Dicerna Pharmaceuticals Inc
Form 10-K
March 10, 2016
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

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

For the fiscal year ended December 31, 2015

or

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

For the transition period from to

Commission File Number: 001-36281

DICERNA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**20-5993609**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

87 Cambridgepark Drive Cambridge, MA 02140

(Address of principal executive offices and zip code)

(617) 621-8097

(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, $0.0001 par value	**The NASDAQ Global Select 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 x

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2) Yes ¨ No x

Based on the closing price of the registrant s Common Stock on the last business day of the registrant s most recently completed second fiscal quarter, which was June 30, 2015, the aggregate market value of its shares (based on a closing price of $13.95 per share) held by non-affiliates was approximately $70.2 million. Shares of the registrant s Common Stock held by each executive officer and director and by each entity or person that owned five percent or more of the registrant s outstanding Common Stock were excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 9, 2016, there were 20,647,983 shares of common stock outstanding.

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DICERNA PHARMACEUTICALS, INC.

2015 ANNUAL REPORT ON FORM 10-K

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Forward-Looking Statements

This Annual Report on Form 10-K includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical fact are forward-looking statements for purposes of this Annual Report on Form 10-K. In some cases, you can identify forward-looking statements by terminology such as may, could, will, would, should, expect, plan, anticipate, believe, estimate, intend, predict, seek, contemplate, potential, ongoing or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the initiation, timing, progress and results of our research and development programs, preclinical studies, any clinical trials and Investigational New Drug (IND) application, New Drug Application (NDA) and other regulatory submissions;
- our ability to identify and develop product candidates for treatment of additional disease indications;
- our or a collaborator s ability to obtain and maintain regulatory approval of any of our product candidates;
- the rate and degree of market acceptance of any approved products candidates;
- the commercialization of any approved product candidates;
- our ability to establish and maintain additional collaborations and retain commercial rights for our product candidates in the collaborations;
- the implementation of our business model and strategic plans for our business, technologies and product candidates;
- our estimates of our expenses, ongoing losses, future revenue and capital requirements;
- our ability to obtain additional funds for our operations;
- our ability to obtain and maintain intellectual property protection for our technologies and product candidates and our ability to operate our business without infringing the intellectual property rights of others;
- our reliance on third parties to conduct our preclinical studies or any future clinical trials;

our reliance on third party supply and manufacturing partners to supply the materials and components for, and manufacture, our research and development, preclinical and clinical trial drug supplies;

our ability to attract and retain qualified key management and technical personnel;

our dependence on our existing collaborator, Kyowa Hakko Kirin Co., Ltd. (KHK), for developing, obtaining regulatory approval for and commercializing product candidates in the collaboration;

our receipt and timing of any milestone payments or royalties under our research collaboration and license agreement with KHK or arrangement with any future collaborator;

our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act;

our financial performance; and

developments relating to our competitors or our industry.

These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these

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forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those set forth in Part I, Item 1A Risk Factors below and for the reasons described elsewhere in this Annual Report on Form 10-K. Any forward-looking statement in this Annual Report on Form 10-K reflects our current view with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our operations, results of operations, industry and future growth. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business and the markets for certain drugs, including data regarding the estimated size of those markets, their projected growth rates and the incidence of certain medical conditions. Information that is based on estimates, forecasts, projections or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained these industry, business, market and other data from reports, research surveys, studies and similar data prepared by third parties, industry, medical and general publications, government data and similar sources. In some cases, we do not expressly refer to the sources from which these data are derived.

Except where the context otherwise requires, in this Annual Report on Form 10-K, we, us, our and the Company re to Dicerna Pharmaceuticals, Inc. and, where appropriate, its consolidated subsidiary.

Trademarks

This Annual Report on Form 10-K includes trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included in this Annual Report on Form 10-K are the property of their respective owners.

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PART I

Item 1. ***Business***

We are an RNA interference-based biopharmaceutical company focused on the discovery and development of innovative treatments for rare inherited diseases involving the liver, for other therapeutic areas in which the liver plays a key role, and for cancers that are genetically defined. We are using our RNA interference (RNAi) technology platform to build a broad pipeline in these therapeutic areas. In many cases we are pursuing targets that have historically been difficult to inhibit using conventional approaches, but where we believe connections between targets and diseases are well understood and documented. We aim to discover, develop and commercialize these novel therapeutics either on our own or in collaboration with pharmaceutical partners, while seeking to retain significant portions of the commercial rights in the rare disease and oncology fields. We have partnered two of our oncology development programs with the global pharmaceutical company Kyowa Hakko Kirin Co., Ltd. (KHK). We are eligible to receive royalties on worldwide net sales for these product candidates. In addition, we have an option to co-promote, in the U.S., a therapeutic targeting the KRAS gene for an equal share of the profits from U.S. net sales.

In choosing which development programs to advance, we apply scientific, clinical, and commercial criteria that we believe allow us to best leverage our RNAi platform and maximize value for our company. Our current development programs are as follows.

Primary Hyperoxaluria Type 1 (PH1). We are developing DCR-PH1 for the treatment of PH1 by targeting the gene encoding the liver enzyme glycolate oxidase. PH1 is known to afflict an estimated one to three people per million of population, and may afflict as many as six to eight people per million of population, and causes severe renal disease and early mortality. In pre-clinical studies, we have shown that, by using our RNAi technology to inactivate the gene encoding glycolate oxidase, we can significantly reduce oxalate levels, the key pathology of PH1. In December 2015, we initiated dosing in our first PH1 clinical trial in normal healthy volunteers, and we expect to begin our first Phase 1 study of DCR-PH1 in patients with PH1 in the first half of 2016. In January 2016, we enrolled our first patient in an international, multicenter, observational study designed to measure biomarkers implicated in PH1. Although the observational study will not include investigational drugs or other interventions, its participants may be considered for enrollment in planned clinical trials of DCR-PH1. We are using our DsiRNA-EX Conjugate technology to develop a subcutaneously injected treatment for PH1 and intend to declare a clinical candidate in the first half of 2016.

Other rare inherited diseases involving the liver. We are investigating a number of other rare diseases involving genes expressed in the liver. We have selected these diseases and disease target genes based on criteria that include having a strong therapeutic hypothesis, a readily-identified patient population, the availability of predictive biomarkers, high unmet medical need, favorable competitive positioning, and a rapid projected path to approval. We are utilizing our DsiRNA-EX Conjugate technology in these rare disease programs.

Other diseases in which the liver plays a key role. We are using our DsiRNA-EX Conjugate technology to develop potential therapeutics for a wide variety of diseases, including chronic liver diseases, cardiovascular

diseases, and viral infection diseases. We have selected these diseases and disease target genes based on criteria that include having a strong therapeutic hypothesis, a readily-identified patient population, the availability of predictive biomarkers, and favorable competitive positioning. For many of these diseases we may seek development partners.

DCR-MYC for MYC-related cancers. We are developing DCR-MYC for the treatment of MYC-related cancers, including hepatocellular carcinoma (HCC) and pancreatic neuroendocrine tumors (PNET). Multiple lines of genetic evidence implicate MYC in the initiation and progression of tumors, including natural variations in the MYC gene that predispose to certain types of cancer, and frequent genetic amplification and overexpression of MYC within tumors. In preclinical studies, inhibition of

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the MYC gene with DCR-MYC has shown strong anti-tumor effects in animal models of human cancers. In the second quarter of 2014, we initiated a multi-center, dose-escalating Phase 1 clinical study of DCR-MYC to assess the safety and tolerability of DCR-MYC in patients with solid tumors, multiple myeloma, or lymphoma who are refractory or unresponsive to standard therapies. In the second quarter of 2015, we announced interim data from this trial, including signs of clinical and metabolic response and tumor shrinkage in two PNET patients. Based on these observations, we announced our intention to expand this on-going phase 1 trial to include a cohort of patients with PNETs. In addition, once the optimal dose of DCR-MYC has been determined, we plan to initiate enrollment of a cohort of patients who will undergo pre- and post-treatment tumor biopsies. Molecular analysis of the MYC gene transcript in these biopsies will allow direct observation of the RNAi-mechanism of action of DCR-MYC. We expect to announce data from the PNET and biopsy cohorts in 2016. In the fourth quarter of 2014, we initiated a global Phase 1b/2 clinical trial of DCR-MYC in patients with advanced hepatocellular carcinoma (HCC). Dose escalation will continue until determination of the MTD, at which point we will initiate an expansion cohort at MTD that includes pre- and post-treatment biopsies, as well as the Phase 2 portion of the study. Molecular analysis of the MYC gene transcript in tumor biopsies will allow direct observation of the RNAi-mechanism of action of DCR-MYC in HCC. We expect to report proof-of-concept data for DCR-MYC in the second half of 2016 based on anticipated results from our two ongoing trials.

Two product candidates in collaboration with KHK, including one for KRAS-related cancers. We are developing, in collaboration with KHK, a therapeutic targeting the KRAS oncogene, a gene that is frequently mutated in numerous cancers, including non-small cell lung cancer, colorectal cancer and pancreatic cancer. Such mutations are associated with aggressive disease and resistance to current therapies. We are also developing, with KHK, a therapeutic targeting a second cancer-related gene, which we are not identifying at this time. KHK is responsible for all preclinical and clinical development activities, including the selection of patient population and disease indications for clinical trials.

DCR-BCAT for ß-catenin and Wnt pathway related tumors. DCR-BCAT is our product candidate for tumors believed to be driven by activating mutations in ß catenin or other tumor-driving genes in the Wnt signaling pathway. In particular, a significant fraction of patients with colorectal carcinoma (CRC) and with HCC are believed to carry activating mutation in ß-catenin or other Wnt pathway genes. In multiple animal models including both CRC and HCC models, DCR-BCAT has shown anti-tumor efficacy in tumors driven by ß-catenin and/or Wnt pathway mutations. DCR-BCAT is based on our DsiRNA-EX technology and is delivered by an advanced version of our EnCore tumor delivery lipid nanoparticle system. We have chosen not to advance DCR-BCAT into IND-enabling studies until we have achieved clinical proof-of-concept with DCR-MYC.

Our drug discovery and development efforts are based on the therapeutic modality of RNAi, a highly potent and specific mechanism for silencing the activity of a targeted gene. In this naturally occurring biological process, double-stranded RNA molecules induce the enzymatic destruction of the messenger RNA (mRNA) of a target gene that contains sequences that are complementary to one strand of the therapeutic double-stranded RNA molecule. Our approach is to design proprietary double-stranded RNA molecules that have the potential to engage the enzyme Dicer and initiate an RNAi process to silence a specific target gene. We refer to these proprietary molecules generally as Dicer substrate short interfering RNAs (DsiRNAs), or as DsiRNA or DsiRNA-EX molecules, depending on the specific structure.

RNAi therapeutics represent a novel advance in drug development. Historically, the pharmaceutical industry has developed small molecules or antibodies to inhibit the activity of disease-causing proteins. This approach is effective

for many diseases; nevertheless, many proteins cannot be inhibited by either small molecules or antibodies. Some proteins lack the binding pockets small molecules require for interaction. Other proteins are solely intracellular and therefore inaccessible to antibody-based therapeutics which are limited to cell surface and extracellular proteins.

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The novel advantage of RNAi is that instead of targeting proteins, RNAi goes upstream to silence the genes themselves. In 2006, the Nobel Prize was awarded for the discovery of RNAi. That same year we incorporated with the goal of developing RNAi-based therapeutics for previously undruggable disease target genes. Rather than seeking to inhibit a protein directly, the better approach may be to prevent its creation in the first place.

We believe our approach to RNAi drug development provides the following qualities and advantages compared to other methods of inducing RNAi.

We initiate RNAi through the Dicer enzyme. DsiRNA and DsiRNA-EX molecules are structured to be processed by the enzyme Dicer, the initiation point for RNAi in the human cell cytoplasm. Unlike earlier generation RNAi molecules, which mimic the output product of Dicer processing, DsiRNA and DsiRNA-EX molecules enter the RNAi pathway prior to Dicer processing. This can result in preferential use of the correct strand of a double-stranded RNA molecule, and therefore increase the efficacy of the RNAi mechanism. We believe this benefit may increase the potency of our DsiRNA and DsiRNA-EX molecules compared to other RNAi-inducing molecules. In addition, due to processing by the Dicer enzyme, our DsiRNA and DsiRNA-EX molecules have multiple sites for chemical modification and conjugation compared to earlier RNAi technologies. At these sites we can use modifications that enhance the drug-like properties on our molecules. Specifically, we can employ modifications that enhance the pharmacokinetic profile and/or suppress immunostimulatory activity.

Our DsiRNA-EX Conjugates enable subcutaneous delivery to the liver. We have developed a proprietary subcutaneous conjugate-based delivery technology for our DsiRNA-EX molecules that is designed to enable convenient subcutaneous delivery for our emerging pipeline of liver-targeted RNAi investigational therapies, and can generally be applied to disease target genes and viral pathogens in the liver. These conjugates do not involve lipid nanoparticles and are built on the DsiRNA-EX platform, using an extension to one end of the double-stranded DsiRNA molecule. These extensions are unique to our technology, enabling a differentiated and independent approach to subcutaneous delivery of RNAi-inducing therapeutics.

In May 2015, we advanced our conjugate platform by extending its observation of potent, durable knockdown of gene expression with DsiRNA-EX Conjugates from mouse models to non-human primates. These data in non-human primates were presented at the 17th Annual TIDES: Oligonucleotide and Peptide Therapeutics from Research through Commercialization conference.

In September 2015, we further advanced our conjugate platform by showing that a single dose of DsiRNA-EX Conjugates significantly below 1 mg/kg can reduce liver gene expression by 50% in mice, and a single dose of 5 mg/kg can yield greater than or equal to 95% reduction in gene expression.

To date, we have demonstrated in vivo gene silencing activity with DsiRNA-EX Conjugate molecules against more than ten liver disease gene targets.

We are driving toward selection of our first DsiRNA-EX Conjugate clinical candidate, in order to advance a program into clinical development in 2017. We intend to use DsiRNA-EX Conjugates in all future programs involving targets in the liver, and intend to declare multiple DsiRNA-EX Conjugate clinical candidates in 2016.

Our EnCore lipid nanoparticle technology enables delivery to solid tumors. We have developed our proprietary EnCore lipid nanoparticle (LNP) technology for delivery of DsiRNA and DsiRNA-EX molecules to tumors. The EnCore system is engineered to accumulate in tumors and mediate delivery of DsiRNA and DsiRNA-EX molecules into tumor cells. We have extensive pre-clinical data, in multiple animal models of human tumors, of effective RNAi delivery mediated by the EnCore system. We utilize this delivery system in our DCR-MYC and DCR-BCAT programs and intend to utilize it for future programs in oncology.

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We believe we have a robust patent portfolio covering our proprietary RNAi platform. As of March 1, 2016, our patent estate included over 20 issued patents and over 70 pending patent applications covering our DsiRNA and DsiRNA-EX payload technologies and our lipid nanoparticle and conjugate delivery technologies.

Our executive management team has extensive experience in the biopharmaceutical industry. In addition, various members of our management team and our board of directors have contributed to the progress of the RNAi field through their substantial involvement in companies such as Cephalon Inc., Genta Inc., GlaxoSmithKline plc, Pfizer Inc., Sanofi, Sirna Therapeutics Inc., and other companies. Our co-founder and chief executive officer, Douglas M. Fambrough III, Ph.D., was a lead venture capital investor and board member of Sirna Therapeutics, an early RNAi company acquired by Merck & Co., Inc. in 2006 for $1.1 billion.

Strategy

We are committed to delivering transformative RNAi-based therapies to patients with rare inherited diseases involving the liver and for cancers that are genetically defined. The key elements of our strategy are as follows.

Create new programs in indication areas with high unmet medical need. We intend to continue to use our proprietary RNAi technology platform to create new, high value pharmaceutical programs. Our primary focus will remain: (1) rare inherited diseases involving the liver; and (2) genetically-defined oncogene targets in oncology. We are also pursuing the use of our DsiRNA-EX Conjugate technology for programs in other therapeutic areas, including disease areas with large population sizes.

Validate our product candidates and our platform in clinical proof-of-concept studies. We expect to announce proof-of-concept clinical data for DCR-MYC in the second half of 2016, clinical data from our single ascending dose DCR-PH1 trial in patients in early 2017, and to initiate proof-of-concept clinical studies in late 2017 using our DsiRNA-EX Conjugate platform. Based on precedents in the RNAi field, we are optimistic that our preclinical data showing the significant knockdown of target mRNA activity may translate into clinical results.

Continue to develop product candidates for rare diseases and oncology while seeking to retain significant portions of the commercial rights.

Enter into additional partnerships with pharmaceutical companies either on our RNAi technology platform or specific indications or therapeutic areas. We may choose to establish partnerships with pharmaceutical companies across multiple programs or indication areas depending on the attractiveness of the opportunities. These partnerships may provide us with further validation of our technology platform, funding to advance our proprietary product candidates, and/or access to development, manufacturing and commercial capabilities.

Continue to invest in our RNAi technology platform. We will continue to invest in expanding and improving our DsiRNA-EX RNAi payload technologies and our conjugate and LNP delivery technologies. Building on what we believe are significant advantages in potency and delivery, we seek to develop product

candidates that will have a profound impact on the lives of patients.

Our RNAi Technology Platform

All of our drug discovery and development efforts are based on the therapeutic modality of RNAi, a highly potent and specific mechanism for silencing the activity of a targeted gene. The RNAi process is triggered by double-stranded RNA molecules containing sequences that are complementary to the sequence of the targeted gene. Our novel and highly potent approach is based on double-stranded RNAs that are aimed to serve as optimal substrates for the RNAi initiating enzyme Dicer, and thus our proprietary RNAi molecules are known as Dicer substrates, which we refer to as DsiRNAs generally or as DsiRNA or DsiRNA-EX molecules, depending on the specific structure. The RNAi machinery, guided by a DsiRNA or DsiRNA-EX molecule (or other double-stranded RNAi-inducing molecules) causes the targeted destruction of specific mRNAs of the complementary

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target gene. Destroying these mRNAs immediately decreases the biological activity from the target gene. A single DsiRNA or DsiRNA-EX molecule incorporated into the RNAi machinery can destroy hundreds or thousands of mRNAs from the targeted gene.

We believe that our DsiRNA and DsiRNA-EX molecules have distinct properties in triggering the RNAi pathway to silence disease-related genes, thereby providing advantages for triggering RNA interference compared to other types of double-stranded RNAs used to induce RNAi. Our DsiRNA and DsiRNA-EX molecules are structured to be optimal for processing by the Dicer enzyme. We believe that other RNAi-inducing molecules currently in development mimic the output of a Dicer enzyme processing event, and thus act at a later point in the RNAi pathway. By contrast, DsiRNA and DsiRNA-EX molecules enter the RNAi pathway through being presented to Dicer itself, the pathway s natural initiation point. By entering the RNAi pathway at that point, we believe that DsiRNA and DsiRNA-EX molecules are able to maximize the efficacy of the RNAi mechanism, making DsiRNA and DsiRNA-EX molecules inherently more potent than traditional RNAi-inducing molecules. This potency advantage derives from the structure of the DsiRNA and DsiRNA-EX molecules and how they interact with the Dicer enzyme. Specifically, the structure of the DsiRNA and DsiRNA-EX molecule is able to indicate to the Dicer enzyme which of the two RNA strands should be used to guide the selective destruction of disease gene target mRNAs by the RNAi machinery. We have found in animal tests that this benefit both increases the potency of our DsiRNA and DsiRNA-EX molecules relative to other RNAi-inducing molecules and enables many more sequences to be used to generate our potent DsiRNAs compared to other RNAi-inducing molecules. We therefore believe that the nature of the interaction of our DsiRNA and DsiRNA-EX molecules with the RNAi pathway intervention facilitates the discovery of new DsiRNA and DsiRNA-EX therapeutic candidates and further strengthens our intellectual property position.

Schematic representation of our DsiRNA

DsiRNAs are precisely-sized double-stranded RNA molecules that are asymmetric. In the form we use for some of our therapeutic programs, the longer strand is 27 bases long and is complementary to the target gene we seek to silence, known as the Guide Strand. The shorter strand is 25 bases long and known as the Passenger Strand. The two strands are complementary across their length, with the two additional bases of the 27-mer forming a two-base overhang at the 3 -end of the molecule. For our product candidates we use chemical modifications (for example, 2 -OMe, 2 -F and phosphorothioates) and we also use two bases of DNA at the 3 end of the Passenger Strand. These DNA bases, along with the two-base overhang on the 27-mer, cause the Dicer enzyme preferentially to take up the Guide Strand, leading to several advantages for DsiRNAs compared to other RNAi-inducing molecules. The DsiRNA structure is utilized in our DCR-MYC and our KHK-partnered oncology programs.

Schematic representation of our DsiRNA-EX

In addition to 25/27-mer duplex DsiRNAs, we have developed the DsiRNA-EX technology, where extensions to one or more of the ends of the RNA strands can provide added functionality including

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sites for conjugation and other modifications. Chemical modifications (for example, 2 -OMe, 2 -F and phosphorothioates) are located on both strands at specific positions. Our DCR-PH1, DCR-BCAT, and all DsiRNA-EX Conjugate programs utilize these structures.

In addition, due to the nature of how the Dicer enzyme processes a DsiRNA or DsiRNA-EX molecule, our DsiRNA and DsiRNA-EX molecules may provide advantages for targeted delivery methods that do not use lipid nanoparticles. Our DsiRNA molecules present chemical conjugation points, which can be used to attach targeting agents or other agents that facilitate delivery or enhance the drug-like properties of the molecules. Our DsiRNA-EX molecules include extensions to one or more of the ends of the RNA strands, which allows even further potential for chemical modification. Notably, the extensions enable the development of subcutaneously delivered molecules that are conjugated to targeting ligands and possess enhanced biological stability, and that can be administered subcutaneously or intravenously without LNPs. These and other favorable features are introduced into the DsiRNA and DsiRNA-EX molecules while maintaining high RNAi activity. Due to how the Dicer enzyme processes a DsiRNA or DsiRNA-EX molecule, we can use stable covalent non-cleavable linkers for conjugation instead of less stable cleavable linkers that other RNAi molecules may require.

Optimization of our DsiRNA and DsiRNA-EX molecules

For therapeutic use in humans, our DsiRNA and DsiRNA-EX molecules are optimized both with respect to base sequence and chemical modifications to increase stability and mask them from mechanisms that recognize foreign RNAs, inducing immune system stimulation. Our optimization process begins with the screening of 300 to 600 RNA sequences predicted to have good activity based on a proprietary DsiRNA prediction algorithm. Through optimization and chemical modification we identify the most active RNAi molecules while engineering in enhanced stability and engineering out immunostimulatory activity. Our DsiRNA and DsiRNA-EX molecules routinely achieve high potencies, with IC50 values (the amount of material required to silence a target gene by 50 percent) typically in the 0.1 to 3.0 picomolar range in *in vitro* studies. Owing to the enzymatic nature of the RNAi pathway, this is 100 to 1,000 times as great as, or greater than, the potency of most traditional small molecule therapeutics. Furthermore, our research and testing to date suggest that our optimized DsiRNA and DsiRNA-EX molecules are significantly reduced in their ability to induce an immune system response in humans.

Our drug delivery technologies

Our process of delivery

From the initial discovery of the RNAi pathway in mammals through more recent attempts at creating RNAi-based therapeutics, drug delivery has been a profound challenge. Most nucleic acids, including our DsiRNA and DsiRNA-EX molecules, are unable to enter cells on their own, but cell entry is required to access the RNAi machinery in the cytoplasm and thus to silence the targeted genes. An effective drug delivery technology is required to ferry the DsiRNA and DsiRNA-EX molecules into cells, through the cell internalization pathway and ultimately release the DsiRNA and DsiRNA-EX molecules into the cell cytoplasm. We believe that our drug delivery technologies overcome these challenges. Effective RNAi drug delivery requires the following three steps: Step 1. Accumulation in the target tissue, Step 2. Binding to and internalization by the target tissue cells, Step 3. Release from the internalization compartment into the cytoplasm.

Subcutaneous delivery to the liver by DsiRNA-EX Conjugates

We believe that the structure of DsiRNA-EX molecules are well suited for direct conjugation to delivery agents. We have developed a delivery system based on conjugation of a targeting agent to the extended region of the DsiRNA-EX

molecules. We call such molecules DsiRNA-EX Conjugates. This system should provide for generalized subcutaneous administration in humans of DsiRNA-EX Conjugates to the hepatocyte cells of the liver. The targeting agent used in our DsiRNA-EX Conjugates is GalNAc (n-acetyl galactosamine), which

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provides for highly specific uptake in hepatocyptes through the hepatocyte-expressed asialoglycoprotein receptor. For example, we have administered DsiRNA-EX Conjugates subcutaneously in mice and have seen IC 50 values substantially below 1.0 milligrams per kilograms of body weight for multiple gene targets, including observations of IC 50 values below 0.3 milligrams per kilogram of body weight

DsiRNA-EX Conjugate Structure

The structure of DsiRNA-EX Conjugates underlying Dicerna s most potent RNAi inducers consists of two RNA strands: a shorter Guide strand with a two-base overhang on its 3 end, and a longer Passenger strand with a four-based tetraloop structure that folds back to form a short stem section. Attached to each of the four tetraloop bases, via a short linker, is a single GalNAc molecule.

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DsiRNA-EX Conjugates yield high-potency gene silencing agents. The data shows a dose response curve for silencing of a therapeutic liver target after subcutaneous administration of a DsiRNA-EX Conjugate in mice. In this example the calculated IC 50 value is <0.3 milligrams per kilogram of body weight.

EnCore lipid nanoparticles are composed of a lipid-DsiRNA or lipid-DsiRNA-EX core surrounded by an envelope of different lipids which mediate the accumulation, internalization and release into the cytoplasm of the DsiRNA or DsiRNA-EX molecules in the core of the particle.

EnCore lipid nanoparticles for delivery

We are using our EnCore lipid nanoparticles (LNPs) for delivery of our DsiRNA and DsiRNA-EX molecules to solid tumors. We believe that the EnCore LNPs effectively mediate all steps required for delivery to tumor cells: accumulation, binding and internalization, and release into the cytoplasm. The EnCore LNPs are

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comprised of a Core of lipid and DsiRNA or DsiRNA-EX molecules, surrounded by an Envelope of chemically distinct lipids that are designed to interact with the target tissue. The Core allows EnCore to carry a large payload of DsiRNA or DsiRNA-EX molecules while simultaneously protecting them from degrading enzymes. The envelope interacts with the target tissue to mediate accumulation, binding and internalization, and release into the cytoplasm. Our EnCore LNPs show preferential delivery to tumor cells, compared to liver cells (the other tissue type commonly associated with LNP-based RNAi delivery) due to the specific lipid composition and nature of the polyethylene coating on the surface of the particles. Our EnCore LNPs also have beneficial properties such as high tolerability (low toxicity), ease of manufacturing, effective RNAi payload loading, and protection of the DsiRNA or DsiRNA-EX payload. We have successfully demonstrated each of these properties of EnCore LNPs and have used them to achieve effective delivery of our DsiRNA and DsiRNA-EX molecules in animal models of cancer.

Delivery to the liver with Arbutus LNP

Our licensing agreement with Arbutus Biopharma Corporation (Arbutus) and one of its subsidiaries enables us to use Arbutus proprietary LNP for delivery of DCR-PH1 to treat PH1. Arbutus lipid nanoparticle system has been shown in other human clinical studies to provide potent, safe and effective RNA delivery to hepatocytes (liver cells). We anticipate that our licensing of Arbutus LNP technology will help streamline the development path for DCR-PH1 and allows us to focus our EnCore LNP efforts on our oncology pipeline.

Our Product Candidates

In choosing clinical programs to pursue using our DsiRNA and drug delivery technologies, we apply the criteria listed below. We believe that our current development programs meet most or all of these criteria.

Strength of therapeutic hypothesis. Our current product candidate gene targets, and those we intend to pursue in the future, are a well-understood part of the disease process where a therapeutic intervention is likely to have substantial benefit for the patient. Because our RNAi technology platform allows us to pursue product candidate gene targets that have historically been difficult to inhibit using conventional approaches, we believe that there are a substantial number of such targets without existing pharmaceuticals on the market.

Readily-identified patient population. We seek disease indications where patients can be readily identified by the presence of characteristic genetic mutations. In the case of genetic diseases, these are heritable genetic traits. In the case of oncology, these are genetic changes that have occurred in tumor cells as part of the tumor-formation process. In both cases, available genetic tests and techniques can identify patients that carry these mutations.

Predictivity of biomarkers for early efficacy assessment. We seek indications where there is a clear relationship between the disease status and an associated biomarker that we can readily measure. This approach will allow us to determine in early stages of clinical development whether our DsiRNA molecules are likely to have the expected biological and clinical effects in patients.

Unmet medical need. We seek to provide patients with significant benefit and alleviation of disease. The indications we choose to approach have high unmet medical need, which is intended to enable us to better access patients and qualify for pricing and reimbursement that justify our development efforts.

Competitive positioning. We seek indications where we believe we have the opportunity to develop either a first-in-class product or a clearly differentiated therapy.

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Rapid development path to approval. To reach commercialization expeditiously and to help ensure our ability to finance development of our product candidates, we have identified indications with the potential for rapid development through marketing approval. Specifically, we believe that certain of our product candidates have the potential to obtain Breakthrough Therapy Designation as well as accelerated approval from the U.S. Food and Drug Administration (FDA).

DCR-PH1 for PH1

PH1 is a rare, inherited autosomal recessive disorder of metabolism in the liver that usually results in severe damage to the kidneys. PH1 is caused by the failure of the liver to metabolize a precursor of oxalate, a highly insoluble metabolic end-product in humans, resulting in excess oxalate and high levels of oxalate in the urine. This oxalate is formed during the metabolic breakdown of hydroxyproline, a naturally occurring component of collagen. In individuals with PH1, crystals of calcium oxalate form in the renal tubules, leading to chronic and painful cases of kidney stones and subsequent fibrosis, known as nephrocalcinosis. Despite the typical interventions of a large daily intake of water to dilute the oxalate and other interventions, many patients eventually enter kidney failure (end-stage renal disease, or ESRD) and become eligible for transplant. While in ESRD, besides having to endure frequent dialysis, patients are afflicted with a build-up of oxalate in the bone, skin, heart and retina with concomitant debilitating complications, a condition known as systemic oxalosis. Some patients show partial disease amelioration with oral pyridoxine supplementation, although disease progression usually continues. Supportive care treatments are available, generally with only minor or no effect on disease progression. Currently, aside from dual liver and kidney organ transplantation, there are no highly efficacious therapeutic options for most patients with PH1. Dual liver and kidney transplantation presents a challenge in identifying a donor and is associated with high co-morbidity rates. Even in those U.S. patients treated with dual liver and kidney transplant, five-year post-transplant survival is 64 percent. For patients treated with kidney transplant alone, five-year survival is 45 percent.

While the true prevalence of PH1 is unknown, according to estimates recently published by the New England Journal of Medicine the prevalence of PH1 is at least one to three per million of population. Based on the frequency of occurrence of disease mutations in the population derived from genome sequence databases, the estimated genetic incidence is six and half per million of population, which we believe suggests that PH1 is under-diagnosed. Roughly consistent with the genetic incidence estimate, the disease is thought to have an incidence of one per 120,000 live births a year in Europe. Certain populations, for example in the Canary Islands (Spain) or Kuwait, have higher incidences due to founder effects or consanguinity. We believe approximately 800 patients total are currently in two distinct disease registries in North America and Europe, although these registries do not capture all afflicted

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patients. Incidence is believed to be similar in Asia. Given the severity of PH1, we believe this disease represents a significant market opportunity. The patient advocacy group, the Oxalosis and Hyperoxaluria Foundation, based in New York City, New York, seeks to represent patients with PH1.

Therapeutic rationale for PH1

We believe that there is a strong rationale for focusing our RNAi technology on the development of product candidates for the treatment of PH1. The hydroxyproline breakdown metabolic pathway that is disrupted in PH1 consists of a number of enzymes. The gene encoding the final enzyme in the pathway, alanine-glyoxylate aminotransferase 1 (AGT1), is mutated in patients with PH1. Under normal circumstances, AGT1 metabolizes oxalate precursors into the harmless amino acid glycine, which is then used by the body or excreted. But when AGT1 function is disrupted due to mutation, oxalate begins to build up, resulting in progressive loss of kidney function and, ultimately, kidney failure. Approximately 50 percent of PH1 patients have kidney failure by age 30 to 35.

Animal studies have shown that intervening one step earlier in the metabolic pathway can reduce or eliminate the abnormally high oxalate production caused by the absence of AGT1 enzyme activity. These studies employ mice in which the gene encoding AGT1 has been genetically deleted to create an animal model of PH1. Similar to human patients, these mice have elevated levels of oxalate in their urine. When the enzyme one step earlier in the metabolic pathway than AGT1 is eliminated by genetic deletion in this animal model of PH1, oxalate levels in the urine are substantially reduced. These studies demonstrate that genetic deletion of the enzyme prior to AGT1 in the pathway prevents the formation of the oxalate precursor and the buildup of oxalate. The enzyme upstream of AGT1 is known as glycolate oxidase (GO) and is encoded by the gene HAO1. In normal animals and humans HAO1 is expressed exclusively or nearly exclusively in the liver.

Preclinical data for DCR-PH1

We are using our DsiRNA-EX technology and licensed lipid nanoparticle delivery technology to develop DCR-PH1, a product candidate designed to specifically inhibit the gene HAO1, which encodes GO. We have generated highly potent and specific DsiRNA-EX molecules targeting HAO1 and believe we have optimized these molecules to enhance their pharmaceutical properties. We have concluded manufacturing scale-up and Good Laboratory Practice (GLP) toxicity studies which allowed filing an IND application with FDA in August, 2015 and CTAs with several countries in Europe; we anticipate initiating clinical trials in the first half of 2016. This past December, we also initiated a study in normal healthy volunteers.

We have demonstrated the efficacy of DCR-PH1 in both mice and in non-human primates (monkeys). The data demonstrate that after a single intravenous dose of 0.3 milligrams per kilogram body weight of DCR-PH1 the average reduction of HAO1 gene expression was 95% in mice and 84% in monkeys soon after dosing. At a much later time, 28 and 29 days after dosing, the target gene expression was still significantly reduced by an average of 54% in mice and 68% in monkeys. These data are supportive of an infrequent clinical dosing regimen.

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DCR-PH1 consists of a DsiRNA-EX payload formulated in a lipid nanoparticle delivery system

A. Long-duration Reduction in Urinary Oxalate after HAO1 Knockdown

B. Urinary Glycolate Elevation a Biomarker of HAO1 mRNA and GO Protein Reduction

In the mouse model of PH1, treatment with DCR-PH1 results in a reduction in levels of urinary oxalate and, as expected by the mechanism of action, elevation in levels of urinary glycolate. Increased urinary glycolate alone may indicate a positive treatment effect; in PH1 patients treated with DCR-PH1, elevation of urinary glycolate may precede reduction in urinary oxalate as accumulated oxalate is flushed out in urine over time.

Phase 1 Clinical Development plan for DCR-PH1

Our development program for DCR-PH1 has multiple on-going components, including an observational study and clinical studies in both patients and healthy volunteers. In January of 2016 we enrolled the first patient in our PH1 observational study for patients with genetically confirmed diagnosis of PH1 and mild to moderate

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renal impairment to (1) characterize the baseline variability and factors that influence changes in urine and blood oxalate and glycolate levels and renal function over time; and (2) better characterize the systemic complications associated with PH1. We anticipate that up to 25 patients will be enrolled. We anticipate a majority of the patients enrolled in the observational study may be considered for enrollment in the Phase 1clinical study in patients. In December 2015, we initiated dosing in our first PH1 clinical trial, which is a Single Ascending Dose (SAD) level trial in normal healthy volunteers and is being conducted in the U.S., and will terminate at a low dose level. Data from the healthy volunteer study will be used to facilitate initiation of clinical studies in patients in the U.S. We expect to begin our first Phase 1 study of DCR-PH1 in patients with PH1 in the first half of 2016 at EU clinical sites. This is an open label study with dose escalation in a Single Ascending Dose (SAD) cohort. After review of the SAD data, and consideration of the competitive environment as well as progress with our DsiRNA-EX Conjugate efforts in PH1, we may initiate dosing of a Multiple Ascending Dose (MAD) level cohorts. We intend for the study to be conducted in the US, EU, and other countries. The primary objective of the Phase 1 study in patients is to determine the safety profile and recommended dose of DCR-PH1. Secondary objectives include the determination of pharmacokinetics (PK) and the pharmacodynamics (PD) profile of DCR-PH1, including changes in urine oxalate levels.

Additional programs under investigation involving the liver

We are investigating a number of other rare diseases and other therapeutic classes involving disease target genes expressed in the liver. We have selected these diseases and disease target genes based on our stated criteria, including having a strong therapeutic hypothesis, a readily-identified patient population, the availability of predictive biomarkers, high unmet medical need, favorable competitive positioning, and a rapid path to approval. We are currently optimizing DsiRNA-EX Conjugate molecules directed toward multiple disease target genes and anticipate in 2016 declaring multiple DsiRNA-EX Conjugates for advancement into IND-enabling studies. We may not disclose the identities of these gene targets, or the diseases we intend to treat, until after an IND has been filed.

DCR-MYC for solid tumors

For the treatment of cancer we are developing the product candidate DCR-MYC, which utilizes our DsiRNA and EnCore LNP technologies to target the oncogene MYC. We believe that DCR-MYC has the potential to be used broadly in solid tumors from many tissues of origin, based on observed patterns of MYC oncogene amplification across diverse tumor types.

There is abundant evidence that the MYC oncogene is a driver of human cancer. The MYC oncogene, originally identified as a transformative agent in naturally-occurring tumor viruses, is one of the most frequently mutated oncogenes found in human cancers. A therapy that reduces or eliminates elevated MYC activity has the potential to generate therapeutic benefits for patients with various tumor types that include MYC amplifications or other elevations of MYC activity. Inhibition of MYC activity has generated strong anti-tumor responses in a variety of animal models of cancer, which we have also observed in our own labs. Genetic techniques in mice which reduce MYC expression or inhibit MYC protein activity have been shown to prevent tumor formation or cause substantial tumor shrinkage, depending on the mouse genetic model of cancer employed in the experiment. These results have been obtained from mouse tumor models where MYC is not responsible for tumor initiation. We believe that this animal model data is supportive of the use of MYC-targeted therapy to treat cancer in humans.

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Association of U.S. cancer patients with aberrant MYC expression

CANCER TYPE	APPROXIMATE PERCENTAGE OF PATIENTS
Liver (hepatocellular)	50%
Breast	80%
Colorectal	70%
Gastric	51-77%
Gynecological	90%
Prostate	80-90%
Small cell lung	18-30%

The frequently observed mutations in the MYC gene usually result in the duplication or higher-order amplification of the MYC oncogene within the tumor cell DNA, resulting in elevated levels of MYC activity. Other types of mutations have also been shown to cause elevated levels of MYC activity, such as chromosomal translocations that result in the activation of the MYC oncogene. In addition, human genetic variants known as single-nucleotide polymorphisms in the MYC gene have been identified that are believed to predispose humans to various cancers. Based on these genetic data in humans, we believe that a therapy that reduces or eliminates elevated MYC activity has the potential to generate therapeutic benefits for patients with various tumor types that include MYC amplifications or other elevations of MYC activity.

Recent molecular work demonstrates that MYC over-expression drives the cancer process by selectively amplifying expression of genes typically expressed by a cell type. Based on this property, MYC is sometimes described as a universal amplifier, which can boost the activity of other cancer-related genes and push a cell to abnormal levels of growth. This model for MYC function suggests that an intervention that could bring down the expression of MYC to normal levels could have therapeutic benefit for cancer patients.

Despite its obvious attractiveness as a therapeutic target, MYC has not been successfully targeted by conventional small molecule drugs and is not amenable to antibody therapeutics. Others have attempted to develop small molecules that inhibit MYC but to date these have not been sufficiently potent and specific to be viable product candidates. We believe that the reason for this is likely due to the absence of a good binding pocket on the MYC protein. MYC is a member of a protein family known as transcription factors, and these proteins generally lack good binding pockets for small molecules. MYC is not amenable to treatment with antibodies; MYC is only found inside the cell and antibodies are limited to extracellular and cell surface targets.

Therapeutic rationale for DCR-MYC in hepatocellular carcinoma (HCC)

For several reasons, we believe that HCC presents an excellent starting point for clinical development of an MYC-targeted therapeutic. First, HCC patients frequently show amplifications of the MYC oncogene, suggesting an important role for MYC activity in a significant fraction of HCC patients. Second, in animal models of disease, we have observed strong anti-tumor responses after treatments with our product candidate DCR-MYC. Finally, there is high unmet medical need for effective treatments for advanced HCC.

Liver cancer is the second leading cause of cancer-related deaths worldwide, with 745,000 deaths per year. HCC is the most common form of liver cancer in adults, accounting for 85-90% of primary liver cancers. Many cases of HCC

result from inflammation associated with infection with the hepatitis B or C virus, which can lead to cirrhosis of the liver. However, non-alcoholic fatty liver disease, associated with obesity and diabetes, is also an important risk factor for HCC.

Early-stage HCC is generally treated with surgery that has the potential to be curative. However, given the non-specific symptoms characteristic of HCC, the majority of patients are diagnosed only after HCC is at an

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advanced stage. Advanced HCC has limited treatment options and is associated with poor patient outcome and high mortality. Chemotherapies have demonstrated poor efficacy in HCC and there is no FDA-approved chemotherapeutic regime. Nexavar (marketed by Amgen Inc. and Bayer AG) is the only FDA-approved drug for the treatment of advanced or unresectable HCC. Unmet medical needs include the identification and development of additional and more effective treatments for patients not eligible for surgical resection, a reduction in relapse rates and an increase in overall survival rates.

Phase 1 clinical development plan for DCR-MYC

We have initiated a clinical development program of DCR-MYC for the treatment of MYC-related cancers. The DCR-MYC development program includes two separate Phase 1 trials: one trial in patients with solid tumors, multiple myeloma or lymphoma, and one trial in patients with advanced Hepatocellular carcinoma (HCC). Each Phase 1 trial is an open label study with two parts. The first part is a standard dose escalation study to determine the maximum tolerated dose. The second part is an expansion cohort treated at the maximum tolerated dose determined from the dose escalation portion of the study. We submitted an IND application for DCR-MYC to the FDA in the second quarter of 2014 for the First in Human Study (FIH) which allows for the enrollment of patients with solid tumors, multiple myeloma, or lymphoma without other alternative therapeutic options. Our FIH Phase 1 trial has a primary objective of determining the safety and tolerability of DCR-MYC in patients and to determine the maximum tolerated dose when administered in a cycle of two weekly infusions followed by one week without an infusion. Secondary objectives of the trial include: (1) evaluating the action in the body of the active ingredient in DCR-MYC (a DsiRNA known as DCR-M1711), such as absorption, distribution, metabolism and elimination over time. (2) observing decreases in the level of MYC transcript when comparing pre- and post-treatment biopsies of tumor tissues; (3) observing a decrease in tumor metabolic activity by imaging techniques, as a biomarker for inhibition of MYC function in tumors; (4) evaluating evidence of anti-tumor activity in patients treated with DCR-MYC; and (5) evaluating the potential use of blood biomarkers to assess activity of DCR-MYC.

The FIH trial enrolled the first patient in the second quarter of 2014. In the second quarter of 2015, we announced interim data from this trial, including signs of clinical and metabolic response and tumor shrinkage in two patients with low to intermediate grade pancreatic neuroendocrine tumors (PNET). Based on these observations, we announced our intention to expand this on-going Phase 1 trial to include a cohort of patients with PNETs. In addition, once the optimal dose of DCR-MYC has been determined, we plan to initiate enrollment of a cohort of patients who will undergo pre- and post-treatment tumor biopsies. Molecular analysis of the MYC gene transcript in these biopsies will allow direct observation of the RNAi-mechanism of action of DCR-MYC.

We expect to report proof-of-concept data for DCR-MYC in the second half of 2016 based on anticipated results from our two ongoing trials.

The second study of DCR-MYC is a Phase 1b/2 trial in patients with locally advanced or metastatic HCC. This study has a primary objective of determining the safety and tolerability of DCR-MYC in patients with late stage HCC and to determine a maximum tolerated dose when administered in a cycle of two weekly infusions followed by one week without an infusion. Secondary objectives of the trial include: (1) evaluating the action in the body of the active ingredient in DCR-MYC, DCR-M1711, such as absorption, distribution, metabolism and elimination over time; (2) observing decreases in the level of MYC transcript when comparing pre- and post-treatment biopsies of tumor tissues; (3) evaluating evidence of anti-tumor activity in patients treated with DCR-MYC; and (4) evaluating the potential use of blood biomarkers to assess activity of DCR-MYC.

The first patient was enrolled in this trial during the first quarter of 2015. We are conducting this trial at sites in the US, Singapore and South Korea. Additional trial sites may be added to the study during the dose escalation or

expansion portions of the trial if needed to meet enrollment goals.

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As with most Phase 1 trials, ours are not designed to yield statistically significant efficacy or molecular marker results. Accordingly, any observed results may be due to chance and not efficacy of DCR-MYC. The principal purpose of our Phase 1 trials will be to provide the basis for design of larger, definitive trials. Those trials will enroll more patients and they will be designed to evaluate potential safety and efficacy of the product candidate with statistical significance.

We have developed an additional product candidate using our DsiRNA-EX technology and the next generation EnCore tumor delivery technology.

Product candidate for ß-catenin and Wnt pathway-related solid tumors

The ß-catenin/Wnt pathway is consistently activated in human tumors, including ~50% of hepatocellular carcinomas (HCC) and ~90% of colorectal cancers (CRC). This is often caused directly by tumorigenic mutations in the APC or ß-catenin /CTNNB1 gene. Robust preclinical and genetic evidence strongly suggests that inhibiting ß-catenin function would yield broad therapeutic benefit in oncology, but efforts to target it using conventional drug modalities have been unsuccessful to-date. DCR-BCAT, our product that contains DsiRNA-EX targeting human ß-catenin formulated in EnCore lipid nanoparticles (LNP) of novel composition, effectively delivered the payload to multiple tumor types including the more clinically relevant CRC liver metastases and caused up to 80% tumor growth inhibition in multiple Wnt/ß-catenin activated colorectal tumor models, and near-complete regression in a model of spontaneous hepatocellular carcinoma (HCC). Importantly, there was no growth inhibition observed when ß-catenin was downregulated in APC/ß-catenin wild type CRC tumors suggests that the ß-catenin DsiRNA efficiently and specifically inhibits the Wnt/ß-catenin pathway. In addition, we also found that the dual targeting of Wnt pathway and MEK using DCR-BCAT and an FDA approved Trametinib resulted in robust anti-tumor activity compared to either of the single agent treatment in preclinical models of CRC with RAS mutations.

Therapeutic rationale for wnt-related solid tumors

Globally, HCC is responsible for over 250,000 deaths annually, and is thus the third most common cause of cancer death with over 500,000 new cases diagnosed per year. Although surgery is the most effective treatment for HCC, tumor recurrence is very high, and the 5-year survival rate remains at only 10%. Because majority of the patients are diagnosed at advanced stage, chemotherapies are frequently ineffective. Targeted therapy, Sorafenib prolonged the overall survival of the HCC patients only by 2-3 months. Thus there is an urgent need for a tolerable, life extending strategies in the management of HCC patients. A promising approach will be to define novel targets for therapeutic strategies based on the identification of molecular pathways responsible for initiating and sustaining HCC. The canonical Wnt signaling pathway is one such signaling mechanism that is frequently activated in this disease and is clearly implicated in tumorigenesis

With 940,000 recorded cases worldwide per year, CRC is the third most common malignancy in the world. Despite efforts to improve early detection and improved therapy, nearly 500,000 patients die from CRC each year worldwide. It has become evident that the main problem in the treatment of CRC is not so much eradication of the primary tumor, but rather the formation of incurable metastases. Its high mortality rates are particularly associated with the occurrence of metastases in the liver. Even when metastatic disease remains limited to the liver, the majority of these are unresectable and the reported rates of successful resection have been found to be less than 20%, and conventional chemotherapy is only marginally effective.

Targeted therapies (current standard of care) such as anti-EGFR treatment and anti-VEGF treatments made some improvement on mCRC treatment strategies compared to chemotherapies. Epidermal growth factor receptor (EGFR) is expressed in approximately 80% of CRCs. But approximately 40% to 50% of colorectal tumors are known to have a

mutated KRAS gene, and 10-20% of CRCs have mutated BRAF gene indicating that these patients are unlikely to benefit from anti-EGFR treatment and therefore these CRC patients are excluded in those treatments, leaving only a small subset of CRC patients eligible for anti-EGFR treatment. Clinical studies

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confirmed the lack of benefit of epidermal growth factor receptor (EGFR)-directed therapy in patients with KRAS/BRAF mutations, limiting treatment options to standard chemotherapeutics with or without VEGF pathway targeted agents. The anti-VEGF therapy is efficacious in mCRCs when combined with chemotherapy, but the overall survival benefit is still very modest. Clinical data also suggest that the VEGF blockade upregulates inflammatory pathways and promote metastasis in the face of VEGF blockade. Improving the outcome in CRC will require overcoming the resistance mechanisms that thwart the anti-VEGF therapy. The CRC patients with KRAS/BRAF wild-type may be able to derive some benefit from anti-EGFR therapy, but it still remains unclear if these patients will definitely respond. MEK inhibitors are being tested in CRC patients too, as MEK is central to the pathogenesis of CRC as a downstream effector of mutant KRAS and BRAF, however the single agent efficacy has been very limited to date. All these suggest that targeting resistance pathways through rational combination strategies may lead to greater efficacy. Several studies have identified the aberrant activation of Wnt signaling as the primary cause of CRCs and as a resistance mechanism in RAS mutant CRCs. Despite this knowledge, none of the therapeutic agents specifically targeting the Wnt pathway has yet been approved to date. Since Wnt pathway is activated in majority of the CRCs (~90%) and HCCs (~50%), we believe that our potent and specific Wnt inhibitor (DCR-BCAT) would reach and treat the liver metastases of CRCs and HCCs effectively. More importantly, we also strongly believe that the rational combination of our DCR-BCAT together with MEK inhibitor would be an effective therapeutic strategy for RAS mutant CRC patients with liver metastases.

Association of U.S. cancer patients with aberrant Wnt activation

CANCER TYPE WITH GENETIC ALTERATUINS	APPROXIMATE PERCENTAGE OF PATIENTS
Colorectal- APC	80%
Colorectal- ß-catenin	10%
Colorectal- KRAS	40-50%
Colorectal- BRAF	10-15%
Colorectal-EGFR	80%
HCC- ß-catenin	40-50%

Product candidate for KRAS-related solid tumors

We believe that the KRAS oncogene represents an excellent target for our RNAi-based therapy because it is a frequently-mutated oncogene found in several common cancers, but it has historically been difficult to inhibit by the pharmaceutical industry. We are pursuing a DsiRNA-based product candidate targeting KRAS in conjunction with our collaborator KHK. Under the terms of our collaboration, KHK is responsible for selection of the clinical product candidate (including delivery system), all preclinical and clinical development activities and the choice of patient population and disease indications for clinical trials. Based on preclinical safety and efficacy data observed to data, KHK has advanced a product candidate resulting from this program into development. KHK has assumed responsibility for preclinical and clinical development of the program and bears the expense of that effort. We have an option to co-promote any KRAS product in the U.S. for an equal share of the profits from U.S. net sales.

Therapeutic rationale for KRAS-related solid tumors

Activating mutations in the KRAS gene are commonly found in a wide variety of tumor types. Among cancer indications with large patient populations, KRAS is found to be mutated in approximately 90 percent of pancreatic cancers, approximately 40 percent of colorectal cancers and approximately 25 percent of non-small cell lung cancers. KRAS mutations are also found in cancers with smaller patient numbers, such as bile duct cancers. In general, the presence of a KRAS mutation correlates with poorer disease prognosis. In the case of

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non-small cell lung cancer, certain therapeutics approved by the FDA and other global regulatory agencies which have demonstrated clinical efficacy in non-small cell lung cancer are known to be ineffective in patients with KRAS mutations. While our collaborator KHK will decide which disease indications to pursue, we believe the potential market for a KRAS therapeutic is highly significant. In the U.S. alone, there are estimated to be over 43,000 cases of pancreatic cancer, 125,000 cases of colorectal cancer and over 202,000 cases of non-small cell lung cancer diagnosed each year.

Association of U.S. cancer patients with activating KRAS mutations

CANCER TYPE	APPROXIMATE PERCENTAGE WITH ACTIVATING KRAS MUTATIONS	IMPLIED PATIENT NUMBERS BASED ON INCIDENCE AND MUTATION FREQUENCY
Pancreatic adenocarcinoma	90%	38,700
Colorectal	40%	50,000
Non-small cell lung	25%	50,500

We believe that our DsiRNA for KRAS-related solid tumors will be developed and used with a companion diagnostic that allows for the selection of patients carrying tumors with KRAS mutations. Clinical diagnostic tests for the presence of KRAS mutations have already been approved by the FDA and other global regulatory agencies and are commercially available.

As with MYC, Numerous studies have indicated that KRAS is a transformative agent in tumor viruses, which led to the identification of the human KRAS oncogene in the 1980s. Yet despite being known as an important drug target since that time, traditional small molecule approaches have not yielded effective KRAS inhibitors. Also, similar to MYC, KRAS is an intracellular protein and thus is not amenable to antibody therapeutics, which are limited to extracellular and cell surface drug targets

In its normal non-mutant form, the KRAS protein plays a key role in the promotion and regulation of cell growth and division. The KRAS protein acts in a keystone position in an intracellular signaling pathway often called the Ras-MAP Kinase pathway. This pathway is responsible for receiving growth-promoting signals from outside the cell and communicating those signals within the cell so that the cell can respond appropriately to the cell growth signals.

Additional product candidates for cancer gene targets

We are developing a second product candidate targeting a cancer-related gene in collaboration with KHK. We have not disclosed the identity of this target. In January 2013 we announced that KHK elected to advance this second therapeutic oncology product candidate from the research to the development stage. The achievement of this milestone triggered a $5.0 million payment from KHK to Dicerna. KHK is responsible for all development costs associated with this product candidate and has worldwide commercialization rights. We are eligible to receive royalties on worldwide net sales of the product candidate and payments of up to $110.0 million based on achievement of certain clinical, regulatory and commercialization milestones.

Strategic Partnerships and Collaborations

KHK research collaboration and license agreement

In December 2009, we entered into a research collaboration and license agreement (the collaboration agreement) with KHK for the research, development and commercialization of drug delivery platforms and DsiRNA molecules for therapeutic targets, primarily in oncology. Under the collaboration agreement, we engaged in the discovery of DsiRNA molecules against KRAS and other gene targets nominated by KHK. In 2011, KHK exercised its option for one additional target, the identity of which has not been publicly disclosed.

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As part of the research we are conducting in the collaboration, we are using our specific RNAi-inducing double-stranded DsiRNA molecules with a lipid nanoparticle drug delivery platform proprietary to KHK. KHK is responsible for all costs it incurs to develop any compound that is directed against a target included in the collaboration that KHK designates for development, subject to our exercise of our co-promotion option with respect to that compound if that compound is directed against KRAS.

We have granted KHK an exclusive license to certain of our technology and patents relating to compounds resulting from the collaboration. KHK has granted us certain non-exclusive licenses in its technology as necessary for us to perform research and development activities as part of the research collaboration.

Under the terms of the collaboration agreement, we have received total payments of $17.5 million. We are entitled to receive up to an additional $110.0 million for each product candidate resulting from the collaboration of certain clinical, regulatory and commercialization milestones. KHK is also obligated to pay us royalties on net sales of products resulting from the research collaboration. These royalties vary depending on the total net sales and range from percentages of net sales in the high single digits to the teens. None of the previously paid milestones are subject to reimbursement.

We have the option to elect to co-promote the KRAS product in the U.S. for an equal share of the profits resulting from U.S. net sales of the product.

If we exercise our option to co-promote a KRAS product in the U.S., the collaboration agreement will remain in effect pursuant to its terms in the U.S. for as long as any product is being sold by either KHK or us in the U.S. For each country outside of the U.S., the agreement will remain in effect pursuant to its terms on a product-by-product and country-by-country basis until the later of the last to expire of any patent rights licensed under the agreement applicable to the manufacture, use or sale of the product or twelve years after the date of the first commercial sale of such product in the applicable country. In the event we do not exercise our option to co-promote an oncogene KRAS product in the U.S., the collaboration agreement will remain in effect pursuant to its terms on a product-by-product and country-by-country basis until the later of the last to expire of any patent rights licensed under the agreement applicable to the manufacture, use or sale of the product or twelve years after the date of the first commercial sale of such product in the applicable country.

KHK may terminate the agreement at any time upon prior written notice to us. We may terminate the agreement if KHK challenges the validity or enforceability of any patents licensed by us to KHK. Either we or KHK may terminate the agreement in the event of the bankruptcy or uncured material breach by the other party.

City of Hope license agreement

In September 2007, we entered into a license agreement with City of Hope (COH), an academic research and medical center, pursuant to which COH has granted to us an exclusive (subject to the exception described below), royalty-bearing, worldwide license under certain patent rights in relation to DsiRNA, including the core DsiRNA patent (U.S. 8,084,599), to manufacture, use, offer for sale, sell and import products covered by the licensed patent rights for the prevention and treatment of any disease in humans. COH is restricted from granting any additional rights to develop, manufacture, use, offer to sell, sell or import products covered by the licensed patent rights for the prevention and treatment of any disease in humans. Prior to entering into the license with us, COH had entered into a non-exclusive license with respect to such patent rights to manufacture, use, import, offer for sale and sell products covered by the licensed patent rights for the treatment or prevention of disease in humans (excluding viruses and delivery of products into the eye or ear). While that non-exclusive license has been terminated, a sublicensee to that non-exclusive license was permitted to enter into an equivalent non-exclusive license which, to our knowledge, is

subsisting with Arrowhead Research Corporation, (Arrowhead) as successor to the non-exclusive license holder. In addition, COH has granted to us an exclusive, royalty-bearing, worldwide license under the licensed patent rights providing certain rights for up to 20 licensed products selected by us for human diagnostic uses, provided that COH has not granted or is not negotiating a license of rights to

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diagnostic uses for such licensed products to a third party. The exclusive licenses granted by COH to us under the agreement are subject to any retained rights of the U.S. government in the licensed patent rights and a royalty-free right of COH to practice the licensed patent rights for educational, research and clinical uses. We have the right to sublicense the licensed patent rights to third parties with COH s written consent. The core DsiRNA patent (U.S. 8,084,599), titled methods and compositions for the specific inhibition of gene expression by double-stranded RNA, describes RNA structures having a 25 to 30 nucleotides sense strand, a blunt end at the 3 end of the sense strand and a one to four nucleotides overhang at the 3 end of the antisense strand. The expiration date of this patent is July 17, 2027. The COH license is applicable to our DCR-MYC and KHK programs.

Pursuant to the terms of the agreement, we paid COH a one-time, non-refundable license fee and issued shares of our common stock to COH and a co-inventor of the core DsiRNA patent. COH is entitled to receive milestone payments in an aggregate amount of up to $5.25 million for each licensed product upon achievement of certain clinical and regulatory milestones. COH is further entitled to receive royalties at a low single-digit percentage of any net sale revenue of the licensed products sold by us and our sublicensees. If we sublicense the licensed patent rights to a third party, COH has the right to receive a double digit percentage of sublicense income, the percentage of which decreases after we have expended $12.5 million in development and commercialization costs. We are also obligated to pay COH an annual license maintenance fee, which may be credited against any royalties due to COH in the same year, and reimburse COH for expenses associated with the prosecution and maintenance of the license patent rights. Royalties shall be paid on a product-by-product and country-by-country basis until the expiration in each country of the last to expire of the licensed patent rights.

Under the agreement, we are obligated to use commercially reasonable efforts to develop and commercialize the licensed products in certain major markets. COH has the right to terminate the agreement in its entirety if we fail to enroll patients for clinical trials of one or more licensed products at various phases before certain specified deadlines unless we exercise the right to extend the deadlines in one-year increments by making a payment of $0.5 million to COH for each one-year extension. We have extended one milestone deadline for three one-year extensions, paying an aggregate of $1.5 million to COH for such extensions.

The agreement will remain in effect pursuant to its terms until all of the obligations under the agreement with respect to the payment of milestones or royalties related to licensed products have terminated or expired. Either party may terminate the license agreement for any uncured material breach by the other party. COH may terminate the agreement upon our bankruptcy or insolvency. We may terminate the agreement without cause upon written notice to COH.

Arbutus Biopharma Corporation license agreement

In November 2014, we entered into a licensing and collaboration agreement with Arbutus to license Arbutus LNP delivery technology for exclusive use in our PH1 development program. We will use Arbutus LNP technology to deliver DCR-PH1, for the treatment of PH1. As of December 31, 2015, we had paid $3.0 million in cumulative license fees. Arbutus is entitled to receive additional payments of $22.0 million in aggregate development milestones, plus a mid-single-digit royalty on future PH1 sales. This partnership also includes a supply agreement with Arbutus providing clinical drug supply and regulatory support.

Under the agreement, we are obligated to use commercially reasonable efforts to develop and commercialize the product.

The agreement will remain in effect pursuant to its terms until all of the obligations under the agreement with respect to the payment of milestones or royalties related to licensed products have terminated or expired. Either party may terminate the license agreement for any uncured material breach by the other party. Arbutus may terminate the

agreement upon our bankruptcy or insolvency. We may terminate the agreement without cause upon written notice to Arbutus.

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In addition to the license agreement, we entered into a development and supply agreement with Arbutus. Arbutus will perform certain development and manufacture processes in accordance with the specifications in development and supply agreement. There is no minimum purchase requirement for the services provided by Arbutus.

Intellectual Property

We invest significant amounts in research and development. Our research and development expenses were approximately $44.0 million, $29.5 million and $11.6 million in 2015, 2014 and 2013, respectively.

We are seeking multifaceted protection for our intellectual property that includes licenses, confidentiality and non-disclosure agreements, copyrights, patents, trademarks and common law rights, such as trade secrets. We enter into confidentiality and proprietary rights agreements with our employees, consultants, collaborators, subcontractors and other third parties and generally control access to our documentation and proprietary information.

Patents and proprietary rights

We own U.S. patents and a number of pending patent applications with claims to methods and compositions of matters that cover various aspects of our RNAi technology and our discovery technologies, including our proprietary DsiRNA and DsiRNA-EX molecules and lipid and DsiRNA-EX conjugate delivery technologies. These U.S. patents include U.S. 8,349,809 (issued in January 2013 with a projected expiration date of January 2030), U.S. 8,513,207 (issued in August 2013 with a projected expiration date of May 2030) and U.S. 8,927,705 (issued in January 2015 with a projected expiration date of July 2030). We also own numerous patents and patent applications covering specific DsiRNA sequences that drive activity against high value disease targets, including MYC, KRAS (U.S. 8,372,816; issued in February 2013, with projected expiration in April 2030), HAO1, CTNNB1 (ß-catenin; U.S. 8,815,825; issued in August 2014, with projected expiration in July 2031), Androgen Receptor (US 8,927,515; issued in January 2015, with projected expiration in September 2031). Further, we own seven U.S. patents expiring by 2017 and numerous patent applications with claims to methods and compositions of matters related to our lipid delivery technology, such as lipid compositions and particle formulations and the EnCore formulation process. We have issued or pending claims to DsiRNA molecules, pharmaceutical compositions/formulations, methods of use, including *in vitro* and *in vivo* methods of reducing target gene expression, methods of treatment, methods of inhibiting cell growth and methods of synthesis.

We jointly own with KHK U.S. and foreign patent applications pursuant to our research collaboration and license agreement claiming developments made in the course of the collaboration focused on delivery of KRAS specific DsiRNA molecules. Depending on the subject matter of future issued claims, we may also jointly own patents issuing from patent applications filed under the research collaboration and license agreement with KHK.

Our strategy around protection of our proprietary technology, including any innovations and improvements, is to obtain worldwide patent coverage with a focus on jurisdictions that represent significant global pharmaceutical markets. Generally, patents have a term of twenty years from the earliest non-provisional priority date, assuming that all maintenance fees are paid, no portion of the patent has been terminally disclaimed and the patent has not been invalidated. In certain jurisdictions, and in certain circumstances, patent terms can be extended or shortened. We are obtaining worldwide patent protection for at least novel molecules, composition of matter, pharmaceutical formulations, methods of use, including treatment of disease, methods of manufacture and other novel uses for the inventive molecules originating from our research and development efforts. We continuously assess whether it is strategically more favorable to maintain confidentiality for the know-how regarding a novel invention rather than pursue patent protection. For each patent application that is filed we strategically tailor our claims in accordance with the existing patent landscape around a particular technology. There can be no assurance that an issued patent will

remain valid and enforceable in a court of law through the entire patent term. Should the validity of a patent be challenged, the legal process associated with defending the

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patent can be costly and time consuming. Issued patents can be subject to oppositions, interferences, post-grant proceedings, and other third party challenges that can result in the revocation of the patent limit patent claims such that patent coverage lacks sufficient breadth to protect subject matter that is commercially relevant. Competitors may be able to circumvent our patents. Development and commercialization of pharmaceutical products can be subject to substantial delays and it is possible that at the time of commercialization any patent covering the product has expired or will be in force for only a short period of time following commercialization.

We cannot predict with any certainty if any third party U.S. or foreign patent rights, other proprietary rights, will be deemed infringed by the use of our technology. Nor can we predict with certainty which, if any, of these rights will or may be asserted against us by third parties. Should we need to defend ourselves and our partners against any such claims, substantial costs may be incurred. Furthermore, parties making such claims may be able to obtain injunctive or other equitable relief, which could effectively block our ability to develop or commercialize some or all of our products in the U.S. and abroad, and could result in the award of substantial damages. In the event of a claim of infringement, we or our partners may be required to obtain one or more licenses from a third party. There can be no assurance that we can obtain a license on a reasonable basis should we deem it necessary to obtain rights to an alternative technology that meets our needs. The failure to obtain a license may have a material adverse effect on our business, results of operations and financial condition.

We also rely on trade secret protection for our confidential and proprietary information. No assurance can be given that we can meaningfully protect our trade secrets on a continuing basis. Others may independently develop substantially equivalent confidential and proprietary information or otherwise gain access to our trade secrets.

See Risk Factors Risks Related to Intellectual Property for a more detailed discussion of the risks to our intellectual property.

It is our policy to require our employees and consultants, outside scientific collaborators, sponsored researchers and other advisors who receive confidential information from us to execute confidentiality agreements upon the commencement of employment or consulting relationships. These agreements provide that all confidential information developed or made known to these individuals during the course of the individual s relationship with the company is to be kept confidential and is not to be disclosed to third parties except in specific circumstances. The agreements provide that all inventions conceived by an employee shall be the property of the company. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

Our success will depend in part on our ability to obtain and maintain patent protection, preserve trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others, both in the U.S. and other territories worldwide.

Additional licenses

In addition to the license agreement with COH described above, we have entered into license agreements for RNA technology that may benefit us as we advance our programs.

Plant Bioscience Limited license agreement

In September 2013, we entered into a commercial license agreement with Plant Bioscience Limited (PBL), pursuant to which PBL has granted to us a nominated-target-limited, worldwide, non-exclusive, fee-bearing license to certain of its U.S. patents (the Baulcombe patent estate) and patent applications to research, discover, develop, manufacture, sell,

import and export, for human diagnostic and therapeutic uses, products incorporating one or more short RNA molecules (SRMs) designed to target and modify the expression of a human gene or

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genes nominated by us from time to time. We are entitled to nominate multiple SRMs and have so far nominated one gene as the first SRM under the agreement. We are not obligated to nominate any additional genes.

We have paid PBL a one-time, non-refundable signature fee and will pay PBL a nomination fee for any additional SRMs nominated by us under the agreement. We are further obligated to pay PBL milestone payments in an aggregate amount of up to $3.85 million for each licensed product upon achievement of certain clinical and regulatory milestones. In addition, PBL is entitled to receive royalties at a low single-digit percentage of any net sale revenue of any licensed products sold by us. The agreement will expire on a country-by-country basis in each country where any licensed products are used, provided, manufactured or sold upon the date of the last to expire of applicable valid claim. Each party may terminate the agreement for any uncured material breach by the other party. We may terminate the agreement at any time for convenience upon prior written notice to PBL. The PBL license is applicable to our DCR-MYC and KHK programs.

Carnegie Institution of Washington license agreement

In January 2009, we entered into a license agreement with the Carnegie Institution of Washington (Carnegie), pursuant to which Carnegie has granted to us a worldwide, non-exclusive license under certain of its patents and patent applications (the Fire and Mello patent estate) relating to genetic inhibition by double-stranded RNA molecules for internal research, screening and development of product candidates for human and non-human diagnostic and therapeutic uses. We have paid Carnegie a one-time upfront fee and will in addition pay an annual license fee during the term of the agreement. We are further obligated to make two one-time additional payments in the aggregate amount of $100,000 upon achievement of the filing with the FDA of an NDA for a licensed product candidate and the first commercial sale of a licensed product candidate or licensed method. Carnegie is entitled to receive royalties on any net sale revenue from licensed product candidates sold by us, with the royalty rate to be further negotiated between Carnegie and us in good faith reflecting customary rates in the industry.

The agreement will terminate with respect to each licensed product candidate upon the last to expire of any valid claim within the licensed patent rights. Each party may terminate the agreement upon any uncured material breach by the other party. We may terminate the agreement at any time for any reason upon written notice to Carnegie. Any patents associated with this license will expire in 2018, removing any obligations.

Manufacturing and Supply

We do not currently own or operate manufacturing facilities for the production of preclinical, clinical or commercial quantities of any of our product candidates. For each product candidate, we currently contract with only one drug product formulation manufacturer for the encapsulation of the oligonucleotide in a lipid nanoparticle and we expect to continue to do so to meet the preclinical and any clinical requirements of our product candidates. We do not have a long term agreement with this third party.

Currently, each of our drug starting materials for our manufacturing activities are supplied by a single source supplier. We have agreements for the supply of such drug materials with manufacturers or suppliers that we believe have sufficient capacity to meet our demands. In addition, we believe that adequate alternative sources for such supplies exist. However, there is a risk that, if supplies are interrupted, it would materially harm our business. We typically order raw materials and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

In November 2014, we entered into a development and supply agreement with Arbutus. Arbutus will perform, or subcontract, certain development and manufacture processes in accordance with the specifications in development and

supply agreement. There is no minimum purchase requirement for the services provided by Arbutus.

KHK is responsible for all manufacturing under our collaboration agreement with KHK both for the KRAS DsiRNA and the oncology program selected by KHK for development under the agreement.

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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 contract manufacturing organizations manufacture our product candidates under current Good Manufacturing Practice (cGMP) conditions. cGMP is a regulatory standard for the production of pharmaceuticals that will be used in humans.

Competition

We believe that our scientific knowledge and expertise in RNAi-based therapies provide us with competitive advantages over the various companies and other entities that are attempting to develop similar treatments. However, we face competition at the technology platform and therapeutic indication levels from both large and small biopharmaceutical companies, academic institutions, governmental agencies and public and private research institutions. Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our success will be based in part upon our ability to identify, develop and manage a portfolio of drugs that are safer and more effective than competing products in the treatment of our targeted patients. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects, are more convenient or are less expensive than any products we may develop.

RNA-based therapeutics

To our knowledge, there are no other companies developing DsiRNA and DsiRNA-EX molecules for therapeutic use. However, there are several companies that are currently developing RNAi-based therapies for various indications. We believe that Arrowhead, Arbutus and Alnylam through their company specific development or through various partnerships with the aforementioned companies are developing RNAi-based therapies that are competing against our current programs or potential future programs.

Among these, Alnylam, in partnership with Genzyme (a Sanofi company), is developing its ALN-TTR program, which is an RNAi-based therapy for the treatment of transthyretin-mediated amyloidosis (ATTR) and is currently in Phase 3 trials. Alnylam has announced it expects to complete enrollment in its APOLLO Phase 3 study of patisiran in ATTR patients with Familial Amyloidotic Polyneuropathy (FAP) in January 2016, Enrollment in its ENDEAVOUR Phase 3 study to evaluate the efficacy and safety of revusiran in ATTR patients with Familial Amyloidotic Cardiomyopathy (FAC) continues and data are expected to be reported from this study in 2018. Alnylam is also developing ALN-TTRsc02 for all forms of ATTR amyloidosis and expects to initiate a Phase 1 study in mid-2016. Alnylam is also developing RNAi-based therapies for other indications, including PH1, paroxysmal nocturnal hemoglobinuria (PNH), acute intermittent porphyria (AIP) hemophilia, porphyria, hypercholesterolemia, hemoglobinopathies, and alpha-1-antitrypsin (AAT) deficiency hepatocyte inclusions, among others. In addition, Alnylam expects to initiate a Phase 1 study for ALN-HBV in mid-2016 and announced its intention to seek strategic partnerships for its Hepatic Infectious Disease therapeutic area. ALN-PCSsc for the treatment of hypercholesterolemia is partnered with The Medicines Company who expect to present initial data from the ORION-1 Phase 2 study in late 2016.

Arbutus also is clinically investigating its RNAi molecules for use in treating serious human diseases, such as cancer and viral infections, including hepatitis B virus (HBV) and Ebola. ARB-1467 for the treatment of HBV is in a Phase II

study that was initiated in December 2015 and Arbutus expects to announce preliminary data in late 2016 Arbutus has rights under Alnylam s intellectual property to develop thirteen RNAi therapeutic products.

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Additionally, Arrowhead is developing ARC-520 for chronic hepatitis B (HBV) and in January 2016, announced the dosing of the first patient in the Phase 2b MONARCH combination study of ARC-520, the treatment of chronic hepatitis B virus (HBV). ARC-AAT for the treatment of liver disease associated with alpha-1 antitrypsin deficiency completed dosing in healthy volunteers and transitioned into patients with PiZZ genotype alpha-1 antitrypsin deficiency. In March 2015 Arrowhead announced the acquisition of Novartis RNAi research and development portfolio and associated assets. The acquisition includes assignment of certain intellectual property owned or controlled by Novartis, including access to non-delivery Alnylam RNAi IP for 30 targets, and three pre-clinical RNAi candidates for which Novartis has developed varying amounts of preclinical data.

In addition to RNAi therapies, there are other intracellular technologies focused on silencing the activity of specific genes by targeting mRNAs copied from them. Companies such as miRagen Therapeutics, Inc., Mirna Therapeutics, Inc., Regulus Therapeutics Inc. and Santaris Pharma A/S, which was acquired by Roche in 2014 and is now known as Roche Innovation Center Copenhagen (RICC), target or inhibit or replace microRNAs, which are approximately 22 nucleotides in length, short, non-coding RNAs, to alter mRNA expression levels. The product candidates being developed by these companies are currently in preclinical and clinical trials for various indications. If our lead product candidates are approved for the indications for which we undertake clinical trials, they will compete with therapies that are either in development or currently marketed, such as the following.

Hepatocellular Carcinoma

There are limited treatments for HCC in the U.S. and abroad. If diagnosed as early-stage HCC, the disease is generally treated with surgical resection of the liver and has the potential to be curative. The majority of patients diagnosed with HCC, however, are in the advanced stages, for which chemotherapies have demonstrated poor efficacy. There is no FDA-approved chemotherapeutic regimen. Nexavar is the only FDA-approved drug for the treatment of advanced or unresectable HCC in our belief. Given the high unmet medical need and the commercial success of Nexavar, numerous targeted therapies for the treatment of hepatocellular carcinoma (HCC) are under development. Targeted therapies represent the largest proportion of the HCC pipeline.

Primary Hyperoxaluria Type 1

The current standard of care for treating PH1 is dual-organ transplant, namely a kidney and liver transplant in patients with PH1, which is often difficult to perform due to lack of donors and the threat of organ rejection. Other treatments include pyridoxine regimens and intensive dialysis, as well as treatments generally used in kidney stone disorders such as high-volume fluid intake and oral citrate. These other treatments do not halt disease progression. OxThera has a competing approach to PH1 treatment, currently in Phase 2 clinical trials, that is not RNAi-based. In January 2016, Alnylam announced their plans to start a Phase 1 clinical trial for ALN-GO1, an investigational RNAi therapeutic for the treatment of PH1. Alnylam also plans to present initial Phase 1 clinical data in late 2016.

Solid tumors

There are a number of pharmaceuticals and biologics that are marketed or in clinical development for the treatment of solid tumors. The most common treatments for solid tumors are various chemotherapeutic agents, radiation therapy and certain targeted therapies. Target therapies include monoclonal antibodies such as Avastin, Erbitux, Herceptin and Vectibix, and small molecules, such as Nexavar, Sutent and Tarceva. Immunotherapy regimens are also on the market and in development for the treatment of solid tumors. In contrast, our proprietary DsiRNA molecules target tumors in which there is dependence on the MYC and KRAS oncogenes. To our knowledge, only one small molecule (salirasib (KD032)) is being evaluated by Kadmon Corporation, LLC in clinical trials for the treatment of KRAS-specific non-small cell lung cancer, pancreatic cancer and other solid tumors. We are not aware of any clinical trial that is

currently evaluating a therapy for the treatment of solid tumors in which the MYC oncogene is specifically targeted.

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Government Regulation and Product Approval

Governmental authorities in the U.S., 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, promotion, storage, record-keeping, advertising, distribution, sampling, marketing, safety, post-approval monitoring and reporting, and export and import of products such as those we are developing. Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the U.S. and will be subject to similar requirements in other countries prior to marketing in those countries. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. government regulation

NDA approval processes

In the U.S., the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (the FDCA) and implementing regulations. Failure to comply with the applicable U.S. requirements at any time during the product development or approval process, or after approval, may result in a delay of approval or subject an applicant to administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

refusal to approve pending applications;

withdrawal of an approval;

imposition of a clinical hold;

issuance of warning or untitled letters;

product recalls;

product seizures;

refusals of government contracts;

total or partial suspension of production or distribution; or

injunctions, fines, restitution, disgorgement, civil penalties or criminal prosecution.

The process required by the FDA before a drug may be marketed in the U.S. generally includes the following:

completion of nonclinical laboratory tests, animal studies and formulation studies conducted according to Good Laboratory Practices (GLPs) or other applicable laws and regulations;

submission to the FDA of an investigational new drug application (IND), which must become effective before human clinical trials may begin;

approval by an institutional review board (IRB) at each clinical site before each trial may be initiated

performance and inspection of adequate and well-controlled human clinical trials and clinical data according to FDA regulations and Good Clinical Practices (GCP) to establish the safety and efficacy of the product candidate for its intended use;

submission of an NDA to FDA and FDA s acceptance of the NDA for filing;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product candidate is produced to assess compliance with current Good Manufacturing Practices (cGMPs) to assure that the facilities, methods and controls are adequate to preserve the product candidate s identity, strength, quality and purity;

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satisfactory completion of an FDA inspection of the major investigational sites to ensure data integrity and assess compliance with good clinical practice (GCP) requirements; and

FDA review and approval of the NDA.

Once a pharmaceutical candidate is identified for development, it enters the preclinical or nonclinical testing stage. Nonclinical tests include laboratory evaluations of product chemistry, stability, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. Some nonclinical testing may continue even after the IND is submitted. In addition to including the results of the nonclinical studies, the IND will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the first phase lends itself to an efficacy determination. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. A clinical hold may occur at any time during the life of an IND and may affect one or more specific studies or all studies conducted under the IND.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with FDA regulations and GCPs. They must be conducted under protocols detailing the objectives of the trial, dosing procedures, research subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol and protocol amendments must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually. Sponsors also must timely report to FDA serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigation brochure or any findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug. All research subjects or their legally authorized representatives must provide their informed consent in writing prior to their participation in a clinical trial. An institutional review board (IRB) at each institution participating in the clinical trial must review and approve the protocol and the informed consent form before a clinical trial commences at that institution, monitor the study until completed and otherwise comply with IRB regulations. Information about most clinical trials must be submitted within specific timeframes to the National Institutes of Health (NIH) to be publicly posted on the ClinicalTrials.gov website.

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

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

Phase 2 Clinical trials are performed on a limited patient population intended 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 and optimal dosage.

Phase 3 Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide an adequate basis for product labeling.

Human clinical trials are inherently uncertain and Phase 1, Phase 2 and Phase 3 testing may not be successfully completed. The FDA, the sponsor, or a data safety monitoring board, may suspend a clinical trial at any time for a variety of reasons, 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 product candidate has been associated with unexpected serious harm to patients.

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During the development of a new product candidate, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to the submission of an IND, at the end of Phase 2 and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date and for the FDA to provide advice on the next phase of development. Sponsors typically use the meeting at the end of Phase 2 to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial that they believe will support the approval of an NDA. If a Phase 2 clinical trial is the subject of discussion at the end of Phase 2 meeting with the FDA, a sponsor may be able to request a Special Protocol Assessment (SPA), the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim.

Concurrent with clinical trials, sponsors usually complete additional animal safety studies and also develop additional information about the chemistry and physical characteristics of the product candidate and finalize a process for manufacturing commercial quantities of the product candidate in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and the manufacturer must develop methods for testing the safety, identity, strength, purity, and quality of the product candidate. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its proposed shelf-life. Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured and tested and will not approve the product unless cGMP compliance is satisfactory. The FDA will also typically inspect one or more clinical sites to assure compliance with FDA regulations and GCPs.

The results of product development, nonclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests and other control mechanisms, 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 user fees, but a waiver of such fees may be obtained under specified circumstances. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant. The FDA typically requires that an NDA include data from two adequate and well-controlled clinical trials, but approval may be based upon a single adequate and well-controlled clinical trial in certain circumstances. The FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. The FDA may refer the NDA to an advisory committee for review and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

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 condition approval on the completion of post approval studies. Such studies may involve clinical trials designed to further assess a product s safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. If FDA determines that it is necessary to ensure the safe use of the drug, FDA may also condition approval on the implementation of a risk evaluation and mitigation strategy, or REMS. The REMS could include medication guides, physician communication

plans or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

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Expedited review and approval

The FDA has various programs, including Fast Track, priority review, breakthrough, and accelerated approval, which are intended to expedite or simplify the process for reviewing product candidates. Generally, product candidates that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. A sponsor can request application of these programs either alone or in combination with each other, depending on the circumstances. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product candidate no longer meets the conditions for qualification or that the time period for FDA review or approval will be shortened. None of the expedited approval programs change the NDA approval standard applied to a product.

New drugs are eligible for Fast Track status if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track status entitles such a drug to expedited review and frequent contact with the FDA review division. Unlike other expedited review programs, Fast Track designation allows FDA to accept for review individual sections of the NDA on a rolling basis. The FDA may also grant a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months from filing of an NDA, rather than the standard review of ten months from filing under current PDUFA guidelines. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

Drug products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA typically requires that a sponsor of a product candidate receiving accelerated approval conduct post-approval clinical trials. As an additional condition of approval, the FDA currently requires pre-approval of all promotional materials, which could adversely impact the timing of the commercial launch of the product.

The FDA may expedite the approval of a designated breakthrough therapy, which is a drug that is intended, to treat a serious or life-threatening disease or condition for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A sponsor may request that a drug be designated as a breakthrough therapy at any time during the clinical development of the product. If FDA designates a drug as a breakthrough therapy, FDA must take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the drug; providing timely advice to the sponsor regarding the development of the drug to ensure that the development program is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; and taking steps to ensure that the design of the clinical trials is as efficient as practicable.

Patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits 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 candidate s approval date. The patent term restoration period

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is generally one half of 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 product candidate is eligible for the extension and the application for extension must be made prior to expiration of the patent. The U.S. 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 intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the U.S. to the first applicant to gain approval of an NDA for a new chemical entity. A product candidate is a new chemical entity if the FDA has not previously approved any other new product candidate containing the same active moiety, which is the molecule or ion responsible for the action of the product candidate substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company for another version of such product candidate 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. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an approved 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, for new indications, dosages or strengths of an existing product candidate. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for product candidates 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.

Orphan drug designation

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

If a product candidate that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product candidate is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications including a full NDA to market the same product candidate for the same indication, except in very limited circumstances, for seven years. Orphan drug exclusivity, however, could also block the approval of one of our product candidates for seven years if a competitor obtains approval of the same product candidate as defined by the FDA prior to us, or if our product candidate is determined to be contained within the competitor s approved orphan product candidate for the same indication or disease.

Pediatric exclusivity, pediatric use and rare pediatric disease priority review vouchers

Under the Best Pharmaceuticals for Children Act (BPCA), certain product candidates may obtain an additional six months of exclusivity if the sponsor submits information requested in writing by the FDA (a

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Written Request) relating to the use of the active moiety of the product candidate in children. The FDA may not issue a Written Request for studies on unapproved or approved indications or where it determines that information relating to the use of a product candidate in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

In addition, the Pediatric Research Equity Act (PREA) requires a sponsor to conduct pediatric studies for most product candidates and biologics, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs, biologics license application and supplements thereto must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must assess the safety and effectiveness of the product candidate for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product candidate is safe and effective. The sponsor or FDA may request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the product candidate or biologic is ready for approval for use in adults before pediatric studies are complete or that additional safety or effectiveness data needs to be collected before the pediatric studies begin. After April 2013, the FDA must send a noncompliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation. PREA does not apply to any drug for an indication for which orphan designation has been granted. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

Under section 529 of the FDCA, FDA will award priority review vouchers to sponsors of certain rare pediatric disease product applications. Section 529 of the FDCA is intended to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Although there are existing incentive programs to encourage the development and study of drugs for rare diseases, pediatric populations, and unmet medical needs, section 529 provides an additional incentive for rare pediatric diseases, which may be used alone or in combination with other incentive programs. Rare pediatric disease is defined as a disease that:

- primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents, which is interpreted as meaning that greater than 50% of the affected population in the U.S. is aged 0 through 18 years; and

- is a rare disease or condition as defined in FDCA, which includes diseases and conditions that affect fewer than 200,000 persons in the United States (U.S.) and diseases and conditions that affect a larger number of persons and for which there is no reasonable expectation that the costs of developing and making available the drug in the U.S. can be recovered from sales of the drug in the U.S.

Under section 529, the sponsor of a human drug application for a rare pediatric disease drug product may be eligible for a voucher that can be used (or sold) to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FDCA or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product. FDA has issued draft Guidance for Industry for Rare Pediatric Disease Priority Review Vouchers.

Post-approval requirements

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product candidate reaches the market. Requirements for additional Phase 4

(post-approval marketing studies) to confirm safety and efficacy may be imposed as a condition of approval. Later discovery of previously unknown problems with a product candidate may result in restrictions on the product candidate, or REMS, or even complete withdrawal of the product candidate from the market. After approval, some types of changes to the approved product candidate, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved

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product candidates that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product candidate based on the results of these post-marketing programs.

Any product candidates manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences with the product candidate;
- submission of periodic reports;
- providing the FDA with updated safety and efficacy information;
- drug sampling, stability and distribution requirements;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes; and
- complying with statutory and regulatory requirements for promotion and advertising.

Drug manufacturers and other entities involved in the manufacture and distribution of approved product candidates are required to register their establishments and provide product listing information to the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and some state agencies for compliance with cGMPs and other laws.

Regulation outside of the U.S.

In addition to regulations in the U.S., we will be subject to regulations of other jurisdictions governing any clinical trials and commercial sales and distribution of our product candidates. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of countries outside of the U.S. before we can commence clinical trials in such countries, and approval of the regulators of such countries or supranational areas, such as the European Union, before we may market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for certain medicines, including those produced by biotechnology or those intended to treat HIV, AIDS, cancer, neurodegenerative disorders, autoimmune and other immune dysfunctions, viral diseases or diabetes and is optional for those medicines which are a significant therapeutic, scientific or technical innovation or whose authorization would be in the interest of public health, provides for the grant of a single marketing authorization that is valid for all European Union

member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessment reports, each member state must decide whether to recognize the approval. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

As in the U.S., we may apply for designation of a product candidate as an orphan drug for the treatment of a specific indication in the European Union before the application for marketing authorization is made. Sponsors of orphan drugs in the European Union can enjoy economic and marketing benefits, including up to ten years of market exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product.

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Reimbursement

Sales of our products will depend, in part, on the extent to which the costs of our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. If these third-party payors do not consider our products to be cost-effective compared to other therapies, they may not cover our products after approved as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

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

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively referred to as the ACA, enacted in March 2010, is expected to have a significant impact on the health care industry. ACA is expected to expand coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, among other things, ACA is expected to expand and increase industry rebates for drugs covered under Medicaid programs and make changes to the

coverage requirements under the Medicare Part D program. We cannot predict the impact of ACA on pharmaceutical companies, as many of the ACA reforms require the promulgation of

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detailed regulations implementing the statutory provisions which has not yet occurred. In addition, although the U.S. Supreme Court upheld the constitutionality of most of the ACA, some states have indicated that they intend to not implement certain sections of the ACA, and some members of the U.S. Congress are still working to repeal parts of the ACA. These challenges add to the uncertainty of the legislative changes enacted as part of ACA.

In addition, in some non-U.S. jurisdictions, the proposed pricing for a product candidate must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union 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 product candidates. Historically, product candidates launched in the European Union do not follow price structures of the U.S. and generally tend to be significantly lower.

Environment

Our third party manufacturers are subject to inspections by the FDA for compliance with cGMP and other U.S. regulatory requirements, including U.S. federal, state and local regulations regarding environmental protection and hazardous and controlled substance controls, among others. Environmental laws and regulations are complex, change frequently and have tended to become more stringent over time. We have incurred, and may continue to incur, significant expenditures to ensure we are in compliance with these laws and regulations. We would be subject to significant penalties for failure to comply with these laws and regulations.

Sales and Marketing

Our current focus is on the development of our existing portfolio, the completion of clinical trials and, if and where appropriate, the registration of our product candidates. We currently do not have marketing, sales and distribution capabilities. If we receive marketing and commercialization approval for any of our product candidates, we intend to market the product either directly or through strategic alliances and distribution agreements with third parties. The ultimate implementation of our strategy for realizing the financial value of our product candidates is dependent on the results of clinical trials for our product candidates, the availability of funds and the ability to negotiate acceptable commercial terms with third parties.

Scientific Advisors

We seek advice from our scientific advisory board, which consists of a number of leading scientists and physicians, on scientific and medical matters. We also seek advice on an as-needed basis from other leading scientists and physicians, who are not on our scientific advisory board, based on their particular knowledge and expertise. Our scientific advisory board meets periodically to assess:

- our research and development programs;
- the design and implementation of our clinical programs;

our patent and publication strategies;

new technologies relevant to our research and development programs; and

specific scientific and technical issues relevant to our business.

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The current members of our scientific advisory board are as follows.

NAME	POSITION AND INSTITUTIONAL AFFILIATION
Mark Behlke, M.D., Ph.D.	Chief Scientific Officer, Integrated DNA Technologies
Frank McCormick, Ph.D., F.R.S., D.Sc. (Hon)	Director, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center
John Rossi, Ph.D.	Co-Founder of Dicerna and Professor and Dean of Irell and Manella Graduate School of Biological Sciences at City of Hope s Beckman Research Institute

Employees

As of December 31, 2015, we had 48 full-time employees, of whom 41 are engaged in research and development and seven in administration. None of our employees is represented by a labor union or covered by a collective bargaining agreement. Geographically, all employees are located in Massachusetts. We consider our relationship with our employees to be good.

Corporate Information

We were incorporated in Delaware in 2006. We maintain our executive offices at 87 Cambridgepark Drive, Cambridge, MA 02140, and our main telephone number is (617) 621-8097. Our website is located at www.dicerna.com, which contains information about us. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated in, this Annual Report on Form 10-K.

We are an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of: (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our initial public offering on February 4, 2014, (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, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the prior June 30th, and (2) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We refer to the Jumpstart Our Business Startups Act of 2012 herein as the JOBS Act, and references herein to emerging growth company shall have the meaning associated with it in the JOBS Act.

Our website address is *http://www.dicerna.com*. The information in, or that can be accessed through, our website is not part of this Annual Report on Form 10-K. Our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K and amendments to those reports are available, free of charge, on or through our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities Exchange Commission (SEC). The public may read and copy any materials we file with the SEC at the SEC s Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Information on the operation of the Public Reference Room can be obtained by calling 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements and other information regarding our filings at *www.sec.gov*.

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Item 1A. Risk Factors

We are providing the following cautionary discussion of risk factors, uncertainties and assumptions that we believe are relevant to our business. These are factors that, individually or in the aggregate, we think could cause our actual results to differ materially from expected and historical results and our forward-looking statements. We note these factors for investors as permitted by Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act), and Section 27A of the Securities Act of 1933, as amended (Securities Act). You should understand that it is not possible to predict or identify all such factors. Consequently, you should not consider this section to be a complete discussion of all potential risks or uncertainties that may substantially impact our business. Moreover, we operate in a competitive and rapidly changing environment. New factors emerge from time to time and it is not possible to predict the impact of all of these factors on our business, financial condition or results of operations.

Risks Related to Our Business

We are a clinical stage biopharmaceutical company with a history of losses, expect to continue to incur significant losses for the foreseeable future and may never achieve or maintain profitability, which could result in a decline in the market value of our common stock.

We are a clinical stage biopharmaceutical company with a limited operating history, focused on the discovery and development of treatments based on the emerging therapeutic modality RNA interference (RNAi), a biological process in which ribonucleic acid (RNA) molecules inhibit gene expression. Since our inception in October 2006, we have devoted our resources to the development of Dicer substrate RNA (DsiRNA) molecules and delivery technologies. We have had significant operating losses since our inception. As of December 31, 2015, we had an accumulated deficit of $196.2 million. For the years ended December 31, 2015, 2014 and 2013, our net loss was $62.8 million, $47.9 million and $18.5 million, respectively. Substantially all of our losses have resulted from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations. Our technologies and product candidates are in early stages of development, and we are subject to the risks of failure inherent in the development of product candidates based on novel technologies.

To date, we have generated revenue primarily from the receipt of upfront research funding, license and option exercise fees and preclinical payments under our research collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd. (KHK). We have not generated, and do not expect to generate, any revenue from product sales for the foreseeable future, and we expect to continue to incur significant operating losses for the foreseeable future due to the cost of research and development, preclinical studies and clinical trials and the regulatory approval process for product candidates. The amount of future losses is uncertain. Our ability to achieve profitability, if ever, will depend on, among other things, us or our existing collaborators, or any future collaborators, successfully developing product candidates, obtaining regulatory approvals to market and commercialize product candidates, manufacturing any approved products on commercially reasonable terms, establishing a sales and marketing organization or suitable third party alternatives for any approved product and raising sufficient funds to finance business activities. If we or our existing collaborators, or any future collaborators, are unable to develop and commercialize one or more of our product candidates or if sales revenue from any product candidate that receives approval is insufficient, we will not achieve profitability, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We will need substantial additional funds to advance development of our product candidates, and we cannot guarantee that we will have sufficient funds available in the future to develop and commercialize our current or future product candidates.

We will need substantial additional funds to expand our development, regulatory, manufacturing, marketing and sales capabilities with other organizations to provide these capabilities for us. We have used substantial funds to develop our product candidates and delivery technologies and will require significant funds to conduct

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further research and development and preclinical testing and clinical trials of our product candidates, to seek regulatory approvals for our product candidates and to manufacture and market products, if any, that are approved for commercial sale. As of December 31, 2015, we had $94.6 million in cash and cash equivalents and held-to-maturity investments. Based on our current operating plan, we believe that our available cash, cash equivalents and held-to-maturity investments will be sufficient to fund our anticipated level of operations for at least the next 12 months. Our future capital requirements and the period for which we expect our existing resources to support our operations may vary significantly from what we expect. Our monthly spending levels vary based on new and ongoing development and corporate activities. Because the length of time and activities associated with successful development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. To execute our business plan, we will need, among other things:

- to obtain the human and financial resources necessary to develop, test, obtain regulatory approval for, manufacture and market our product candidates;
- to build and maintain a strong intellectual property portfolio and avoid infringing intellectual property of third parties;
- to establish and maintain successful licenses, collaborations and alliances;
- to satisfy the requirements of clinical trial protocols, including patient enrollment;
- to establish and demonstrate the clinical efficacy and safety of our product candidates;
- to obtain regulatory approvals;
- to manage our spending as costs and expenses increase due to preclinical studies and clinical trials, regulatory approvals, manufacturing scale-up and commercialization;
- to obtain additional capital to support and expand our operations; and
- to market our products to achieve acceptance and use by the medical community in general.

If we are unable to obtain funding on a timely basis or on acceptable terms, we may have to delay, reduce or terminate our research and development programs and preclinical studies or clinical trials, if any, limit strategic opportunities or undergo reductions in our workforce or other corporate restructuring activities. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies or product candidates that we would otherwise pursue on our own. We do not expect to realize revenue from product sales, milestone payments or royalties in the foreseeable future, if at all. Our revenue sources are, and

will remain, extremely limited unless and until our product candidates are clinically tested, approved for commercialization and successfully marketed. To date, we have primarily financed our operations through the sale of securities, debt financings, credit and loan facilities and payments received under our collaboration and license agreement with KHK. We will be required to seek additional funding in the future and intend to do so through either collaborations, equity offerings or debt financings, credit or loan facilities or a combination of one or more of these funding sources. Our ability to raise additional funds will depend on financial, economic and other factors, many of which are beyond our control. Additional funds may not be available to us on acceptable terms or at all. If we raise additional funds by issuing equity securities, our stockholders will suffer dilution and the terms of any financing may adversely affect the rights of our stockholders. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, may involve restrictive covenants limiting our flexibility in conducting future business activities, and, in the event of insolvency, debt holders would be repaid before holders of equity securities receive any distribution of corporate assets.

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Our quarterly operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expense related to our product candidates or future development programs;
- results of clinical trials, or the addition or termination of clinical trials or funding support by us, our existing collaborators or any future collaborator or licensing partner;
- the timing of the release of results from any clinical trials conducted by us or our collaborator KHK;
- our execution of any collaboration, licensing or similar arrangement, and the timing of payments we may make or receive under such existing or future arrangements or the termination or modification of any such existing or future arrangements;
- any intellectual property infringement lawsuit or opposition, interference, re-examination, post-grant review, inter partes review, nullification, derivation action, or cancellation proceeding in which we may become involved;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- if any of our product candidates receive regulatory approval, market acceptance and demand for such product candidates;
- if any of our third-party manufacturers fail to execute on our manufacturing requirements;
- regulatory developments affecting our product candidates or those of our competitors;
- disputes concerning patents, proprietary rights, or license and collaboration agreements that negatively impact our receipt of milestone payments or royalties or require us to make significant payments arising from licenses, settlements, adverse judgments or ongoing royalties;

expenditures as we respond to and defend against complaints and potential litigation, including Alnylam s lawsuit alleging misappropriation of confidential information; and

changes in general market and economic conditions.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Our approach to the discovery and development of innovative therapeutic treatments based on novel technologies is unproven and may not result in marketable products.

We plan to develop a pipeline of product candidates using our DsiRNA molecules and delivery technologies for rare inherited diseases involving the liver and cancers that are genetically defined. We believe that product candidates identified with our drug discovery and delivery platform may offer an improved therapeutic approach to small molecules and monoclonal antibodies, as well as several advantages over earlier generation RNAi molecules. However, the scientific research that forms the basis of our efforts to develop product candidates based on the therapeutic modality RNAi and the identification and optimization of DsiRNA is relatively new. Further, the scientific evidence to support the feasibility of developing therapeutic treatments based on RNAi and DsiRNA is both preliminary and limited.

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Relatively few product candidates based on RNAi have been tested in animals or humans, and a number of clinical trials conducted by other companies using RNAi technologies have not been successful. We may discover that DsiRNA does not possess certain properties required for a drug to be effective, such as the ability to remain stable in the human body for the period of time required for the drug to reach the target tissue or the ability to cross the cell wall and enter into cells within the target tissue for effective delivery. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these necessary drug-like properties into DsiRNA. We may spend substantial funds attempting to introduce these properties and may never succeed in doing so. In addition, product candidates based on DsiRNA may demonstrate different chemical and pharmacological properties in patients than they do in laboratory studies. Even if product candidates, such as DCR-PH1 and DCR-MYC, have successful results in animal studies, they may not demonstrate the same chemical and pharmacological properties in humans and may interact with human biological systems in unforeseen, ineffective or harmful ways. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

Further, the U.S. Food and Drug Administration (FDA) has relatively limited experience with RNAi and DsiRNA based therapeutics. No regulatory authority has granted approval to any person or entity, including us, to market and commercialize therapeutics using RNAi or DsiRNA, which may increase the complexity, uncertainty and length of the regulatory approval process for our product candidates. We and our current collaborators, or any future collaborators, may never receive approval to market and commercialize any product candidate. Even if we or a collaborator obtain regulatory approval, the approval may be for disease indications or patient populations that are not as broad as we intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. We or a collaborator may be required to perform additional or unanticipated clinical trials to obtain approval or be subject to post-marketing testing requirements to maintain regulatory approval. If our technologies based on DsiRNA prove to be ineffective, unsafe or commercially unviable, our entire platform and pipeline would have little, if any, value, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

The market may not be receptive to our product candidates based on a novel therapeutic modality, and we may not generate any future revenue from the sale or licensing of product candidates.

Even if approval is obtained for a product candidate, we may not generate or sustain revenue from sales of the product due to factors such as whether the product can be sold at a competitive cost and otherwise accepted in the market. The product candidates that we are developing are based on new technologies and therapeutic approaches. Market participants with significant influence over acceptance of new treatments, such as physicians and third-party payors, may not adopt a treatment based on DsiRNA technology, and we may not be able to convince the medical community and third-party payors to accept and use, or to provide favorable reimbursement for, any product candidates developed by us or our existing collaborator or any future collaborators. Market acceptance of our product candidates will depend on, among other factors:

- the timing of our receipt of any marketing and commercialization approvals;
- the terms of any approvals and the countries in which approvals are obtained;
- the safety and efficacy of our product candidates;

the prevalence and severity of any adverse side effects associated with our product candidates;

limitations or warnings contained in any labeling approved by the FDA or other regulatory authority;

relative convenience and ease of administration of our product candidates;

the willingness of patients to accept any new methods of administration;

the success of our physician education programs;

the availability of adequate government and third-party payor reimbursement;

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the pricing of our products, particularly as compared to alternative treatments; and

availability of alternative effective treatments for the disease indications our product candidates are intended to treat and the relative risks, benefits and costs of those treatments.

With our focus on the emerging therapeutic modality RNAi, these risks may increase to the extent the space becomes more competitive or less favored in the commercial marketplace. Additional risks apply in relation to any disease indications we pursue which are classified as rare diseases and allow for orphan drug designation by regulatory agencies in major commercial markets, such as the U.S., the European Union and Japan. For instance, we are in the preliminary stages of developing a treatment for the rare genetic disorder Primary Hyperoxaluria Type 1 (PH1) with the gene encoding the liver metabolic enzyme glycolate oxidase as our target. Because of the small patient population for a rare disease, if pricing is not approved or accepted in the market at an appropriate level for an approved product with orphan drug designation, such drug may not generate enough revenue to offset costs of development, manufacturing, marketing and commercialization despite any benefits received from the orphan drug designation, such as market exclusivity, assistance in clinical trial design or a reduction in user fees or tax credits related to development expense. Market size is also a variable in disease indications not classified as rare. Our estimates regarding potential market size for any indication may be materially different from what we discover to exist at the time we commence commercialization, if any, for a product, which could result in significant changes in our business plan and have a material adverse effect on our business, financial condition, results of operations and prospects.

If a product candidate that has orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product candidate is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same product candidate for the same indication, except in very limited circumstances, for seven years. Orphan drug exclusivity, however, could also block the approval of one of our product candidates for seven years if a competitor obtains approval of the same product candidate as defined by the FDA or if our product candidate is determined to be contained within the competitor s product candidate for the same indication or disease.

As in the U.S., we may apply for designation of a product candidate as an orphan drug for the treatment of a specific indication in the European Union before the application for marketing authorization is made. Sponsors of orphan drugs in the European Union can enjoy economic and marketing benefits, including up to ten years of market exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product.

Our product candidates are in early stages of development and may fail in development or suffer delays that materially adversely affect their commercial viability.

We have no products on the market and all of our product candidates are in early stages of development. Our ability to achieve and sustain profitability depends on obtaining regulatory approvals, including institutional review board (IRB) approval to conduct clinical trials at particular sites, and successfully commercializing our product candidates, either alone or with third parties, such as our collaborators KHK and Arbutus Biopharma Corporation. Before obtaining regulatory approval for the commercial distribution of our product candidates, we or a collaborator must conduct extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Preclinical testing and clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. The start or end of a clinical study is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparative drug or required prior therapy, clinical outcomes or financial constraints. For instance, delays or difficulties in patient

enrollment or difficulties in retaining trial participants can result in increased costs, longer development times or termination of a clinical trial. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the

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disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the eligibility criteria for the clinical trial, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites and the availability of effective treatments for the relevant disease.

A product candidate can unexpectedly fail at any stage of preclinical and clinical development. The historical failure rate for product candidates is high due to scientific feasibility, safety, efficacy, changing standards of medical care and other variables. The results from preclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. We, the FDA, IRB, an independent ethics committee, or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects participating in such trials are being exposed to unacceptable health risks or adverse side effects. Similarly, an IRB or ethics committee may suspend a clinical trial at a particular trial site. We may not have the financial resources to continue development of, or to enter into collaborations for, a product candidate if we experience any problems or other unforeseen events that delay or prevent regulatory approval of, or our ability to commercialize, product candidates, including:

- negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours, leading to a decision or requirement to conduct additional preclinical testing or clinical trials or abandon a program;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;
- delays in submitting INDs or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs to commence a clinical trial, or a suspension or termination of a clinical trial once commenced;
- conditions imposed by the FDA or comparable foreign authorities, such as the European Medicines Agency (EMA), regarding the scope or design of our clinical trials;
- delays in enrolling research subjects in clinical trials;
- high drop-out rates of research subjects;
- inadequate supply or quality of drug product or product candidate components or materials or other supplies necessary for the conduct of our clinical trials;
- greater than anticipated clinical trial costs;

poor effectiveness of our product candidates during clinical trials;

unfavorable FDA or other regulatory agency inspection and review of a clinical trial site;

failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;

delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or

varying interpretations of data by the FDA and similar foreign regulatory agencies.

To date, our revenue has been primarily derived from our research collaboration and license agreement with KHK, and we are dependent on KHK for the successful development of product candidates in the collaboration.

In December 2009, we entered into a research collaboration and license agreement with KHK for the research, development and commercialization of DsiRNA molecules and drug delivery technologies for

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therapeutic targets, primarily in oncology. Under the research collaboration and license agreement with KHK, KHK has paid us a total of $17.5 million. During the first two years of the collaboration, we worked together with KHK to optimize KHK s lipid nanoparticles for tumor delivery and to identify DsiRNAs optimized against oncology and KRAS targets. Based on the results of this research, KHK exercised options to advance two separate DsiRNAs into the development stage, including one with a KRAS target. For each product candidate under the research collaboration and license agreement, we have the potential to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of such product candidate. The success of our collaboration programs with KHK depends entirely upon the efforts of KHK. Except for certain co-promotion and profit sharing rights we retain with respect to the KRAS product candidate if it is approved for marketing and commercialization in the U.S., KHK has sole discretion in determining and directing the efforts and resources, including the ability to discontinue all efforts and resources, it applies to the development and, if approval is obtained, commercialization and marketing of the product candidates covered by the collaboration. KHK may not be effective in obtaining approvals for the product candidates developed under the collaboration arrangement or in marketing, or arranging for necessary supply, manufacturing or distribution relationships for, any approved products. Under the research collaboration and license agreement, KHK may change its strategic focus or pursue alternative technologies in a manner that results in reduced, delayed or no revenue to us. KHK has a variety of marketed products and product candidates under collaboration with other companies, including some of our competitors, and its own corporate objectives may not be consistent with our best interests. If KHK fails to develop, obtain regulatory approval for or ultimately commercialize any product candidate under our collaboration or if KHK terminates our collaboration, our business, financial condition, results of operations and prospects could be materially and adversely affected. In addition, any dispute or litigation proceedings we may have with KHK in the future could delay development programs, create uncertainty as to ownership of intellectual property rights, distract management from other business activities and generate substantial expense.

If third parties on which we depend to conduct our preclinical studies, or any future clinical trials, do not perform as contractually required, fail to satisfy regulatory or legal requirements or miss expected deadlines, our development program could be delayed with materially adverse effects on our business, financial condition, results of operations and prospects.

We rely on third party clinical investigators, contract research organizations (CROs), clinical data management organizations and consultants to design, conduct, supervise and monitor preclinical studies of our product candidates and will do the same for any clinical trials. Because we rely on third parties and do not have the ability to conduct preclinical studies or clinical trials independently, we have less control over the timing, quality and other aspects of preclinical studies and clinical trials than we would if we conducted them on our own. These investigators, CROs and consultants are not our employees and we have limited control over the amount of time and resources that they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw time and resources from our programs. The third parties with which we contract might not be diligent, careful or timely in conducting our preclinical studies or clinical trials, resulting in the preclinical studies or clinical trials being delayed or unsuccessful.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA and certain foreign regulatory authorities, such as the European Medicines Agency (EMA), require preclinical studies to be conducted in accordance with applicable Good Laboratory Practices (GLPs) and clinical trials to be conducted in accordance with applicable FDA regulations and good clinical practices (GCPs), including requirements for

conducting, recording and reporting the results of preclinical 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. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

Because we rely on third party manufacturing and supply partners, our supply of research and development, preclinical studies and clinical trial materials may become limited or interrupted or may not be of satisfactory quantity or quality.

We rely on third party supply and manufacturing partners to supply the materials and components for, and manufacture, our research and development, preclinical study and clinical trial drug supplies. For example, pursuant to our development and supply agreement, a third party manufactures lipid nanoparticles that we are seeking to use for delivery of DCR-PH1 to the liver. In the event that we are unable to use the technology we licensed to deliver DCR-PH1 to the liver or if the third party experiences difficulty in manufacturing lipid nanoparticles, our DCR-PH1 program would suffer delays, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We do not own manufacturing facilities or supply sources for such components and materials. Our manufacturing requirements include lipid nanoparticle components and oligonucleotide, each of which we procure from a single source supplier on a purchase order basis. In addition, for each product candidate we currently contract with only one drug product formulation manufacturer for the encapsulation of the oligonucleotide in a lipid particle. There can be no assurance that our supply of research and development, preclinical study and clinical trial drugs and other materials will not be limited, interrupted, restricted in certain geographic regions or of satisfactory quality or continue to be available at acceptable prices. In particular, any replacement of our drug product formulation manufacturer could require significant effort and expertise because there may be a limited number of qualified replacements.

The manufacturing process for a product candidate is subject to FDA and foreign regulatory authority review. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities in order to comply with regulatory standards, such as current Good Manufacturing Practices (cGMPs). In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget.

We expect to continue to rely on third party manufacturers if we receive regulatory approval for any product candidate. To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance. If we are unable to obtain or maintain third-party manufacturing for product candidates, or to do so on commercially reasonable terms, we may not be able to develop and commercialize our product candidates successfully. Our or

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a third party s failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- an inability to initiate or continue preclinical studies or clinical trials of product candidates under development;
- delay in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of a collaborator;
- subjecting manufacturing facilities of our product candidates to additional inspections by regulatory authorities;
- requirements to cease distribution or to recall batches of our product candidates; and
- in the event of approval to market and commercialize a product candidate, an inability to meet commercial demands for our products.

We may not successfully engage in strategic transactions, including any additional collaborations we seek, which could adversely affect our ability to develop and commercialize product candidates, impact our cash position, increase our expense and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as collaborations, acquisitions of companies, asset purchases and out- or in-licensing of product candidates or technologies. In particular, in addition to our current arrangements with KHK and Arbutus, we will evaluate and, if strategically attractive, seek to enter into additional collaborations, including with major biotechnology or pharmaceutical companies. The competition for collaborators is intense, and the negotiation process is time-consuming and complex. Any new collaboration may be on terms that are not optimal for us, and we may be unable to maintain any new or existing collaboration if, for example, development or approval of a product candidate is delayed, sales of an approved product candidate do not meet expectations or the collaborator terminates the collaboration. Any such collaboration, or other strategic transaction, may require us to incur non-recurring or other charges, increase our near- and long-term expenditures and pose significant integration or implementation challenges or disrupt our management or business. These transactions would entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of our business and diversion of our management s time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected collaboration, acquisition or integration costs, write-downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the collaboration or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and have a material adverse effect on our business, results of

operations, financial condition and prospects. Conversely, any failure to enter any collaboration or other strategic transaction that would be beneficial to us could delay the development and potential commercialization of our product candidates and have a negative impact on the competitiveness of any product candidate that reaches market.

We face competition from entities that have developed or may develop product candidates for our target disease indications, including companies developing novel treatments and technology platforms based on modalities and technology similar to ours. If these companies develop technologies or product candidates more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to develop and successfully commercialize product candidates may be adversely affected.

The development and commercialization of drugs is highly competitive. We compete with a variety of multinational pharmaceutical companies and specialized biotechnology companies, as well as technology being

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developed at universities and other research institutions. Our competitors have developed, are developing or will develop product candidates and processes competitive with our product candidates. Competitive therapeutic treatments include those that have already been approved and accepted by the medical community and any new treatments that enter the market. We are aware of multiple companies that are working in the field of RNAi therapeutics, including a major pharmaceutical company, Takeda Pharmaceutical Company Limited, and biopharmaceutical companies such as Alnylam, which in March 2014 acquired Sirna Therapeutics, Inc. from Merck & Co., Inc., Arbutus, with which we have license and development and supply agreements, Arrowhead, Silence Therapeutics plc, RXi Pharmaceuticals Corporation, Quark Pharmaceuticals, Inc., Marina Biotech, Inc., Benitec Biopharma Limited and Arcturus Therapeutics. In particular, Arrowhead holds a non-exclusive license to the same patent rights of City of Hope (COH) and Integrated Data Technologies, Inc. (IDT) as we are licensed under our license agreement with COH. As a result, we cannot rely on those patent rights to prevent Arrowhead or third parties working with Arrowhead from developing, marketing and selling products that compete directly with our product candidates. In March 2015 Arrowhead announced the acquisition of Novartis RNAi research and development portfolio and associated assets. The acquisition includes assignment of certain intellectual property owned or controlled by Novartis, including access to non-delivery Alnylam RNAi IP for 30 targets, and three pre-clinical RNAi candidates for which Novartis has developed varying amounts of preclinical data.

We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop product candidates. There are also competitors to our proprietary product candidates currently in development, some of which may become commercially available before our product candidates. For example, Alnylam announced in the third quarter of 2014 a new RNAi-based program for treatment of PH1. OxThera also has a competing approach to PH1 treatment, currently in Phase 2 clinical trials, that is not RNAi-based. The drug candidates of either Alnylam or OxThera may become commercially available before or perform more effectively than DCR- PH1, our investigational treatment for PH1.

We also compete with companies working to develop antisense and other RNA-based drugs. Like RNAi therapeutics, antisense drugs target messenger RNA (mRNA) with the objective of suppressing the activity of specific genes. The development of antisense drugs is more advanced than that of RNAi therapeutics, and antisense technology may become the preferred technology for products that target mRNAs. Significant competition also exists from companies such as Alnylam and Arrowhead to discover and develop safe and effective means to deliver therapeutic RNAi molecules, such as DsiRNAs, to the relevant cell and tissue types.

If our lead product candidates are approved for the indications we are currently pursuing, they will compete with a range of therapeutic treatments that are either in development or currently marketed. For example, Nexavar, marketed by Amgen Inc. and Bayer AG, is currently in use for the treatment of hepatocellular carcinoma (HCC). Given the high unmet medical need and the commercial success of Nexavar, numerous targeted therapies for the treatment of HCC are under development. Targeted therapies represent the largest proportion of the HCC pipeline. There are also a number of pharmaceuticals and biologics that are marketed or in clinical development for the treatment of solid tumors. The most common treatments for solid tumors are various chemotherapeutic agents, radiation therapy and certain targeted therapies. Targeting therapies include monoclonal antibodies such as Avastin, Erbitux and Herceptin, and small molecules, such as Affinitor, Sutent and Tarceva. Immunotherapy regimens are also on the market and in development for the treatment of solid tumors. In addition, we believe that Kadmon Corporation, LLC is evaluating salirasib (KD032) in clinical trials for the treatment of KRAS-specific non-small cell lung cancer, pancreatic cancer and other solid tumors.

Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we have. If we successfully obtain approval for any product candidate, we will face competition based on many different factors, including safety and effectiveness, ease with which our products can be

administered and the extent to which patients accept relatively new routes of administration, timing and scope of regulatory approvals, availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position of our products. Competing products could

present superior treatment alternatives, including by being more effective, safer, less expensive or marketed and sold more effectively than any products we may develop. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. Competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan.

Any inability to attract and retain qualified key management and technical personnel would impair our ability to implement our business plan.

Our success largely depends on the continued service of key management and other specialized personnel, including Douglas M. Fambrough, III, Ph.D., our chief executive officer, Theodore T. Ashburn, M.D., Ph.D, our senior vice president, product strategy and operations, Pankaj Bhargava, M.D., our chief medical officer, Bob D. Brown, Ph.D., our chief scientific officer, John Jack Green, our interim chief financial officer, and James B. Weissman, our chief business officer. The loss of one or more members of our management team or other key employees or advisors could delay our research and development programs and materially harm our business, financial condition, results of operations and prospects. The relationships that our key managers have cultivated within our industry make us particularly dependent upon their continued employment with us. We are dependent on the continued service of our technical personnel because of the highly technical nature of our product candidates and technologies and the specialized nature of the regulatory approval process. Because our management team and key employees are not obligated to provide us with continued service, they could terminate their employment with us at any time without penalty. We do not maintain key person life insurance policies on any of our management team members or key employees. Our future success will depend in large part on our continued ability to attract and retain other highly qualified scientific, technical and management personnel, as well as personnel with expertise in clinical testing, manufacturing, governmental regulation and commercialization. We face competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations.

If our product candidates advance into clinical trials, we may experience difficulties in managing our growth and expanding our operations.

We have limited experience in drug development and did not begin our first clinical trial of a product candidate until 2014. As our product candidates enter and advance through preclinical studies and any clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

If any of our product candidates are approved for marketing and commercialization and we are unable to develop sales, marketing and distribution capabilities on our own or enter into agreements with third parties to perform these functions on acceptable terms, we will be unable to successfully commercialize any such future products.

We currently have no sales, marketing or distribution capabilities or experience. If any of our product candidates is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or enter into collaborations with third parties to perform these services. If we decide to market our products directly, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our approved

products or decide to co-promote products with collaborators, we will need

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to establish and maintain marketing and distribution arrangements with third parties, and there can be no assurance that we will be able to enter into such arrangements on acceptable terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition, results of operations and prospects could be materially adversely affected.

If we fail to comply with U.S. and foreign regulatory requirements, regulatory authorities could limit or withdraw any marketing or commercialization approvals we may receive and subject us to other penalties that could materially harm our business.

The company, our product candidates, our suppliers, and our contract manufacturers, distributors, and contract testing laboratories are subject to extensive regulation by governmental authorities in the European Union, the United States, and other countries, with the regulations differing from country to country.

Even if we receive marketing and commercialization approval of a product candidate, we and our third-party services providers will be subject to continuing regulatory requirements, including a broad array of regulations related to establishment registration and product listing, manufacturing processes, risk management measures, quality and pharmacovigilance systems, post-approval clinical studies, labeling, advertising and promotional activities, record keeping, distribution, adverse event reporting, and import and export of pharmaceutical products. We are required to submit safety and other post market information and reports and are subject to continuing regulatory review, including in relation to adverse patient experiences with the product and clinical results that are reported after a product is made commercially available, both in the U.S. and any foreign jurisdiction in which we seek regulatory approval. The FDA and certain foreign regulatory authorities, such as the EMA, have significant post-market authority, including the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials to evaluate safety risks related to the use of a product or to require withdrawal of the product from the market. The FDA also has the authority to require a risk evaluation and mitigation strategies (REMS) plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. The EMA now routinely requires risk management plans (RMPs) as part of the marketing authorization application process, and such plans must be continually modified and updated throughout the lifetime of the product as new information becomes available. In addition, the relevant governmental authority of any European Union member state can request an RMP whenever there is a concern about a risk affecting the benefit risk balance of the product. The manufacturer and manufacturing facilities we use to make a future product, if any, will also be subject to periodic review and inspection by the FDA and other regulatory agencies, including for continued compliance with cGMP requirements. The discovery of any new or previously unknown problems with our third-party manufacturers, manufacturing processes or facilities may result in restrictions on the product, manufacturer or facility, including withdrawal of the product from the market. If we rely on third-party manufacturers, we will not have control over compliance with applicable rules and regulations by such manufacturers. Any product promotion and advertising will also be subject to regulatory requirements and continuing regulatory review. If we or our collaborators, manufacturers or service providers fail to comply with applicable continuing regulatory requirements in the U.S. or foreign jurisdictions in which we seek to market our products, we or they may be subject to, among other things, fines, warning and untitled letters, clinical holds, delay or refusal by the FDA or foreign regulatory authorities to approve pending applications or supplements to approved applications, suspension, refusal to renew or withdrawal of regulatory approval, product recalls, seizures or administrative detention of products, refusal to permit the import or export of products, operating restrictions and total or partial suspension of production or distribution, injunction, restitution, disgorgement, debarment, civil penalties and criminal prosecution.

Price controls imposed in foreign markets may adversely affect our future profitability.

In some countries, particularly member states of the European Union, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take

considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our RNAi therapeutic candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of any product candidate approved for marketing is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, financial condition, results of operations or prospects could be adversely affected.

Our business entails a significant risk of product liability and our ability to obtain sufficient insurance coverage could harm our business, financial condition, results of operations or prospects.

Our business exposes us to significant product liability risks inherent in the development, testing, manufacturing and marketing of therapeutic treatments. Product liability claims could delay or prevent completion of our development programs. If we succeed in marketing products, such claims could result in an investigation by certain regulatory authorities, such as FDA or foreign regulatory authorities, of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management s time and our resources, substantial monetary awards to trial participants or patients and a decline in our stock price. We currently have product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to marketing any of our product candidates. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include, but is not limited to, intentional failures to comply with FDA regulations or applicable laws, regulations, guidance or codes of conduct set by foreign governmental authorities or self-regulatory industry organizations, provide accurate information to any governmental authorities such as FDA, comply with manufacturing standards we may establish, comply with federal and state healthcare fraud and abuse laws and regulations, 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, regulations, guidance and codes of conduct intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws, regulations, guidance and codes of conduct 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, including debarment or disqualification of those employees from participation in FDA regulated activities, and serious harm to our reputation. 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 be in compliance with such

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laws, regulations, guidance or codes of conduct. 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, exclusion from government programs, or other sanctions.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such events could cause interruptions of our operations. For instance, the loss of preclinical data or data from any future clinical trial involving our product candidates could result in delays in our development and regulatory filing efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing involve the use of hazardous materials and various chemicals. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge, Massachusetts, that are required for our research, development and manufacturing activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing these materials in our Cambridge facilities comply with the relevant guidelines of Cambridge, the Commonwealth of Massachusetts and the Occupational Safety and Health Administration of the U.S. Department of Labor. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of animals and biohazardous materials. 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 these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological or hazardous materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate any of these laws or regulations.

Our information technology systems could face serious disruptions that could adversely affect our business.

Our information technology and other internal infrastructure systems, including corporate firewalls, servers, leased lines and connection to the Internet, face the risk of systemic failure that could disrupt our operations. A significant disruption in the availability of our information technology and other internal infrastructure systems could cause interruptions in our collaborations with our partners and delays in our research and development work.

Our current operations are concentrated in one location and any events affecting this location may have material adverse consequences.

Our current operations are located in our facilities situated in Cambridge. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics, power shortage,

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telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize the facilities, may have a material adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. Loss of access to these facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption may have a material adverse effect on our business, financial position, results of operations and prospects.

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

We have incurred substantial losses during our history, do not expect to become profitable for the foreseeable future and may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. We may be unable to use these losses to offset income before such unused losses expire. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an ownership change, which is generally defined as a greater than 50 percentage point 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 and other pre-change tax attributes to offset its post-change income may be further limited. We have not performed an analysis on whether we have experienced any ownership changes in the past. It is possible that we have experienced an ownership change, including pursuant to the initial public offering of our common stock, which closed on February 4, 2014, and our net operating losses are subject to such limitation. As of December 31, 2015, we had U.S. federal and Massachusetts net operating loss carryforwards of $92.5 million and $77.6 million, respectively. Any limit on these loss carryforwards if we have or do experience an ownership change could have an adverse effect on our business, financial position, results of operations and prospects.

The investment of our cash and cash equivalents and held-to-maturity investments is subject to risks which may cause losses and affect the liquidity of these investments.

As of December 31, 2015, we had $94.6 million in cash and cash equivalents and held-to-maturity investments. We historically have invested substantially all of our available cash and cash equivalents in corporate bonds, commercial paper, securities issued by the U.S. government, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. These investments are subject to general credit, liquidity, market and interest rate risks, including the impact of U.S. sub-prime mortgage defaults that have affected various sectors of the financial markets and caused credit and liquidity issues. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our condensed consolidated financial statements.

In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

Changes in accounting rules and regulations, or interpretations thereof, could result in unfavorable accounting charges or require us to change our compensation policies.

Accounting methods and policies for biopharmaceutical companies, including policies governing revenue recognition, research and development and related expenses and accounting for stock-based compensation, are subject to review,

interpretation and guidance from our auditors and relevant accounting authorities, including the Securities and Exchange Commission and the Public Company Accounting Oversight Board. Changes to

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accounting methods or policies, or interpretations thereof, may require us to reclassify, restate or otherwise change or revise our financial statements, including those contained in this Annual Report on Form 10-K.

Risks Related to Intellectual Property

If we are not able to obtain and enforce patent protection for our technologies or product candidates, development and commercialization of our product candidates may be adversely affected.

Our success depends in part on our ability to obtain and maintain patents and other forms of intellectual property rights, including in-licenses of intellectual property rights of others, for our product candidates, methods used to manufacture our product candidates and methods for treating patients using our product candidates, as well as our ability to preserve our trade secrets, to prevent third parties from infringing upon our proprietary rights and to operate without infringing upon the proprietary rights of others. As of March 1, 2016, our patent estate, including the patents and patent applications that we have licensed from COH, along with one of their affiliates, included over 20 issued patents and over 70 pending patent applications supporting commercial development of our DsiRNA molecules and delivery technologies. We may not be able to apply for patents on certain aspects of our product candidates or delivery technologies in a timely fashion or at all. Our existing issued and granted patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technology. There is no guarantee that any of our pending patent applications will result in issued or granted patents, that any of our issued or granted patents will not later be found to be invalid or unenforceable or that any issued or granted patents will include claims that are sufficiently broad to cover our product candidates or delivery technologies or to provide meaningful protection from our competitors. Moreover, the patent position of biotechnology and pharmaceutical companies can be highly uncertain because it involves complex legal and factual questions. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our current and future proprietary technology and product candidates are covered by valid and enforceable patents or are effectively maintained as trade secrets. If third parties disclose or misappropriate our proprietary rights, it may materially and adversely impact our position in the market.

The U.S. Patent and Trademark Office (USPTO) and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case. The standards applied by the USPTO and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology and pharmaceutical patents. As such, we do not know the degree of future protection that we will have on our proprietary products and technology. While we will endeavor to try to protect our product candidates with intellectual property rights such as patents, as appropriate, the process of obtaining patents is time-consuming, expensive and sometimes unpredictable.

In addition, there are numerous recent changes to the patent laws and proposed changes to the rules of the USPTO which may have a significant impact on our ability to protect our technology and enforce our intellectual property rights. For example, the Leahy-Smith America Invents Act (AIA) enacted in 2011 involves significant changes in patent legislation. The U.S. Supreme Court has ruled on several patent cases in recent years, some of which cases either narrow the scope of patent protection available in certain circumstances or weaken the rights of patent owners in certain situations. The 2013 decision by the U.S. Supreme Court in *Association for Molecular Pathology v. Myriad Genetics, Inc.* precludes a claim to a nucleic acid having a stated nucleotide sequence which is identical to a sequence found in nature and unmodified. We currently are not aware of an immediate impact of this decision on our patents or

patent applications because we are developing nucleic acid products that are not found in nature. However, this decision has yet to be clearly interpreted by courts and by the USPTO. We cannot assure you that the interpretations of this decision or subsequent rulings will not adversely impact our patents or

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patent applications. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Once granted, patents may remain open to opposition, interference, re-examination, post-grant review, inter partes review, nullification or derivation action in court or before patent offices or similar proceedings for a given period before or after allowance or grant, during which time third parties can raise objections against such initial grant. In the course of such proceedings, which may continue for a protracted period of time, the patent owner may be compelled to limit the scope of the allowed or granted claims thus attacked, or may lose the allowed or granted claims altogether. Our patent risks include that:

- Others may, or may be able to, make, use or sell compounds that are the same as or similar to our product candidates but that are not covered by the claims of the patents that we own or license.
- We or our licensors, collaborators or any future collaborators may not be the first to file patent applications covering certain aspects of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- A third party may challenge our patents and, if challenged, a court may not hold that our patents are valid, enforceable and infringed.
- A third party may challenge our patents in various patent offices and, if challenged, we may be compelled to limit the scope of our allowed or granted claims or lose the allowed or granted claims altogether.
- Any issued patents that we own or have licensed will provide us with any competitive advantages, or may be challenged by third parties.
- We may not develop additional proprietary technologies that are patentable.
- The patents of others could harm our business.
- Our competitors could conduct research and development activities in countries where we will not have enforceable patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.

Intellectual property rights of third parties could adversely affect our ability to commercialize our product candidates, and we might be required to litigate or obtain licenses from third parties in order to develop or market our product candidates. Such litigation could be costly and licenses may be unavailable on commercially reasonable terms.

Research and development of RNAi-based therapeutics and other oligonucleotide-based therapeutics has resulted in many patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. Our efforts are based on RNAi technology that we have licensed (DsiRNA) and that we have developed internally and own (DsiRNA-EX). We have chosen this approach to increase our likelihood of technical success and our freedom to operate. We have obtained grants and issuances of RNAi, RNAi therapeutic and DsiRNA patents and have licensed other patents from third parties on an exclusive or non-exclusive basis. The issued patents and pending patent applications in the U.S. and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics and DsiRNA therapeutics. Specifically, we own and have licensed a portfolio of patents, patent applications and other intellectual property covering: (1) certain aspects of the structure and uses of DsiRNA and DsiRNA-EX molecules, including their manufacture and use as

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therapeutics, and RNAi-related mechanisms, (2) chemical modifications to DsiRNA and DsiRNA-EX molecules that improve their properties and suitability for therapeutic uses, (3) DsiRNA and DsiRNA-EX molecules directed to specific gene sequences and drug targets as treatments for particular diseases and (4) delivery technologies, such as in the field of lipid nanoparticles and lipid nanoparticle formulation, and chemical modifications such as conjugation to targeting moieties.

The RNAi-related intellectual property landscape, including patent applications in prosecution where no definitive claims have yet issued, is still evolving, and it is difficult to conclusively assess our freedom to operate. Other companies are pursuing patent applications and possess issued patents broadly directed to RNAi compositions, methods of making and using RNAi and to RNAi-related delivery and modification technologies. Our competitive position may suffer if patents issued to third parties cover our products, or our manufacture or uses relevant to our commercialization plans. In such cases, we may not be in a position to commercialize products unless we enter into a license agreement with the intellectual property right holder, if available, on commercially reasonable terms or successfully pursue litigation, opposition, interference, re-examination, post-grant review, inter partes review, nullification, derivation action, or cancellation proceeding to limit, nullify or invalidate the third party intellectual property right concerned. Even if we are successful in limiting, nullifying, or invalidating third party intellectual property rights through such proceedings, we may incur substantial costs and could require significant time and attention of our personnel.

While we believe our intellectual property allows us to pursue our current development programs, the biological process of RNAi is a natural process and cannot be patented. Several companies in the space are pursuing alternate methods to exploit this phenomenon and have built their intellectual property around these methods. For example, Alnylam controls three patent families containing both pending patent applications and issued patents (e.g., U.S. Patent Numbers 8,853,384 and 9,074,213, and European Patent EP 1 352 061 B1) that pertain to RNAi. These are referred to in their corporate literature as the Tuschl family (e.g. patents and applications claiming priority to WO2002/044321, filed Nov. 29, 2001, and their priority filings) and the Kreutzer-Limmer family (e.g. patents and applications claiming priority to WO 2002/044895, filed Jan. 29, 2000, WO 2002/055693, filed Jan. 9, 2002, and their priority filings). Both families contain patent applications still in prosecution, with the applicants actively seeking to extend the reach of this intellectual property in ways that might strategically impact our business. Additional areas of intellectual property pursued by Alnylam and others include oligonucleotide delivery-related technologies (such as conjugation to targeting moieties) and oligonucleotides directed to specific gene targets.

Patent applications in the U.S. and elsewhere are generally published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our products or platform technology could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our products or the use of our products. Third party intellectual property right holders may also bring patent infringement claims against us. No such infringement actions have been brought against us. We cannot guarantee that we will be able to successfully settle or otherwise resolve any future infringement claims. If we are unable to successfully settle future claims on terms acceptable to us, we may be required to engage in or continue costly, unpredictable and time-consuming litigation and may be prevented from or experience substantial delays in marketing our products. If we fail in any such dispute, in addition to being forced to pay damages, we may be temporarily or permanently prohibited from commercializing any of our product candidates that are held to be infringing. We might also be forced to redesign product candidates so that we no longer infringe the third party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

As the field of RNAi therapeutics matures, patent applications are being processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation in the courts and other proceedings, such as

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interference, re-examination, opposition, post-grant review, inter partes review, nullification, derivation action, or cancellation proceedings, in various patent offices relating to patent rights in the RNAi therapeutics field. In many cases, the possibility of appeal or opposition exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims or if third parties are successful in obtaining claims that cover our DsiRNA technology or any of our product candidates. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi therapeutics.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need to apply to our DsiRNA and DsiRNA-EX therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for DsiRNA drugs we wish to develop. Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may be unable to market products or perform research and development or other activities covered by these patents.

We license patent rights from third-party owners or licensees. If such owners or licensees do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, or if they retain or license to others any competing rights, our competitive position and business prospects may be adversely affected.

We do, and will continue to, rely on intellectual property rights licensed from third parties to protect our technology. We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have a license from COH (on behalf of itself and IDT) to certain patent rights, which provide platform intellectual property for research and development of our DsiRNA molecules employed in our DCR-MYC programs and collaborative programs with KHK. Pursuant to this agreement, we have a worldwide license from COH (subject to the pre-existing non-exclusive license) for the exploitation of key intellectual property rights in this respect, and COH and IDT retain ownership of the patents and patent applications to which we are licensed under the agreement. In addition, we have an exclusive worldwide license from Arbutus to their LNP technology for delivery of certain therapeutics to treat PH1, and Arbutus retains ownership of its patents. This technology could be important to us as we are seeking to use it to deliver DCR-PH1 to the liver. If we are unable to do so, our DCR-PH1 program would suffer delays, which could have a material adverse effect on our business, financial condition, results of operations and prospects. We also may license additional third-party intellectual property in the future. Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue litigation less aggressively than we would. Further, we may not obtain exclusive rights, which would allow for third parties to develop competing products. Without protection for, or exclusive right to, the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. In addition, we sublicense our rights under our third-party licenses to KHK and may sublicense such rights to current or future collaborators or any future strategic partners. Any impairment of these sublicensed rights could result in reduced revenue under our collaboration agreement with KHK or result in termination of an agreement by one or more of our collaborators or any future strategic partners.

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Certain third parties may also have rights in the patents related to DsiRNA included in the license granted to us by COH, including the core DsiRNA patent (U.S. 8,084,599), which could allow them to develop, market and sell product candidates in competition with ours.

To the extent that we do not have exclusive rights in the patents covered by the license granted to us by COH, we cannot prevent third parties from developing DsiRNA based product candidates in competition with ours. Prior to entering into the license with us, COH had entered into a non-exclusive license with a third party with respect to such patent rights to manufacture, use, import, offer for sale and sell products covered by the licensed patent rights for the treatment or prevention of disease in humans (excluding viruses and delivery of products into the eye or ear). While we believe that such non-exclusive license has been terminated, COH has informed us that a sublicensee to that non-exclusive license was permitted to enter into an equivalent non-exclusive license which, to our knowledge, is subsisting with Arrowhead, as successor to the non-exclusive license holder. As successor to the non-exclusive license holder, we believe that Arrowhead has substantially similar access to the same patent rights related to DsiRNA technology granted to us under our license with COH. Arrowhead is developing RNA-based therapeutics for the treatment of diseases of the liver, which may directly compete with our product candidates. In addition, the U.S. government has certain rights to the inventions covered by the patent rights and COH, as an academic research and medical center, has the right to practice the licensed patent rights for educational, research and clinical uses. If Arrowhead or another party develops, manufactures, markets and sells any product covered by the same patent rights and technologies that compete with ours, it could significantly undercut the value of any of our product candidates, which would materially adversely affect our revenue, financial condition and results of operations.

We may be unable to protect our intellectual property rights throughout the world.

Obtaining a valid and enforceable issued or granted patent covering our technology in the U.S. and worldwide can be extremely costly. In jurisdictions where we have not obtained patent protection, competitors may use our technology to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but where it is more difficult to enforce a patent as compared to the U.S. Competitor products may compete with our future products in jurisdictions where we do not have issued or granted patents or where our issued or granted patent claims or other intellectual property rights are not sufficient to prevent competitor activities in these jurisdictions. The legal systems of certain countries, particularly certain developing countries, make it difficult to enforce patents and such countries may not recognize other types of intellectual property protection, particularly that relating to biopharmaceuticals. This could make it difficult for us to prevent the infringement of our patents or marketing of competing products in violation of our proprietary rights generally in certain jurisdictions. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

We generally file a provisional patent application first (a priority filing) at the USPTO. A U.S. utility application and international application under the Patent Cooperation Treaty (PCT) are usually filed within twelve months after the priority filing. Based on the PCT filing, national and regional patent applications may be filed in the European Union, Japan, Australia and Canada and, depending on the individual case, also in any or all of, inter alia, China, India, South Korea, Singapore, Taiwan and South Africa. We have so far not filed for patent protection in all national and regional jurisdictions where such protection may be available. In addition, we may decide to abandon national and regional patent applications before grant. Finally, the grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications might in some jurisdictions be refused by the relevant registration authorities, while granted by others. It is also quite common that depending on the country, various scopes of patent protection may be granted on the same product candidate or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws in the U.S., and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from

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effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition from others in those jurisdictions. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position in the relevant jurisdiction may be impaired and our business and results of operations may be adversely affected.

We or our licensors, collaborators or any future strategic partners may become subject to third party claims or litigation alleging infringement of patents or other proprietary rights or seeking to invalidate patents or other proprietary rights, and we may need to resort to litigation to protect or enforce our patents or other proprietary rights, all of which could be costly, time consuming, delay or prevent the development and commercialization of our product candidates, or put our patents and other proprietary rights at risk.

We or our licensors, collaborators or any future strategic partners may be subject to third-party claims for infringement or misappropriation of patent or other proprietary rights. We are generally obligated under our license or collaboration agreements to indemnify and hold harmless our licensors or collaborators for damages arising from intellectual property infringement by us. If we or our licensors, collaborators or any future strategic partners are found to infringe a third party patent or other intellectual property rights, we could be required to pay damages, potentially including treble damages, if we are found to have willfully infringed. In addition, we or our licensors, collaborators or any future strategic partners may choose to seek, or be required to seek, a license from a third party, which may not be available on acceptable terms, if at all. Even if a license can be obtained on acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. If we fail to obtain a required license, we or our collaborator, or any future collaborator, may be unable to effectively market product candidates based on our technology, which could limit our ability to generate revenue or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. In addition, we may find it necessary to pursue claims or initiate lawsuits to protect or enforce our patent or other intellectual property rights. The cost to us in defending or initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management s attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts and limit our ability to continue our operations.

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our products or our technology, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on one or more of our products or certain aspects of our platform technology. Such a loss of patent protection could have a material adverse impact on our business. Patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without legally infringing our

patents or other intellectual property rights.

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If we fail to comply with our obligations under any license, collaboration or other agreements, we may be required to pay damages and could lose intellectual property rights that are necessary for developing and protecting our product candidates and delivery technologies or we could lose certain rights to grant sublicenses.

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor s rights. In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patent protection for certain aspects of our product candidates and delivery technologies, we also consider trade secrets, including confidential and unpatented know-how important to the maintenance of our competitive position. We protect trade secrets and confidential and unpatented know-how, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants that obligate them to maintain confidentiality and assign their inventions to us. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts in the U.S. and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We are also subject both in the U.S. and outside the U.S. to various regulatory schemes regarding requests for the information we provide to regulatory authorities, which may include, in whole or in part, trade secrets or confidential commercial information. While we are likely to be notified in advance of any disclosure of such information and would likely object to such disclosure, there can be no assurance that our challenge to the request would be successful.

We are currently, and may be in the future, subject to claims that we or our employees or consultants have wrongfully used or disclosed alleged trade secrets of our employees or consultants former employers or their clients. These claims may be costly to defend and if we do not successfully do so, we may be required to pay monetary damages, may be prohibited from using some of our research and development, and may lose valuable intellectual property rights or personnel.

Many of our employees were previously employed at universities or biotechnology or pharmaceutical companies, including our competitors or potential competitors. From time to time we have received

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correspondence from other companies alleging the improper use or disclosure, or inquiring regarding the use or disclosure, by certain of our employees who have previously been employed elsewhere in our industry, including with our competitors, of their former employer s trade secrets or other proprietary information.

Responding to these allegations can be costly and disruptive to our business, even when the allegations are without merit, and can be a distraction to management. On June 10, 2015, Alnylam Pharmaceuticals, Inc. filed a complaint against us in the Superior Court of Middlesex County, Massachusetts, alleging misappropriation of confidential information and trade secrets, as well as other related claims, in connection with our hiring of a number of former employees of Sirna Therapeutics, Inc., or Sirna, which at the time was a subsidiary of Merck & Co., Inc., and in connection with our discussion with Merck to acquire Sirna, which was subsequently acquired by Alnylam. We may be subject to additional claims in the future that these or other of our employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail in defending current or future claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, personnel, or the ability to use some of our research and development. A loss of intellectual property, key research personnel, or their work product could hamper our ability to commercialize, or prevent us from commercializing, our product candidates, which could severely harm our business.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Government Regulation

We may be unable to obtain U.S. or foreign regulatory approval and, as a result, unable to commercialize our product candidates.

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, packaging, advertising and promotion, pricing, marketing, sampling, and distribution of drugs. Rigorous preclinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the U.S. and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

We have very limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA as well as foreign regulatory authorities, such as the EMA. The time required to obtain FDA and foreign regulatory approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are not always applied predictably or uniformly and can change. Any analysis we perform of data from preclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future

legislation or administrative action, or from changes in the policy of FDA or foreign regulatory authorities during the period of product development, clinical trials and

regulatory review by the FDA or foreign regulatory authorities. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign laws, regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Because the drugs we are developing may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. While we believe the product candidates that we are currently developing are regulated as new drugs under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA or foreign regulatory authorities of any regulatory filings that we may submit. Moreover, the FDA or foreign regulatory authorities may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. Regulatory authority also may impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy (REMS) plan as part of an NDA or biologics license application (BLA) or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug or biologic, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process varies among countries and may include all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Moreover, the time required to obtain approval may differ from that required to obtain FDA approval. Approval by the FDA does not ensure approval by regulatory authorities outside the U.S. and vice versa.

If we or our existing or future collaborators, manufacturers or service providers fail to comply with healthcare laws and regulations, we or they could be subject to enforcement actions, which could affect our ability to develop, market and sell our products and may harm our reputation.

We and our collaborators are subject to federal, state, and foreign healthcare laws and regulations pertaining to fraud and abuse and patients rights. These laws and regulations include, but are not limited to:

- the U.S. federal anti-kickback law, which prohibits, among other things, persons from soliciting, receiving, offering or providing remuneration, directly or indirectly, to induce either the referral of an individual for a

healthcare item or service, or the purchasing or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid;

the U.S. federal false claims law, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government funded programs

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such as Medicare or Medicaid that are false or fraudulent, and which may apply to us by virtue of statements and representations made to customers or third parties;

the Federal Food, Drug and Cosmetic Act and other laws, which prohibit promotion of drugs prior to FDA approval and prohibit dissemination of information about unapproved uses of approved drugs, with very specific and limited exceptions;

the U.S. federal Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) Act, which prohibit executing a scheme to defraud healthcare programs, impose requirements relating to the privacy, security, and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;

the federal Open Payments regulations under the National Physician Payment Transparency Program have been issued under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, and will require that manufacturers of pharmaceutical and biological drugs covered by Medicare, Medicaid, and Children s Health Insurance Programs report all consulting fees, travel reimbursements, research grants, and other payments or gifts with values over $10 made to physicians and teaching hospitals; and

state laws comparable to each of the above federal laws, such as, for example, anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to patient data privacy and security.

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, any of which could adversely our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management s attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our products successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others:

adverse regulatory inspection findings;

warning or untitled letters;

voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;

restrictions on, or prohibitions against, marketing our products;

restrictions on, or prohibitions against, importation or exportation of our products;

suspension of review or refusal to approve pending applications or supplements to approved applications;

exclusion from participation in government-funded healthcare programs;

exclusion from eligibility for the award of government contracts for our products;

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FDA debarment of individuals at our Company;

suspension or withdrawal of product approvals;

seizure or administrative detention of products;

injunctions; and

civil and criminal penalties and fines.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we intend to monitor these regulations, our programs are currently in the early stages of development and we will not be able to assess the impact of price regulations for a number of years. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product in that country.

Our ability to commercialize any products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. However, there may be significant delays in obtaining coverage for newly-approved drugs. Moreover, eligibility for coverage does not necessarily signify that a drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution costs. Also, interim payments for new drugs, if applicable, may be insufficient to cover our costs and may not be made permanent. Thus, even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Because our programs are in the early stages of development, we are unable at this time to determine their cost effectiveness or the likely level or method of reimbursement. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are seeking greater upfront discounts, additional rebates and other concessions to reduce the prices for pharmaceutical products. If the price we are able to charge for any products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

We currently expect that certain/some drugs we develop may need to be administered under the supervision of a physician on an outpatient basis. Under currently applicable U.S. law, certain drugs that are not usually self-administered (including injectable drugs) may be eligible for coverage under the Medicare Part B program if certain requirements, including the following, have been satisfied:

they are furnished incident to a physician s services;

they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice;

they are included or approved for inclusion in certain Medicare-designated pharmaceutical compendia; and

they have been approved by the FDA.

Under current law, as a condition of receiving Medicare Part B reimbursement for a manufacturer s eligible drugs or biologicals, the manufacturer is required to participate in other government healthcare programs,

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including the Medicaid Drug Rebate Program (MDRP) and the 340B Drug Discount Program. Average prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Reimbursement rates under Medicare Part B would depend in part on whether the newly approved product would be eligible for a unique billing code. Self-administered drugs are typically reimbursed under Medicare Part D, and drugs that are administered in a hospital setting are typically reimbursed under Medicare Part A under a bundled payment. It is difficult for us to predict how Medicare coverage and reimbursement policies will be applied to our products in the future and coverage and reimbursement under different federal healthcare programs are not always consistent. Medicare reimbursement rates may also reflect budgetary constraints placed on the Medicare program.

Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for new drugs that we develop and for which we obtain regulatory approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the U.S. and other major healthcare markets have been proposed, and such efforts have expanded substantially in recent years. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

For example, in the U.S., Congress passed the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (ACA), which contains provisions that affect companies in the pharmaceutical industry and other healthcare-related industries in a variety of ways. Provisions that may affect pharmaceutical companies include, but are not limited to, the following.

- Mandatory rebates for drugs sold under the Medicaid program have been increased, and the rebate requirement has been extended to drugs used in risk-based Medicaid managed care plans.

- The 340B Drug Discount Program has been extended to require discounts for covered outpatient drugs sold to certain children s hospitals, critical access hospitals, freestanding cancer hospitals, rural referral centers, and sole community hospitals.

- Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the Donut Hole.

- Pharmaceutical companies are required to pay an annual non-tax-deductible fee to the federal government based on each company s market share of prior year total sales of branded drugs to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal healthcare

program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

For product candidates classified as biologics, marketing approval for a follow-on biologic product may not become effective until 12 years after the date on which the reference innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for biosimilar manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability if our products are classified as biologics.

In addition, in recent years, U.S. Congress has enacted various laws seeking to reduce the federal debt level and contain healthcare expenditures. For example, the Budget Control Act of 2011 (BCA) called for the

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establishment of a Joint Select Committee on Deficit Reduction, tasked with reducing the federal debt level. However, because the Committee did not draft a proposal by the BCA s deadline, President Obama issued a sequestration order on March 1, 2013 that imposed automatic spending cuts on various federal programs. Under the Bipartisan Budget Act of 2013 and a bill signed by the President on February 15, 2014, sequestration has been extended through fiscal year 2024. Medicare payments to providers are subject to such cuts, although the BCA generally limited the Medicare cuts to two percent. For fiscal year 2024, however, Medicare sequestration amounts will be realigned such that there will be a 4.0 percent sequester for the first six months and a zero percent sequester for the second six months.

The financial impact of the U.S. healthcare reform legislation over the next few years will depend on a number of factors, including the policies reflected in implementing regulations and guidance and changes in sales volumes for products affected by the legislation. Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further federal and state legislative, regulatory, or judicial developments are likely, and we expect ongoing initiatives in the U.S. to reduce healthcare expenditures. 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.

The healthcare industry is heavily regulated in the U.S. at the federal, state, and local levels, and our failure to comply with applicable requirements may subject us to penalties and negatively affect our financial condition.

As a healthcare company, our operations, clinical trial activities and interactions with healthcare providers may be subject to extensive regulation in the U.S., particularly if the company receives FDA approval for any of its products in the future. For example, if we receive FDA approval for a product for which reimbursement is available under a federal healthcare program (e.g., Medicare, Medicaid), it would be subject to a variety of federal laws and regulations, including those that prohibit the filing of false or improper claims for payment by federal healthcare programs (e.g. the False Claims Act), prohibit unlawful inducements for the referral of business reimbursable by federal healthcare programs (e.g. the Anti-Kickback Statute), and require disclosure of certain payments or other transfers of value made to U.S.-licensed physicians and teaching hospitals (the Physician Payments Sunshine Act). We are not able to predict how third parties will interpret these laws and apply applicable governmental guidance and may challenge our practices and activities under one or more of these laws. If our past or present operations are found to be in violation of any of these laws, we could be subject to civil and criminal penalties, which could hurt our business, our operations and financial condition.

Similarly, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) prohibits, among other offenses, knowingly and willfully executing a scheme to defraud any health care benefit program, including private payors, or 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 items or services under a health care benefit program. To the extent that the company acts as a business associate to a healthcare provider, the company may also be subject to the privacy and security provisions of HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, which restricts the use and disclosure of patient-identifiable health information, mandates the adoption of standards relating to the privacy and security of patient-identifiable health information, and requires the reporting of certain security breaches to healthcare provider customers with respect to such information. Additionally, many states have enacted similar laws that may impose more stringent requirements on entities like ours. Failure to comply with applicable laws and regulations could result in substantial penalties and adversely affect the company s financial condition and results of operations.

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending.

U.S. federal government agencies currently face potentially significant spending reductions. The Budget Control Act of 2011 (BCA) established a Joint Select Committee on Deficit Reduction, which was tasked with

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achieving a reduction in the federal debt level of at least $1.2 trillion. That committee did not draft a proposal by the BCA s deadline. As a result, automatic cuts (sequestration) in various federal programs were scheduled to take place, beginning in January 2013, although the American Taxpayer Relief Act of 2012 delayed the BCA s automatic cuts until March 1, 2013. While the Medicare program s eligibility and scope of benefits are generally exempt from these cuts, Medicare payments to providers and Part D health plans are not exempt. The BCA did, however, provide that the Medicare cuts to providers and Part D health plans would not exceed two percent. President Obama issued the sequestration order on March 1, 2013, and cuts went into effect on April 1, 2013. Additionally, the Bipartisan Budget Act of 2013 extended sequestration for Medicare for another two years, through 2023, and a bill signed by the President on February 15, 2014, further extended these cuts for an additional year, through fiscal year 2024. On January 21, 2014, President Obama signed the fiscal year 2014 omnibus appropriations bill, modifying for fiscal year 2014 and fiscal year 2015 the cuts that went into effect under the sequester on March 1, 2013.

The situation with the federal budget remains in flux. From October 1, 2013 through October 16, 2013, the U.S. federal government ceased the majority of its operations after Congress failed to enact legislation appropriating funds for fiscal year 2014. On October 17, 2013, President Obama signed into law the Continuing Appropriations Act of 2014, which included a continuing resolution to fund the government until January 15, 2014 and suspended the statutory debt ceiling until February 7, 2014. After extending the government funding expiration date to January 18, 2014, Congress passed a $1.1 trillion spending bill that was signed into law on January 17, 2014 and funds the government through September 30, 2014. While on December 9, 2014, Congress passed the Consolidated and Further Continuing Appropriations Act of 2015, which funds the government through September 30, 2015, this new law is a temporary measure that does not resolve the debt-limit issue. Many Members of Congress have made public statements indicating that some or all of these budget-related deadlines should be used as leverage to negotiate additional cuts in federal spending. The Medicare program is frequently mentioned as a target for spending cuts. The full impact on our business of any future cuts in Medicare or other programs would be uncertain. If federal spending is reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

If any of our product candidates receives marketing approval and we or others later identify undesirable side effects caused by the product candidate, our ability to market and derive revenue from the product candidates could be compromised.

In the event that any of our product candidates receive regulatory approval and we or others identify undesirable side effects, adverse events or other problems caused by one of our products, any of the following adverse events could occur, which could result in the loss of significant revenue to us and materially and adversely affect our results of operations and business:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we may need to recall the product or change the way the product is administered to patients;

additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof;

we may be subject to fines, restitution or disgorgement of profits or revenues, injunctions, or the imposition of civil penalties or criminal prosecution;

regulatory authorities may require the addition of labeling statements, such as a black box warning or a contraindication;

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regulatory authorities may require us to implement a REMS, or to conduct post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product; we may be required to create a Medication Guide outlining the risks of such side effects for distribution to patients;

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

the product may become less competitive; and

our reputation may suffer.

Risks Related to Our Common Stock

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

We are an emerging growth company as defined in the Jumpstart Our Business Act (JOBS Act). For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including (1) not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act of 2002 (Sarbanes-Oxley Act), (2) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and (3) exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31, or if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, in which case we would no longer be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share 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.

Our stock price may be volatile and purchasers of our common stock could incur substantial losses.

Our stock price is volatile. From January 30, 2014, the first day of trading of our common stock, through March 9, 2016, our stock had high and low closing sale prices in the range of $46.00 and $4.96 per share. The market price for our common stock may be influenced by many factors, including the other risks described in this section titled Risk

Factors and the following:

the success of competitive products or technologies;

results of preclinical studies and clinical trials of our product candidates, or those of our competitors, our existing collaborator or any future collaborators;

regulatory or legal developments in the U.S. and other countries, especially changes in laws or regulations applicable to our products;

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introductions and announcements of new products by us, our commercialization partners, or our competitors, and the timing of these introductions or announcements;

actions taken by regulatory agencies with respect to our products, clinical studies, manufacturing process or sales and marketing terms;

actual or anticipated variations in our financial results or those of companies that are perceived to be similar to us;

the success of our efforts to acquire or in-license additional technologies, products or product candidates;

developments concerning our collaborations, including but not limited to those with our sources of manufacturing supply and our commercialization partners;

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

developments concerning our collaborations, including those with our sources of manufacturing supply and our commercialization partners;

our ability or inability to raise additional capital and the terms on which we raise it;

the recruitment or departure of key personnel;

changes in the structure of healthcare payment systems;

market conditions in the pharmaceutical and biotechnology sectors;

actual or anticipated changes in earnings estimates or changes in stock market analyst recommendations regarding our common stock, other comparable companies or our industry generally;

our failure or the failure of our competitors to meet analysts projections or guidance that we or our competitors may give to the market;

fluctuations in the valuation of companies perceived by investors to be comparable to us;

announcement and expectation of additional financing efforts;

speculation in the press or investment community;

trading volume of our common stock;

sales of our common stock by us or our stockholders;

the absence of lock-up agreements in connection with the follow-on public offering of our common stock with the holders of substantially all of our outstanding shares;

the concentrated ownership of our common stock;

changes in accounting principles;

terrorist acts, acts of war or periods of widespread civil unrest;

natural disasters and other calamities;

general economic, industry and market conditions; and

developments concerning complaints or litigation against us.

In addition, the stock markets in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme volatility that has been often unrelated to the operating performance of the issuer. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance.

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The future issuance of equity or of debt securities that are convertible into equity will dilute our share capital.

On May 27, 2015, we completed an issuance and sale of 2,750,000 shares of our common stock at an offering price of $17.75 per share. We may choose to raise additional capital in the future, depending on market conditions, strategic considerations and operational requirements. To the extent that additional capital is raised through the issuance of shares or other securities convertible into shares, our stockholders will be diluted. Future issuances of our common stock or other equity securities, or the perception that such sales may occur, could adversely affect the trading price of our common stock and impair our ability to raise capital through future offerings of shares or equity securities. We cannot predict the effect, if any, that future sales of common stock or the availability of common stock for future sales will have on the trading price of our common stock.

The employment agreements with our executive officers may require us to pay severance benefits to officers who are terminated in connection with a change of control of us, which could harm our financial condition.

Our executive officers are parties to employment agreements providing, in the event of a termination of employment in connection with a change of control of us, for significant cash payments for severance and other benefits and acceleration of vesting of up to all outstanding stock options. The accelerated vesting of options could result in dilution to our existing stockholders and reduce the market price of our common stock. The payment of these severance benefits could harm our financial condition. In addition, these potential severance payments may discourage or prevent third parties from seeking a business combination with us.

If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our stock, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our target studies and operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

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

As of March 9, 2016, our executive officers and directors, together with holders of five percent or more of our outstanding common stock and their respective affiliates, beneficially own, in the aggregate, approximately 73.6 percent of our outstanding common stock, including shares subject to outstanding options and warrants that are exercisable within 60 days after such date, based on the Forms 3 and 4 and Schedules 13D and 13G filed by them with the SEC. As a result, these stockholders, if acting together, will continue to have significant influence over the outcome of corporate actions requiring stockholder approval, including the election of directors, any merger, consolidation or sale of all or substantially all of our assets and any other significant corporate transaction. The interests of these stockholders may not be the same as or may even conflict with the interests of our other stockholders. For example, these stockholders could delay or prevent a change of control of our company, even if such a change of control would benefit our other stockholders, which could deprive our stockholders of an opportunity to receive a premium for their common stock as part of a sale of our company or our assets and might affect the prevailing market price of our common stock. The significant concentration of stock ownership may adversely affect the trading price of our common stock due to investors perception that conflicts of interest may exist or arise.

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Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a prohibition on actions by our stockholders by written consent;
- a requirement that special meetings of stockholders, which the Company is not obligated to call more than once per calendar year, be called only by the chairman of our board of directors, our chief executive officer, our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors, or, subject to certain conditions, by our secretary at the request of the stockholders holding of record, in the aggregate, shares entitled to cast not less than ten percent of the votes at a meeting of the stockholders (assuming all shares entitled to vote at such meeting were present and voted);
- advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings; and
- the authority of the board of directors to issue preferred stock with such terms as the board of directors may determine.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, as amended, which prohibits a person who owns in excess of 15 percent of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 percent of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

We incur increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company we incur, and particularly after we are no longer an emerging growth company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the NASDAQ and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, we expect that these rules and regulations make it more difficult and more expensive for us to

obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors. However, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

We are not currently required to comply with the SEC s rules that implement Section 404(b) of the Sarbanes-Oxley Act (Section 404(b)), and are therefore not required to make a formal assessment of the

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effectiveness of our internal control over financial reporting for that purpose. Pursuant to Section 404(b), we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404(b) within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404(b). If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. In addition, if we are not able to continue to meet these requirements, we may not be able to remain listed on The NASDAQ Market.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be sole source of gain of our stockholders for the foreseeable future.

We may incur significant costs from class action litigation due to our historical or expected stock volatility.

Our stock price has fluctuated and may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. This risk is especially relevant to us because pharmaceutical and biotechnology companies have experienced significant stock price volatility in recent years. When the market price of a stock has been volatile as our stock price has been and may be, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

Our amended and restated bylaws designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated bylaws provide that, subject to limited exceptions, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, as amended, our amended and restated certificate of incorporation or our amended and restated bylaws, any action to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or our amended and restated bylaws, any action to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or our amended and restated bylaws or any other action asserting

a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation

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described above. This choice of forum provision may limit a stockholder s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Our stockholders may experience significant dilution as a result of future equity offerings and exercise of outstanding options.

On May 27, 2015, we completed an issuance and sale of 2,750,000 shares of our common stock at an offering price of $17.75 per share. In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any offering at a price per share that is equal to or greater than the price paid by our existing shareholders, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share paid by our existing stockholders.

In addition, we have a significant number of securities convertible into, or allowing the purchase of, our common stock. As of March 9, 2016, 650,272 shares of common stock were reserved for future issuance under our stock incentive plans. As of that date, there were also stock options and awards to purchase 5,055,943 shares of our common stock outstanding and warrants to purchase 87,901 shares of our common stock outstanding. The exercise price of outstanding options or warrants having an exercise price per share that is less than the offering price per share paid by our existing stockholders will increase dilution to such stockholders.

Future sales of our common stock in the public market could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market, or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. As of March 9, 2016, we have 20,647,983 shares of common stock outstanding, all of which shares, other than shares held by our directors and certain officers, were eligible for sale in the public market, subject in some cases to compliance with the requirements of Rule 144, including the volume limitations and manner of sale requirements. In addition, shares of common stock issuable upon exercise of outstanding options and shares reserved for future issuances under our stock incentive plans will become eligible for sale in the public market to the extent permitted by applicable vesting requirements and subject in some cases to compliance with the requirements of Rule 144.

Item 1B. *Unresolved Staff Comments*

None.

Item 2. *Properties*

Our corporate headquarters are located in Cambridge, Massachusetts, where we lease 37,084 square feet of office and laboratory space. The lease term for our office and laboratory space in Cambridge, Massachusetts, commenced in

December 2014 for a lease term of six years.

We believe that suitable additional or alternative space will be available as needed on commercially reasonable terms.

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Item 3. ***Legal Proceedings***

We are not currently a party to or aware of any proceedings that we believe will have, individually or in the aggregate, a material adverse effect on our business, financial condition or results of operations.

On June 10, 2015, Alnylam Pharmaceuticals, Inc. (Alnylam) filed a complaint against the Company in the Superior Court of Middlesex Country, Massachusetts. The complaint alleges misappropriation of confidential, proprietary, and trade secret information, as well as other related claims, in connection with the Company s hiring of a number of former employees of Merck & Co., Inc. (Merck) and its discussions with Merck regarding the acquisition of its subsidiary, Sirna Therapeutics, Inc. (Sirna), which was subsequently acquired by Alnylam. The complaint seeks among other things, damages, attorneys fees, and an order permanently enjoining the Company from disclosing or using any of Alnylam s confidential information or trade secrets. An unfavorable resolution of this matter could potentially cause us to incur significant legal fees and other costs to defend this action, and could potentially have a material adverse effect on our business, financial condition, and results of operations or prospects, potentially delay or limit our ability to use some of our research and development programs, and potentially result in paying monetary damages. We believe, however, that Alnylam s allegations lack merit, we have filed an answer denying all liability, and we intend to continue to vigorously defend all claims asserted. We expect that a liability is not probable. Accordingly, we cannot reasonably estimate any range of potential future charges, and we have not recorded any accrual for a contingent liability associated with this legal proceeding.

Item 4. ***Mine Safety Disclosures***

Not applicable.

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PART II

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

Market Information for Common Stock

Our common stock has been publicly traded on The NASDAQ Global Select Market under the symbol DRNA since January 30, 2014. Prior to that time, there was no public market for our common stock. As a result, we have not set forth information with respect to the high and low prices of our common stock for any full fiscal quarter during 2013 fiscal year. The following table sets forth the high and low sale prices per share for our common stock on The NASDAQ Global Select Market for the periods indicated:

Year Ended December 31, 2015:	**High**	**Low**
First Quarter	$ 27.33	$ 16.55
Second Quarter	$ 25.26	$ 12.50
Third Quarter	$ 15.17	$ 7.61
Fourth Quarter	$ 15.93	$ 7.66
Year Ended December 31, 2014:		
First Quarter (from January 30, 2014)	$ 46.00	$ 27.11
Second Quarter	$ 28.25	$ 15.00
Third Quarter	$ 22.40	$ 12.55
Fourth Quarter	$ 16.82	$ 8.00

Holders of Record

As of March 9, 2016, there were approximately 16 holders of record of our common stock. Because many of our shares of common stock are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

Dividend Policy

We currently intend to retain future earnings, if any, for use in the operation of our business and to fund future growth. We have never declared or paid cash dividends on our common stock and we do not intend to pay any 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 in light of conditions then existing, including factors such as our results of operations, financial condition and requirements, business conditions and covenants under any applicable contractual arrangements.

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Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return on our common stock since January 30, 2014 (the date our stock became publicly traded on The NASDAQ Global Select Market) to the NASDAQ composite and NASDAQ biotechnology indices. The graph assumes an initial investment of $100 on January 30, 2014. The stock price performance on the following graph is not necessarily indicative of future stock price performance. This performance graph shall not be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the Exchange Act), or incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

Recent Sales of Unregistered Securities

We did not sell any securities during the fiscal year ended December 31, 2015, which were not registered under the Securities Act of 1933, as amended (Securities Act).

Use of Proceeds from Initial Public Offering of Common Stock

On February 4, 2014, we completed the initial public offering of our common stock and sold and issued a total of 6,900,000 shares of our common stock, including 900,000 shares sold pursuant to the exercise in full by the underwriters of the option to purchase additional shares, at a public offering price of $15.00 per share for aggregate gross proceeds of $103.5 million before deducting underwriting commissions and discounts and offering expenses payable by us. The shares of common stock were registered under the Securities Act on a registration statement on Form S-1 (File No. 333-193150). The SEC declared the registration statement effective on January 29, 2014. Shares of our common stock began trading on The NASDAQ Global Select Market on January 30, 2014. On February 4, 2014, following the sale of 6,900,000 shares of our common stock, our initial public offering ended. There has been no material change in the planned use of proceeds from our initial public

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offering as described in the final prospectus dated as of January 29, 2014 for the initial public offering and filed with the SEC pursuant to Rule 424(b) under the Securities Act on January 30, 2014.

The net proceeds to us from the IPO, including the shares sold pursuant to the exercise in full by the underwriters of the option to purchase additional shares, were used for preclinical studies and Phase 1 clinical trials for DCR-MYC and DCR-PH1 to evaluate safety and biological markers of efficacy in oncology patients in patients with Primary Hyperoxaluria 1. The remaining net proceeds were used for continued technology platform development, general corporate purposes and working capital

Purchases of Equity Securities by the Issuer and Affiliated Parties

None.

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Item 6. ***Selected Financial Data***

DICERNA PHARMACEUTICALS, INC. AND SUBSIDIARIES

SELECTED FINANCIAL DATA

	YEARS ENDED DECEMBER 31,		
	2015	**2014**	**2013**
Results of operations			
Revenue	$ 184	$	$
Operating expenses:			
Research and development	43,971	29,453	11,558
General and administrative	19,240	15,648	5,820
Total operating expenses	63,211	45,101	17,378
Loss from operations	(63,027)	(45,101)	(17,378)
Other income (expense):			
Preferred stock warrant re-measurement		(2,559)	126
Loss on extinguishment of debt		(143)	(318)
Interest income	188	63	4
Interest expense		(199)	(952)
Total other income (expense)	188	(2,838)	(1,140)
Net loss	$ (62,839)	$ (47,939)	$ (18,518)
Less: Accretion and dividends on redeemable convertible preferred stock		204	2,388
Net loss attributable to common stockholders	(62,839)	(48,143)	(20,906)
Net loss per share attributable to common stockholders Basic and diluted	$ (3.09)	$ (3.00)	$ (709.57)
Weighted average shares outstanding Basic and diluted	20,320,628	16,070,054	29,463
Financial condition			
Cash and cash equivalents	$ 56,058	$ 26,067	$ 46,595
Held-to-maturity investments	$ 38,551	$ 72,556	$
Total assets	$ 100,023	$ 103,605	$ 49,794
Long-term debt including of current portion	$	$	$ 4,847
Total stockholders equity / (deficit)	$ 91,022	$ 98,340	$ (68,919)

The financial data included within the tables above should be read in conjunction with our consolidated financial statements and related notes and the *Management s Discussion and Analysis of Financial Condition and Results of Operations* sections of this Form 10-K.

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

The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those discussed here. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this section as well as factors described in Part I, Item 1A Risk Factors.

Overview

We are an RNA interference-based biopharmaceutical company focused on the discovery and development of innovative treatments for rare inherited diseases involving the liver, for other therapeutic areas in which the liver plays a key role, and for cancers that are genetically defined. We are using our RNA interference (RNAi) technology platform to build a broad pipeline in these therapeutic areas. In many cases, we are pursuing targets that have historically been difficult to inhibit using conventional approaches, but where we believe connections between targets and diseases are well understood and documented. We aim to discover, develop and commercialize these novel therapeutics either on our own or in collaboration with pharmaceutical partners, while seeking to retain significant portions of the commercial rights in the rare disease and oncology fields.

In the rare disease field, we are developing a proprietary treatment, DCR-PH1, for the rare and serious inherited disorder Primary Hyperoxaluria Type 1 (PH1). In December 2015, we initiated dosing in our first PH1 clinical trial in normal healthy volunteers, and we expect to begin our first Phase 1 study of DCR-PH1 in patients with PH1 in the first half of 2016. In December 2015, we also initiated an international, multicenter, observational study designed to measure biomarkers implicated in PH1, and enrolled our first patient in this observational study in January 2016. The FDA and the European Medicines Agency (EMA) have both granted Orphan Drug Designation to DCR-PH1. We also have discovery and early development programs against a series of additional rare inherited diseases involving the liver where we are utilizing our DsiRNA-EX Conjugate technology. In other therapeutic areas involving the liver, we are using our DsiRNA-EX Conjugate technology to develop potential therapeutics for a wide variety of diseases, including chronic liver diseases, cardiovascular diseases, and viral infection diseases. We have selected these diseases and disease target genes based on criteria that include having a strong therapeutic hypothesis, a readily-identified patient population, the availability of predictive biomarkers, and favorable competitive positioning. For many of these diseases we may seek development partners. In oncology, we are currently directing our development efforts towards our proprietary product candidate DCR-MYC for the treatment of MYC-related cancers, including hepatocellular carcinoma (HCC). In the second quarter of 2014, we initiated a multi-center, dose-escalating Phase 1 clinical study of DCR-MYC to assess the safety and tolerability of DCR-MYC in patients with solid tumors, multiple myeloma, or lymphoma who are refractory or unresponsive to standard therapies. In the fourth quarter of 2014 we initiated a global Phase 1b/2 clinical trial of DCR-MYC in patients with advanced HCC with the first patient dosed in January 2015. In the second quarter of 2015, we announced plans to expand our ongoing Phase 1 study of DCR-MYC in solid tumors, multiple myeloma, or lymphoma to include a cohort of patients with pancreatic neuroendocrine tumors (PNETs) following early signs of clinical and metabolic response and tumor shrinkage in PNET patients. In addition, once the optimal dose of DCR-MYC has been determined, we plan to initiate enrollment of a cohort of patients who will undergo pre- and post-treatment tumor biopsies. Molecular analysis of the MYC gene transcript in these biopsies will allow direct observation of the RNAi-mechanism of action of DCR-MYC. We expect to announce data from the PNET and biopsy cohorts in 2016.

As part of our collaboration with Kyowa Hakko Kirin Co., Ltd. (KHK), a global pharmaceutical company, we are developing a product candidate that targets the oncogene KRAS, which is frequently mutated in numerous major cancers, including non-small cell lung cancer, colorectal cancer, and pancreatic cancer. KHK is responsible for global development of the KRAS program, including all development expenses. For the KRAS product candidate, we retain an option to co-promote in the U.S. for an equal share of the profits from U.S. net sales. We are also developing, with KHK, a therapeutic candidate targeting a second cancer-related gene, which we are not identifying at this time. For

each product candidate in our collaboration with KHK, we have the potential to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of each such product candidate. We expect that our strategy to partner the development of

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product candidates will help us fund the costs of clinical development and enable us to diversify risk across a number of programs. KHK is responsible for all preclinical and clinical development activities, including the selection of patient population and disease indications for clinical trials.

Since our inception in October 2006, we have devoted substantial resources to the research and development of DsiRNA molecules and drug delivery technologies and the protection and enhancement of our intellectual property estate. We have no products approved for sale and all of our revenue to date has been collaboration revenue or government grant revenue. To date, we have funded our operations primarily through public offerings of our common stock, private placements of preferred stock and convertible debt securities, from research funding, license fees, option exercise fees, preclinical payments under our research collaboration and license agreement with KHK, from government grants, and from a secured term loan from Hercules Technology II, L.P. (Hercules loan). More particularly, since our inception and through December 31, 2015, we have raised an aggregate of $278.8 million to fund our operations, of which approximately $45.4 million was from the May 2015 follow-on offering of common stock, $0.2 million was from a federal government grant from the National Institutes of Health (NIH) covering our work on cancer treatment research, $92.7 million was from the initial public offering of our common stock, which closed on February 4, 2014, $110.5 million was from the sale of preferred stock and convertible debt securities (including $3.0 million from the 2013 bridge note financing), $17.5 million was through our collaboration and license agreement with KHK, $0.5 million was from a federal government grant for our Qualifying Therapeutic Discovery Project in November 2010 and $12.0 million was from borrowings under the Hercules loan. On April 7, 2014, we repaid the remaining amount of the Hercules loan of approximately $3.6 million. As of December 31, 2015, we had cash and cash equivalents and held-to-maturity investments of $94.6 million and we also had $1.1 million in assets held in restriction.

On February 4, 2014, we completed the initial public offering of our common stock, in which we issued and sold a total of 6,900,000 shares of common stock, including 900,000 shares sold pursuant to the exercise in full by the underwriters of an option to purchase additional shares, at a public offering price of $15.00 per share. We received net proceeds of approximately $92.7 million after deducting the underwriting commissions and discounts and offering expenses payable by us. All of the shares of our preferred stock were converted into shares of common stock and our warrants to purchase preferred stock became exercisable to purchase common stock immediately prior to the completion of our initial public offering.

On May 27, 2015, we completed a follow-on offering of our common stock, in which we issued and sold a total of 2,750,000 shares of common stock, at a public offering price of $17.75 per share. We received net proceeds of approximately $45.4 million after deducting underwriting commissions and discounts and offering expenses payable by us.

Since inception, we have incurred significant operating losses. Our net loss was $62.8 million, $47.9 million and $18.5 million for the years ended December 31, 2015, 2014 and 2013, respectively. Substantially all of our operating losses resulted from expenses incurred in connection with our research and clinical programs and from general and administrative costs associated with our operations. We recognized $0.2 million in revenue for the year ended December 31, 2015 and no revenue for the years ended December 31, 2014 and 2013. Our revenue to date has been generated through our research collaboration and license agreement with KHK and government grants. We have not generated any commercial product revenue. As of December 31, 2015, we had an accumulated deficit of $196.2 million. We expect to continue to incur significant and increasing losses in the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

advance our product candidates into preclinical development;

conduct any clinical trials of DCR-PH1, DCR-MYC and other potential product candidates;

continue our research and development efforts, including to expand our pipeline and to enhance our technology platform;

increase research and development related activities for the discovery and development of additional product candidates;

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manufacture clinical study materials and develop large-scale manufacturing capabilities;

seek regulatory approval for our product candidates that successfully complete clinical trials;

maintain, expand and protect our intellectual property portfolio;

add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and

operate as a public company.

We do not expect to generate substantial revenue from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which is subject to significant uncertainty and which could take several years. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Until such time, if ever, that we generate product revenue, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings and research collaboration and license agreements. We may be unable to raise capital or enter into such other arrangements when needed or on favorable terms. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our product candidates.

Collaboration agreement

In December 2009, we entered into a research collaboration and license agreement with KHK for the research, development and commercialization of DsiRNA molecules and drug delivery technologies for therapeutic targets in oncology. We have granted KHK an exclusive, worldwide, royalty-bearing and sub-licensable license to our DsiRNA molecules and drug delivery technologies and intellectual property for two programs, KRAS and a second undisclosed oncology target. Under the research collaboration and license agreement, KHK is responsible for activities to develop, manufacture and commercialize the selected DsiRNA-based compounds and pharmaceutical products containing such compounds. For the KRAS product candidate, we have an option to co-promote in the U.S. for an equal share of the profits from U.S. net sales. In addition, for each product candidate under the research collaboration and license agreement, we have the potential to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of such product candidate.

Since the initiation of the research collaboration and license agreement, of the various targets in the collaboration, two target programs, including the initial target KRAS, have been nominated by KHK for formal development studies. Both programs utilize our specific RNAi-inducing double-stranded DsiRNA molecules and a lipid nanoparticle drug delivery technology proprietary to KHK. As of December 31, 2015, we have received total payments to date of $17.5 million from KHK under the research collaboration and license agreement.

License agreement

In September 2007, we entered into a license agreement with City of Hope (COH), an independent academic research and medical center, pursuant to which COH has granted to us an exclusive (subject to certain exceptions described below), royalty-bearing, worldwide license under certain patent rights in relation to DsiRNA, including the core

DsiRNA patent (U.S. 8,084,599), to manufacture, use, offer for sale, sell and import products covered by the licensed patent rights for the prevention and treatment of any disease in humans. COH is restricted from granting any additional rights to develop, manufacture, use, offer to sell, sell or import products covered by the licensed patent rights for the prevention and treatment of any disease in humans. In addition, COH has granted to us an exclusive, royalty-bearing, worldwide license under the licensed patent rights providing certain rights for up to 20 licensed products selected by us for human diagnostic uses, provided that COH has not granted or is not negotiating a license of rights to diagnostic uses for such licensed products to a third party. The core DsiRNA patent (U.S. 8,084,599), titled methods and compositions for the specific

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inhibition of gene expression by double-stranded RNA, describes RNA structures having a 25 to 30 nucleotides sense strand, a blunt end at the 3 end of the sense strand and a one to four nucleotides overhang at the 3 end of the antisense strand. The expiration date of this patent is July 17, 2027.

Pursuant to the terms of the agreement, we paid COH a one-time, non-refundable license fee and issued shares of our common stock to COH and a co-inventor of the core DsiRNA patent. COH is entitled to receive milestone payments in an aggregate amount within the range of $5.0 million to $10.0 million upon achievement of certain clinical and regulatory milestones. COH is further entitled to receive royalties at a low single-digit percentage of any net sale revenue of the licensed products sold by us and our sublicensees. If we sublicense the licensed patent rights to a third party, COH has the right to receive a double digit percentage of sublicense income, the percentage of which decreases after we have expended $12.5 million in development and commercialization costs. We are also obligated to pay COH an annual license maintenance fee, which may be credited against any royalties due to COH in the same year, and reimburse COH for expenses associated with the prosecution and maintenance of the license patent rights. The license agreement will remain in effect until the expiration of the last to expire of the patents or copyrights licensed under the agreement. We have not included our obligations to make future milestone payments on our balance sheet because the achievement and timing of the related milestones is not probable and estimable.

In September 2013, we entered into a commercial license agreement with Plant Bioscience Limited (PBL), pursuant to which PBL has granted a license to us for certain of its U.S. patents and patent applications to research, discover, develop, manufacture, sell, import and export, products incorporating one or more short RNA molecules (SRMs).

We have paid PBL a one-time, non-refundable signature fee and will pay PBL a nomination fee for any additional SRMs nominated by us under the agreement. We are further obligated to pay PBL milestone payments upon achievement of certain clinical and regulatory milestones. In addition, PBL is entitled to receive royalties on any net sale revenue of any licensed product candidates sold by us. During 2014, the Company paid $0.1 million to PBL upon the commencement of our MYC clinical trial.

In November 2014, we entered into a licensing and collaboration agreement with Arbutus to license Arbutus LNP delivery technology for exclusive use in our PH1 development program. We will use Arbutus LNP technology to deliver DCR-PH1, for the treatment of PH1. As of December 31, 2015, we had paid a total of $3.0 million in license fees to Arbutus. Arbutus is entitled to receive additional payments of $22.0 million in aggregate development milestones, plus a mid-single-digit royalty on future PH1 sales. This partnership also includes a supply agreement with Arbutus providing clinical drug supply and regulatory support.

In December 2014, we licensed all of our non-U.S. intellectual property rights to a non-U.S. wholly-owned subsidiary, and, in December 2015, we licensed our U.S. intellectual property rights to the same wholly-owned subsidiary.

Financial Operations Overview

Revenue

Our revenue to date has been generated primarily through research funding, license fees, option exercise fees and preclinical development payments under our research collaboration and license agreement with KHK and government grants. We have not generated any commercial product revenue. For each product candidate under our research collaboration and license agreement with KHK, we are also entitled to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of such product candidate. We did not receive any royalty payments during 2015 or 2014.

In April 2015, the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH), awarded us a grant related to cancer treatment research. The project period for this grant covers a three month period which commenced in April 2015, with total funds available of approximately $0.2 million. The payment of the NIH grant award was based upon subcontractor and internal costs incurred that are specifically covered by

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the grant and, where applicable, a facilities and administrative rate that provides funding for overhead expenses. During the year ended December 31, 2015, we recognized $0.2 million of revenue associated with the NIH grant award. We did not have revenue for the years ended December 31, 2014 and 2013, respectively.

In the future, we may generate revenue from a combination of research and development payments, license fees and other upfront payments, milestone payments, product sales and royalties in connection with our collaboration with KHK or future collaborations and licenses. We expect that any revenue we generate will fluctuate in future periods as a result of the timing of our or a collaborator s achievement of preclinical, clinical, regulatory and commercialization milestones, if at all, the timing and amount of any payments to us relating to such milestones and the extent to which any of our product candidates are approved and successfully commercialized by us or a collaborator. If we, KHK or any future collaborator fails to develop product candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

Research and development expenses

Research and development expenses consist of costs associated with our research activities, including discovery and development of our DsiRNA and DsiRNA-EX molecules and drug delivery technologies, clinical and pre-clinical development activities and our research activities under our research collaboration and license agreement with KHK. Our research and development expenses include:

- direct research and development expenses incurred under arrangements with third parties, such as contract research organizations, contract manufacturing organizations, and consultants;
- platform-related lab expenses, including lab supplies, license fees, consultants and our scientific advisory board;
- employee-related expenses, including salaries, benefits and stock-based compensation expense; 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 they are 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. A significant portion of our research and development costs are not tracked by project as they benefit multiple projects or our technology platform.

In the second quarter of 2014, we initiated a multi-center, dose-escalating Phase 1 clinical study of DCR-MYC to assess the safety and tolerability of DCR-MYC in patients with solid tumors, multiple myeloma, or lymphoma who are refractory or unresponsive to standard therapies, and in the fourth quarter of 2014 we initiated a global phase 1b/2 clinical trial of DCR-MYC in patients with advanced HCC with the first patient dosed in January 2015. In the second quarter of 2015, we announced an expansion of our DCR-MYC ongoing Phase 1 trial to include a cohort of patients with pancreatic neuroendocrine tumors (PNETs) following early signs of clinical and metabolic response and tumor

shrinkage in PNET patients. Once the maximum tolerated dose (MTD) of DCR-MYC has been determined, we plan to initiate enrollment of a cohort of patients who will undergo pre- and post-treatment tumor biopsies. We expect to report proof-of-concept data for DCR-MYC in the second half of 2016 based on anticipated results from our two ongoing trials. In December 2015, we initiated dosing in our first PH1 clinical trial, which is a Single Ascending Dose (SAD) trial in normal healthy volunteers and is being conducted in the U.S. Data from the healthy volunteer study will be used to facilitate initiation of clinical studies in patients in the U.S. We expect to begin our first Phase 1 study of DCR-PH1 in patients with PH1 in the first half of 2016 at EU clinical sites. In December 2015, we also initiated an international, multicenter, observational study designed to measure biomarkers implicated in PH1. Although the observational study will not include investigational drugs or other interventions, its participants may be considered for enrollment in planned clinical trials of DCR-PH1. The process of conducting preclinical studies and clinical trials necessary to obtain regulatory approval is costly and time-consuming. We, KHK or any future collaborator may never succeed in obtaining marketing approval for any of our product candidates. The probability of success for

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each product candidate may be affected by numerous factors, including preclinical data, clinical data, competition, manufacturing capability and commercial viability. All of our research and development programs are at an early stage and successful development of future product candidates from these programs is highly uncertain and may not result in approved products. Completion dates and completion costs can vary significantly for each future product candidate and are difficult to predict. We anticipate we will make determinations as to which product candidates to pursue and how much funding to direct to each product candidate on an ongoing basis in response to our ability to maintain or enter into collaborations with respect to each product candidate, the scientific and clinical success of each product candidate as well as ongoing assessments as to the commercial potential of product candidates. We will need to raise additional capital and may seek additional collaborations in the future in order to advance our various product candidates. Additional private or public financings may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a material adverse effect on our financial condition and our ability to pursue our business strategy.

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 travel expenses, professional fees for legal, audit, tax and other professional services and allocated facility-related costs not otherwise included in research and development expenses.

Interest income

Interest income consists of interest income earned on our cash and cash equivalents, held-to-maturity investments and assets held in restriction.

Interest expense

Interest expense consists of interest expense on the Hercules loan, which was repaid in full in April 2014.

Preferred stock warrant re-measurement

Preferred stock warrant re-measurement is associated with warrants to purchase preferred stock issued to lenders under our convertible notes and the Hercules loan. The re-measurement consists of the change in value calculated using the Black-Scholes option pricing model to estimate the fair value of the warrants. We base the estimates in the Black-Scholes option pricing model, in part, on subjective assumptions, including stock price volatility, risk-free interest rate, dividend yield and the fair value of the preferred stock underlying the warrants. The re-measurement gain or loss associated with the change in the fair value of the preferred stock warrant liability each reporting period is recognized as a component of other income (expense). Upon the completion of our initial public offering of our common stock on February 4, 2014, the preferred stock warrant liability was reclassified as a component of equity and is no longer subject to re-measurement. The fair value of the preferred stock warrants as of the closing date of the initial public offering was $3.1 million.

Critical Accounting Policies and Significant Judgments and Estimates

Our management s discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles general accepted in the U.S. (GAAP) and in accordance with the rules and regulations of the SEC. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and

the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the revenue and expenses incurred during the reported periods. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses, revenue recognition, deferred revenue and stock-based compensation. 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

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sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in the notes to our consolidated financial statements appearing in this Annual Report on Form 10-K, we believe that the following critical accounting policies are most important to understanding and evaluating our reported financial results.

Revenue recognition

Collaborative research and development and multiple-deliverable arrangements

We have generated our revenue primarily through our research collaboration and license agreement with KHK and government grants. The terms of the research collaboration and license agreement with KHK include multiple deliverables by us (e.g., license rights and research and development services) in exchange for consideration to us of some combination of research funding, license fees, option exercise fees, payments based upon the achievement of specified milestones and royalty payments based on product sales derived from the collaboration.

We recognize revenue when all of the following four criteria are met: (1) persuasive evidence that an arrangement exists; (2) delivery of the products or services has occurred; (3) the selling price is fixed or determinable; and (4) collectability is reasonably assured. Multiple-deliverable arrangements, such as license and development agreements, are analyzed to determine whether the deliverables can be separated or whether they must be accounted for as a single unit of accounting. When deliverables are separable, consideration received is allocated to the separate units of accounting based on the relative selling price method and the appropriate revenue recognition principles are applied to each unit. When we determine that an arrangement should be accounted for as a single unit of accounting, we must determine the period over which the performance obligations will be performed and revenue will be recognized.

At the inception of each arrangement that includes payments for optional research or milestones, we evaluate whether each option or milestone is substantive and at risk to both parties on the basis of the contingent nature of the option or milestone. This evaluation includes an assessment of whether: (1) the consideration is commensurate with either the entity s performance to achieve the milestone or the enhancement of the value of the delivered items; (2) as a result of a specific outcome resulting from the entity s performance to achieve the milestone; (3) the consideration relates solely to past performance; and (4) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. Substantive options and milestones are recognized as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met.

License fees are initially recorded as deferred revenue upon receipt and then recognized as revenue over our performance period. Research and development service revenue is recognized over the research term as the research and development services are provided. The cost of such services is reflected in research and development costs in the period in which it is incurred. Assuming all other revenue recognition criteria are met, milestone payments are recognized as revenue when the milestone is achieved or is probable of achievement. Royalty payments are recognized as revenue based on contract terms and reported sales of licensed products, when reported sales are reliably measurable and collectability is reasonably assured.

Preferred stock warrant liability

As of December 31, 2013, we had outstanding warrants for the purchase of shares of Series A and Series B preferred stock as well as warrants issued in the Series C bridge loan that became exercisable for shares of Series C preferred

stock, (Series C warrants), upon the closing of our sale of Series C preferred stock in July 2013. We account for freestanding warrants related to shares that are redeemable or contingently redeemable, or

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for purchases of preferred stock that are not indexed to our stock, as liabilities. The warrants are recorded at fair value, estimated using the Black-Scholes option-pricing model, at each balance sheet date with changes in the fair value of the liability recorded in the statement of operations.

Pursuant to the terms of these warrants, upon the conversion of the class of preferred stock underlying the warrant, the warrants automatically become exercisable for shares of our common stock based upon the conversion ratio of the underlying class of preferred stock. The consummation of our initial public offering resulted in the conversion of all classes of our preferred stock into common stock. Upon the conversion of the underlying classes of preferred stock, our outstanding warrants to purchase Series A, Series B and Series C preferred stock were reclassified as a component of equity and are no longer subject to re-measurement.

Net operating loss and research and development tax credit carryforwards

We file U.S. federal income tax returns and Massachusetts state tax returns. The deferred tax assets were primarily comprised of federal and state tax net operating losses and tax credit carryforwards and were recorded using enacted tax rates expected to be in effect in the years in which these temporary differences are expected to be utilized. As of December 31, 2015, the Company has approximately $92.5 million of federal and $77.6 million of state net operating loss carryforwards, and $2.1 million of federal and $1.4 million of Massachusetts research and development credits that expire starting in 2028. As of December 31, 2015, we had $1.4 million of unrecognized tax benefits, of which $1.4 million would affect income tax expense if recognized, before consideration of our valuation allowance.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to historical or future ownership percentage change rules provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of certain net operating loss and tax credit carryforwards before their utilization. However, due to uncertainties surrounding our ability to generate future taxable income to realize these tax assets, a full valuation allowance has been established to offset our deferred tax assets.

Redeemable convertible preferred stock

We have issued preferred stock in the past to raise capital. We initially record preferred stock redeemable outside of our control outside of stockholders equity (deficit) at the value of the proceeds received or fair value, if lower, net of issuance costs. Subsequently, if it is probable that the preferred stock will become redeemable, we adjust the carrying value to the redemption value over the period from the issuance date to the earliest possible redemption date.

Stock-based compensation and common stock valuation

Stock-based compensation

We estimate the fair value of our stock-based awards to employees and non-employees using the Black-Scholes option-pricing model, which requires the input of highly subjective assumptions, including: (1) the expected volatility of our stock, (2) the expected term of the award, (3) the risk-free interest rate and (4) expected dividends. Due to the lack of a public market history for the trading of our common stock before and after the completion of our initial public offering and a lack of company specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For these analyses, we have selected companies with comparable characteristics to ours, including factors such as enterprise value, risk profiles, position within the industry and historical share price information, sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected

companies shares during the equivalent period of the calculated expected term of our stock-based awards. We have estimated the expected life of our employee stock

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options using the simplified method, whereby the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted.

We are also required to estimate forfeitures at the time of grant and revise those estimates in subsequent periods if actual forfeitures differ from estimates. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

Common stock valuations before the initial public offering

We have historically granted stock options at exercise prices not less than the fair value of our common stock. As there was no public market for our common stock before our initial public offering, the estimated fair value of our common stock was previously determined by our board of directors. Stock options granted after the completion of initial public offering are valued using our common stock price as stated on The NASDAQ Global Select Market on the grant date. We have periodically determined, for financial reporting purposes, the estimated per share fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation* (Practice Aid). We performed these contemporaneous valuations as of January 31, 2012 and August 31, 2013. In conducting the contemporaneous valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects and operating performance at each valuation date. Within the contemporaneous valuations performed, a range of factors, assumptions and methodologies were used. The significant factors included:

- the prices of our preferred stock sold to or exchanged between outside investors in arm s length transactions, and the rights, preferences and privileges of our preferred stock as compared to those of our common stock, including the liquidation preferences of our preferred stock;
- our results of operations, financial position and the status of research and development efforts;
- the composition of, and changes to, our management team and board of directors;
- the lack of liquidity of our common stock as a private company;
- our stage of development and business strategy and the material risks related to our business and industry;
- the achievement of enterprise milestones, including entering into collaboration and license agreements;
- the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies;

any external market conditions affecting the life sciences and biotechnology industry sectors;

the likelihood of achieving a liquidity event for the holders of our common stock and stock options, such as an initial public offering or a sale of our company, given prevailing market conditions;

the state of the initial public offering market for similarly situated privately held biotechnology companies; and

any recent contemporaneous valuations prepared by our board of directors and management in accordance with methodologies outlined in the Practice Aid.

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Stock option grants on December 4, 2013 and December 30, 2013

For the stock options granted by us on December 4, 2013 and December 30, 2013, our board of directors determined that the fair value of common stock of $3.42 per share calculated in the contemporaneous valuation as of August 31, 2013 reasonably reflected the per share fair value of our common stock on each of the grant dates. However, in the context and given the anticipated proximity of our initial public offering, for financial reporting purposes, in early January 2014 we conducted a retrospective valuation as of December 31, 2013, which reasonably assumed that examination of contemporaneous information would have concluded a price range consistent with the then estimated price range for our initial public offering of $11.00 to $13.00 per share. The retrospective valuation as of December 31, 2013 indicated that the fair value of our common stock on December 31, 2013 was $7.42 per share. The valuation concluded that, with such contemporaneous information, the fair value of our common stock as of December 31, 2013 was $7.42 per share primarily due to feedback from investment bankers that we had an increased probability of executing a successful initial public offering in the first quarter of 2014 and feedback from investment bankers that public investors could potentially price our common stock in the range of $11.00 to $13.00 per share in such an initial public offering. Accordingly, we recognized a stock-based compensation charge of less than $0.1 million in relation to the December 4, 2013 and December 30, 2013 option grants for the quarter ended December 31, 2013 based on the grant date fair value of our common stock as determined by the retrospective valuation.

Held-to-Maturity Investments

We account for our investment in marketable securities in accordance with FASB ASC 320, Investments Debt and Equity Securities. We determine the appropriate classification of investments at the time of purchase and re-evaluate such designation as of each balance sheet date. Debt securities carried at amortized cost are classified as held-to-maturity when we have the positive intent and ability to hold the securities to maturity. At December 31, 2015 and 2014, all of our investments were classified as held-to-maturity.

Emerging growth company status

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

Recent Accounting Pronouncements

Leases

In February 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2016-02, Leases (Topic 842). The ASU requires lessees to put most leases on their balance sheets as a liability for the obligation to make lease payments and as a right-of-use asset, but recognize expenses on the income statements in a manner similar to today s accounting. The guidance also eliminates the current real estate-specific provisions for all entities. For calendar-year public entities, the guidance becomes effective in 2019 and interim periods within that year. Early adoption is permitted for all entities. The Company has not chosen early adoption for this ASU and is currently evaluating its effect on the Company s consolidated financial statements.

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Income Taxes

In November 2015, the FASB issued ASU 2015-17, Income Taxes: Balance Sheet Classification of Deferred Taxes (Topic 740). ASU 2015-17 simplifies the presentation of deferred income taxes by eliminating the separate classification of deferred income tax assets and liabilities into current and noncurrent amounts in the consolidated balance sheet statement of financial position. The amendments in the update require that all deferred tax assets and liabilities be classified as noncurrent in the consolidated balance sheet. The amendments in this update are effective for annual periods beginning after December 15, 2017, and interim periods therein and may be applied either prospectively or retrospectively to all periods presented. Early adoption is permitted. The Company has early adopted this standard in the fourth quarter of 2015 on a prospective basis, and it did not have an effect on the Company s consolidated financial statements.

Revenue Recognition

In May 2014, the FASB issued ASU 2014-09, Revenue from Contracts with Customers (Topic 606). ASU 2014-09 amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in Accounting Standards Codification Topic 605, Revenue Recognition, and creates a new Topic 606, Revenue from Contracts with Customers. This guidance was originally pronounced to become effective for fiscal years beginning after December 15, 2016, with early adoption not permitted. On July 9, 2015, the FASB decided to defer the effective date of the ASU by one year. As a result, the Company will be required to apply the new revenue standard to annual reporting periods beginning after December 15, 2017, and would be permitted to adopt the ASU early, but not before the original public organization effective date (annual periods beginning after December 15, 2016). Two adoption methods are permitted: retrospectively to all prior reporting periods presented, with certain practical expedients permitted; or retrospectively with the cumulative effect of initially adopting the ASU recognized at the date of initial application. The Company has not yet determined which adoption method it will utilize or the effect, if any, the adoption of this guidance will have on its consolidated financial statements through December 31, 2015 as the Company has yet to record revenue from contracts with customers.

Comparison of the years ended December 31, 2015 and 2014

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

	FOR THE YEARS ENDED DECEMBER 31,		INCREASE (DECREASE)	
	2015	2014		
Total revenue	$ 184	$	$ 184	100%
Expenses:				
Research and development	43,971	29,453	14,518	49%
General and administrative	19,240	15,648	3,592	23%
Total expenses	63,211	45,101	18,110	40%
Loss from operations	(63,027)	(45,101)	(17,926)	(40)%
Other income (expense)	188	(2,838)	3,026	107%
Net loss	$ (62,839)	$ (47,939)	$ (14,900)	(31)%

Revenue

During the year ended December 31, 2015, we recognized $0.2 million of revenue associated with the NIH grant award. We did not have revenue for the year ended December 31, 2014. We do not expect to generate any product revenue for the foreseeable future.

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Research and development expenses

The following table summarizes our research and development expenses incurred during the years ended December 31, 2015 and 2014 (in thousands):

	FOR THE YEARS ENDED DECEMBER 31,		INCREASE
	2015	2014	
Direct research and development expenses	$ 15,529	$ 11,068	$ 4,461
Platform-related expenses	14,066	9,984	4,082
Employee-related expenses	11,340	7,694	3,646
Facilities, depreciation and other expenses	3,036	707	2,329
Total	$ 43,971	$ 29,453	$ 14,518

Research and development expenses were $44.0 million and $29.5 million for the years ended December 31, 2015 and 2014, respectively. For the year ended December 31, 2015, direct research and development expenses were $15.5 million compared to $11.1 million in the prior year. The increase of $4.4 million was the result of increased costs related to pre-clinical and clinical start-up activities for DCR-PH1, as well as increased costs related to DCR-MYC manufacturing for clinical development and our clinical trials, including our global Phase 1b/2 trial in patients with advanced HCC, which was initiated in the fourth quarter of 2014, offset by a reduction in license fees paid to a collaboration partner. For the year ended December 31, 2015, platform-related expenses were $14.1 million compared to $10.0 million in the prior year. The increase of $4.1 million was primarily due to increased expenses related to discovery and early development of future programs, offset by a decrease to non-employee stock-based compensation of $1.5 million. Employee-related expenses were $11.3 million in 2015 compared to $7.7 million in the prior year. The increase of $3.6 million was primarily due to additional headcount, along with an increase in stock-based compensation of $1.6 million. Facilities, depreciation and other expenses have increased by $2.3 million for the year ended December 31, 2015 due to increased occupancy costs. We expect our research and development expenses to continue to increase in 2016 as we continue spending on our development programs and clinical trials.

General and administrative expenses

General and administrative expenses were $19.2 million and $15.6 million for the years ended December 31, 2015 and 2014, respectively. The increase of $3.6 million was primarily due to an increase in payroll-related expenses of $0.7 million, an increase in stock-based compensation of $1.5 million, and an increase in professional fees of $1.9 million, primarily from legal costs incurred related to the Alnylam complaint. We expect that general and administrative expenses will continue to increase in 2016 as we incur additional costs to support the expanding operations.

Other income (expense)

Other income (expense) was $0.2 million and $(2.8) million for the years ended December 31, 2015 and 2014, respectively. The change was primarily due to a decrease in expense related to the re-measurement of the preferred stock warrant liability of $2.6 million, and a decrease in interest expense of $0.3 million due to the Hercules loan being repaid in full in April 2014.

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Comparison of the years ended December 31, 2014 and 2013

The following table summarizes the results of our operations for the years ended December 31, 2014 and 2013 (in thousands, except percentages):

	FOR THE YEARS ENDED DECEMBER 31,		INCREASE (DECREASE)	
	2014	2013		
Total revenue	$	$	$	
Expenses:				
Research and development	29,453	11,558	17,895	155%
General and administrative	15,648	5,820	9,828	169%
Total expenses	45,101	17,378	27,723	160%
Loss from operations	(45,101)	(17,378)	(27,723)	(160)%
Other expense	(2,838)	(1,140)	(1,698)	(149)%
Net loss	$ (47,939)	$ (18,518)	$ (29,421)	(159)%

Revenue

We did not recognize any revenue for the years ended December 31, 2014 and 2013. We do not expect to generate any product revenue for the foreseeable future.

Research and development expenses

The following table summarizes our research and development expenses incurred during the years ended December 31, 2014 and 2013 (in thousands):

	FOR THE YEARS ENDED DECEMBER 31,		INCREASE (DECREASE)
	2014	2013	
Direct research and development expenses	$ 11,068	$ 4,164	$ 6,904
Platform-related expenses	9,984	3,492	6,492
Employee-related expenses	7,694	2,871	4,823
Facilities, depreciation and other expenses	707	1,031	(324)
Total	$ 29,453	$ 11,558	$ 17,895

Research and development expenses were $29.5 million and $11.6 million for the years ended December 31, 2014 and 2013, respectively. For the year ended December 31, 2014, direct research and development expenses increased by $6.9 million compared to the prior year as a result of the initiation of the clinical trials related to DCR-MYC and an increase in research activities related to DCR-PH1, of which $3.0 million related to license fees paid to Arbutus for the LNP delivery of DCR-PH1. For the year ended December 31, 2014, platform-related expenses increased by $6.5

million compared to the prior year primarily due to increased expenses related to discovery and early development of future programs, along with an increase in non-employee stock-based compensation of $1.7 million. Employee-related expenses increased by $4.8 million for the year ended December 31, 2014 compared to the prior year primarily due to additional hiring during the period, along with an increase in stock-based compensation of $2.4 million. Facilities, depreciation and other expenses have decreased by $0.3 million for the year ended December 31, 2014 due to a reduction in occupancy costs. We expect our research and development expenses to continue to increase in the future as we continue spending on our development programs and clinical trials.

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General and administrative expenses

General and administrative expenses were $15.6 million and $5.8 million for the years ended December 31, 2014 and 2013, respectively. The increase of $9.8 million, or 169 percent, was primarily due to an increase in payroll-related expenses of $3.6 million, which includes an increase in stock-based compensation of $2.6 million, an increase in professional fees of $2.9 million and an increase in non-employee stock-based compensation of $1.1 million. The remaining increase in general and administrative expenses during 2014 was primarily due to the transition and increased costs associated with operating as a public company. We expect that general and administrative expenses will continue to increase in the future as we expand our operating activities and incur additional costs associated with being a publicly-traded company. These increases will likely include legal, accounting and filing fees, directors and officers liability insurance premiums and fees associated with investor relations.

Other expense

Other expense was $2.8 million and $1.1 million for the years ended December 31, 2014 and 2013, respectively. The increase of $1.7 million, or 149 percent, was primarily due to the re-measurement of the preferred stock warrant liability of $2.7 million, which was partially offset by a decrease in interest and other expenses of $1.0 million. The decrease in interest expense was due to the Hercules loan being repaid in full in April 2014.

Liquidity and Capital Resources

Since our inception and through December 31, 2015, we have raised an aggregate of $278.8 million to fund our operations, of which approximately $45.4 million was from the May 2015 follow-on offering of common stock, $0.2 million was from a federal government grant from the NIH covering our work on cancer treatment research, $92.7 million was from the initial public offering of our common stock, which closed on February 4, 2014, $110.5 million was from the sale of preferred stock and convertible debt securities (including $3.0 million from the 2013 bridge note financing), $17.5 million was through our collaboration and license agreement with KHK, $0.5 million was from a federal government grant for our Qualifying Therapeutic Discovery Project in November 2010 and $12.0 million was from borrowings under the Hercules loan. On April 7, 2014, we repaid the remaining amount of the Hercules loan of approximately $3.6 million. As of December 31, 2015, we had cash and cash equivalents and held-to-maturity investments of $94.6 million and $1.1 million in assets held in restriction.

On May 27, 2015, we closed a follow-on offering of 2,750,000 shares of common stock at a price to the public of $17.75 per share, resulting in net proceeds to the Company of $45.4 million after deducting underwriting discounts and commissions of approximately $2.9 million, and costs of the offering of approximately $0.4 million.

On February 4, 2014, we closed our initial public offering, in which we issued and sold a total of 6,900,000 shares of our common stock, including 900,000 shares sold pursuant to the exercise in full by the underwriters of their option to purchase additional shares, at a public offering price of $15.00 per share, and received net proceeds of approximately $92.7 million after deducting underwriting commissions and discounts and offering expenses payable by us.

We granted to Hercules a security interest in certain of our assets. In connection with the loan and security agreement, as amended, we issued to Hercules warrants to purchase 21,000 shares of Series A preferred stock and 26,400 shares of Series B preferred stock, respectively, each at an exercise price of $25.00 per share. The warrants became exercisable to purchase our common stock immediately prior to the closing of our initial public offering. On February 11, 2014, Hercules net exercised these warrants in exchange for a total of 12,702 shares of our common stock. On April 7, 2014, we repaid the remaining amount of the Hercules loan in full for a total payment of $3.6 million.

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In addition to our existing cash and cash equivalents, for each product candidate under our research collaboration and license agreement with KHK, we are entitled to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of such product candidate. Our ability to earn these milestone payments and the timing of achieving these milestones is dependent upon the outcome of our research and development and regulatory activities and is uncertain at this time. Our right to receive the payment of certain milestones under our agreement with KHK is our only committed external source of funds.

Cash flows

As of December 31, 2015, we had $94.6 million in cash and cash equivalents and held-to-maturity investments and $1.1 million in assets held in restriction.

The following table shows a summary of our cash flows for the years ended December 31, 2015, 2014 and 2013 (in thousands).

	FOR THE YEARS ENDED DECEMBER 31,		
	2015	**2014**	**2013**
Net cash used in operating activities	$ (48,799)	$ (34,764)	$ (10,944)
Net cash provided by (used in) investing activities	33,001	(75,761)	(413)
Net cash provided by financing activities	45,789	89,997	54,282
Increase (decrease) in cash and cash equivalents	$ 29,991	$ (20,528)	$ 42,925

Operating activities

Net cash used in operating activities for years ended December 31, 2015 and 2014 was $48.8 million and $34.8 million, respectively. The increase in cash used in operating activities of $14.0 million was due primarily to an increase in our net loss of $14.9 million, partially offset by non-cash items and changes in working capital totaling $0.9 million, including non-cash items of $2.7 million in 2014 for the loss on extinguishment of debt and the increase in the fair value of preferred stock warrant, which did not occur in 2015.

Net cash used in operating activities was $34.8 million and $10.9 million for the years ended December 31, 2014 and 2013, respectively. The increase in cash used in operating activities of $23.8 million was due primarily to an increase in our net loss of $29.4 million, partially offset by non-cash items and changes in working capital totaling $5.6 million, including a payment of $5.0 million received in 2013 under a license agreement related to an option exercise fee and preclinical payments earned in December 2012.

Investing activities

Net cash provided by investing activities for the year ended December 31, 2015 was $33.0 million compared to net cash used in investing activities of $75.8 million in the year ended December 31, 2014. The increase in net cash provided by investing activities for 2015, compared to 2014, relates to an increase in maturities of held-to-maturity investments, a decrease in purchases of held-to-maturity investments, a decrease in purchases of property and equipment, and a decrease in assets held in restriction.

Net cash used in investing activities for the years ended December 31, 2014 and 2013 was $75.8 million and $0.4 million, respectively. Net cash used in investing activities for the periods presented relates to net purchases of held-to-maturity investments, purchases of property and equipment, primarily laboratory equipment, and an increase in assets held in restriction.

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Financing activities

Net cash provided by financing activities for the years ended December 31, 2015 and 2014 was $45.8 million and $90.0 million, respectively. In 2015, net proceeds from our follow-on offering was $45.4 million and proceeds from other issuance of common stock was $0.4 million. In 2014, net proceeds from our initial public offering was $94.1 million and proceeds from other issuance of common stock was $0.9 million, partially offset by the repayment of principal payments related to the Hercules loan for $5.0 million.

Net cash provided by financing activities for the years ended December 31, 2014 and 2013 was $90.0 million and $54.3 million, respectively. In 2014, net proceeds from our initial public offering was $94.1 million and proceeds from other issuance of common stock was $0.9 million, partially offset by the repayment of principal payments related to the Hercules loan for $5.0 million. In 2013, we had net proceeds of $56.8 million from the issuance of redeemable convertible preferred stock and net proceeds of $3.0 million from a bridge loan financing, which were offset by $4.1 million of repayments on long-term debt, and $1.4 million of deferred issuance payments.

Funding requirements

We expect that our primary uses of capital will continue to be third-party clinical research and development services and manufacturing costs, compensation and related expenses, laboratory and related supplies, legal and other regulatory expenses and general overhead costs, including the costs to defend the Alnylam trade secret misappropriation claim against us. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates and the extent to which we may enter into additional collaborations with third parties to participate in their development and commercialization, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated development activities. However, we continue to believe that our cash and cash equivalents as of December 31, 2015 excluding any potential option exercise fees or milestone payments, will be sufficient to meet our anticipated cash requirements for at least the next twelve months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect.

Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially as a result of a number of factors. Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the receipt of milestone payments under our research collaboration and license agreement with KHK;
- the terms and timing of any other collaboration, licensing and other arrangements that we may establish;
- the initiation, progress, timing and completion of preclinical studies and clinical trials for our potential product candidates;
- the number and characteristics of product candidates that we pursue;

the progress, costs and results of our preclinical studies and clinical trials;

the outcome, timing and cost of regulatory approvals;

delays that may be caused by changing regulatory requirements;

the cost and timing of hiring new employees to support our continued growth;

the costs involved in filing and prosecuting patent applications and enforcing and defending patent claims;

the costs of filing and prosecuting intellectual property rights and enforcing and defending any intellectual property-related claims;

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the costs of responding to and defending ourselves against complaints and potential litigation, including the Alnylam complaint of misappropriation of confidential information (see Legal Proceedings);

the costs and timing of procuring clinical and commercial supplies of our product candidates;

the extent to which we acquire or in-license other product candidates and technologies; and

the extent to which we acquire or invest in other businesses, product candidates or technologies.

Until such time, if ever, we generate product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings and research collaboration and license agreements. We may be unable to raise capital or enter into such other arrangements when needed or on favorable terms, or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our product candidates.

Contractual Obligations and Commitments

The following is a summary of our significant contractual obligations as of December 31, 2015 (in thousands).

		PAYMENTS DUE BY PERIOD			
CONTRACTUAL OBLIGATIONS	TOTAL	LESS THAN 1 YEAR	MORE THAN 1 YEAR AND LESS THAN 3	MORE THAN 3 YEARS AND LESS THAN 5	MORE THAN 5 YEARS
Existing operating lease obligations(1)	$ 8,006	$ 1,536	$ 3,211	$ 3,259	$

(1) Total commitments includes future minimum lease payments under our existing non-cancelable operating lease for our office and laboratory space in Cambridge, Massachusetts, as executed on July 11, 2014 with an average rent of approximately $0.1 million per month.

We also have obligations to make future payments to COH, PBL and Arbutus that become due and payable on the achievement of certain development, regulatory and commercial milestones. We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not probable and estimable.

Off-balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the Securities and Exchange Commission.

Segment Reporting

We view our operations and manage our business as one segment, which is the discovery, research and development of treatments based on our RNAi technology platform.

Item 7A. ***Quantitative and Qualitative Disclosure About Market Risk***

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. Some of the securities that we invest in may have market risk related to changes in interest rates. As of December 31, 2015, we had cash and cash equivalents and held-to-maturity investments of $94.6 million. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term maturities of our cash and cash equivalents and held-to-maturity investments and the low risk profile of our investments an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our cash and cash equivalents and held-to-maturity investments. To minimize the risk in the future, we intend to maintain our portfolio of cash and cash equivalents and held-to-maturity investments in a variety of securities, including commercial paper, money market funds, government and non-government debt securities and corporate obligations.

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Item 8. ***Financial Statements and Supplementary Data***

DICERNA PHARMACEUTICALS, INC.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of

Dicerna Pharmaceuticals, Inc.

Cambridge, Massachusetts

We have audited the accompanying consolidated balance sheets of Dicerna Pharmaceuticals, Inc. and its subsidiaries (the Company) as of December 31, 2015 and 2014, and the related consolidated statements of operations, redeemable convertible preferred stock and stockholders equity, and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company s management. Our responsibility is to express an opinion on the 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. The Company is not required to have, nor were we engaged to perform, an audit of its 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, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, such consolidated financial statements present fairly, in all material respects, the financial position of Dicerna Pharmaceuticals, Inc. and its subsidiaries as of December 31, 2015 and 2014, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2015, in conformity with accounting principles generally accepted in the United States of America.

/s/ Deloitte & Touche LLP

Boston, Massachusetts

March 10, 2016

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DICERNA PHARMACEUTICALS, INC.

Consolidated Balance Sheets

(In thousands, except share data and par value)

	DECEMBER 31,	
	2015	2014
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 56,058	$ 26,067
Held-to-maturity investments	38,551	70,055
Prepaid expenses and other current assets	1,532	1,194
Total current assets	96,141	97,316
NONCURRENT ASSETS:		
Property and equipment net	2,684	2,165
Held-to-maturity investments		2,501
Assets held in restriction	1,116	1,380
Other noncurrent assets	82	243
Total noncurrent assets	3,882	6,289
TOTAL ASSETS	$ 100,023	$ 103,605
LIABILITIES AND STOCKHOLDERS EQUITY		
CURRENT LIABILITIES:		
Accounts payable	$ 2,621	$ 1,237
Accrued expenses and other current liabilities	6,376	3,845
Deferred rent	4	77
Total current liabilities	9,001	5,159
NONCURRENT LIABILITIES:		
Security deposit		106
Total noncurrent liabilities		106
TOTAL LIABILITIES	9,001	5,265
COMMITMENTS AND CONTINGENCIES (Note 15)		
STOCKHOLDERS EQUITY:		
Preferred stock, $0.0001 par value 5,000,000 shares authorized; no shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively		
Common stock, $0.0001 par value 150,000,000 shares authorized; 20,594,575 and 17,786,867 shares issued and outstanding at December 31, 2015 and 2014, respectively	2	3
Additional paid-in capital	287,263	231,741

Accumulated deficit	(196,243)	(133,404)
Total stockholders equity	91,022	98,340
TOTAL LIABILITIES AND STOCKHOLDERS EQUITY	$ 100,023	$ 103,605

The accompanying notes are an integral part of these consolidated financial statements.

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DICERNA PHARMACEUTICALS, INC.

Consolidated Statements of Operations

(In thousands, except share data and per share data)

	YEARS ENDED DECEMBER 31,		
	2015	**2014**	**2013**
Revenues	$ 184	$	$
Operating expenses:			
Research and development	43,971	29,453	11,558
General and administrative	19,240	15,648	5,820
Total operating expenses	63,211	45,101	17,378
Loss from operations	(63,027)	(45,101)	(17,378)
Other income (expense):			
Preferred stock warrant liability re-measurement		(2,559)	126
Loss on extinguishment of debt		(143)	(318)
Interest income	188	63	4
Interest expense		(199)	(952)
Total other income (expense)	188	(2,838)	(1,140)
Net loss	$ (62,839)	$ (47,939)	$ (18,518)
Less: Accretion and dividends on redeemable convertible preferred stock		204	2,388
Net loss attributable to common stockholders	$ (62,839)	$ (48,143)	$ (20,906)
Net loss per share attributable to common stockholders basic and diluted	$ (3.09)	$ (3.00)	$ (709.57)
Weighted average shares outstanding basic and diluted	20,320,628	16,070,054	29,463

The accompanying notes are an integral part of these consolidated financial statements.

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DICERNA PHARMACEUTICALS, INC.

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders Equity

(In thousands, except share data and par value)

	SERIES A REDEEMABLE CONVERTIBLE PREFERRED STOCK $0.0001 PAR VALUE		SERIES B REDEEMABLE CONVERTIBLE PREFERRED STOCK $0.0001 PAR VALUE		SERIES C REDEEMABLE CONVERTIBLE PREFERRED STOCK $0.0001 PAR VALUE		COMMON STOCK $0.0001 PAR VALUE		ADDITIONAL PAID-IN CAPITAL	ACCUMULATED DEFICIT	STO
	SHARES	AMOUNT	SHARES	AMOUNT	SHARES	AMOUNT	SHARES	AMOUNT			
January 1,	855,996	29,728	1,162,021	34,520			27,853	1		(64,720)	
eries C ck, net of s of $220					8,142,891	56,780					
eries C ck, in f bridge					428,526	3,000					
preferred e costs		47		58		16			(121)		
dends		962		1,305					(40)	(2,227)	
ribution of ckholders		(9,337)		(6,833)					16,170		
stricted k							15				
f unvested mmon stock									(5)		
n									495		
ommon							10,358		46		
										(18,518)	
December 31,	855,996	21,400	1,162,021	29,050	8,571,417	59,796	38,226	1	16,545	(85,465)	
Common itial public of fees and s of $10,751							6,900,000	1	92,749		
of common t							12,702				

on of urchase eemable referred varrant to mmon stock									3,088	
preferred e costs						204			(204)	
f preferred mon stock	(855,996)	(21,400)	(1,162,021)	(29,050)	(8,571,417)	(60,000)	10,589,434	1	110,451	
stricted k							4,000			
n									8,237	
ommon							239,853		824	
non stock ployee stock n							2,652		51	
										(47,939)
December 31,	$		$			$	17,786,867	$ 3	$ 231,741	$ (133,404)
Common ublic of fees and s of $445							2,750,000		45,438	
stricted k							6,388			
n									9,732	
ommon							29,506		149	
restricted withholding								(1)	(75)	
non stock ployee stock n							21,814		278	
										(62,839)
December 31,	$		$			$	20,594,575	$ 2	$ 287,263	$ (196,243)

The accompanying notes are an integral part of these consolidated financial statements.

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DICERNA PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows

(In thousands)

	YEARS ENDED DECEMBER 31,		
	2015	**2014**	**2013**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$ (62,839)	$ (47,939)	$ (18,518)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	727	848	740
Net amortization of premium/discount on investments	134		
Stock-based compensation	9,732	8,237	495
Loss on extinguishment of debt		143	318
Increase (Decrease) in fair value of preferred stock warrant		2,559	(126)
Changes in operating assets and liabilities:			
Research and license receivable			5,018
Prepaid expenses and other assets	(177)	(1,171)	57
Accounts payable	1,384	(97)	116
Accrued expenses and other liabilities	2,313	2,684	1,016
Deferred rent	(73)	(28)	(60)
Net cash used in operating activities	(48,799)	(34,764)	(10,944)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Changes in assets held in restriction	264	(1,116)	
Purchases of property and equipment	(1,134)	(2,013)	(413)
Maturities of held-to-maturity investments	70,000	9,995	
Purchases of held-to-maturity investments	(36,129)	(82,627)	
Net cash provided by (used in) investing activities	33,001	(75,761)	(413)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from stock option exercise and issuances under Employee Stock Purchase Plan	427	875	46
Proceeds from public offering of common stock, net of costs	45,438	94,148	
Repurchase of restricted common stock			(5)
Settlement of restricted stock for tax withholding	(76)		
Payments of deferred issuance costs			(1,399)
Proceeds from issuance of redeemable convertible preferred stock			57,000
Redeemable preferred stock issuance costs			(220)
Proceeds from bridge loan financing			3,000
Repayments of long-term debt principal		(5,026)	(4,140)

Net cash provided by financing activities	45,789	89,997	54,282
INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS	29,991	(20,528)	42,925
CASH AND CASH EQUIVALENTS Beginning of year	26,067	46,595	3,670
CASH AND CASH EQUIVALENTS End of year	$ 56,058	$ 26,067	$ 46,595
NONCASH INVESTING ACTIVITIES:			
Property and equipment purchases included in accrued expenses	$ 112	$	$
NONCASH FINANCING ACTIVITIES:			
Accretion of redeemable convertible preferred stock	$	$ 204	$ 2,388
Deemed contribution of preferred stockholders	$	$	$ 16,170
Conversion of bridge loan financing	$	$	$ 3,000
Tenant allowances	$	$	$ 104
SUPPLEMENTAL CASH FLOW INFORMATION:			
Warrant conversion to common stock	$	$ 3,088	$
Cash paid for interest	$	$ 194	$ 771

The accompanying notes are an integral part of these consolidated financial statements.

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DICERNA PHARMACEUTICALS, INC.

Notes to Consolidated Financial Statements

(In thousands, except share and per share data)

1. Description of Business and Basis of Presentation

Nature of business

Dicerna Pharmaceuticals, Inc., and its subsidiaries, (the Company) is a biopharmaceutical company focused on the discovery and development of innovative treatments for rare inherited diseases involving the liver and for cancers that are genetically defined. The Company is using its proprietary RNA interference (RNAi) technology platform to build a broad pipeline in these therapeutic areas. The Company intends to discover, develop and commercialize novel therapeutics either on its own or in collaboration with pharmaceutical partners.

The Company continues to be subject to a number of risks common to companies in similar stages of development. Principal among these risks are the uncertainties of technological innovations, which are particularly high in the field of drug discovery and development, dependence on key individuals, development of the same or similar technological innovations by the Company s competitors and protection of proprietary technology.

The Company s ability to fund its planned preclinical and clinical operations, including completion of its clinical trials, is expected to depend on the amount and timing of cash receipts under any future collaborations, financing transactions, its existing collaboration agreement, as well as any product sales.

In February 2014, the Company completed the sale of 6,900,000 shares of common stock in an initial public offering of its common stock (the IPO) at a price to the public of $15.00 per share, resulting in net proceeds to the Company of $92.7 million after deducting underwriting discounts and commissions of approximately $7.2 million and offering expenses paid by the Company of approximately $3.5 million. In connection with the close of the IPO, all of the outstanding shares of Series A mandatorily redeemable, convertible preferred stock (Series A preferred stock), Series B mandatorily redeemable, convertible preferred stock (Series B preferred stock) and Series C mandatorily redeemable, convertible preferred stock (Series C preferred stock) were converted into shares of common stock on a one-for-one basis immediately prior to the closing of the IPO.

In May 2015, the Company completed the sale of 2,750,000 shares of common stock in a public offering of its common stock at a price to the public of $17.75 per share, resulting in proceeds to the Company of $45.4 million after deducting underwriting discounts and commissions of approximately $2.9 million and offering costs incurred by the Company of approximately $0.4 million.

2. Summary of Significant Accounting Policies

Basis of presentation and consolidation

The accompanying consolidated financial statements have been prepared under accounting principles generally accepted in the United States of America, or GAAP, and include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Significant judgments and estimates

The preparation of these financial statements is in conformity with GAAP which requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the revenues and expenses incurred during the reporting periods. On an ongoing basis, the Company evaluates judgments and estimates, including those related to accrued expenses, revenue recognition, deferred revenue and stock-based compensation. The Company bases its estimates on historical experience and on various other factors that the Company believes 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. Changes in

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estimates are reflected in reported results for the period in which they become known. Actual results could differ materially from those estimates.

Cash equivalents

Cash equivalents include all highly liquid investments maturing within 90 days from the date of purchase. Cash equivalents consist of money market funds as of December 31, 2015 and 2014 and are valued at cost, plus accrued interest, which approximates fair value.

Held-to-Maturity Investments

The Company accounts for its investments in marketable securities in accordance with FASB ASC 320, *Investments Debt and Equity Securities*. The Company determines the appropriate classification of investments at the time of purchase and re-evaluates such designation as of each balance sheet date. Debt securities carried at amortized cost are classified as held-to-maturity when the Company has the positive intent and ability to hold the securities to maturity. At December 31, 2015 and 2014, all of the Company s investments are classified as held-to-maturity.

Assets held in restriction

As of December 31, 2015, assets held in restriction was comprised of a money market collateral account that is restricted and secures the Company s outstanding letter of credit of $1.1 million for the operating lease for office and laboratory space. The letter of credit is required to be maintained throughout the term of the Company s lease which expires on December 1, 2020. As of December 31, 2014, assets held in restriction were comprised of a money market collateral account that is restricted and two certificates of deposit that mature annually, and secure the Company s outstanding letters of credit of $1.1 million and $0.3 million for the operating leases for office and laboratory space, respectively. The letters of credit are required to be maintained throughout the term of the Company s leases which expire on December 1, 2020 and April 9, 2015, as amended, respectively.

Concentrations of credit risk

Financial instruments that subject the Company to significant concentrations of credit risk consist of cash and cash equivalents, assets held in restriction and held-to-maturity investments. All of the Company s cash and cash equivalents, assets held in restriction and held-to-maturity investments are invested in money market funds or U.S. Treasury or agency securities that management believes to be of high credit quality. During 2015, one counterparty accounted for all of the Company s revenue.

Deferred stock issuance costs

Deferred stock issuance costs, which consisted of direct incremental legal and professional accounting fees relating to the Company s IPO, totaling $1.8 million, were initially capitalized in 2013 and subsequently offset against IPO proceeds in 2014, when the offering was completed. No amounts were deferred as of December 31, 2015 and 2014.

Property and equipment

Property and equipment are stated at cost. Major betterments are capitalized whereas expenditures for maintenance and repairs which do not improve or extend the life of the respective assets are charged to operations as incurred. Depreciation is provided using the straight-line method over the estimated useful lives:

ASSET CATEGORY	USEFUL LIVES
Office and computer equipment	3-5 years
Laboratory equipment	5 years
Furniture and fixtures	5 years
Leasehold improvements	5 years or the remaining term of lease, if shorter

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Impairment of long-lived assets

Long-lived assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of the asset may not be recoverable. When such events occur, the Company compares the carrying amounts of the assets to their undiscounted expected future cash flows. If this comparison indicates that there is an impairment, the amount of the impairment is calculated as the difference between the carrying value and fair value of the related asset. For the years ended December 31, 2015, 2014 and 2013, no impairments have been recorded.

Segment and geographic information

Operating segments are defined as components (business activity from which it earns revenue and incurs expenses) of an enterprise about which discrete financial information is available and regularly reviewed by the chief operating decision maker in deciding how to allocate resources and in assessing performance. The Company, through its Chief Executive Officer in his role as chief operating decision maker, views its operations and manages its business as one operating segment. All material long-lived assets of the Company are located in the United States.

Revenue recognition

The Company generates revenue from research collaboration and license agreements with third parties which contain multiple deliverables. The deliverables in the agreements include (a) the use of the Company s technology and (b) research and development of product candidates. Such agreements may provide for consideration to the Company in the form of up-front payments, research and development services, milestone payments and royalties. Revenue is recognized when the following criteria have been met: (1) pervasive evidence of an arrangement exists; (2) delivery has occurred or services have been rendered and risk of loss has passed; (3) the seller s price to the buyer is fixed or determinable; and (4) collectability is reasonably assured. Multiple-deliverable arrangements are analyzed to determine whether the deliverables can be separated or whether they must be accounted for as a single unit of accounting. When deliverables are separable, consideration received is allocated to the separate units of accounting based on the relative selling price method and the appropriate revenue recognition principles are applied to each unit.

At the inception of each arrangement that includes payments for optional research or milestones, the Company evaluates whether each option or milestone is substantive and at risk to both parties on the basis of the contingent nature of the option or milestone. This evaluation includes an assessment of whether (1) the consideration is commensurate with either the entity s performance to achieve the milestone or the enhancement of the value of the delivered item(s); (2) as a result of a specific outcome resulting from the entity s performance to achieve the milestone; (3) the consideration relates solely to past performance; and (4) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. Substantive options and milestones are recognized as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met.

When the Company determines that an arrangement should be accounted for as a single unit of accounting, it must determine the period over which the performance obligations will be performed and revenue will be recognized. The Company s revenue to date results from a research collaboration and license agreement entered into in December 2009 and an NIH grant awarded in 2015. Non-refundable up-front license fees under the agreement were initially recorded as deferred revenue upon receipt and are being recognized as revenue over the Company s performance period as defined in the agreement. Research and development service revenue is recognized over the research term as the research and development services are provided. The cost of such services is reflected in research and development costs in the period in which it is incurred.

Royalty payments are recognized as revenue based on contract terms and reported sales of licensed products, when reported sales are reliably measurable and collectability is reasonably assured.

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Grant revenue is recognized in the period during which the related grant research and activities are incurred, provided that the conditions under which the grant was provided have been met and the Company only has perfunctory obligations outstanding. Any amounts received in advance of revenue recognition are classified as deferred revenue in the consolidated balance sheets. Costs associated with grants are included in research and development expenses in the consolidated statements of operations.

Research and development costs

Research and development costs consist of expenses incurred in performing research and development activities, including compensation and benefits for full-time research and development employees, an allocation of facility expenses, overhead expenses and other outside expenses. Research and development costs are expensed as incurred. Research and development costs that are paid in advance of performance are deferred as a prepaid expense and amortized over the service period as the services are provided.

Preferred stock warrant liability

Freestanding warrants related to shares that are redeemable, contingently redeemable, or for purchases of preferred stock that are not indexed to the Company s own stock are classified as a liability on the Company s balance sheet. The preferred stock warrants were recorded at fair value, estimated using the Black-Scholes option-pricing model for the year ended December 31, 2013 and until the conversion date of February 4, 2014, and marked to market at each balance sheet date with changes in the fair value of the liability recorded in the statements of operations. After the closing of the IPO, the preferred stock warrants were no longer classified as a liability subject to re-measurement as the preferred stock warrants became warrants to purchase shares of common stock. There were no preferred stock warrants outstanding as of December 31, 2015 and 2014.

Deferred Rent

Deferred rent consists of rent escalation payment terms, tenant improvement allowances and other incentives received from landlords related to the Company s operating leases. Rent escalation represents the difference between actual operating lease payments due and straight-line rent expense, which is recorded by the Company over the term of the lease. Tenant improvement allowances and other incentives are recorded as deferred rent and amortized as a reduction of periodic rent expense, over the term of the applicable lease.

Redeemable convertible preferred stock

The Company initially records preferred stock that may be redeemed at the option of the holder or based on the occurrence of events not under the Company s control outside of stockholders equity at the value of the proceeds received or fair value, if lower, net of issuance costs. Subsequently, if it is probable that the preferred stock will become redeemable, the Company adjusts the carrying value to the redemption value over the period from the issuance date to the earliest possible redemption date using the effective interest method. If it is not probable that the preferred stock will become redeemable, the Company does not adjust the carrying value. In the absence of retained earnings these accretion charges are recorded against additional paid-in-capital, if any, and then to accumulated deficit.

Common stock valuation

Due to the absence of an active market for the Company s common stock prior to the IPO, the Company utilized methodologies in accordance with the framework of the American Institute of Certified Public Accountants Technical

Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its common stock. In determining the exercise prices for options granted, the Company has considered the fair value of the common stock as of the measurement date. The fair value of the common stock has been determined at each award grant date based upon a variety of factors, including the illiquid nature

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of the common stock, arm s-length sales of the Company s capital stock (including redeemable convertible preferred stock), the effect of the rights and preferences of the preferred stockholders, and the prospects of a liquidity event. Among other factors are the Company s financial position and historical financial performance, the status of technological developments within the Company s research, the composition and ability of the current research and management team, an evaluation or benchmark of the Company s competition, and the current business climate in the marketplace. Significant changes to the key assumptions underlying the factors used could result in different fair values of common stock at each valuation date.

Stock-based compensation

The Company accounts for stock options granted as share-based awards at fair value, which is measured using the Black-Scholes option pricing model. The fair value measurement date for employee awards is the date of grant. The fair value measurement date for nonemployee awards is generally the date the performance of services is completed. Share-based compensation costs are recognized as expense over the requisite service period, which is generally the vesting period, on a straight-line basis for all time-vested awards.

For performance-based stock awards, compensation costs are recorded when the Company determines that the achievement of such performance conditions is deemed probable. This determination requires significant judgment by management. At the probable date, the Company records a cumulative expense catch-up, with the remaining compensation cost being amortized over the remaining vesting period.

The Company accounts for restricted stock awards granted to employees at fair value, which is measured based upon the quoted closing market price per share on the date of grant, adjusted for assumed forfeitures. The compensation costs are recognized over the vesting period, commencing when the Company determines that it is probable that the awards will vest.

Share-based awards to non-employees are re-measured at each reporting date and compensation costs are recognized as services are rendered, generally on a straight-line basis. The Company believes that the fair value of these awards is more reliably measurable than the fair value of the services rendered.

Income taxes

The Company records deferred tax assets and liabilities for the expected future tax consequences of temporary differences between the Company s financial statement carrying amounts and the tax basis of assets and liabilities using enacted tax rates expected to be in effect in the years in which the differences are expected to reverse. A valuation allowance is provided to reduce the net deferred tax assets to the amount that will more likely than not be realized.

The Company also assesses the probability that the positions taken or expected to be taken in its income tax returns will be sustained by taxing authorities. A more likely than not (more than 50 percent) recognition threshold must be met before a tax benefit can be recognized. Tax positions that are more likely than not to be sustained are reflected in the Company s financial statements. Tax positions are measured as the largest amount of tax benefit that is greater than 50 percent likely of being realized upon settlement with a taxing authority that has full knowledge of all relevant information. The difference between the benefit recognized for a position and the tax benefit claimed on a tax return is referred to as an unrecognized tax benefit. Potential interest and penalties associated with such uncertain tax positions are recorded as a component of income tax expense.

Net loss per common share

The Company computes basic net loss per common share by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding. During periods where the Company earns net income, the Company allocates participating securities a proportional share of net income determined by dividing total weighted average participating securities by the sum of the total weighted average

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common shares and participating securities (the two-class method). The Company s preferred stock and vested restricted stock participate in any dividends declared by the Company and are therefore considered to be participating securities. Participating securities have the effect of diluting both basic and diluted earnings per share during periods of income. During periods where the Company incurred net loss, the Company allocates no loss to participating securities because they have no contractual obligation to share in the losses of the Company. The Company computes diluted net loss per common share after giving consideration to the dilutive effect of stock options, warrants and unvested restricted stock that are outstanding during the period, except where such non-participating securities would be anti-dilutive.

Comprehensive loss

The Company has no comprehensive loss items other than net loss.

Guarantees and indemnifications

The Company is not a guarantor under any agreements.

The Company leases office space under an operating lease. The Company has standard indemnification arrangements under these leases that require the Company to indemnify the landlord against losses, liabilities, and claims incurred in connection with the premises covered by the Company s lease, the Company s use of the premises, property damage or personal injury, and breach of the agreement.

Through December 31, 2015, the Company had not experienced any losses related to this indemnification obligation and no claims with respect thereto were outstanding. The Company does not expect material claims related to this indemnification obligation, and consequently, concluded that the fair value of this obligation is negligible and no related liabilities were established.

The Company has indemnified, under pre-determined conditions and limitations, a counterparty for infringement of third-party intellectual property rights by the Company. The Company does not believe, based on information available, that it is probable that any material amounts will be paid under these indemnification provisions.

As permitted under Delaware law, the Company indemnifies its officers, directors, and employees for certain events or occurrences while the officer or director is, or was, serving at the Company s request in such capacity. The term of the indemnification is for the officer s or director s lifetime.

Recent Accounting Pronouncements

Leases

In February 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) 2016-02, Leases (Topic 842). The ASU requires lessees to put most leases on their balance sheets as a liability for the obligation to make lease payments and as a right-of-use asset, but recognize expenses on the income statements in a manner similar to today s accounting. The guidance also eliminates the current real estate-specific provisions for all entities. For calendar-year public entities, the guidance becomes effective in 2019 and interim periods within that year. Early adoption is permitted for all entities. The Company has not chosen early adoption for this ASU and is currently evaluating its effect on the Company s consolidated financial statements.

Income Taxes

In November 2015, the FASB issued ASU 2015-17, Income Taxes: Balance Sheet Classification of Deferred Taxes (Topic 740). ASU 2015-17 simplifies the presentation of deferred income taxes by eliminating the separate classification of deferred income tax assets and liabilities into current and noncurrent amounts in the consolidated balance sheet statement of financial position. The amendments in the update require that all deferred tax assets and liabilities be classified as noncurrent in the consolidated balance sheet. The amendments in this update are

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effective for annual periods beginning after December 15, 2017, and interim periods therein and may be applied either prospectively or retrospectively to all periods presented. Early adoption is permitted. The Company has early adopted this standard in the fourth quarter of 2015 on a prospective basis, and it did not have an effect on the Company s consolidated financial statements.

Revenue Recognition

In May 2014, the FASB issued ASU 2014-09, Revenue from Contracts with Customers (Topic 606). ASU 2014-09 amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in Accounting Standards Codification Topic 605, Revenue Recognition, and creates a new Topic 606, Revenue from Contracts with Customers. This guidance was originally pronounced to become effective for fiscal years beginning after December 15, 2016, with early adoption not permitted. On July 9, 2015, the FASB decided to defer the effective date of the ASU by one year. As a result, the Company will be required to apply the new revenue standard to annual reporting periods beginning after December 15, 2017, and would be permitted to adopt the ASU early, but not before the original public organization effective date (annual periods beginning after December 15, 2016). Two adoption methods are permitted: retrospectively to all prior reporting periods presented, with certain practical expedients permitted; or retrospectively with the cumulative effect of initially adopting the ASU recognized at the date of initial application. The Company has not yet determined which adoption method it will utilize or the effect, if any, the adoption of this guidance will have on its consolidated financial statements through December 31, 2015 as the Company has yet to record revenue from contracts with customers.

3. Net Loss Per Share Attributable to Common Stockholders

The following table summarizes the computation of basic and diluted net loss per share attributable to common stockholders of the Company (in thousands, except share and per share data):

	YEARS ENDED DECEMBER 31,		
	2015	**2014**	**2013**
Net loss	$ (62,839)	$ (47,939)	$ (18,518)
Accretion of preferred stock issuance costs to redemption value		(204)	(121)
Accrued dividends on preferred stock			(2,267)
Net loss attributable to common stockholders basic and diluted	$ (62,839)	$ (48,143)	$ (20,906)
Weighted-average number of common shares basic and diluted	20,320,628	16,070,054	29,463
Net loss per share attributable to common stockholders basic and diluted	$ (3.09)	$ (3.00)	$ (709.57)

The following potentially dilutive securities outstanding during the period, prior to the use of the treasury stock method or if-converted method, have been excluded from the computation of diluted weighted-average common shares outstanding, because such securities had an anti-dilutive impact since the Company has a net loss attributable to common stockholders:

	AS OF DECEMBER 31,		
	2015	**2014**	**2013**
Options to purchase common stock	4,297,300	2,764,144	403,959
Warrants to purchase common stock	87,901	80,722	2,198
Warrants to purchase redeemable convertible preferred stock		12,763	91,543
Redeemable convertible preferred stock		1,015,426	5,634,458
Unvested restricted stock	68,656	92,932	7

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4. Held-to-maturity Investments

The Company invests its excess cash balances in short-term and long-term fixed-income investments. The Company determines the appropriate classification of investments at the time of purchase and re-evaluates such designation as of each balance sheet date. Debt securities carried at amortized cost are classified as held-to-maturity when the Company has the positive intent and ability to hold the securities to maturity.

The following tables provide information relating to held-to-maturity investments:

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
At December 31, 2015:				
Held-to-maturity investments				
U.S. Government treasury	$ 38,551	$	$ (47)	$ 38,504
Total held-to-maturity investments	$ 38,551	$	$ (47)	$ 38,504

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
At December 31, 2014:				
Held-to-maturity investments				
U.S. Government treasury and agency securities	$ 72,556	$ 2	$ (26)	$ 72,532
Total held-to-maturity investments	$ 72,556	$ 2	$ (26)	$ 72,532

The amortized cost and fair value of held-to-maturity investments by contractual maturities at December 31, 2015, are as follows:

	Held-to-Maturity	
	Amortized Cost	Fair Value
Maturing in one year or less	$ 38,551	$ 38,504
Total	$ 38,551	$ 38,504

5. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consists of the following:

	AS OF DECEMBER 31,	
	2015	2014
Prepaid expenses	$ 1,479	$ 1,115
Interest receivable and other current assets	53	79
Prepaid expenses and other current assets	$ 1,532	$ 1,194

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6. Property and Equipment, Net

Property and equipment, net consists of the following:

	AS OF DECEMBER 31, 2015	2014
Office and computer equipment	$ 705	$ 503
Laboratory equipment	4,161	3,209
Leasehold improvements	257	887
Furniture and fixtures	477	624
Property and equipment at cost	5,600	5,223
Less accumulated depreciation	(2,916)	(3,058)
Property and equipment net	$ 2,684	$ 2,165

Depreciation expense for the years ended December 31, 2015, 2014 and 2013 was $0.7 million, $0.7 million and, $0.5 million, respectively.

7. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consists of the following:

	AS OF DECEMBER 31, 2015	2014
Other accrued expenses	$ 4,284	$ 2,362
Accrued compensation and benefits	2,092	1,483
Accrued expenses and other current liabilities	$ 6,376	$ 3,845

8. Long-term Debt

On March 26, 2009, as amended in June 2011, the Company entered into a loan and security agreement with an independent finance company, Hercules Technology II, LP (Hercules), for up to $7.0 million. The Hercules loan, which has since been repaid, was collateralized by a security interest in all tangible assets. The applicable annual interest rate was 10.15% from December 31, 2013 through April 7, 2014, the date the Company repaid the remaining amount of the Hercules loan in full for a total amount of $3.6 million.

In connection with the Hercules loan, the Company issued warrants to Hercules for the purchase of an aggregate of 21,000 shares of the Series A preferred stock and 26,400 shares of the Series B preferred stock each at an exercise price of $25.00 per share. Immediately prior to the closing of the IPO on February 4, 2014, all of the outstanding shares of the Series A, Series B and Series C preferred stock were automatically converted into shares of common stock on a one-for-one basis. The fair value of the warrants was classified as a liability in the accompanying consolidated balance sheet as of December 31, 2013. After the conversion of Series A and Series B preferred stock,

the fair value of the warrants was reclassified as a part of stockholders equity. The re-measurement of the liability continued until the date of the closing of the IPO. The fair value of the outstanding Hercules warrants as of the IPO closing date was $0.8 million and was determined using the Black-Scholes option-pricing model with the following assumptions:

	FEBRUARY 4, 2014
Stock price	$ 32.66
Expected option term (in years)	3.0
Expected volatility	62%
Risk-free interest rate	0.7%
Expected dividend yield	0.0%

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On February 11, 2014, Hercules net exercised the warrants in exchange for a total of 12,702 shares of common stock. There were no Series A and Series B warrants outstanding at December 31, 2015 and 2014.

The adjustment to this preferred stock warrant liability related to the Hercules warrants was recorded in other income (expense) and amounted to $0, $(0.7) million and $0.2 million for the years ended December 31, 2015, 2014 and 2013, respectively.

9. Bridge Loan Financing

On June 26, 2013, the Company issued convertible notes and warrants for the purchase of preferred stock in the next qualified financing to then existing preferred and common stockholders for approximately $3.0 million (bridge loan financing). The notes were due to mature on June 26, 2018, unless previously converted or repaid. In the event the Company were to obtain financing through the issuance of equity securities, including an IPO, prior to the maturity date, the notes would automatically convert into shares of the equity issued in such a qualified financing and at the lowest price per share of the equity securities issued and sold in that financing. If a liquidation event were to occur prior to June 26, 2018, the notes could be converted at the option of the holder for an amount equal to two times the outstanding principal balance of the notes in cash or the issuance of Series B preferred stock equal to the outstanding principal balance of the notes divided by 0.9. The notes had an interest rate of 7% per year, payable at the earlier of the notes conversion or maturity.

The purpose of this bridge loan financing was to provide operating cash to the Company until it completed the issuance of the Series C in July 2013, at which time the notes were converted into 428,526 shares of Series C preferred shares at $7.00 per share and the related accrued interest of $20 became payable.

In connection with the issuance of the bridge loan financing, the Company issued warrants for the purchase of an aggregate of 85,703 shares of the Company s preferred stock in the next qualified financing at an exercise price of $7.00 per share. The warrants are immediately exercisable and expire 5 years from the date of issuance. The Company estimated the fair value of the warrants at the date of issuance to be $0.3 million. The fair value of the warrants was recorded as a discount to the convertible notes upon issuance, and was initially classified as a liability in the accompanying consolidated balance sheets. The issuance date fair value was determined using the Black-Scholes option-pricing model with the following assumptions: risk-free interest rate of approximately 1.2%, expected life of 5 years, volatility of 64%, and no expected dividends. After the conversion of Series C preferred stock, the fair value of the warrants related to Series C preferred stock outstanding immediately prior to the closing of the IPO was reclassified as a part of stockholders equity (deficit). The re-measurement of the Series C preferred stock warrant liability continued until the closing date of the IPO.

The estimated fair value of the outstanding Series C warrants at the IPO closing date and December 31, 2013 was $2.3 million and $0.4 million, respectively. The estimated fair values were determined using the Black-Scholes option-pricing model with the following assumptions:

	FEBRUARY 4, 2014	DECEMBER 31, 2013
Stock price	$ 32.66	$ 8.84
Expected option term (in years)	4.4	4.5
Expected volatility	65%	64%
Risk-free interest rate	1.5%	1.3%

Expected dividend yield	0.0%	0.0%

There were no Series C warrants outstanding at December 31, 2015 and 2014. As of the closing of the IPO on February 4, 2014, the conversion of Series C preferred stock into common stock triggered the conversion all Series C warrants into common share warrants. As of December 31, 2015 and 2014 there were 85,703 common share warrants outstanding.

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The adjustment to this preferred stock warrant liability was recorded in other income (expense) and for the years ended December 31, 2015, 2014, and 2013 amounted to $0, $(1.9) million and $(0.1) million, respectively.

The bridge loan discount was amortized to interest expense using the effective interest method over the loan repayment term, and the unamortized discount of $0.3 million was reflected as a loss on extinguishment of the bridge loan in the accompanying statement of operations, when the notes were converted to Series C in July 2013.

10. Revenue

NIH Grants In April 2015, the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH), awarded the Company a grant related to cancer treatment research. The project period for this grant covers a three month period which commenced in April 2015, with total funds available of approximately $0.2 million. The payment of the NIH grant award was based upon subcontractor and internal costs incurred that are specifically covered by the grant, and where applicable, a facilities and administrative rate that provides funding for overhead expenses. During the year ended December 31, 2015, the Company recognized $0.2 million of revenue associated with the NIH grant award.

Collaboration and License Agreements In December 2009, the Company entered into a research collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd. (KHK) for the research, development and commercialization of drug delivery systems and DsiRNA pharmaceuticals for therapeutic targets primarily in oncology. The Company granted KHK an exclusive, worldwide, royalty-bearing and sub-licensable license to the DsiRNA and drug delivery technologies and intellectual property for certain selected DsiRNA-based compounds. Under the agreement, KHK is responsible for activities to develop, manufacture and commercialize the selected DsiRNA-based compounds and pharmaceutical products containing such compounds.

Since the initiation of the research collaboration and license agreement two target programs, including the initial target KRAS, have been nominated by KHK for formal development studies. Both target programs utilize the Company s specific RNAi-inducing double-stranded DsiRNA molecules and a lipid nanoparticle drug delivery system proprietary to KHK.

The Company is entitled to receive up to $110.0 million in regulatory, clinical and commercialization milestone payments, and royalties on net sales of each product candidate under the KHK agreement. Since contract inception, the Company has received payments totaling $17.5 million.

The deliverables at the effective date of the agreement include delivery of intellectual property, conducting the KRAS research and development program, and providing KHK the exclusive option right to reserve additional targets. The Company concluded the performance of additional research for each additional target, if exercised by KHK, is not a deliverable of the agreement at inception because it is a substantive option and is not priced at a significant and incremental discount. The performance period is the expected period over which the services of the combined unit are performed which spans from the contract inception through the end of 2011.

The Company has no further obligations under the research collaboration and license agreement related to the KRAS target or the additional target.

11. Redeemable Convertible Preferred Stock

The consummation of the IPO on February 4, 2014 resulted in the conversion of all of the shares of the Company s Series A, Series B and Series C preferred stock into shares of common stock. Each share of Series A, Series B and

Series C preferred stock was automatically converted into common stock on a one-for-one basis. The conversion of Series A, Series B and Series C preferred stock resulted in the issuance of 10,589,434 shares of common stock.

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After the conversion of Series C preferred stock, the fair value of the warrants related to Series C preferred stock outstanding immediately prior to the closing of the IPO was reclassified as a part of stockholders equity. The re-measurement of the Series C preferred stock warrant liability continued until the closing date of the IPO. The fair value of the Series C preferred stock warrants as of the IPO closing date was $2.3 million and was determined using the Black-Scholes option-pricing model with the following assumptions:

	FEBRUARY 4, 2014
Stock price	$ 32.66
Expected option term (in years)	4.39
Expected volatility	65%
Risk-free interest rate	1.52%
Expected dividend yield	0.00%

The adjustment to the Series C preferred stock warrant liability was recorded in other income (expense) and amounted to $0 and ($1.9) million for the years ended December 31, 2015 and 2014, respectively.

12. Common Stock and Stock Option Plan

Common stock

Prior to the IPO, voting, dividend and liquidation rights of the holders of the common stock were subject to and qualified by the rights, powers and preferences of the holders of the preferred stock.

Voting

The holders of the common stock are entitled to one vote for each share of common stock held at all meetings of stockholders. The number of authorized shares of common stock may be increased or decreased (but not below the number of shares thereof) by the affirmative vote of the holders of shares of capital stock of the Company representing a majority of the votes represented by all outstanding shares of capital stock of the Company entitled to vote.

Stock option plan

On July 1, 2007, the Board of Directors approved the 2007 Employee, Director, and Consultant Stock Plan, which provides for the grant of qualified incentive stock options, nonqualified stock options, and restricted stock to employees, directors, and non-employees. On May 5, 2010, the Board of Directors approved the Fourth Amended and Restated 2007 Employee, Director, and Consultant Stock Plan (the 2007 Plan), which authorizes further issuances of up to 30,254 shares of the Company s common stock. On October 14, 2010, the Board of Directors approved the retirement of the 2007 Plan and adopted the 2010 Employee Director and Consultant Equity Incentive Plan (the 2010 Plan). The 2010 Plan, as adopted, authorizes further issuances of up to 45,214 shares of the Company s common stock. On February 9, 2012, the Board of Directors approved an amendment to the 2010 Plan to increase the number of shares authorized for purchase by 4,800 shares, thereby providing for the purchase of up to 49,014 shares of the Company s common stock. On July 30, 2013, the Board of Directors approved an amendment to the 2010 Plan to increase the number of shares authorized for purchase by 1,715,851 shares, thereby providing for the purchase of up to 1,764,865 shares of the Company s common stock. The stock options generally vest 25% after 12 months, followed by ratable vesting over 36 months and expire 10 years from the grant date. On January 14, 2014, the Board of Directors approved the retirement of the 2010 Plan and adopted the 2014 Performance Incentive Plan (the 2014 Plan). The 2014

Plan, as adopted, authorizes the issuances of up to 1,900,000 shares of the Company s common stock, with an additional 4% of the total outstanding common shares becoming available at each year ending December 31. In June 2015, the 2014 plan was amended to increase the replenishment percentage from 4% to 5% of outstanding common shares annually and to allow the reissuance thereunder of awards and grants that expire or are canceled, terminated,

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forfeited or fail to vest under the 2007 Plan and the 2010 Plan. The stock options for new hires generally vest 25% after 12 months, followed by ratable vesting over 36 months and expire 10 years from the grant date.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option-pricing model that uses the assumptions noted in the table below. Expected volatility for the Company s common stock was determined based on an average of the historical volatility of a peer group of similar companies. The Company has limited stock option exercise information, as such; the expected term of stock options granted was calculated using the simplified method, which represents the average of the contractual term of the stock option and the weighted-average vesting period of the stock option. The assumed dividend yield is based upon the Company s expectation of not paying dividends in the foreseeable future. The risk-free rate for periods within the expected life of the stock option is based upon the U.S. Treasury yield curve in effect at the time of grant.

The assumptions used in the Black-Scholes option-pricing model for stock options granted during the years ended December 31, 2015, 2014 and 2013 are as follows:

	DECEMBER 31,					
	2015		2014		2013	
Expected option term (in years)	5.5	6.3	5.5	6.3		6.0
Expected volatility	67%	71%	64%	65%	64%	69%
Risk-free interest rate	1.5%	1.9%	1.7%	2.0%	1.2%	1.9%
Expected dividend yield		0.0%		0.0%		0.0%

The weighted-average grant date fair value of stock options granted during the years ended December 31, 2015, 2014 and 2013 was $9.67, $9.62, and $2.52 per share, respectively. As of December 31, 2015, there was $18.6 million of unrecognized compensation cost related to unvested employee stock options which are expected to be recognized over a weighted-average period of approximately 3 years. The intrinsic value of stock options exercised was $0.4 million, $3.2 million and $0 for the years ended December 31, 2015, 2014 and 2013, respectively. Cash received from stock option exercises for the year ended December 31, 2015 was $0.1 million.

On September 24, 2013, the Board of Directors approved the repricing of all of the then outstanding 24,811 stock options, with an original per-share weighted average exercise price of $45.16, to a new per-share exercise price of $3.42, which represented the current per-share fair market value. The repricing was treated by the Company as an exchange of the original awards for new awards. The incremental fair value of the modification, which was $30, was recognized in the statement of operations in 2013, representing the value of vested awards.

A summary of stock option activity for employee and non-employee awards under the Plan are presented below:

	NUMBER OF OPTIONS	WEIGHTED-AVERAGE PRICE PER SHARE	WEIGHTED-AVERAGE REMAINING CONTRACTUAL TERM (YEARS)
OUTSTANDING January 1, 2015	3,604,713	$ 11.28	9.1
Granted	1,160,626	15.39	

Exercised	(29,506)		4.98	
Forfeited/Canceled	(336,408)		13.46	
OUTSTANDING December 31, 2015	4,399,425		12.24	8.1
EXERCISABLE December 31, 2015	2,058,772		11.05	7.5
Vested and expected to vest as of December 31, 2015	4,281,737	$	12.22	8.1

Under the Company s 2014 stock option plans, the Company has reserved 429,821 shares of common stock for future issuance at December 31, 2015.

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Stock options granted to non-employees

In September 2013, the Company granted stock options to purchase 132,500 shares of common stock to non-employees with an initial fair value of $0.3 million. These options vest ratably over forty-eight months from the initial vesting date of July 30, 2013. Based on the terms of the non-employee stock option agreements, the Company recorded stock-based compensation expense of $0.2 million, $1.9 million and $0 during the years ended December 31, 2015, 2014 and 2013, respectively. The assumptions used to estimate fair value were as follows:

	DECEMBER 31,				
	2015		2014		2013
Stock price	$ 8.21	$24.43	$ 9.37	$41.12	$ 7.42
Expected option term (in years)	4.37	5.29	0.25	6.86	7.0
Expected volatility	66%	73%	56%	68%	66%
Risk-free interest rate	1.2%	1.6%	0.1%	2.3%	2.8%
Expected dividend yield	0.0%		0.0%		0.0%

As of December 31, 2015, there were 26,250 unvested stock options held by non-employees. The remaining unrecognized compensation cost related to unvested non-employee stock options is dependent on the valuation inputs used on each re-measurement date and will be recognized over a weighted-average period of thirty months.

Restricted common stock

During 2014, the Company issued a total of 44,000 shares of the Company s restricted common stock, of which 4,000 were fully-vested at grant date. The fair value of these shares were $0.7 million at the grant date.

As of December 31, 2015 and 2014 the unrecognized compensation cost related to restricted common stock was $0.4 million and $0.5 million, respectively. The total fair value of restricted stock awards that vested during the years ended December 31, 2015, 2014 and 2013 (measured on the date of vesting) was $0.2 million, $0.1 million and $0.

A summary of the Company s restricted common stock is presented below:

	SHARES	WEIGHTED-AVERAGE GRANT DATE FAIR VALUE PER SHARE
Nonvested January 1, 2014		$
Issued	44,000	16.30
Vested	(4,000)	14.34
Nonvested December 31, 2014	40,000	16.30
Issued		
Vested	(10,000)	16.30

Nonvested	December 31, 2015	30,000	$	16.30

Stock-based compensation expense is classified in the statements of operations as follows:

	YEAR ENDED DECEMBER 31,		
	2015	2014	2013
Research and development	$ 4,202	$ 4,183	$ 124
General and administrative	5,530	4,054	371
Total	$ 9,732	$ 8,237	$ 495

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13. Fair Value Measurements

Fair value is an exit price, representing the amount that would be received from the sale of an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. Valuation techniques used to measure fair value are performed in a manner to maximize the use of observable inputs and minimize the use of unobservable inputs. As a basis for considering such assumption the accounting literature establishes a three-tier value hierarchy which prioritizes the inputs used in measuring fair value as follows: (Level 1) observable inputs, such as quoted prices in active markets; (Level 2) inputs other than the quoted prices in active markets that are observable either directly or indirectly; and (Level 3) unobservable inputs for which there is little or no market data, which requires the Company to develop its own assumptions.

A summary of the Company s assets that are measured or disclosed at fair value on a recurring basis as of December 31, 2015 and 2014 are presented below:

Description	At December 31, 2015	(Level 1)	(Level 2)	(Level 3)
Cash equivalents				
Money market fund	$ 45,557	$ 45,557	$	$
Held-to-maturity investments				
U.S. treasury securities	38,504		38,504	
Assets held in restriction				
Money market fund	1,116		1,116	
Total	$ 85,177	$ 45,557	$ 39,620	$

Description	At December 31, 2014	(Level 1)	(Level 2)	(Level 3)
Cash equivalents				
Money market fund	$ 20,425	$ 20,425	$	$
Held-to-maturity investments				
U.S. treasury securities and government agency bonds	72,532		72,532	
Assets held in restriction				
Money market fund and certificate of deposit	1,380		1,380	
Total	$ 94,337	$ 20,425	$ 73,912	$

The Company s cash equivalents, primarily money market accounts are classified within Level 1 of the fair value hierarchy because they are valued using quoted prices as of December 31, 2015 and 2014, respectively.

The Company s assets held in restriction bore interest at the prevailing market rates for instruments with similar characteristics and, accordingly, the carrying value of these instruments also approximated their fair value and the financial instruments were classified within Level 2 of the fair value hierarchy because the inputs to the fair value

measurement are valued using observable inputs as of December 31, 2015 and 2014, respectively.

The Company s held-to-maturity investments bore interest at the prevailing market rates for instruments with similar characteristics. The financial instruments were classified within Level 2 of the fair value hierarchy because the inputs to the fair value measurement are valued using observable inputs as of December 31, 2015 and 2014, respectively.

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For the years ended December 31, 2015 and 2014, there were no transfers between Level 1 and Level 2.

The fair value of the preferred stock warrant liability was determined using the Black-Scholes option-pricing model until the IPO conversion date of February 4, 2014. After the closing of the IPO, the remaining preferred stock warrant liability was no longer subject to re-measurement as the warrants to purchase the Company s preferred stock became warrants to purchase shares of the Company s common stock. As of the IPO closing date, the fair value of the preferred stock warrants was based significantly on the fair value of the Company s publicly traded common stock and other observable inputs and was reclassified to Level 2.

The fair value of the preferred stock warrant prior to the closing of the IPO was based significantly on the fair value of the preferred stock, which was developed using unobservable inputs, and was classified within Level 3. The following table provides a roll-forward of the Company s liabilities measured at fair value on a recurring basis using unobservable inputs (Level 3):

BALANCE January 1, 2013	331
Issuance of preferred stock warrants	324
Change in fair value of warrant liability	(126)
BALANCE December 31, 2013	529
Change in fair value of warrant liability	2,559
Transfers to Level 2	(3,088)
BALANCE December 31, 2014	$

There were no preferred stock warrants outstanding as of December 31, 2015 and 2014, respectively.

14. Income Taxes

The Company has no current and no deferred income tax expense for the year ended December 31, 2015, and $0.1 million of current and no deferred income tax expense for 2014. The Company did not record a federal income tax provision or benefit for the year ended December 31, 2015 and 2014, respectively.

The reconciliation between income taxes computed at the federal statutory income tax rate and the provision for (benefit from) income taxes is as follows:

	YEARS ENDED DECEMBER 31,		
	2015	2014	2013
Federal statutory rate	34.0%	34.0%	34.0%
Effect of:			
Impact of foreign rate differential	(12.6)		
Change in valuation allowance	(24.4)	(32.0)	(35.4)
Research and development tax credit	0.9	0.8	2.5
Stock-based compensation	(0.9)	(2.6)	(1.3)
Other	3.0	(0.2)	0.2

Total	0.0%	0.0%	0.0%

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The components of the deferred tax assets are as follows:

	As of December 31, 2015	2014
Deferred tax assets:		
Net operating loss carryforwards	$ 37,017	$ 41,846
Capitalized research and development costs	2,431	2,646
Research and development credit carryforwards	3,510	2,360
Stock compensation	5,369	2,479
Depreciation and other costs	(74)	372
Net deferred tax assets	48,253	49,703
Valuation allowance	(48,253)	(49,703)
Net deferred tax assets	$	$

Management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its net deferred tax assets and determined that it is more likely than not that the Company will not recognize the benefits of the net deferred tax assets. As a result, the Company has a valuation allowance at December 31, 2015 and 2014. The valuation allowance increased in 2014 and decreased in 2015 by $18.7 million and $1.4 million, primarily due to the increase in the Company s net operating loss carryforwards, capitalized costs and stock compensation for 2014 and a decrease in 2015 as a result of prior year losses utilized to offset an intercompany gain. As of December 31, 2015, the Company has approximately $92.5 million of federal and $77.6 million of state net operating loss carryforwards, and $2.1 million of federal and $1.4 million of Massachusetts tax credits that expire starting in 2028.

Realization of the future tax benefits is dependent on many factors, including the Company s ability to generate taxable income within the net operating loss carryforward period. Under the provisions of the Internal Revenue Code, certain substantial changes in the Company s ownership, including a sale of the Company or significant changes in ownership due to sales of equity, may have limited, or may limit in the future, the amount of net operating loss carryforwards, which could be used annually to offset future taxable income.

As of December 31, 2015, the Company had $1.4 million of unrecognized tax benefits, of which $1.4 million would affect income tax expense if recognized, before consideration of the Company s valuation allowance. The Company does not expect the unrecognized tax benefits to change significantly over the next 12 months. The Company recognizes both interest and penalties associated with uncertain tax positions as a component of income tax expense. As of December 31, 2015 and 2014, the Company has not accrued any penalties or made provisions for interest.

A reconciliation of the gross unrecognized tax benefit is as follows (in thousands):

	Year Ended December 31, 2015	2014
Unrecognized tax benefits at the beginning of the period	$ 1,216	$ 865
Additions for current tax positions	421	220

Changes for previous tax positions	(207)	131
Unrecognized tax benefits at the end of the period	$ 1,430	$ 1,216

The Company files income tax returns in the United States and Commonwealth of Massachusetts. The tax years 2007 through 2015 remain open to examination by these jurisdictions, as carryforward attributes generated in past years may be adjusted in a future period. The Company is not currently under examination by the Internal

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Revenue Service or any other jurisdiction for these years. The Company has not recorded any interest or penalties for unrecognized tax benefits since its inception.

In December 2014, the Company licensed all of its non-U.S. intellectual property rights to a non-U.S. wholly-owned subsidiary and, in December 2015, the Company licensed its U.S. intellectual property rights to the same wholly-owned subsidiary. For financial reporting purposes 2015 loss before provision for income taxes includes foreign losses of $23.0 million.

15. Commitments and Contingencies

Facility lease

On July 11, 2014, the Company executed a non-cancelable operating lease for office and laboratory space in Cambridge, Massachusetts. The lease agreement obligates the Company to future minimum payments totaling $9.5 million over a six-year lease term. Rent expense is recorded on the straight-line basis and, therefore, the Company had a deferred rent obligation in the amount of $4 and $10 as of December 31, 2015 and 2014, respectively. The lease commenced on December 1, 2014. As part of the lease agreement, the Company established a $1.1 million letter of credit, secured by a restricted money market account which was included in assets held in restriction at December 31, 2015 and 2014.

On April 9, 2015, the Company terminated its lease and sub-lease at 480 Arsenal Street in Watertown. The transactions did not have a material impact on the Company s financial statements. The associated letter of credit was cancelled by the bank during the second quarter of 2015, and a $0.3 million certificate of deposit that secured the letter of credit was redeemed and transferred to cash and cash equivalents.

Rent expense was $1.7 million, $0.7 million and $0.9 million for the years ended December 31, 2015, 2014 and 2013, respectively.

Under the current lease agreement, future minimum payments payable are approximately as follows:

PERIOD ENDING DECEMBER 31	OPERATING LEASES
2016	$ 1,536
2017	1,582
2018	1,629
2019	1,678
2020	1,581
Total	$ 8,006

City of Hope license agreement

In September 2007, the Company entered into a license agreement with City of Hope, an independent academic research and medical center (the Medical Center). In consideration for the right to develop, manufacture, and commercialize products based on certain of the Medical Center s intellectual property, the Company paid a one-time, non-refundable license fee and issued shares of common stock as consideration for the license.

The Company is required to pay an annual license maintenance fee, reimburse the Medical Center for patent costs incurred, and pay an amount within the range of $5.0 million to $10.0 million upon the achievement of certain milestones, and royalties on future sales, if any. There were no sublicense and other fees accrued at December 31, 2015, and 2014. The license agreement will remain in effect until the expiration of the last patents or copyrights licensed under the agreement or until all obligations under the agreement with respect to payment of milestones have terminated or expired. The Company may terminate the license agreement at any time upon

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90 days written notice to the Medical Center. The Company recorded research and development expense, related to the agreement with the Medical Center, of $0.1 million, $0.1 million and $0.5 million in 2015, 2014 and 2013, respectively.

Plant Bioscience Limited license agreement

In September 2013, the Company entered into a commercial license agreement with Plant Bioscience Limited (PBL), pursuant to which PBL has granted to the Company a license to certain of its U.S. patents and patent applications to research, discover, develop, manufacture, sell, import and export, products incorporating one or more short RNA molecules (SRMs).

The Company has paid PBL a one-time, non-refundable signature fee and will pay PBL a nomination fee for any additional SRMs nominated by the Company under the agreement. The Company is further obligated to pay PBL milestone payments upon achievement of certain clinical and regulatory milestones. During 2014, the Company paid $0.1 million to PBL based on meeting a clinical milestone. In addition, PBL is entitled to receive royalties of any net sales revenue of any licensed product candidates sold by the Company. Research and development expense related to this agreement was $0, $0.1 million and $0.1 million in 2015, 2014 and 2013, respectively.

Arbutus Biopharma Corporation license agreement

In November 2014, the Company signed a licensing and collaboration agreement with Arbutus to license Arbutus LNP delivery technology for exclusive use in the Company s primary hyperoxaluria type 1 (PH1) development program. The Company will use Arbutus LNP technology to deliver DCR-PH1, for the treatment of PH1. As of December 31, 2015, the Company paid $3.0 million in cumulative license fees. Arbutus is entitled to receive additional payments of $22.0 million in aggregate development milestones, plus a mid-single-digit royalty on future PH1 sales. This new partnership also includes a supply agreement with Arbutus providing clinical drug supply and regulatory support.

16. Litigation

On June 10, 2015, Alnylam Pharmaceuticals, Inc. (Alnylam) filed a complaint against the Company in the Superior Court of Middlesex County, Massachusetts. The complaint alleges misappropriation of confidential, proprietary, and trade secret information, as well as other related claims, in connection with the Company s hiring of a number of former employees of Merck & Co., Inc. (Merck) and its discussions with Merck regarding the acquisition of its subsidiary, Sirna Therapeutics, Inc. (Sirna), which was subsequently acquired by Alnylam. The complaint seeks among other things, unspecified damages, attorneys fees, and an order permanently enjoining the Company from disclosing or using any of Alnylam s confidential information or trade secrets.

The Company believes that these allegations lack merit, has filed an answer denying all liability and intends to continue to vigorously defend all claims asserted. At this time, the Company has not recorded a liability in connection with these matters because it believes that any potential loss is neither probable nor reasonably estimable.

From time to time, the Company may be subject to various claims and legal proceedings. If the potential loss from any claim, asserted or unasserted, or legal proceeding is considered probable and the amount is reasonably estimable, the Company will accrue a liability for the estimated loss. There were no litigation liabilities outstanding as of December 31, 2015 and December 31, 2014.

17. Employee Benefit Plan

The Company has a 401(k) retirement plan in which substantially all employees are eligible to participate. Eligible employees may elect to contribute up to the maximum limits, as set by the Internal Revenue Service, of their eligible compensation. The Company made discretionary plan contributions of $0.4 million, $0.2 million and $0.1 million in 2015, 2014 and 2013, respectively.

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18. Quarterly Financial Data (Unaudited)

	FIRST QUARTER	SECOND QUARTER	THIRD QUARTER	FOURTH QUARTER	TOTAL YEAR
2015					
Revenue	$	$ 184	$	$	$ 184
Net loss	(14,084)	(16,176)	(16,944)	(15,635)	(62,839)
Net loss attributable to common stockholders	(14,084)	(16,176)	(16,944)	(15,635)	(62,839)
Net loss per share attributable to common stockholders basic and diluted	$ (0.79)	$ (0.86)	$ (0.82)	$ (0.76)	$ (3.09)

	FIRST QUARTER	SECOND QUARTER	THIRD QUARTER	FOURTH QUARTER	TOTAL YEAR
2014					
Revenue	$	$	$	$	$
Net loss	(10,804)	(11,355)	(11,193)	(14,587)	(47,939)
Net loss attributable to common stockholders	(11,008)	(11,355)	(11,193)	(14,587)	(48,143)
Net loss per share attributable to common stockholders basic and diluted	$ (1.02)	$ (0.64)	$ (0.63)	$ (0.82)	$ (3.00)

Full year amounts may not sum due to rounding.

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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 ensure that information required to be disclosed in our periodic and current reports that we file under the Securities Exchange Act of 1934, as amended (Exchange Act), with the Securities and Exchange Commission (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 chief executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

As of the end of the period covered by this Annual Report on Form 10-K, we carried out an evaluation, under the supervision and with the participation of our management, including the chief executive officer and the chief financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures pursuant to Exchange Act Rule 13a-15. Based upon, and as of the date of, this evaluation, the chief executive officer and the chief financial officer concluded that our disclosure controls and procedures were effective. Accordingly, management believes that the financial statements included in this report fairly present in all material respects our financial condition, results of operations and cash flows for the periods presented.

Management s Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act). Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31,

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2015 based on the guidelines established in Internal Control Integrated Framework 2013 issued by the Committee of Sponsoring Organizations of the Treadway Commission. Our internal control over financial reporting includes policies and procedures that provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

Based on that evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2015.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm as we are an emerging growth company as of December 31, 2015, as defined in the Jumpstart Our Business Startups Act of 2012.

Changes in Internal Control Over Financial Reporting

We continuously seek to improve the efficiency and effectiveness of our internal controls. This results in refinements to processes throughout the Company. There was no change in our internal control over financial reporting during the quarter ended December 31, 2015, which was identified in connection with our management s evaluation required by Exchange Act Rules 13a-15(f) and 15d-15(f) that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations on the Effectiveness of Controls

Our management, including the chief executive officer and chief financial officer, does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all error and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the company have been detected. These inherent limitations include the realities that judgments in decision making can be faulty and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by management override of the control. 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 the 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.

Item 9B. ***Other Information***

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 definitive proxy statement for our 2016 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission (SEC) pursuant to Regulation 14A (Proxy Statement) not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, and is incorporated herein by reference.

Information regarding our audit committee financial expert will be set forth in the Proxy Statement and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics applicable to all employees, including the principal executive officer, principal financial officer and principal accounting officer or controller, or persons performing similar functions. The Code of Business Conduct and Ethics is posted on our website at *www.dicerna.com*. Amendments to, and waivers from, the Code of Business Conduct and Ethics that apply to any of these officers, or persons performing similar functions, and that relate to any element of the code of ethics definition enumerated in Item 406(b) of Regulation S-K will be disclosed at the website address provided above and, to the extent required by applicable regulations, on a current report on Form 8-K.

Item 11. ***Executive Compensation***

The information required by this item will be set forth in the 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 in the 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 Proxy Statement and is incorporated herein by reference.

Item 14. ***Principal Accountant Fees and Services***

The information required by this item will be set forth in the Proxy Statement and is incorporated herein by reference.

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PART IV

Item 15. *Exhibits and Financial Statement Schedules*

(1) *Consolidated Financial Statements:*

The following consolidated financial statements are filed as part of this Annual Report on Form 10-K under Item 8 Financial Statements and Supplementary Data.

(2) *Financial Statement Schedules:* None

(3) *Exhibits.*

Except as so indicated in Exhibit 32.1, the following exhibits are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K.

Exhibit Number	Description of Documents
3.1(1)	Amended and Restated Certificate of Incorporation of the Company.
3.2(1)	Amended and Restated Bylaws of the Company.
4.1(2)	Specimen Common Stock Certificate.
4.2(3)	Form of Warrant to Purchase Common Stock.
4.3(3)	Form of Warrant to Purchase Preferred Stock.
4.4(3)	Amended and Restated Registration Rights Agreement dated as of July 30, 2013, by and among the Company and the investors named therein.
10.1(3)	2007 Employee, Director and Consultant Stock Plan, as amended (the 2007 Plan).++
10.2(3)	Form of Restricted Stock Agreement under the 2007 Plan.++

10.3(3)	Form of Incentive Stock Option Agreement under the 2007 Plan.++
10.4(3)	Form of Non-Qualified Stock Option Agreement under the 2007 Plan.++
10.5(3)	2010 Employee, Director and Consultant Equity Incentive Plan, as amended (the 2010 Plan).++
10.6(3)	Form of Stock Option Grant Notice and Stock Option Agreement under the 2010 Plan.++
10.7(3)	Form of Restricted Stock Agreement under the 2010 Plan.++
10.8(2)	2014 Employee Stock Purchase Plan.++
10.9(2)	Form of Indemnification Agreement by and between the Company and each of its directors.++
10.10(3)	Employment Agreement dated as of May 6, 2010, by and between the Company and Douglas M. Fambrough, III, Ph.D.++

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10.11(3)	Employment Agreement dated as of May 1, 2008, by and between the Company and Bob D. Brown, Ph.D.++
10.12(3)	Employment Agreement dated as of December 5, 2011, by and between the Company and James B. Weissman.++
10.13(3)	Letter agreement dated as of June 2, 2009, by and between the Company and David M. Madden.++
10.14(3)	Letter agreement dated as of February 28, 2011, by and between the Company and Dennis H. Langer M.D., J.D.++
10.15(3)	Transition Agreement dated as of September 8, 2009, as amended by Amendment to Transition Agreement dated as of February 1, 2010 and Second Amendment to the Transition Agreement dated as of July 29, 2013, by and between the Company and James C. Jenson, Ph.D.++
10.16(4)	Employment agreement dated as of November 24, 2013, by and between the Company and James E. Dentzer.++
10.17(2)	Loan and Security Agreement dated as of March 25, 2009, as amended by Amendment No. 1 to Loan and Security Agreement dated as of May 28, 2010, and Second Amendment to Loan and Security Agreement dated as of June 28, 2011, by and between the Company and Hercules Technology II, L.P.
10.18(5)	Research Collaboration and License Agreement dated as of December 21, 2009, as amended by Amendment No. 1 to Research Collaboration and License Agreement dated as of December 2, 2010, by and between the Company and Kyowa Hakko Kirin Co., Ltd.
10.19(2)	Exclusive License Agreement dated as of September 28, 2007, by and between the Company and City of Hope.
10.20(2)	Commercial License Agreement dated as of September 2, 2013, by and between the Company and Plant Bioscience Limited.
10.21(2)	Lease Agreement dated as of March 14, 2008, as amended by First Amendment to Lease dated as of September 12, 2008 and Second Amendment to Lease dated as of July 3, 2013, by and between the Company and ARE-480 Arsenal Street, LLC.
10.22(2)	Letter agreement dated as of January 24, 2014, by and between the Company and James E. Dentzer.++
10.23(6)	Lease agreement dated as of July 11, 2014, by and between the Company and King 87 CPD LLC
10.24(7)	Employment Agreement dated as of March 7, 2014, by and between the Company and Pankaj Bhargava, M.D.++
10.25(7)	Letter Agreement dated as of September 12, 2014, by and between the Company and Bruce Peacock.++
10.26(7)	Employment Agreement dated as of November 22, 2014, by and between the Company and Theodore Ashburn, M.D., Ph.D.++
10.27(7)	License Agreement dated as of November 16, 2014 by and between the Company, on one hand, and Protiva Biotherapeutics Inc. and Tekmira Pharmaceuticals Corporation, on the other hand.
10.28(7)	Development and Supply Agreement dated as of November 16, 2014 by and between Protiva Biotherapeutics Inc. and Tekmira Pharmaceuticals Corporation, on one hand, and the Company, on the other hand.
10.29(8)	

	Underwriting Agreement dated as of May 20, 2015 by and between the Company, Jeffries LLC and Leerink Partners LLC.
10.30(9)	Amended and Restated 2014 Performance Incentive Plan.++
10.31(10)	Form of Incentive Stock Option Agreement under the Amended and Restated 2014 Performance Incentive Plan.++

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10.32(10)	Form of Non-Qualified Stock Option Agreement under the Amended and Restated 2014 Performance Incentive Plan.++
10.33(10)	Separation Agreement dated as of December 15, 2015 by and between the Company and James E. Dentzer.++
10.34(10)	Offer Letter dated as of January 14, 2016 by and between the Company and John Jack Green.++
21.1(7)	Subsidiaries of the Company.
23.1(10)	Consent of Independent Registered Accounting Firm.
24	Power of Attorney (reference is made to the signature page).
31.1(10)	Certification of the Company s principal executive officer required by Rule 13a-14(a) or Rule 15d-14(a).
31.2(10)	Certification of the Company s principal financial officer required by Rule 13a-14(a) or Rule 15d-14(a).
32.1*	Section 1350 Certifications.
101.INS(10)	XBRL Report Instance Document
101.SCH(10)	XBRL Taxonomy Extension Schema Document
101.CAL(10)	XBRL Taxonomy Calculation Linkbase Document
101.LAB(10)	XBRL Taxonomy Label Linkbase Document
101.PRE(10)	XBRL Taxonomy Presentation Linkbase Document
101.DEF(10)	XBRL Taxonomy Extension Definition Linkbase Document

Confidential treatment with respect to specific portions of this Exhibit has been requested, and such portions are omitted and have been filed separately with the Securities and Exchange Commission.

++ Management contract or compensatory plan or arrangement.

* Exhibit 32.1 is being furnished and shall not be deemed to be filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (Exchange Act), or otherwise subject to the liability of that section, nor shall such exhibit be deemed to be incorporated by reference in any registration statement or other document filed under the Securities Act of 1933, as amended, or the Exchange Act, except as otherwise stated in such filing.

(1) Incorporated by reference to the indicated exhibit in the Company s Current Report on Form 8-K filed on February 5, 2014.

(2) Incorporated by reference to the indicated exhibit in the Company s Amendment No. 3 to Registration Statement on Form S-1 (No. 333-193150) filed on January 28, 2014.

(3) Incorporated by reference to the indicated exhibit in the Company s Registration Statement on Form S-1 (No. 333-193150) filed on December 31, 2013.

(4) Incorporated by reference to the indicated exhibit in the Company s Amendment No. 1 to Registration Statement on Form S-1 (No. 333-193150) filed on January 17, 2014.

(5) Incorporated by reference to the indicated exhibit in the Company s Amendment No. 5 to Registration Statement on Form S-1 (No. 333-193150) filed on January 29, 2014.

(6) Incorporated by reference to the indicated exhibit in the Company s Registrant s Quarterly Report on Form 10-Q filed on November 6, 2014 (File No. 001-36281) for the quarterly period ended September 30, 2014.

(7)

Incorporated by reference to the indicated exhibit in the Company s Annual Report on Form 10-K filed on March 12, 2015 (File No. 001-36281) for the annual period ended December 31, 2014.

(8) Incorporated by reference to the indicated exhibit in the Company s Current Report on Form 8-K filed on May 22, 2015.

(9) Incorporated by reference to the indicated exhibit in the Company s Current Report on Form 8-K filed on July 7, 2015.

(10) Filed herewith.

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SIGNATURES

Pursuant to 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, in Cambridge, Commonwealth of Massachusetts on March 10, 2016.

By: /s/ Douglas M. Fambrough, III
Douglas M. Fambrough, III, Ph.D.

Chief Executive Officer and Director (Principal Executive Officer)

By: /s/ John B. Green, CPA
John B. Green, CPA

Interim Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)

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POWER OF ATTORNEY

KNOW ALL PERSON BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Douglas M. Fambrough, III, Ph.D. and John B. Green and each of them, as his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K and to file the same, with all 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 connection therewith, as fully to all intents and purposes as he might or could do in person, hereby ratify and confirming all that said attorneys-in-fact and agents, or any of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed by the following persons in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Douglas M. Fambrough, III	Chief Executive Officer and Director	March 10, 2016
Douglas M. Fambrough, III, Ph.D.	(Principal Executive Officer)	
/s/ John B. Green, CPA	Chief Financial Officer	March 10, 2016
John B. Green, CPA	(Principal Financial Officer and Principal Accounting Officer)	
/s/ David M. Madden	Chairman	March 10, 2016
David M. Madden		
/s/ Brian K. Halak	Director	March 10, 2016
Brian K. Halak, Ph.D.		
/s/ Stephen J. Hoffman	Director	March 10, 2016
Stephen J. Hoffman, M.D., Ph.D.		
/s/ Peter Kolchinsky	Director	March 10, 2016
Peter Kolchinsky, Ph.D.		
/s/ Dennis H. Langer	Director	March 10, 2016
Dennis H. Langer, M.D., J.D.		

/s/ Bruce Peacock	Director	March 10, 2016

Bruce Peacock

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Except as so indicated in Exhibit 32.1, the following exhibits are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K.

Exhibit Number	Description of Documents
3.1(1)	Amended and Restated Certificate of Incorporation of the Company.
3.2(1)	Amended and Restated Bylaws of the Company.
4.1(2)	Specimen Common Stock Certificate.
4.2(3)	Form of Warrant to Purchase Common Stock.
4.3(3)	Form of Warrant to Purchase Preferred Stock.
4.4(3)	Amended and Restated Registration Rights Agreement dated as of July 30, 2013, by and among the Company and the investors named therein.
10.1(3)	2007 Employee, Director and Consultant Stock Plan, as amended (the 2007 Plan).++
10.2(3)	Form of Restricted Stock Agreement under the 2007 Plan.++
10.3(3)	Form of Incentive Stock Option Agreement under the 2007 Plan.++
10.4(3)	Form of Non-Qualified Stock Option Agreement under the 2007 Plan.++
10.5(3)	2010 Employee, Director and Consultant Equity Incentive Plan, as amended (the 2010 Plan).++
10.6(3)	Form of Stock Option Grant Notice and Stock Option Agreement under the 2010 Plan.++
10.7(3)	Form of Restricted Stock Agreement under the 2010 Plan.++
10.8(2)	2014 Employee Stock Purchase Plan.++
10.9(2)	Form of Indemnification Agreement by and between the Company and each of its directors.++
10.10(3)	Employment Agreement dated as of May 6, 2010, by and between the Company and Douglas M. Fambrough, III, Ph.D.++
10.11(3)	Employment Agreement dated as of May 1, 2008, by and between the Company and Bob D. Brown, Ph.D.++
10.12(3)	Employment Agreement dated as of December 5, 2011, by and between the Company and James B. Weissman.++
10.13(3)	Letter agreement dated as of June 2, 2009, by and between the Company and David M. Madden.++
10.14(3)	Letter agreement dated as of February 28, 2011, by and between the Company and Dennis H. Langer M.D., J.D.++
10.15(3)	Transition Agreement dated as of September 8, 2009, as amended by Amendment to Transition Agreement dated as of February 1, 2010 and Second Amendment to the Transition Agreement dated as of July 29, 2013, by and between the Company and James C. Jenson, Ph.D.++
10.16(4)	Employment agreement dated as of November 24, 2013, by and between the Company and James E.

	Dentzer.++
10.17(2)	Loan and Security Agreement dated as of March 25, 2009, as amended by Amendment No. 1 to Loan and Security Agreement dated as of May 28, 2010, and Second Amendment to Loan and Security Agreement dated as of June 28, 2011, by and between the Company and Hercules Technology II, L.P.

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10.18(5)	Research Collaboration and License Agreement dated as of December 21, 2009, as amended by Amendment No. 1 to Research Collaboration and License Agreement dated as of December 2, 2010, by and between the Company and Kyowa Hakko Kirin Co., Ltd.
10.19(2)	Exclusive License Agreement dated as of September 28, 2007, by and between the Company and City of Hope.
10.20(2)	Commercial License Agreement dated as of September 2, 2013, by and between the Company and Plant Bioscience Limited.
10.21(2)	Lease Agreement dated as of March 14, 2008, as amended by First Amendment to Lease dated as of September 12, 2008 and Second Amendment to Lease dated as of July 3, 2013, by and between the Company and ARE-480 Arsenal Street, LLC.
10.22(2)	Letter agreement dated as of January 24, 2014, by and between the Company and James E. Dentzer.++
10.23(6)	Lease agreement dated as of July 11, 2014, by and between the Company and King 87 CPD LLC
10.24(7)	Employment Agreement dated as of March 7, 2014, by and between the Company and Pankaj Bhargava, M.D.++
10.25(7)	Letter Agreement dated as of September 12, 2014, by and between the Company and Bruce Peacock.++
10.26(7)	Employment Agreement dated as of November 22, 2014, by and between the Company and Theodore Ashburn, M.D., Ph.D.++
10.27(7)	License Agreement dated as of November 16, 2014 by and between the Company, on one hand, and Protiva Biotherapeutics Inc. and Tekmira Pharmaceuticals Corporation, on the other hand.
10.28(7)	Development and Supply Agreement dated as of November 16, 2014 by and between Protiva Biotherapeutics Inc. and Tekmira Pharmaceuticals Corporation, on one hand, and the Company, on the other hand.
10.29(8)	Underwriting Agreement dated as of May 20, 2015 by and between the Company, Jefferies LLC and Leerink Partners LLC.
10.30(9)	Amended and Restated 2014 Performance Incentive Plan.++
10.31(10)	Form of Incentive Stock Option Agreement under the Amended and Restated 2014 Performance Incentive Plan.++
10.32(10)	Form of Non-Qualified Stock Option Agreement under the Amended and Restated 2014 Performance Incentive Plan.++
10.33(10)	Separation Agreement dated as of December 15, 2015 by and between the Company and James E. Dentzer.++
10.34(10)	Offer Letter dated as of January 14, 2016 by and between the Company and John Jack Green.++
21.1(7)	Subsidiaries of the Company.
23.1(10)	Consent of Independent Registered Accounting Firm.
24	Power of Attorney (reference is made to the signature page).
31.1(10)	

	Certification of the Company s principal executive officer required by Rule 13a-14(a) or Rule 15d-14(a).
31.2(10)	Certification of the Company s principal financial officer required by Rule 13a-14(a) or Rule 15d-14(a).
32.1*	Section 1350 Certifications.
101.INS(10)	XBRL Report Instance Document
101.SCH(10)	XBRL Taxonomy Extension Schema Document

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101.CAL(10)	XBRL Taxonomy Calculation Linkbase Document
101.LAB(10)	XBRL Taxonomy Label Linkbase Document
101.PRE(10)	XBRL Taxonomy Presentation Linkbase Document
101.DEF(10)	XBRL Taxonomy Extension Definition Linkbase Document

Confidential treatment with respect to specific portions of this Exhibit has been requested, and such portions are omitted and have been filed separately with the Securities and Exchange Commission.

++ Management contract or compensatory plan or arrangement.

* Exhibit 32.1 is being furnished and shall not be deemed to be filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (Exchange Act), or otherwise subject to the liability of that section, nor shall such exhibit be deemed to be incorporated by reference in any registration statement or other document filed under the Securities Act of 1933, as amended, or the Exchange Act, except as otherwise stated in such filing.

(1) Incorporated by reference to the indicated exhibit in the Company s Current Report on Form 8-K filed on February 5, 2014.

(2) Incorporated by reference to the indicated exhibit in the Company s Amendment No. 3 to Registration Statement on Form S-1 (No. 333-193150) filed on January 28, 2014.

(3) Incorporated by reference to the indicated exhibit in the Company s Registration Statement on Form S-1 (No. 333-193150) filed on December 31, 2013.

(4) Incorporated by reference to the indicated exhibit in the Company s Amendment No. 1 to Registration Statement on Form S-1 (No. 333-193150) filed on January 17, 2014.

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(6) Incorporated by reference to the indicated exhibit in the Company s Registrant s Quarterly Report on Form 10-Q filed on November 6, 2014 (File No. 001-36281) for the quarterly period ended September 30, 2014.

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(8) Incorporated by reference to the indicated exhibit in the Company s Current Report on Form 8-K filed on May 22, 2015.

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(10) Filed herewith.