

Dicerna Pharmaceuticals Inc  
Form 424B5  
December 15, 2017  
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**Filed Pursuant to Rule 424(b)(5)  
Registration No. 333-214082**

## **PROSPECTUS SUPPLEMENT**

(To prospectus dated October 31, 2016)

**5,714,286 Shares**

### **Common Stock**

We are offering 5,714,286 shares of our common stock. Our common stock is listed on The NASDAQ Global Select Market under the symbol DRNA. On December 14, 2017, the last reported sale price of our common stock on The NASDAQ Global Select Market was \$7.31 per share.

**Investing in our common stock involves a high degree of risk. Please read Risk Factors beginning on page S-12 of this prospectus supplement and in the other documents incorporated by reference into this prospectus supplement.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.**

|  | <b>PER<br/>SHARE</b> | <b>TOTAL</b>     |
|--|----------------------|------------------|
| Public Offering Price                      | \$ 7.00              | \$ 40,000,002.00 |
| Underwriting Discounts and Commissions (1) | \$ 0.42              | \$ 2,400,000.12  |
| Proceeds to Dicerna (Before Expenses)      | \$ 6.58              | \$ 37,600,001.88 |

- (1) The underwriters will also be reimbursed for certain expenses incurred in this offering. See Underwriting for details.

Delivery of the shares of common stock is expected to be made on or about December 18, 2017. We have granted the underwriters an option for a period of 30 days to purchase up to an additional 857,143 shares of our common stock. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$2,760,000.18 and the total proceeds to us, before expenses, will be \$43,240,002.82.

***Joint Book-Running Managers***

**Stifel**

**Evercore ISI**

***Co-Lead Managers***

**H.C. Wainwright & Co.**

**SunTrust Robinson Humphrey**

**Prospectus Supplement dated December 14, 2017**

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**ABOUT THIS PROSPECTUS SUPPLEMENT**

In this prospectus, the terms Dicerna, Company, we, us, our and similar terms refer to Dicerna Pharmaceuticals, Delaware corporation, and its subsidiaries unless the context otherwise requires.

This prospectus supplement and the accompanying base prospectus is part of a shelf registration statement on Form S-3 that we filed with the Securities and Exchange Commission ( SEC ).

We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering and also adds to and updates information contained in the accompanying base prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying base prospectus; and (2) the accompanying base prospectus, including the documents incorporated by reference therein, which provides general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying base prospectus, you should rely on this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in this prospectus the statement in the document having the later date modifies or supersedes the earlier statement as our business, financial condition, results of operations and prospects may have changed since the earlier dates.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and in any free writing prospectus that we may authorize for use in connection with this offering. We have not, and the underwriters have not, authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We and the underwriters are not making an offer to sell or soliciting an offer to buy our securities in any jurisdiction in which an offer or solicitation is not authorized or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus, the documents incorporated by reference into this prospectus, and in any free writing prospectus that we may authorize for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus, the documents incorporated by reference into this prospectus, and any free writing prospectus that we may authorize for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus entitled Where You Can Find More Information and Incorporation of Certain Documents by Reference.

Other than in the U.S., no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons outside the U.S. who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus outside the U.S. This prospectus does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus by any

person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

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This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference in this prospectus are the property of their respective owners.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been or will be filed as exhibits to the registration statement of which this prospectus is a part or as exhibits to documents incorporated by reference herein, and you may obtain copies of those documents as described below under the headings **Where You Can Find More Information** and **Incorporation of Certain Documents by Reference**.

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**PROSPECTUS SUPPLEMENT SUMMARY**

*This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in the securities covered by this prospectus. For a more complete understanding of Dicerna and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus, including the information incorporated by reference in this prospectus and the information included in any free writing prospectus that we have authorized for use in connection with this offering, including the information referred to under the heading *Risk Factors* in this prospectus supplement beginning on page S-12 and in the other periodic reports incorporated by reference herein.*

**Overview**

Dicerna is a biopharmaceutical company focused on the discovery and development of innovative subcutaneously delivered ribonucleic acid interference ( RNAi )-based pharmaceuticals using our GalXC RNAi platform for the treatment of diseases involving the liver, including rare diseases, chronic liver diseases, cardiovascular diseases and viral infectious diseases. Within these therapeutic areas, we believe our GalXC RNAi platform will allow us to build a broad pipeline of therapeutics with commercially attractive pharmaceutical properties, including a subcutaneous route of administration, infrequent dosing (e.g., dosing that is monthly or quarterly, and potentially even less frequent), high therapeutic index, and specificity to a single target gene.

All of our GalXC 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 ribonucleic acid ( mRNA ) of a target gene that contains sequences that are complementary to one strand of the therapeutic double-stranded ribonucleic acid ( RNA ) molecule. The Company's 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. These proprietary molecules are generally referred to as Dicer Substrate short-interfering RNAs ( DsiRNAs ). Our GalXC RNAi platform utilizes a particular Dicer Substrate structure configured for subcutaneous delivery to the liver. Due to the enzymatic nature of RNAi, a single GalXC molecule incorporated into the RNAi machinery can destroy hundreds or thousands of mRNAs from the targeted gene.

The GalXC RNAi platform supports Dicerna's long-term strategy to retain, subject to the evaluation of potential licensing opportunities as they may arise, a full or substantial ownership stake and to invest internally in diseases with focused patient populations, such as certain rare diseases. We see such diseases as representing opportunities that carry a relatively higher probability of success, with genetically and molecularly defined disease markers, high unmet need, a limited number of Centers of Excellence to facilitate reaching these patients, and the potential for more rapid clinical development programs. For more complex diseases with multiple gene dysfunctions and larger patient populations, we plan to pursue collaborations that can provide the enhanced scale, resources and commercial infrastructure required to maximize these prospects.

**Development Programs**

In choosing which development programs to advance, we apply scientific, clinical, and commercial criteria that we believe allow us to best leverage our GalXC RNAi platform and maximize value. The Company is focusing its efforts on three priority therapeutic programs that currently have a Clinical Trial Application ( CTA ) filed or are in Investigational New Drug Application ( IND )/CTA enabling studies and on a series of programs in the



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clinical candidate selection stage that may be elevated into IND/CTA enabling studies in the future, either on our own or in partnership with larger pharmaceutical companies. Our three priority programs are: DCR-PHXC for the treatment of primary hyperoxaluria ( PH ); a program against an undisclosed rare disease; and DCR-HBVS for the treatment of chronic hepatitis B virus ( HBV ) infection. Our programs in clinical candidate selection include a program for the treatment of hypercholesterolemia, for which DCR-PCSK9 has been selected as a provisional clinical candidate, and multiple programs targeting undisclosed targets in chronic liver diseases, cardiovascular diseases and additional rare diseases. On October 16, 2017, we announced that we had submitted a CTA for DCR-PHXC to the Medicines and Healthcare products Regulatory Agency ( MHRA ) in the United Kingdom ( UK ) and that we have dosed the first subjects in the study on December 6, 2017. We expect to file additional CTAs and/or INDs for our therapeutic programs in 2018 and 2019.

The table below sets forth the state of development of our various GalXC RNAi platform product candidates as of December 11, 2017.

Our current GalXC RNAi platform development programs are as follows:

**Primary Hyperoxaluria.** We are developing DCR-PHXC for the treatment of all types of PH. PH is a family of rare inborn errors of metabolism in which the liver produces excessive levels of oxalate, which in turn causes damage to the kidneys and to other tissues in the body. In preclinical models of PH, DCR-PHXC reduces oxalate production to near-normal levels, ameliorating the disease condition.

On October 16, 2017, we announced that we had submitted a CTA for DCR-PHXC to the MHRA in the UK and we have dosed the first subjects in the study on December 6, 2017. Our Phase 1 trial is a randomized, single-blind, placebo-controlled, single-ascending dose study, enrolling up to 25 healthy volunteer subjects and up to 16 patients with PH. The primary objective of the study is to evaluate the safety and tolerability of single doses of DCR-PHXC, with participants being enrolled into as many as five sequential cohorts of increasing doses. Patients with PH will be dosed after safety has been established at the same dose level in normal healthy volunteers. Secondary endpoints include the pharmacokinetics of DCR-PHXC and its pharmacodynamic effects on oxalate biomarkers in plasma and urine. We expect to have clinical proof-of-concept data in the second half of 2018. We also plan to

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submit additional CTAs in other European countries later this year and an investigational new drug application ( IND ) in the U.S. by the end of February 2018.

On July 15, 2017, in a series of presentations at the 12<sup>th</sup> International Workshop on Primary Hyperoxaluria for Professionals, Patients and Families in Tenerife, Spain ( 1<sup>st</sup> International Workshop ), we presented new preclinical data suggesting the potential utility of DCR-PHXC for treating all forms of PH. In particular, we presented research from animal models demonstrating how DCR-PHXC inhibits the lactate dehydrogenase A ( *LDHA* ) gene, which we have identified as potentially being an optimal therapeutic target in patients with PH. *LDHA* inhibition was shown in animal models to reduce oxalate to normal or near-normal levels in PH types 1, 2 and ethylene glycol-induced hyperoxaluria (a model for idiopathic PH).

*LDHA* reduction has a near-linear correlation with oxalate reduction and offers a minimal metabolic intervention. These benefits of *LDHA* inhibition may translate into consistent therapeutic activity even in the event of a missed dose. There are numerous case reports of *LDHA* deficiency naturally occurring in humans, with no reported adverse effects due to deficiency in the liver.

To facilitate DCR-PHXC development, we have completed our Primary HYperoxaluria Observational Study ( PHYOS ), an international, multicenter, observational study in patients with a genetically confirmed diagnosis of PH, type 1 ( PH1 ). PHYOS is collecting data on key biochemical parameters implicated in the pathogenesis of PH1. We hope to use the data to better understand the baseline PH1 disease state, which will help guide long-term drug development plans. At the 12<sup>th</sup> International Workshop, we reported interim data from the study 's 20 enrolled patients with a median age at screening of 21 years (range 12-61 years). The patients had been diagnosed at a median age of 7 years (range 1-59 years), and 14 patients (74%) had a medical history of renal stones. Over the six-month observation period, the variability (coefficient of variation) between 24-hour urine measurements of oxalate at different time points was 28%. These data will help our clinical team design future clinical studies using 24-hour urinary oxalate excretion as a surrogate marker for clinical benefit. We expect to publish data from PHYOS in 2018.

**An undisclosed rare disease involving the liver.** We are developing a GalXC-based therapeutic, targeting a liver-expressed gene involved in a serious rare disease. For competitive reasons, we have not yet publicly disclosed the target gene or disease. We have selected this target gene and disease based on criteria that include having a strong therapeutic hypothesis, a readily-identifiable patient population, the availability of a potentially predictive biomarker, high unmet medical need, favorable competitive positioning and what we believe is a rapid projected path to approval. The disease is a genetic disorder, where mutations in the disease gene lead to the production of an abnormal protein. The protein causes progressive liver damage and fibrosis, in some cases leading to cirrhosis and liver failure, and we believe that silencing of the disease gene will prevent production of the abnormal protein and thereby slow or stop progression of the liver fibrosis. Greater than 100,000 people in the US are believed to be homozygous for the mutation that causes the liver disease, and at least 10% of those people, and potentially a significantly higher fraction, are believed to have liver fibrotic disease as a consequence. We plan to seek a risk-sharing collaborative partner for the program before we file an IND application and/or CTA for this program, which we expect to be prepared to file in the second quarter of 2018.

**Chronic Hepatitis B Virus infection.** Current therapies for HBV rarely lead to a long-term immunological cure as measured by the clearance of HBV surface antigen ( HBsAg ) and sustained HBV deoxyribonucleic acid ( DNA ) suppression in patient plasma or blood. We have declared a GalXC RNAi platform-based

product candidate, DCR-HBVS, and are conducting formal non-clinical development studies. We expect to file an IND or a CTA approximately at the end of 2018. DCR-HBVS targets HBV messenger RNA. Based on preclinical studies, and only if we receive

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appropriate regulatory approval to begin human clinical trials, we hope to determine the potential of DCR-HBVS to reduce HBsAg expression and HBV DNA in HBV patients in a commercially attractive subcutaneous dosing paradigm.

**Hypercholesterolemia (PCSK9 targeted therapy).** We are using our GalXC RNAi platform to develop a therapeutic that targets the PCSK9 gene for the treatment of hypercholesterolemia. The Company has selected a provisional clinical candidate for the program, but is continuing to explore ways to further optimize the program. PCSK9 is a validated target for hypercholesterolemia, and there are U.S. Food and Drug Administration (FDA)-approved therapies targeting PCSK9 that are based on monoclonal antibody technology. Based on preclinical studies, we believe that our GalXC RNAi platform has the potential to produce a PCSK9-targeted therapy with attractive commercial properties, such as small subcutaneous injection volumes and less frequent dosing.

**Additional pipeline programs.** We have applied our GalXC technology to multiple gene targets across our disease focus areas of chronic liver diseases, cardiovascular diseases and rare diseases. Pursuant to our strategy, we are seeking collaborations with larger pharmaceutical companies to advance our programs in the areas of chronic liver diseases and cardiovascular diseases. Both these disease areas represent large and diverse patient populations, requiring complex clinical development and commercialization paths that we believe can be more effectively be pursued in partnership with larger pharmaceutical companies more experienced in these types of programs. For our additional rare diseases, we are continuing to assess their potential for clinical success and market opportunity while optimizing our GalXC molecules. For our additional pipeline programs (including PCSK9), we may utilize more advanced versions of our GalXC technology, that further improve pharmaceutical properties of the GalXC molecules, including enhancing the duration of action.

In addition to our GalXC development programs, on October 27, 2017, we entered into a collaborative research and license agreement with Boehringer Ingelheim International GmbH, a wholly-owned subsidiary of C.H. Boehringer Sohn AG & Co. KG (BI) (the BI Agreement), pursuant to which the Company and BI will jointly research and develop product candidates that target a specific disease-linked gene in the hepatocytes for the treatment of nonalcoholic steatohepatitis (NASH) using our GalXC platform. The BI Agreement is for the development of product candidates against one target gene with an option for BI to add the development of product candidates that target a second gene. We will work exclusively with BI to develop the product candidates against the undisclosed target gene. We will be responsible for the discovery and initial profiling of the product candidates, including primary pre-clinical studies, synthesis, and delivery. BI will be responsible for evaluating and selecting the product candidates for further development. If BI selects one or more product candidates, it will be responsible for further pre-clinical development, clinical development, manufacturing and commercialization of those products. Also pursuant to the BI Agreement, we granted BI a worldwide license in connection with the research and development of the product candidates and will transfer to BI intellectual property rights of the product candidates selected by BI for clinical development and commercialization. We also may provide assistance to BI in order to help BI further develop selected product candidates. Under the terms of the BI Agreement, BI paid a non-refundable upfront payment of \$10.0 million. During the term of the research program, BI will reimburse us the cost of materials and third party expenses that have been included in the preclinical studies up to an agreed-upon limit. We are eligible to receive up to \$191.0 million in potential development and commercial milestones. We are also eligible to receive royalty payments on potential global net sales, subject to certain adjustments, tiered from high single digits up to low double-digits. BI's option to add a second target would provide for an option fee payment and success-based development and commercialization milestones and royalty payments to us.

We are party to a collaboration for our early generation of Dicer Substrate RNAi technology, non-GalXC technology, against two targets, the KRAS oncogene and an additional undisclosed gene, with the global pharmaceutical company Kyowa Hakko Kirin Co., Ltd. ( KHK ), to use for development in oncology and formulated using KHK s proprietary drug delivery system. KHK has provided us with notice of termination

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related to the non-KRAS program, and the Company expects that KHK will provide notice of termination related to the KRAS program.

We also have developed a wholly owned clinical candidate, DCR-BCAT, targeting the  $\beta$ -catenin oncogene. DCR-BCAT is based on an extended version of our earlier generation Dicer Substrate RNAi technology and is delivered by our LNP tumor delivery system, EnCore™. We plan to out-license or spin out the DCR-BCAT opportunity, given our focus on our GalXC platform-based programs.

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 Genta Inc., GlaxoSmithKline plc, Pfizer Inc., Sirna Therapeutics, Inc. ( Sirna ), NPS Pharmaceuticals, 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, an early RNAi company acquired by Merck & Co., Inc. ( Merck ) in 2006 for \$1.1 billion. He played a pivotal role in the restructuring of Ribozyme Pharmaceuticals into Sirna, the management of the company as a member of its Board of Directors, and the execution of its 2006 acquisition by Merck.

## **Risk Factors**

Our business is subject to numerous risks, which are highlighted in and incorporated in the section entitled Risk Factors in this prospectus.

## **Our Corporate Information**

We were incorporated in Delaware in October 2006. Our mailing address is 87 Cambridgepark Drive, Cambridge, MA 02140 where our principal executive offices are located, and our main telephone number is (617) 621-8097. We maintain a website at [dicerna.com](http://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 into, this prospectus and should not be considered part of this prospectus.

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**RECENT DEVELOPMENTS**

On October 16, 2017, we announced that we had submitted a CTA for DCR-PHXC to the MHRA in the UK and on December 7, 2017, we announced the dosing of the first human in DCR-PHXC-101, the Company's Phase 1 clinical trial of DCR-PHXC. We also plan to submit an IND for DCR-PHXC in the U.S. by the end of February 2018.

On October 27, 2017, we entered into a collaborative research and license agreement with BI, pursuant to which the Company and BI will jointly research and develop product candidates that target a specific disease-linked gene in the hepatocytes for the treatment of NASH using our GalXC platform.

The Company has selected a target for an additional GalXC-based therapeutic targeting a liver-expressed gene involved in a serious rare disease. Our undisclosed rare disease is a genetic disorder involving the liver, where mutations in the disease gene lead to the production of an abnormal protein. The protein causes progressive liver damage and fibrosis, in some cases leading to cirrhosis and liver failure, and we believe that silencing of the disease gene will prevent production of the abnormal protein and thereby slow or stop progression of the liver fibrosis. Greater than 100,000 people in the U.S. are believed to be homozygous for the mutation that causes the liver disease, and at least 10% of those people, and potentially a significantly higher fraction, are believed to have liver fibrotic disease as a consequence. We plan to seek a risk sharing collaborative partner for the program before we file an IND and/or CTA for this program, which we expect to be prepared to file in the second quarter of 2018.

KHK has provided notice of termination related to the non-KRAS program, and the Company expects that KHK will provide notice of termination related to the KRAS program. Our collaboration with KHK is for our early generation of Dicer Substrate RNAi technology, non-GalXC technology.

**Contingent Optional Conversion of Redeemable Convertible Preferred Stock**

On December 13, 2017, the Company entered into a letter agreement (the "Letter Agreement") with the holders (the "Preferred Holders") of all of the outstanding shares of the Company's redeemable convertible preferred stock (the "Redeemable Convertible Preferred"). Pursuant to the Letter Agreement, the Preferred Holders agreed, contingent upon the completion of this offering, to convert all of their shares of Redeemable Convertible Preferred, to the extent not subject to Conversion Blockers, into common stock at a conversion price of \$3.19 per share of Redeemable Convertible Preferred and agreed, if applicable, to the repurchase of any residual shares of Redeemable Convertible Preferred that would be converted into common stock but for the Conversion Blockers (the "Residual Shares") for \$0.0001 per share. Assuming the completion of this offering and the consummation of the transactions contemplated by the Letter Agreement, after the conversion and repurchase, no shares of Redeemable Convertible Preferred will remain outstanding.

Conversion Blockers refers to the beneficial ownership limitations in the Company's Certificate of Designation of the Redeemable Convertible Preferred, which include (i) a 19.99% blocker provision to comply with NASDAQ Listing Rules, (ii) if so elected by a holder, a 9.99% blocker provision that will prohibit beneficial ownership of more than 9.99% of the outstanding shares of the Company's common stock or voting power at any time, and (iii) ownership limitations resulting from applicable regulatory restrictions.

The Letter Agreement also provides for Preferred Holders to waive and amend certain provisions in an amended and restated registration rights agreement by and among the Company and the Preferred Holders party thereto (the "Registration Rights Agreement"). In consideration for the Preferred Holders agreeing to the optional conversion of the Redeemable Convertible Preferred and to a waiver under and certain amendments to the Registration Rights Agreement, the Company agreed to issue to the Preferred Holders pre-funded warrants (the



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Pre-Funded Warrants ) exercisable in part or in whole at any time upon grant for shares of the Company s common stock at a price per share of \$0.0001 per share. Each Preferred Holder may elect to receive shares of our common stock in lieu of the Pre-Funded Warrants, subject to any applicable Conversion Blockers. Under the Letter Agreement, the number of shares allocable to each Preferred Holder will be calculated based on the sum of (i) dividend accruals on the Redeemable Convertible Preferred that such Preferred Holders would have been entitled to receive up to and including March 31, 2018, calculated immediately prior to the effectiveness of the optional conversion, and (ii) any Residual Shares repurchased, or to be repurchased, from such Preferred Holder by the Company as described above (the Additional Investor Shares ). The calculation assumes (1) a conversion price of \$3.19 per share of Redeemable Convertible Preferred; (2) application of a dividend rate of 12% per annum from April 11, 2017 to October 27, 2017; and (3) application of a dividend rate of 8% per annum commencing from October 28, 2017 through March 31, 2018.

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**THE OFFERING**

|   |   |
|---|---|
| <b>Common stock offered by us</b>   | 5,714,286 shares  |
| <b>Underwriters option to purchase additional shares</b>  | We have granted the underwriters an option to purchase up to 857,143 additional shares of our common stock. This option is exercisable, in whole or in part, for a period of 30 days from the date of this prospectus supplement. |
| <b>Common stock to be outstanding immediately after this offering</b>   | 26,577,933 shares (as more fully described in the notes following this table) (27,435,076 shares if the underwriters exercise their option to purchase additional shares in full).  |
| <b>Common stock to be outstanding after this offering, giving effect to the conversion of certain of our Redeemable Convertible Preferred Use of Proceeds</b> | 50,012,136 shares (50,964,411 shares if the underwriters exercise their option to purchase additional shares in full).  |

We currently intend to use the net proceeds from this offering, for preclinical studies and clinical trials, with the remainder of any net proceeds from sales of securities being used for continued technology platform development, working capital and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in businesses, products or technologies that are complementary to our own. We regularly consider such opportunities but are not currently negotiating any such transactions. See Use of Proceeds.

**Risk Factors**

Investing in our securities involves a high degree of risk. See Risk Factors beginning on page S-12 of this prospectus supplement and the other information included in, or incorporated by reference into, this prospectus for a discussion of certain factors that you should carefully consider before deciding to invest in shares of our common stock.

**NASDAQ Global Select Market Symbol**

Our common stock is listed on The NASDAQ Global Select Market under the symbol DRNA.

The number of shares of our common stock shown above to be outstanding immediately after this offering is based on 20,863,647 shares outstanding as of December 12, 2017 and excludes:

87,901 shares of our common stock issuable upon the exercise of outstanding warrants as of December 12, 2017, at a weighted average exercise price of \$13.08 per share;

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23,434,203 shares of our common stock issued as a result of the conversion of certain of our Redeemable Convertible Preferred, assuming conversion immediately following the completion of this offering;

772,452 shares of our common stock issuable upon (i) the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or (ii) the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants, assuming issuance immediately following the completion of this offering;

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6,139,382 shares of our common stock issuable upon the exercise of outstanding options as of December 12, 2017, at a weighted average exercise price of \$8.57 per share; and

509,752 shares of our common stock available for future issuance pursuant to our existing stock incentive plans as of December 12, 2017.

The number of shares of our common stock shown above to be outstanding after this offering, giving effect to the conversion of certain of our Redeemable Convertible Preferred, is based on 20,863,647 shares outstanding as of December 12, 2017 and excludes:

87,901 shares of our common stock issuable upon the exercise of outstanding warrants as of December 12, 2017, at a weighted average exercise price of \$13.08 per share;

772,452 shares of our common stock issuable upon (i) the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or (ii) the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants, assuming issuance immediately following the completion of this offering;

6,139,382 shares of our common stock issuable upon the exercise of outstanding options as of December 12, 2017, at a weighted average exercise price of \$8.57 per share; and

509,752 shares of our common stock available for future issuance pursuant to our existing stock incentive plans as of December 12, 2017.

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**RISK FACTORS**

*An investment in our securities is speculative in nature and involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks discussed below, together with those risks included in our most recent annual report on Form 10-K and our subsequent reports filed with the SEC, including our most recent quarterly report on Form 10-Q, which are incorporated by reference into this prospectus, as well as the other information in this prospectus, the information and documents incorporated by reference and in any free writing prospectus that we have authorized for use in connection with this offering. If any of the identified risks actually occur, they could materially adversely affect our business, financial condition, operating results or prospects and the trading price of our securities. Additional risks and uncertainties that we do not presently know or that we currently deem immaterial may also impair our business, financial condition, operating results and prospects and the trading price of our securities. As a result, you could lose all or part of your investment. You should also be aware that this document and other public statements we make may contain statements that do not relate strictly to historical fact, any of which may be forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995.*

**Additional Risks Related to This Offering**

*We have broad discretion in the use of the net proceeds from this offering.*

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways with which you may not agree. Accordingly, you will be relying on the judgment of our management with regard to the use of the net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that the net proceeds will be invested or otherwise used in a way that does not yield a favorable, or any, return for the Company.

*Investors in this offering will experience immediate and substantial dilution in the net tangible book value per share of the common stock they purchase.*

Since the price per share of our common stock being offered is higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. See the section entitled "Dilution" in this prospectus for a more detailed discussion of the dilution you will incur immediately after this offering if you purchase common stock in this offering. In addition, we have a significant number of options and a number of warrants outstanding. If the holders of these options or warrants exercise such options or warrants, you may incur further dilution.

*Our stockholders may experience significant dilution as a result of future equity offerings and exercise of outstanding options, warrants, the conversion of the Redeemable Convertible Preferred and the potential issuance of Pre-Funded Warrants and/or common stock in connection with such conversion.*

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 other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, 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 in this offering.

In addition, we have a significant number of securities convertible into, or allowing the purchase of, our common stock. On April 11, 2017, we issued 700,000 shares of Redeemable Convertible Preferred that are convertible at any time into shares of our common stock at an initial price of \$3.19 per share, subject to proportionate

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adjustment for any stock split, stock dividend, combination or other similar recapitalization event (the Conversion Price ), and through September 30, 2017, we have issued an additional 40,126 shares of Redeemable Convertible Preferred as dividends paid in kind. As of December 12, 2017, 509,752 shares of common stock were reserved for future issuance under our stock incentive plans. Our stock incentive plans also provide for annual increases in the number of shares available for issuance. As of that date, there were also options to purchase 6,139,382 shares of our common stock outstanding and warrants to purchase 87,901 shares of our common stock outstanding. The exercise of outstanding options or warrants having an exercise price per share that is less than the offering price per share in this offering will increase dilution to investors in this offering. If the conversion and redemption of the Redeemable Convertible Preferred described under the heading Recent Developments contained in this prospectus supplement occurs, up to 740,126 shares of Redeemable Convertible Preferred will convert into our common stock at the Conversion Price, a price per share that is less than the offering price per share in this offering. In addition, in connection with such conversion and repurchase, we will issue Pre-Funded Warrants to certain of the holders of the Redeemable Convertible Preferred exercisable for shares of our common stock at an exercise price of \$0.0001 per share.

### ***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 December 12, 2017, we had 20,863,647 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 warrants and shares reserved for future issuance 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.

### ***We cannot assure you that the conversion of the Redeemable Convertible Preferred will occur, or if it does occur, that none of our Redeemable Convertible Preferred will remain outstanding following this offering.***

While each of the Preferred Holders has committed to convert such Preferred Holder's shares of Redeemable Convertible Preferred and to consent to the redemption of its remaining shares of Redeemable Convertible Preferred, if applicable, the conversion and redemption of all shares of Redeemable Convertible Preferred is contingent on a number of factors, including the consummation of this offering.

Under the terms of the Certificate of Designation that governs the Redeemable Convertible Preferred, the Redeemable Convertible Preferred generally ranks, with respect to liquidation, dividends and redemption, senior to other securities and, so long as any shares of Redeemable Convertible Preferred remain outstanding, the approval of the holders of a majority of the Redeemable Convertible Preferred is required in order for the Company to, undertake certain major corporate transactions.

In addition, holders of Redeemable Convertible Preferred also have certain redemption and conversion rights, including the right to request redemption by the Company after the seventh anniversary of the closing of the private placement of the Redeemable Convertible Preferred (the Private Placement ).

Our obligations to the holders of Redeemable Convertible Preferred could limit our ability to obtain additional financing or increase our borrowing costs, which could have an adverse effect on our financial condition. These preferential rights could also result in divergent interests between the holders of shares of Redeemable Convertible



Preferred and holders of our common stock. See Risks Related to Our Redeemable Convertible Preferred.

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**Risks Related to Our Business**

*We will need to raise 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 to raise substantial additional funds to expand our development, regulatory, manufacturing, marketing and sales capabilities, whether internally or through other organizations. We have used substantial funds to develop our product candidates and delivery technologies and will require significant funds to conduct 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 are approved for commercial sale. As of September 30, 2017, we had \$75.9 million in cash and cash equivalents and held-to-maturity investments. Based on our current operating plan and liquidity, including the receipt of net proceeds of \$69.3 million in connection with the issuance of the Company's Redeemable Convertible Preferred on April 11, 2017 and the receipt of upfront proceeds in connection with the BI Agreement, we believe that our available cash, cash equivalents and held-to-maturity investments will be sufficient to fund our planned level of operations for at least the 12-month period following November 2, 2017. 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 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. Failure to obtain funding on a timely basis or on acceptable terms would have a negative impact on our financial condition, and 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 financed our operations primarily through the sale of securities, debt financings, and credit and loan facilities. For example, on April 11, 2017, we issued and sold 700,000 shares of our newly designated Redeemable Convertible Preferred to the investors in the Private Placement for aggregate gross proceeds of \$70.0 million. We will be required to seek additional funding in the future and intend to do so through a combination of public or private equity offerings, debt financings and research collaborations and license agreements. Our ability to raise additional funds will depend on financial, economic and other factors, many of which are beyond our control. For example, a number of factors, including the timing and outcomes of

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our clinical activities, our status as a smaller reporting company under SEC regulations, our capital structure, which currently consists of common stock and redeemable convertible preferred stock, as well as conditions in the global financial markets, may present significant challenges to accessing the capital markets at a time when we would like or require, and at an increased cost of capital. 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.

***We are a 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 biopharmaceutical company with a limited operating history focused on the discovery and development of treatments based on the emerging therapeutic modality RNAi, a biological process in which RNA molecules inhibit gene expression. Since our inception in October 2006, we have devoted our resources to the development of DsiRNA molecules and delivery technologies. We have had significant operating losses since our inception. As of September 30, 2017, we had an accumulated deficit of \$300.2 million. For the nine months ended September 30, 2017 and for the years ended December 31, 2016, 2015 and 2014, our net loss attributable to common stockholders was \$57.3 million, \$59.5 million, \$62.8 million and \$47.9 million, respectively. Substantially all of our operating losses have resulted from expenses incurred in connection with our research and development 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.

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.

***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 licensor;

the timing of the release of results from any clinical trials conducted by us or our collaborator BI;

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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 or misappropriation lawsuit or opposition, interference, re-examination, post-grant review, inter partes review, nullification, derivation action, or cancellation proceeding in which we may become involved, including Alnylam Pharmaceuticals, Inc. ( Alnylam )'s lawsuit alleging misappropriation of confidential information and trade secrets;

additions and departures of key personnel;

strategic decisions by us and 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; and

changes in general market and economic conditions.

If our quarterly operating results fluctuate or fall below the expectations of investors or securities analysts, the price of our common stock could fluctuate or decline 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 subcutaneously delivered RNAi based pharmaceuticals using our GalXC RNAi platform for the treatment of rare diseases involving the liver and for other therapeutic areas involving the liver such as chronic liver diseases, as well as cardiovascular diseases and viral infectious diseases. 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 is relatively new. The scientific evidence to support the feasibility of developing therapeutic treatments based on RNAi and GalXC is both preliminary and

limited.

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 GalXC does not possess certain properties required for a drug to be safe and 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 GalXC. We may spend substantial funds attempting to introduce these properties and may never succeed in doing so. In addition, product candidates based on GalXC may demonstrate different chemical and pharmacological properties in patients than they do in laboratory studies. Even if product candidates, such as DCR-PHXC, 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.

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Further, the FDA has relatively limited experience with RNAi or GalXC based therapeutics. No regulatory authority has granted approval to any person or entity, including us, to market and commercialize therapeutics using RNAi or GalXC, 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 GalXC prove to be ineffective, unsafe or commercially unviable, our entire platform and pipeline would have little, if any, value, which would 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 numerous factors, including whether the product can be sold at a competitive price and otherwise is 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 GalXC technology, and we may not be able to convince the medical community and third-party payors, including health insurers, to accept and use, or to provide favorable coverage or 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 physicians and patients to accept any new methods of administration;

the success of our physician education programs;



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

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

our ability to compliantly market and sell our products; 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 market becomes more competitive or less favorable to this approach. Additional risks apply to any disease indications we pursue which are for rare diseases. 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 rare disease product, such drug may not generate enough revenue to offset costs of development, manufacturing, marketing and commercialization. This may be true despite any benefits received from our efforts to obtain orphan drug designation by regulatory agencies in major commercial markets, such as the U.S., the EU and Japan. These benefits may include market

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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 that are not classified as rare. Our estimates regarding potential market size for any indication may be materially different from what we discover to exist if we ever get to the point of product commercialization, 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 that 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 ( EU ) before the application for marketing authorization is made. Sponsors of orphan drugs in the EU 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. The respective orphan designation and exclusivity frameworks in the U.S. and in the EU are subject to change, and any such changes may affect our ability to obtain EU or U.S. orphan designations in the future.

***Our product candidates are in early stages of development and may fail or suffer delays that materially and 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 ethics committee approval to conduct clinical trials at particular sites, and successfully commercializing our product candidates, either alone or with third parties, such as our collaborator BI. 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 and 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 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 many factors, including scientific feasibility, safety, efficacy and changing standards of medical care. 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, the applicable Institutional Review Board ( 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 individuals 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

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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 individuals in clinical trials;

high drop-out rates of study participants;

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; and

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

***We are dependent on BI for the successful development of product candidates in the collaboration.***

On October 27, 2017, we entered into the BI Agreement to jointly research and develop candidate products using the GalXC platform to target specific disease-linked genes in the hepatocytes for the treatment of NASH. Under the terms of the BI Agreement, BI paid us a non-refundable upfront payment of \$10 million and we will be eligible to receive up to \$191 million in development and commercial milestones and royalty payments on global net sales. The success of our collaboration program with BI and the realization of the milestone and royalty payments under the BI Agreement depends entirely upon the efforts of BI may not be successful in obtaining approvals for the product candidates developed under the collaboration arrangements or in marketing, or arranging for necessary supply, manufacturing or distribution relationships for, any approved products. BI may change its strategic focus or pursue alternative technologies in a manner that results in reduced, delayed or no revenue to us. BI has a variety of marketed products and product candidates under collaboration with other companies, including some of our competitors, and their own corporate objectives may not be consistent with our interests. BI fails to develop, obtain regulatory approval for or ultimately commercialize any product candidate under our collaborations or if BI terminates our collaboration, our business, financial condition, results of operations and prospects could be materially and adversely affected. In addition, if we have a dispute or enter into litigation with BI in the future, it could delay development programs, create uncertainty as to ownership of intellectual property rights, distract management from other business activities and generate substantial expense.

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***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, compliance 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, compliant, 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 as well as applicable laws and regulations. The FDA and certain foreign regulatory authorities, such as the EMA, require preclinical studies to be conducted in accordance with applicable good laboratory practices and clinical trials to be conducted in accordance with applicable FDA regulations and applicable good clinical practices, 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 companies and organizations to supply the materials, components and manufacturing services for our research and development, preclinical study and clinical trial drug supplies.

We do not own or lease manufacturing facilities or supply sources for such components and materials. Our manufacturing requirements include oligonucleotides and custom amidites, some of which we procure from a single source supplier on a purchase order basis. In addition, for each product candidate we contract with only one manufacturer for the formulation and filling of drug product. 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 substance manufacturer could require significant effort and expertise because there may be a limited number of qualified replacements.

If we are at any time unable to provide an uninterrupted supply of our product candidates or, following regulatory approval, any products to patients, we may lose patients, physicians may elect to utilize competing therapeutics instead of our products, and our clinical trials may be adversely affected, which could materially and adversely affect

our clinical trial outcome.

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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 ( cGMP ). In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations regarding quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may experience shortages resulting in delayed shipments, supply constraints and/or stock-outs of our products, 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 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 BI, City of Hope ( COH ), Carnegie Institution of Washington ( Carnegie ) and Plant Bioscience Limited ( PBL ), 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 do not

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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 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 developed at universities and other research institutions. Our competitors have developed, are developing or may develop product candidates and processes competitive with our product candidates, some of which may become commercially available before any of 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 many 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 acquired Sirna from Merck in March 2014, Arbutus Biopharma Corporation, Arrowhead Pharmaceuticals, Inc. ( Arrowhead ), Silence Therapeutics plc, RXi Pharmaceuticals Corporation, Quark Pharmaceuticals, Inc., WAVE Life Sciences Ltd., Benitec Biopharma Limited and Arcturus Therapeutics. In particular, Arrowhead holds a non-exclusive license to the same patent rights of 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 some of 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 preclinical 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.

We also compete with companies working to develop antisense and other RNA-based drugs. Like RNAi therapeutics, antisense drugs target 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.

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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 and physicians 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; Bob D. Brown, Ph.D., our chief scientific officer; Ralf Rosskamp, M.D., our chief medical officer; John B. Green, our 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 complex 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 very limited experience with clinical trials of product candidates. 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, 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 are approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize

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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, legal 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 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, compliant 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 and 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 EU, the U.S., 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 of 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, import and export of pharmaceutical products, pricing, sales and marketing, and fraud and abuse requirements. 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 strategy ( 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 EU 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

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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, inability to participate in government programs including Medicare and Medicaid, and total or partial suspension of production or distribution, injunction, restitution, disgorgement, debarment, civil penalties and criminal prosecution.

We have a subsidiary physically located in the UK, which we established in order to allow us to conduct clinical trials in EU member states. On June 23, 2016, the UK held a referendum in which voters approved an exit from the EU, commonly referred to as Brexit. The withdrawal of the UK from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the UK provides a notice of withdrawal pursuant to the EU Treaty. On March 29, 2017, the Prime Minister of the UK delivered a formal notice of withdrawal to the EU. On May 22, 2017, the Council of the EU (the Council), adopted a decision authorizing the opening of Brexit negotiations with the UK and formally nominated the European Commission as EU negotiator. The Council also adopted negotiating directives for the talks. It appears likely that the UK's withdrawal from the EU will involve a process of lengthy negotiations between the UK and EU member states to determine the future terms of the UK's relationship with the EU. This could lead to a period of uncertainty and could impact our regulatory process in Europe, as well as require us to close our subsidiary in the UK and establish a new subsidiary elsewhere in the EU.

### ***Price controls imposed in foreign markets and downward pricing pressure in the U.S. may adversely affect our future profitability.***

In some countries, particularly member states of the EU, 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, in the U.S. and elsewhere, 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 EU 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 the 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 related litigation, a diversion of management's time and our resources, substantial monetary awards to clinical trial participants or patients and a decline in our stock price.



We currently have product liability insurance that we believe is

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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 or U.S. health care laws and 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 the 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 program, health care professional, 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 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 third parties with which we do business, including 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 or the theft of Company or patient confidential information.***

Despite the implementation of security measures, our internal computer systems and those of third parties with which we do business, including 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. Certain data breaches must also be reported to affected individuals and the government, and in some cases to the media, under provisions of the U.S. federal Health Insurance Portability and Accountability Act ( HIPAA ), as amended by the Health Information Technology for Economic and Clinical Health Act ( HITECH ), other U.S. federal and state law, and requirements of non-U.S. jurisdictions, including the European Union Data Protection Directive, and financial penalties may also apply. 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 of the Company or patients, 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

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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 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, telecommunication failure or other natural or manmade accidents or incidents that prevent us from fully utilizing 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,

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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. Additionally, we may experience an ownership change upon conversion of our Redeemable Convertible Preferred to common stock. As of December 31, 2016, we had significant U.S. federal and Massachusetts net operating loss carryforwards. 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 September 30, 2017, we had \$75.9 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. For example, the impact of U.S. sub-prime mortgage defaults in recent years 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 SEC. Changes to accounting methods or policies, or interpretations thereof, may require us to reclassify, restate or otherwise change or revise our consolidated financial statements, including those contained in our Annual Reports 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 November 1, 2017, our worldwide patent estate, not including the patents and patent applications that we have licensed from third parties, included over 20 issued patents or allowed patent applications and over 100 pending patent applications supporting commercial development of our RNAi 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

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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 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 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 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 U.S. 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;



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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;

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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 from others may not 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; and

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 and that we have developed internally and own. 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-based patents and have licensed other patents from third parties on exclusive and non-exclusive bases. 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. 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 RNAi molecules, including their manufacture and use as therapeutics, and RNAi-related mechanisms, (2) chemical modifications to RNAi molecules that improve their properties and suitability for therapeutic uses, (3) RNAi 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

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RNAi. These are referred to in their corporate literature as the Tuschl family (e.g. patents and applications claiming priority to WO2002/044321, filed November 29, 2001, and their priority filings) and the Kreutzer-Limmer family (e.g. patents and applications claiming priority to WO 2002/044895, filed January 29, 2000, WO 2002/055693, filed January 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. In addition, Silence Therapeutics owns patents directed to certain chemical modifications of RNAi molecules, including U.S. Patent Number 9,222,092, with a priority date of August 5, 2002.

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 product candidates or platform technology could have been filed by others without our knowledge. Additionally, pending claims in patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our product candidates or the use of our product candidates. Third party intellectual property right holders may also bring patent infringement claims against us. No such patent 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 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 RNAi 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 therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for 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.



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***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 DsiRNA molecules employed in our 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. 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 certain of our rights under our third-party licenses to BI and may sublicense such rights to current or future collaborators. Any impairment of these sublicensed rights could result in reduced revenue under our collaboration agreement with BI or result in termination of an agreement by one or more of our collaborators or any future strategic partners.

***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 certain of our GalXC products. 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 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 and 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

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where we have patent protection, but where it is more difficult to enforce a patent as compared to the U.S. We also may face competition 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 EU, 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 be refused in some jurisdictions, while granted by others. 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 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, our licensors or existing or future collaborators 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, our licensors or existing or future collaborators 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, our licensors or existing or future collaborators 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, our licensors or existing or future collaborators 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, our licensors or existing or future collaborators 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

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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 patent 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 patent 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.

***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

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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 work, 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 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 filed a complaint against us in the Superior Court of Middlesex County, Massachusetts (the Court). The complaint alleges misappropriation of confidential, proprietary, and trade secret information, as well as other related claims, in connection with our 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 Court has set a trial date of April 23, 2018. This matter has caused us to incur significant legal fees and other costs to defend against this action and will continue to do so through the trial and potentially beyond. We believe, however, that Alnylam's allegations lack merit. In response to the complaint, we filed an answer denying all liability, and we will continue to vigorously defend all claims asserted. We expect that a finding of liability against us 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. However, an unfavorable resolution 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. In addition, if an unfavorable resolution had a material adverse impact on our ability to meet our obligations under the BI Agreement, we could be required to repay to BI certain future milestone payments, excluding the upfront payment, R&D reimbursement and certain other payments paid or to be paid to us by BI. As we believe Alnylam's suit is without merit and intended only to cause competitive harm, we filed a countersuit in the case against Alnylam for damages, and on August 8, 2017, we filed a complaint in the Federal District court for the District of Massachusetts asserting a federal antitrust claim against Alnylam.

We may be subject to additional claims in the future that these or other employees of the Company have, or we have, inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former

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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 work. 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, 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. Any trademark litigation could be expensive. 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 collaborators 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, may be unable to commercialize our product candidates.***

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, development, testing, manufacture, quality control, approval, labeling, packaging, promotion, storage, record-keeping, advertising, distribution, sampling, pricing, sales and marketing, safety, post-approval monitoring and reporting, and export and import 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 the 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 ( FDCA ), the FDA could decide to reclassify them, namely 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

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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.

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 authorities 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 REMS plan as part of an NDA or biologics license application 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 coverage and 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 or may become 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 statute, 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 act, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government funded programs 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 FDCA 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;



HIPAA and HITECH, 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 Physician Payment Sunshine Act ( Open Payments ) requires that, among others, manufacturers of pharmaceutical and biological drugs covered by Medicare, Medicaid, and Children's Health Insurance Programs report certain payments and other transfers of value to U.S.-licensed physicians and teaching hospitals unless an exception applies; and

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state and foreign laws comparable to each of the above federal laws, such as, for example, state anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance or transparency reporting 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 affect 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. Achieving and sustaining compliance with applicable laws and regulations may also be costly to us in terms of money, time and resources. In addition, many of the laws with which we must comply contain provisions added or amended by 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. The current Administration and the U.S. Congress have expressed a desire to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA, which has contributed to the uncertainty of the ongoing implementation and impact of the ACA and also underscores the potential for additional health care reform going forward.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign healthcare 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;

limitations on our ability to secure or maintain adequate coverage and reimbursement for our proprietary product candidates from government (including U.S. federal health care programs) and private payors;

exclusion from participation in government-funded healthcare programs (including Medicare and Medicaid);

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

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.

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*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, coverage 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, their coverage prospects, or the likely level or method of reimbursement, if covered. 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. Moreover, legislation and regulations affecting the pricing of pharmaceuticals may change before regulatory agencies approve our proposed products for marketing and could further limit pricing approvals for, and reimbursement of, our products from government authorities and third-party payers. For example, the current Administration has indicated support for possible new measures related to drug pricing. New government legislation or regulations related to pricing or a government or third-party payer decision not to approve pricing for, or provide adequate coverage and reimbursements of, our products hold the potential to limit severely market acceptance of such 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 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 (the Medicare program that generally covers physician-administered, outpatient drugs) for a manufacturer's eligible drugs or biologicals, the manufacturer is required to participate in other government healthcare programs, including the Medicaid Drug

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Rebate Program and the 340B Drug Pricing Program. The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to entities eligible to participate in the 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, outpatient drugs are typically reimbursed by Medicare under Medicare Part D, and drugs that are administered in an inpatient 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., the ACA 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 Pricing 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; and

if the FDA were to reclassify any of our existing product candidates or choose to classify any of our future product candidates as biologics, then 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, the FDA may approve a biosimilar product to enter the market, which is likely to

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reduce the pricing for the innovator product and could affect our profitability if our products are classified as biologics.

In addition, in recent years, the 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 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. For example, the current Administration and the U.S. Congress have expressed a desire to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA, which has contributed to the uncertainty of the ongoing implementation and impact of the ACA and also underscores the potential for additional health care reform going forward. There is still uncertainty with respect to the impact the current Administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold. We cannot assure you that the ACA, as currently enacted or as amended in the future, will not adversely affect our business and financial results. Moreover, 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 federal false claims act), prohibit unlawful inducements for the referral of business reimbursable by federal healthcare programs (e.g. the federal anti-kickback statute), and require disclosure of certain payments or other transfers of value made to U.S.-licensed physicians and teaching hospitals (Open Payments). 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, 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 that engages in electronic transactions, the Company may also be subject to the privacy and security provisions of HIPAA, as amended by HITECH, which restricts the use and disclosure of patient-identifiable health



information, mandates the adoption of standards relating to the privacy and security of patient-

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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.***

The U.S. federal budget remains in flux, which could, among other things, cut Medicare payments to providers. 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 is uncertain. In addition, we cannot predict any impact that the current Administration may have on the federal budget. 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 ( NIH ), 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 receive 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 not be able to secure or maintain adequate coverage and reimbursement for our proprietary product candidates from government (including U.S. federal health care programs) and private payors;

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;

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.

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**Risks Related to Our Common Stock**

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

We are an emerging growth company as defined in the Jumpstart Our Business Startups Act ( 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 the prior June 30 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, under certain circumstances, 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 is 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 December 12, 2017, the closing sale price of our common stock has ranged between a high of \$46.00 per share and a low of \$2.45 per share. The market price for our common stock may be influenced by many factors, including the other risks described in this Risk Factors section and the following:

the success or failure 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;

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

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

actions taken by regulatory agencies with respect to our or our competitors' product candidates, 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;

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

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

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

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;

sales of our common stock by us or our stockholders;

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

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 often been 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.

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

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.

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***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 the Company, 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 the Company, 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 September 30, 2017, our executive officers and directors, together with holders of five percent or more of our outstanding common stock and their respective affiliates, beneficially owned, in the aggregate, approximately 75% of our outstanding common stock, assuming conversion of all Redeemable Convertible Preferred, after application of the Conversion Blockers, and 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. Subsequent to the consummation of the conversion and repurchase of the Redeemable Convertible Preferred that is contingent upon the completion of this offering, certain holders of the Redeemable Convertible Preferred will also hold Pre-Funded Warrants exercisable for shares of common stock at an exercise price of \$0.0001 per share. In addition, if any of the stockholders participate in this offering, their ownership may be further increased. 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.

***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 amended and restated certificate of incorporation and our amended and restated 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

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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, such as the Redeemable Convertible Preferred, 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 and if we ever cease to be a smaller reporting 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 rules of the SEC that implement Section 404(b) of the Sarbanes-Oxley Act. Pursuant to Section 404 of the Sarbanes-Oxley Act ( Section 404 ), we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company and a smaller reporting 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 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

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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. 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 Global Select 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 common 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 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.

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### ***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 November 1, 2017, we had 20,848,503 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.

### **Risks Related to Our Redeemable Convertible Preferred**

#### ***The issuance of shares of our Redeemable Convertible Preferred reduces the relative voting power of holders of our common stock and dilutes the ownership of such holders, and the conversion of our Redeemable Convertible Preferred may adversely affect the market price of our common stock.***

Holders of our Redeemable Convertible Preferred are entitled to vote, on an as-converted basis, together with holders of our common stock on all matters submitted to a vote of the holders of our common stock. As a result, the issuance of the Redeemable Convertible Preferred effectively reduces the relative voting power of the holders of our common stock. Moreover, the conversion of the Redeemable Convertible Preferred to common stock, which is described under the heading *Recent Developments*, is expected to occur in connection with the consummation of this offering. would dilute the ownership interest of existing holders of our common stock, and any sales in the public market pursuant to the registration rights granted to the holders of the Redeemable Convertible Preferred of the common stock issuable upon conversion of the Redeemable Convertible Preferred could adversely affect prevailing market prices of our common stock. Sales by such holders of a substantial number of shares of our common stock in the public market, or the perception that such sales might occur, could have a material adverse effect on the price of our common stock.

#### ***The holders of shares of the Redeemable Convertible Preferred may exercise significant influence over us.***

After application of the Conversion Blockers, holders of the Redeemable Convertible Preferred owned approximately 72% of our shares of common stock on an as-converted basis as of September 30, 2017. Holders of our Redeemable Convertible Preferred are entitled to vote, on an as-converted basis, together with holders of our common stock on all matters submitted to a vote of the holders of our common stock. As a result, the holders of shares of the Redeemable Convertible Preferred have the ability to significantly influence the outcome of any matter submitted for the vote of the holders of our common stock.

In addition, under the terms of the Certificate of Designation that governs the Redeemable Convertible Preferred, the Redeemable Convertible Preferred generally ranks, with respect to liquidation, dividends and redemption, senior to other securities and, so long as any shares of Redeemable Convertible Preferred remain outstanding, the approval of the holders of a majority of the Redeemable Convertible Preferred is required in order for the Company to, among other things, (i) amend, modify or fail to give effect to any right of holders of the Redeemable Convertible Preferred, (ii) change the authorized number of Redeemable Convertible Preferred or issue additional Redeemable Convertible Preferred or create a new class or series of equity securities or securities convertible into equity securities with equal or superior rights, preferences or privileges to those of the Redeemable Convertible Preferred in terms of liquidation preference, dividend rights or certain governance rights, (iii) issue shares of common stock or securities convertible into common stock while we have insufficient shares to effect the conversion of the Redeemable Convertible

Preferred into common stock, (iv) declare or pay dividends or redeem or repurchase any capital stock (other than certain repurchases from employees, directors, advisors or consultants upon termination of service) or (v) incur certain indebtedness in excess of \$10 million.

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One of the holders of Redeemable Convertible Preferred was also granted a one-time right to nominate a director, Adam M. Koppel M.D., Ph.D. Dr. Koppel joins Brian K. Halak, Ph.D., Peter Kolchinsky, Ph.D., and Stephen J. Hoffman, M.D., Ph.D. on our board of directors as directors affiliated with or formerly affiliated with holders of Redeemable Convertible Preferred. Notwithstanding the fact that all directors are subject to fiduciary duties to us and to applicable law, the interests of these directors could potentially differ from the interests of our security holders as a whole or of our other directors.

***The holders of Redeemable Convertible Preferred have rights, preferences and privileges that are not held by, and are preferential to, the rights of our common stockholders.***

Upon our liquidation, dissolution or winding up, the holders of the Redeemable Convertible Preferred will be entitled to receive out of our assets, in preference to the holders of the common stock and any junior preferred stock, an amount per share equal to the greater of (i) the sum of the Accrued Value plus an amount equal to all accrued or declared and unpaid dividends on the Redeemable Convertible Preferred that have not previously been added to the Accrued Value, or (ii) the amount that such shares would have been entitled to receive if they had converted into common stock immediately prior to such liquidation, dissolution or winding up. In addition, upon consummation of a specified change of control transaction, each holder of Redeemable Convertible Preferred will be entitled to receive in preference to the holders of common stock and any junior preferred stock, an amount equal to the greater of (i) 101% of the sum of the Accrued Value plus an amount equal to all accrued or declared and unpaid dividends on the Redeemable Convertible Preferred that have not previously been added to the Accrued Value, or (ii) the amount that such shares would have been entitled to receive if they had converted into common stock immediately prior to such event. These provisions may make it more costly for a potential acquirer to engage in a business combination transaction with us. Provisions that have the effect of discouraging, delaying or preventing a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock and could also affect the price that some investors are willing to pay for our common stock. If there are insufficient assets to pay in full such amounts, then the available assets will be ratably distributed to the holders of the Redeemable Convertible Preferred in accordance with the respective amounts that would be payable on such shares if all amounts payable thereon were paid in full. This will reduce the remaining amount of our assets, if any, available to distribute to holders of our common stock. The holders of Redeemable Convertible Preferred also have a preferential right to receive cumulative dividends on the Accrued Value of each share of Redeemable Convertible Preferred at an initial rate of 12% per annum, compounded quarterly, and subject to downward adjustment upon achievement of certain milestones. This dividend rate was adjusted down to 8% following our entry into the BI Agreement on October 27, 2017, as discussed above. Dividends on the Redeemable Convertible Preferred are payable in kind and will accrue on the Accrued Value of each share of Redeemable Convertible Preferred until the earlier of conversion, redemption, consummation of a change of control, a liquidation event, or upon failure to mandatorily convert due to the Conversion Blockers or applicable regulatory restrictions.

In addition, the holders of Redeemable Convertible Preferred also have certain redemption and conversion rights, including the right to request redemption by the Company after the seventh anniversary of the closing of the Private Placement.

Our obligations to the holders of Redeemable Convertible Preferred could limit our ability to obtain additional financing or increase our borrowing costs, which could have an adverse effect on our financial condition. These preferential rights could also result in divergent interests between the holders of shares of Redeemable Convertible Preferred and holders of our common stock.





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*Sales of shares issued in recent placements may cause the market price of our shares to decline.*

In connection with the Private Placement, we issued 700,000 shares of Redeemable Convertible Preferred, which are convertible at any time into shares of our common stock at an agreed conversion rate. We have agreed to grant the holders of Redeemable Convertible Preferred certain demand, shelf and piggyback registration rights with respect to the shares of common stock issuable upon conversion of the Redeemable Convertible Preferred. Such registration rights will continue subsequent to the conversion and repurchase of the Redeemable Convertible Preferred with respect to the shares of common stock issued in such conversion and any shares issued upon exercise of the Pre-Funded Warrants issued in connection with the conversion. Upon the effectiveness of such registration statements, all shares of common stock issuable upon conversion of the Redeemable Convertible Preferred or upon the exercise of the Pre-Funded Warrants may be freely sold in the open market. The sale of a significant amount of these shares in the open market or the perception that these sales may occur could cause the market price of our common stock to decline or become highly volatile.

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**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

This prospectus includes and incorporates by reference forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 and releases issued by the SEC and within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). All statements other than statements of historical fact are forward-looking statements for purposes of this prospectus. In some cases, you can identify forward-looking statements by terminology such as may, could, will, would, should, expect, plan, anticipate, believe, predict, seek, contemplate, project, continue, potential, ongoing, goal, or the negative of these terms or comparable terminology. These forward-looking statements include, but are not limited to, statements about:

how long we expect to maintain liquidity to fund our planned level of operations and our ability to obtain additional funds for our operations;

the initiation, timing, progress and results of our research and development programs, preclinical studies, any clinical trials and IND, CTA, 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 product 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 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, BI, 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 BI or any future arrangements with any other collaborators;

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

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materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. In evaluating such forward-looking statements, you should specifically consider various factors that may cause actual results to differ materially from current expectations, including the risks outlined under the heading **Risk Factors** contained in this prospectus and any related free writing prospectus, and in any other documents incorporated herein or therein (including in our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q). Any forward-looking statement in this prospectus 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 prospectus 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.

## **Trademarks**

This prospectus includes trademarks, service marks and trade names owned by us or by other companies. All trademarks, service marks and trade names included in this prospectus are the property of their respective owners.

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**USE OF PROCEEDS**

We estimate that the net proceeds received by us from this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately \$37.2 million, or approximately \$42.8 million, if the underwriters exercise their option to purchase additional shares in full.

We currently intend to use the net proceeds from this offering for preclinical studies and clinical trials, with the remainder of any net proceeds from sales of securities being used for continued technology platform development, working capital and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in businesses, products or technologies that are complementary to our own. We regularly consider such opportunities but are not currently negotiating any such transactions. The amount and timing of these expenditures will depend on a number of factors, such as the timing, scope, progress and results of our research and development efforts, the timing and progress of any partnership efforts, and the competitive environment for our product candidates.

As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering, if any. As a result, our management will have broad discretion regarding the timing and application of the net proceeds from this offering. Pending the application of the net proceeds, we intend to invest the net proceeds in short-term, investment grade, interest-bearing securities.

**Table of Contents****CAPITALIZATION**

The following table sets forth our cash, cash equivalents and held-to-maturity investments and capitalization as of September 30, 2017 on:

An actual basis;

On a pro forma basis, giving effect to (i) the conversion of 721,578 shares of our Redeemable Convertible Preferred into an aggregate of 22,620,441 shares of our common stock, assuming conversion immediately prior to the completion of this offering; (ii) the issuance, but not the exercise, of Pre-Funded Warrants exercisable for 1,586,221 shares of our common stock, at an exercise price of \$0.0001 per share, assuming issuance of the Pre-Funded Warrants immediately prior to the completion of this offering and assuming that no Preferred Holders elect to receive shares of our common stock in lieu of Pre-Funded Warrants; and (iii) the repurchase of 18,548 Residual Shares for \$0.0001 per share, assuming repurchase immediately prior to the completion of this offering; and

On a pro forma as-adjusted basis, giving effect to (i) the conversion of 755,146 shares of our Redeemable Convertible Preferred into an aggregate of 23,434,203 shares of our common stock, assuming conversion immediately following the completion of this offering; (ii) the issuance, but not the exercise, of Pre-Funded Warrants exercisable for 772,452 shares of our common stock, at an exercise price of \$0.0001 per share, assuming issuance of the Pre-Funded Warrants immediately following the completion of this offering and assuming that no Preferred Holders elect to receive shares of our common stock in lieu of Pre-Funded Warrants; and (iii) the sale and issuance of 5,714,286 shares of our common stock by us in this offering, at an offering price of \$7.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table together with the section of our Quarterly Report on Form 10-Q for the period ended September 30, 2017 entitled Management's Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related notes incorporated by reference into this prospectus supplement.

|  | <b>Actual<br/>September 30,<br/>2017</b> | <b>Pro<br/>Forma</b> | <b>Pro Forma<br/>As-Adjusted</b> |
|--|--|----------------------|----------------------------------|
|  |  | (in thousands)       |                                  |
| Cash and held-to-maturity investments  | \$ 75,919                                | \$ 75,919            | \$ 113,109                       |
| Redeemable Convertible Preferred Stock<br>(740,126 shares outstanding, actual; no shares<br>outstanding, pro forma; no shares outstanding,<br>pro forma as-adjusted) | \$ 75,983                                | \$                   | \$                               |
| Common stock (150,000,000 shares<br>authorized; 20,847,754 shares outstanding,   | \$ 2                                     | \$ 4                 | \$ 5                             |

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|   |              |              |              |
|---|--------------|--------------|--------------|
| actual; 43,468,195 shares outstanding, pro<br>forma; 49,996,243 shares outstanding, pro<br>forma as-adjusted) |              |              |              |
| Pre-funded warrants   | \$           | \$ 8,140     | \$ 5,647     |
| Additional paid-in capital  | \$ 296,434   | \$ 364,274   | \$ 403,957   |
| Accumulated deficit   | \$ (300,215) | \$ (300,215) | \$ (300,215) |
| Stockholders (deficit) equity   | \$ (3,779)   | \$ 72,204    | \$ 109,394   |
| Total capitalization  | \$ 72,204    | \$ 72,204    | \$ 109,394   |

Assumes that no Preferred Holders elect to receive shares of our common stock in lieu of Pre-Funded Warrants. Pursuant to the Letter Agreement, each Preferred Holder may elect to receive shares of our common stock in lieu of all or a portion of the Pre-Funded Warrants that would otherwise be issued to such Preferred Holder.

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The number of shares of our common stock shown above to be outstanding immediately after the completion of this offering excludes, as of September 30, 2017:

87,901 shares of our common stock issuable upon the exercise of outstanding warrants, at a weighted average exercise price of \$13.08 per share;

772,452 shares of our common stock issuable upon (a) the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or (b) the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants, assuming issuance immediately following the completion of this offering;

6,134,301 shares of our common stock issuable upon the exercise of outstanding options, at a weighted average exercise price of \$8.62 per share; and

599,505 shares of our common stock available for future issuance pursuant to our existing stock incentive plans.

The number of shares of our common stock shown above to be outstanding after the conversion of the Redeemable Convertible Preferred excludes, as of September 30, 2017:

87,901 shares of our common stock issuable upon the exercise of outstanding warrants, at a weighted average exercise price of \$13.08 per share;

1,586,221 shares of our common stock issuable upon (a) the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or (b) the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants, assuming issuance immediately prior to the completion of this offering;

6,134,301 shares of our common stock issuable upon the exercise of outstanding options, at a weighted average exercise price of \$8.62 per share; and

599,505 shares of our common stock available for future issuance pursuant to our existing stock incentive plans.

**Table of Contents****DILUTION**

If you invest in our common stock, you will experience dilution to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value as of September 30, 2017 was approximately \$72.2 million, or \$1.60 per share of our common stock. Net tangible book value per share as of September 30, 2017 is equal to our total tangible assets minus total liabilities, all divided by the number of shares of common stock outstanding as of September 30, 2017, adjusted for (i) the conversion of 755,146 shares of Redeemable Convertible Preferred into 23,434,203 shares of our common stock, assuming conversion immediately following this offering, and (ii) the issuance of 772,452 shares of our common stock issuable upon (a) the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or (b) the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants, assuming issuance immediately following the completion of this offering.

After giving effect to the sale of 5,714,286 shares of our common stock in this offering at a public offering price of \$7.00 per share, and after deducting estimated offering commissions and expenses payable by us, our as adjusted net tangible book value would have been approximately \$109.4 million, or approximately \$2.15 per share of common stock, as of September 30, 2017. This represents an immediate increase in net tangible book value of approximately \$0.55 per share to existing stockholders and an immediate dilution of approximately \$4.85 per share to investors in this offering. The following table illustrates this calculation on a per share basis.

|  |         |
|--|---------|
| Public offering price per share  | \$ 7.00 |
| Net tangible book value per share as of September 30, 2017   | \$ 1.60 |
| Increase in net tangible book value per share after this offering  | \$ 0.55 |
| As adjusted net tangible book value per share as of September 30, 2017, after giving effect to this offering | \$ 2.15 |
| Dilution per share to new investors purchasing shares in this offering                                       | \$ 4.85 |

The information in this section assumes that the underwriters do not exercise their option to purchase additional shares. If the underwriters exercise their option to purchase additional shares in full, our pro forma net tangible book value per share at September 30, 2017 after giving effect to this offering would have been \$2.23 per share, and the dilution in pro forma net tangible book value per share to investors in this offering would have been \$4.77 per share.

The number of shares of our common stock shown above to be outstanding after this offering is based on 20,847,754 shares outstanding as of September 30, 2017, 24,206,655 shares of common stock issuable upon: the conversion of certain of our Redeemable Convertible Preferred, the repurchase of the Residual Shares, the exercise of the Pre-Funded Warrants, at an exercise price of \$0.0001 per share, and/or the election of the Preferred Holders to receive shares of our common stock in lieu of Pre-Funded Warrants; and excludes:

87,901 shares of our common stock issuable upon the exercise of outstanding warrants as of September 30, 2017, at a weighted average exercise price of \$13.08 per share;

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6,134,301 shares of our common stock issuable upon the exercise of outstanding options as of September 30, 2017, at a weighted average exercise price of \$8.62 per share; and

599,505 shares of our common stock available for future issuance pursuant to our existing stock incentive plans as of September 30, 2017.

The above illustration of dilution per share to investors participating in this offering assumes no exercise of outstanding options to purchase our common stock or outstanding warrants to purchase shares of our common stock. The exercise of outstanding options and warrants having an exercise price per share that is less than the offering price per share in this offering will increase dilution to investors in this offering.

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**Table of Contents****UNDERWRITING**

Subject to the terms and conditions set forth in an underwriting agreement, each underwriter named below has agreed to purchase from us the aggregate number of shares of common stock set forth opposite its name below. Stifel, Nicolaus & Company, Incorporated and Evercore Group L.L.C. are the representatives of the underwriters.

| <b>Underwriter</b>                       | <b>Number of Shares</b> |
|--|-------------------------|
| Stifel, Nicolaus & Company, Incorporated | 2,285,715               |
| Evercore Group L.L.C.                    | 2,285,715               |
| H.C. Wainwright & Co., LLC               | 571,428                 |
| SunTrust Robinson Humphrey, Inc.         | 571,428                 |
| <b>Total</b>                             | <b>5,714,286</b>        |

The underwriting agreement provides that the obligations of the underwriters are subject to various conditions. The nature of the underwriters' obligations commit them to purchase and pay for all of the shares of common stock listed above if any are purchased.

The underwriters expect to deliver the shares of common stock to purchasers on or about December 18, 2017.

**Option to Purchase Additional Shares**

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 857,143 additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions.

**Commissions and Discounts**

The underwriters initially propose to offer the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the underwriter.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds, before expenses, to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 857,143 shares of our common stock.

|  | <b>Per Share</b> | <b>Without Option</b> | <b>Total With Option</b> |
|--|------------------|-----------------------|--------------------------|
| Public offering price                  | \$ 7.00          | \$ 40,000,002.00      | \$ 46,000,003.00         |
| Underwriting discounts and commissions | \$ 0.42          | \$ 2,400,000.12       | \$ 2,760,000.18          |
| Proceeds, before expenses, to us       | \$ 6.58          | \$ 37,600,001.88      | \$ 43,240,002.82         |

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$410,000, which amount includes up to \$15,000 that we have agreed to reimburse the underwriters for

fees and expenses of their counsel.

**Indemnification of the Underwriters**

We will indemnify the underwriters against some civil liabilities, including liabilities under the Securities Act of 1933, as amended (the Securities Act), and liabilities arising from breaches of our representations and warranties contained in the underwriting agreement. If we are unable to provide this indemnification, we will contribute to payments the underwriters may be required to make in respect of those liabilities.

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### **No Sales of Similar Securities**

We and our directors and executive officers have agreed that, subject to certain exceptions, without the prior written consent of Stifel, Nicolaus & Company, Incorporated and Evercore Group L.L.C., we and they will not, during the period ending 90 days after the date of this prospectus supplement (the Lock-Up Period), directly or indirectly:

sell, offer to sell, contract to sell or lend, effect any short sale or establish or increase a put equivalent position or liquidate or decrease any call equivalent position on, pledge, hypothecate or grant any security interest in or in any other way transfer or dispose of, any shares of common stock or securities convertible into or exercisable or exchangeable for common stock;

enter into any swap, hedge or similar agreement or arrangement that transfers in whole or in part, the economic risk of ownership of the common stock or securities convertible into or exercisable or exchangeable for common stock, whether now owned or hereafter acquired;

engage in any short selling of the common stock or securities convertible into or exercisable or exchangeable for common stock;

make any demand for, or exercise any right with respect to, the registration under the Securities Act of the offer and sale of any shares of common stock or securities convertible into or exercisable or exchangeable for common stock, or cause to be filed a registration statement, prospectus or prospectus supplement (or an amendment or supplement thereto) with respect to any such registration; or

publicly announce any intention to do any of the foregoing.

The exceptions to such agreements permit parties, among other things and subject to restrictions, to: (a) make certain gifts, (b) make transfers to any corporation, partnership, limited liability company or other legal entity all of the beneficial ownership interests of which are held by such party or certain of his or her family members, (c) if the party is a corporation, partnership, limited liability company or other business entity, make transfers to partners, members or stockholders of such party, (d) make transfers by operation of law, including pursuant to a domestic order or a negotiated settlement, (e) exercise an option to purchase shares of common stock granted under any of our stock incentive plans or stock purchase plans, provided that the underlying shares of common stock shall continue to be subject to the restrictions on transfer, (f) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act of 1934 (the Exchange Act) for the transfer of common stock, provided that such plan does not provide for any sales or transfers of common stock during the Lock-up Period and that no filing under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such plan or its establishment, and (g) make transfers of shares of common stock acquired in the offering or on the open market following the offering, provided that no filing under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer or disposition.

### **Nasdaq Global Select Market Listing**

Our common stock is quoted on the Nasdaq Global Select Market under the symbol DRNA.

**Passive Market-Making**

In connection with the offering, the underwriters may engage in passive market-making transactions in the common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M under the Exchange Act during the period before the commencement of offers or sales of common stock and extending through the completion and distribution. A passive market-maker must display its bids at a price not in excess of the highest independent bid of the security. However, if all independent bids are lowered below the passive market-maker's bid, that bid must be lowered when specified purchase limits are exceeded.

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### **Short Sales, Stabilizing Transactions, and Penalty Bids**

In order to facilitate this offering, persons participating in this offering may engage in transactions that stabilize, maintain, or otherwise affect the price of our common stock during and after this offering. Specifically, the underwriters may engage in the following activities in accordance with the rules of the Securities and Exchange Commission.

*Short sales.* Short sales involve the sales by the underwriters of a greater number of shares than they are required to purchase in the offering. Covered short sales are short sales made in an amount not greater than the underwriters option to purchase additional shares from us in this offering. The underwriters may close out any covered short position by either exercising their option to purchase shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares from us in this offering. Naked short sales are any short sales in excess of such over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

*Stabilizing transactions.* The underwriters may make bids for or purchases of the shares for the purpose of pegging, fixing, or maintaining the price of the shares, so long as stabilizing bids do not exceed a specified maximum.

*Penalty bids.* If the underwriters purchase shares in the open market in a stabilizing transaction or syndicate covering transaction, they may reclaim a selling concession from the underwriters and selling group members who sold those shares as part of this offering. Stabilization and syndicate covering transactions may cause the price of the shares to be higher than it would be in the absence of these transactions. The imposition of a penalty bid might also have an effect on the price of the shares if it discourages presales of the shares.

The transactions above may occur on the Nasdaq Global Select Market or otherwise. Neither we nor the underwriters make any representation or prediction as to the effect that the transactions described above may have on the price of the shares. If these transactions are commenced, they may be discontinued without notice at any time.

### **Other Relationships**

The underwriters and their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and certain of their affiliates have in the past performed and may in the future perform various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.



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**NOTICE TO INVESTORS**

**Notice to Canadian Residents**

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

**Notice to United Kingdom Residents**

The underwriters have represented and agreed that:

it has not made or will not make an offer of the securities to the public in the United Kingdom within the meaning of section 102B of the Financial Services and Markets Act 2000 (as amended) (FSMA) except to legal entities which are authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities or otherwise in circumstances which do not require the publication by us of a prospectus pursuant to the Prospectus Rules of the Financial Services Authority (FSA);

it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of section 21 of FSMA) to persons who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 or in circumstances in which section 21 of FSMA does not apply to us; and

it has complied with and will comply with all applicable provisions of FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

**Notice to Switzerland Residents**

The securities will not be offered, directly or indirectly, to the public in Switzerland and this prospectus does not constitute a public offering prospectus as that term is understood pursuant to article 652a or 1156 of the Swiss Federal Code of Obligations.

**Notice to European Economic Area Residents**

In relation to each Member State of the European Economic Area (the EEA) which has implemented the European Prospectus Directive (each, a Relevant Member State), an offer of our shares may not be made to the public in a Relevant Member State other than:

to any legal entity which is a qualified investor, as defined in the European Prospectus Directive;

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to fewer than 150 natural or legal persons (other than qualified investors as defined in the European Prospectus Directive), subject to obtaining the prior consent of the relevant dealer or dealers nominated by us for any such offer; or

in any other circumstances falling within Article 3(2) of the European Prospectus Directive, provided that no such offer of our shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the European Prospectus Directive or supplement prospectus pursuant to Article 16 of the European Prospectus Directive.

For the purposes of this description, the expression an offer to the public in relation to the securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the expression may be varied in that Relevant Member State by any measure implementing the European Prospectus Directive in that member state, and the expression European Prospectus Directive means Directive 2003/71/EC (and amendments hereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

## **Notice to Israel Residents**

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728-1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728-1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the Addressed Investors); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728-1968, subject to certain conditions (the Qualified Investors). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728-1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728-1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728-1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728-1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728-1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

We have not authorized and do not authorize the making of any offer of securities through any financial intermediary on our behalf, other than offers made by the underwriters and their respective affiliates, with a view to the final placement of the securities as contemplated in this document. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of shares on our behalf or on behalf of the underwriters.

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**Electronic Offer, Sale and Distribution of Shares**

A prospectus in electronic format may be made available on the websites maintained by the underwriters or selling group members, if any, participating in this offering and the underwriters participating in this offering may distribute prospectuses electronically. The underwriters may agree to allocate a number of shares to the underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters and selling group members that will make internet distributions on the same basis as other allocations. Other than the prospectus in electronic format, the information on these websites is not part of this prospectus or the registration statement of which this prospectus forms a part, has not been approved or endorsed by us or any underwriter in its capacity as underwriter, and should not be relied upon by investors.

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**LEGAL MATTERS**

Sidley Austin LLP, Palo Alto, California, will provide us with an opinion as to the validity of the shares of common stock offered by this prospectus. This opinion may be conditioned upon and may be subject to assumptions regarding future actions required to be taken by us and any underwriters, dealers or agents in connection with the issuance and sale of the securities. Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, is counsel for the underwriters in connection with this offering.

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**EXPERTS**

The consolidated financial statements incorporated in this prospectus by reference from the Company's Annual Report on Form 10-K, have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

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**WHERE YOU CAN FIND MORE INFORMATION**

This prospectus is part of a registration statement that we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and the securities being offered hereby. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to the filings. You should review the complete document to evaluate these statements.

We are subject to the information reporting requirements of the Exchange Act. In accordance with the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Such reports, proxy statements and other information filed by us are available to the public free of charge at [www.sec.gov](http://www.sec.gov). You may also read and copy any document we file with the SEC at the public reference facilities maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the public reference facilities by calling the SEC at 1-800-SEC-0330.

We also make these documents available on our website at [dicerna.com](http://dicerna.com). Our website and the information contained or connected to our website is not incorporated by reference in this prospectus, and you should not consider it part of this prospectus.



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**INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE**

SEC rules permit us to incorporate by reference information in this prospectus. This means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is considered to be part of this prospectus, except for information superseded by information contained in this prospectus or in any subsequently filed incorporated document. This prospectus incorporates by reference the documents set forth below that we have previously filed with the SEC (Commission File No. 001-36281), other than information in such documents that is deemed to be furnished and not filed. These documents contain important information about Dicerna and its business and financial condition.

Annual Report on Form 10-K for the year ended December 31, 2016 filed on March 30, 2017, as amended;

our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which was filed on November 2, 2017;

our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, which was filed on August 10, 2017;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, which was filed on May 8, 2017;

our Current Reports on Form 8-K filed on March 30, 2017, April 12, 2017, July 12, 2017, and November 2, 2017; and

our Definitive Proxy Statement on Schedule 14A, filed with the SEC on May 23, 2017, as amended.

All documents filed by us pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act subsequent to the date of this prospectus supplement and prior to the completion of this offering and after the date of the initial registration statement and prior to the effectiveness of the registration statement shall be deemed to be incorporated by reference in this prospectus and to be a part hereof from the date of filing of such documents.

Any statement contained herein or in a document incorporated or deemed to be incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus, modifies or supersedes such earlier statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

Documents incorporated by reference are available from us without charge, excluding all exhibits unless specifically incorporated by reference as an exhibit to this prospectus. Prospective investors may obtain documents incorporated by reference in this prospectus by requesting them in writing or by telephone from us at our executive offices at:

Dicerna Pharmaceuticals, Inc.

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87 Cambridgepark Drive

Cambridge, MA 02140

(617) 621-8097

Attention: Investor Relations and Corporate Communications

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PROSPECTUS

**\$150,000,000**

**Common Stock**

**Preferred Stock**

**Debt Securities**

**Warrants**

**Other Rights**

**Units**

From time to time, we may sell up to an aggregate total offering price of \$150,000,000 of our shares of Common Stock, Preferred Stock, Debt Securities, Warrants, other Rights or Units, in each case in one or more issuances and at prices and on terms that we will determine at the time of the offering.

This prospectus describes the general manner in which any of these securities may be offered using this prospectus. We will specify in an accompanying prospectus supplement the terms of the securities offered and other details regarding the offering thereof.

Our common stock is listed on The NASDAQ Global Select Market under the symbol DRNA.

**We are an emerging growth company as defined by the Jumpstart Our Business Startups Act of 2012 and, as such, we are subject to reduced public company reporting requirements. Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading Risk Factors on page 6 of this prospectus and under any similar heading in the documents that are incorporated by reference into this prospectus, as well as Special Note Regarding Forward-Looking Statements on page 3 of this prospectus.**

The securities covered by this prospectus may be sold directly by us to investors, through agents designated by us from time to time or through underwriters or dealers at prices and on terms to be determined at the time of offering. We will include in an applicable prospectus supplement the names of any underwriters or agents and any applicable commissions or discounts. Additional information on the methods of sale appears under Plan of Distribution in this

prospectus. We will also describe in an applicable prospectus supplement the way(s) in which we expect to use the net proceeds we receive from any sale.

**Neither the U.S. Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus or any accompanying prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.**

**This prospectus may not be used to offer or sell any securities unless accompanied by a prospectus supplement.**

**The date of this prospectus is October 31, 2016.**

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**You should rely only on the information contained or incorporated by reference in this prospectus and in an applicable prospectus supplement to this prospectus. We have not authorized any other person to provide you with different or additional information. If anyone provides you with different, additional or inconsistent information, you should not rely on it. We do not take responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not making an offer to sell these securities or soliciting any offer to buy these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus, any applicable prospectus supplement or any free writing prospectus we authorize to be delivered to you is accurate only as of the date of that document or any other date set forth in that document. Additionally, any information we have incorporated by reference in this prospectus or in any applicable prospectus supplement is accurate only as of the date of the document incorporated by reference or other date set forth in that document, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any sale of securities. Our business, financial condition, results of operations, cash flow and prospects may have changed since that date.**

**This prospectus, any applicable prospectus supplement and the information incorporated herein or therein by reference contains market data, industry statistics and other data that have been obtained or compiled from information made available by independent third parties. We have not independently verified the accuracy and completeness of such data. This prospectus, any applicable prospectus supplement and the information incorporated herein or therein by reference include trademarks, service marks and trade names owned by us or other companies. Solely for convenience, we may refer to our trademarks included or incorporated by reference in this prospectus, any applicable prospectus supplement or any free writing prospectus without the <sup>TM</sup> or <sup>®</sup> symbols, but any such references are not intended to indicate that we will not assert, to the fullest extent permitted under applicable law, our rights to our trademarks or other intellectual property. All trademarks, service marks and trade names included or incorporated by reference in this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.**

**When used in this prospectus, the terms Dicerna, we, our and us refer to Dicerna Pharmaceuticals, Inc., a Delaware corporation, and its subsidiaries, unless otherwise specified or the context otherwise requires.**

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**ABOUT THIS PROSPECTUS**

This prospectus forms a part of a registration statement that we have filed with the U.S. Securities and Exchange Commission ( SEC ) using a shelf registration process.

By using a shelf registration statement, we may, from time to time, offer and sell the securities described in this prospectus with an aggregate total offering price not exceeding \$150 million in one or more offerings.

This prospectus describes the general manner in which we may offer the securities described in this prospectus. Each time we sell securities pursuant to the registration statement of which this prospectus forms a part we will provide an applicable prospectus supplement that will contain specific information about the offering and the securities offered, and may also add, update or change information contained in this prospectus. If there is any inconsistency between information in this prospectus and any accompanying prospectus supplement, you should rely on the information in the most recent applicable prospectus supplement and documents incorporated by reference herein and therein. This prospectus may not be used to offer to sell, solicit an offer to buy or consummate a sale of our securities unless it is accompanied by a prospectus supplement.

This prospectus, together with any accompanying prospectus supplement, contains important information you should know before investing in our securities, including important information about us and the securities being offered. You should carefully read both documents, as well as the additional information contained in the documents described under **Where You Can Find More Information** and **Incorporation of Certain Information by Reference** in both this prospectus and the applicable prospectus supplement, and in particular the annual quarterly and current reports and other documents we file with the SEC. Neither this prospectus nor any accompanying prospectus supplement is an offer to sell these securities or is soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

**WHERE YOU CAN FIND MORE INFORMATION**

We have filed with the SEC a registration statement on Form S-3 under the Securities Act of 1933, as amended (the Securities Act ), with respect to the securities offered by this prospectus and the applicable prospectus supplement. This prospectus and the applicable prospectus supplement do not contain all of the information set forth in the registration statement and its exhibits and schedules in accordance with SEC rules and regulations. For further information with respect to us and the securities being offered by this prospectus and the applicable prospectus supplement, you should read the registration statement, including its exhibits and schedules. Statements contained in this prospectus and the applicable prospectus supplement, including documents that we have incorporated by reference, as to the contents of any contract or other document referred to are not necessarily complete, and, with respect to any contract or other document filed as an exhibit to the registration statement or any other such document, each such statement is qualified in all respects by reference to the corresponding exhibit. You should review the complete contract or other document to evaluate these statements. You may obtain copies of the registration statement and its exhibits via the SEC's EDGAR database or our website, or at the offices of the SEC, where they may be examined without charge at the Public Reference Room, at the address listed below, or obtained upon payment of the prescribed fees.

We file annual, quarterly and current reports, proxy statements and other documents with the SEC under the U.S. Securities Exchange Act of 1934, as amended (the Exchange Act ). The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers, including us, that file electronically with the SEC. You may obtain documents that we file with the SEC at [www.sec.gov](http://www.sec.gov) and





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read and copy them at the SEC's Public Reference Room at 100 F Street N.E., Washington, DC 20549 (information on operation of the Public Reference Room is available by calling the SEC at 1-800-SEC-0330).

We also make these documents available on our website at [dicerna.com](http://dicerna.com). Our website and the information contained or connected to our website is not incorporated by reference in this prospectus or any prospectus supplement, and you should not consider it part of this prospectus or any prospectus supplement.

### **INCORPORATION OF CERTAIN INFORMATION BY REFERENCE**

SEC rules permit us to incorporate information by reference in this prospectus and the applicable prospectus supplement. This means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is considered to be part of this prospectus and the applicable prospectus supplement, except for information superseded by information contained in this prospectus or the applicable prospectus supplement itself or in any subsequently filed incorporated document. This prospectus and the applicable prospectus supplement incorporate by reference the documents set forth below that we have previously filed with the SEC (Commission File No. 001-36281), other than information in such documents that is deemed to be furnished and not filed. These documents contain important information about us and our business and financial condition.

Annual Report on Form 10-K for the year ended December 31, 2015;

Quarterly Reports on Form 10-Q for the quarters ended March 31, 2016 and June 30, 2016;

Current Reports on Form 8-K filed with the SEC on January 5, 2016, January 20, 2016, March 10, 2016, April 18, 2016, June 15, 2016 (excluding Item 7.01 therein), July 11, 2016 and October 13, 2016;

Definitive Proxy Statement on Form DEF 14A filed with the SEC on April 29, 2016; and

the description of our Common Stock contained in our Registration Statement on Form 8/A, dated January 28, 2014, including any amendments or reports filed for the purpose of updating such description.

All documents that we file (but not those that we furnish) pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended (the Exchange Act), after the date of the initial registration statement of which this prospectus is a part and prior to the effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus and will automatically update and supersede the information in this prospectus, and any previously filed documents. All documents that we file (but not those that we furnish) pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act on or after the date of this prospectus and prior to the termination of the offering of any of the securities covered under this prospectus shall be deemed to be incorporated by reference into this prospectus and will automatically update and supersede the information in this prospectus, the applicable prospectus supplement and any previously filed documents.

Any statement contained herein or in a document incorporated or deemed to be incorporated by reference in this prospectus or the applicable prospectus supplement shall be deemed to be modified or superseded for purposes of this

prospectus and such applicable prospectus supplement to the extent that a statement contained in this prospectus or such applicable prospectus supplement, or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus and such applicable prospectus supplement, modifies or supersedes such earlier statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus or such applicable prospectus supplement.

Documents incorporated by reference are available from us without charge, excluding all exhibits unless specifically incorporated by reference as an exhibit to this prospectus and the applicable prospectus supplement.

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Prospective investors may obtain documents incorporated by reference in this prospectus and the applicable prospectus supplement by requesting them in writing or by telephone from us at our executive offices at:

Dicerna Pharmaceuticals, Inc.

87 Cambridgepark Drive

Cambridge, MA 02140

(617) 621-8097

Attention: Investor Relations and Corporate Communications

**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

Certain statements contained or incorporated by reference in this prospectus, any applicable prospectus supplement and any related free writing prospectus constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and releases issued by the SEC and within the meaning of Section 27A of the Securities Act, and Section 21E of the Exchange Act. From time to time, we publish forward-looking statements relating to matters such as anticipated financial performance, business prospects, technological developments, new products, research and development activities and other aspects of our present and future business operations as well as similar matters.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by such forward-looking statements. While it is impossible to identify or predict all such matters, these differences may result from:

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;

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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;

developments relating to our competitors or our industry; and

our use of net proceeds from this offering.

In some cases, you can identify forward-looking statements by terminology such as expect, anticipate, estimate, continue, plan, believe, could, intend, predict, project, potential, may, should, will or the negative similar import regarding our expectations. Forward-looking statements are only predictions and actual events or results may differ materially. Although we believe that our expectations are based on reasonable assumptions within the bounds of our current knowledge of our industry, business and operations, we cannot guarantee that actual results will not differ materially from our expectations. In evaluating such forward-looking statements, you should specifically consider various factors, including the risks outlined under the heading Risk Factors contained in this prospectus, the applicable prospectus supplement and any related free writing prospectus, and in any other documents incorporated herein or therein. The discussion of these risks and uncertainties is not necessarily a complete or exhaustive list of all risks facing us at any particular point in time. We operate in a highly competitive, highly regulated and rapidly changing environment, and our business is in a state of evolution. Therefore, it is likely that over time new risks will emerge and the nature and certain elements of existing risks will change. It is not possible for management to predict all such risk factors or changes therein or to assess either the impact of all such risk factors on our business or the extent to which any individual risk factor, combination of factors or new or altered factors may cause results to differ materially from those contained in any forward-looking statement. Forward-looking statements represent our estimates and assumptions only as of the date such forward-looking statements are made. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein and therein by reference, and with the understanding that our actual future results may materially differ from what we expect.

Except as required by law, forward-looking statements speak only as of the date they are made. We do not have a policy of updating or revising forward-looking statements and we assume no obligation to update any statements as a result of new information or future events or developments. It should not be assumed that our silence over time means that actual events are bearing out as expressed or implied in forward-looking statements.



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**ABOUT THE COMPANY**

*The following highlights information about the registrant and our business contained elsewhere or incorporated by reference in this prospectus. It is not complete and does not contain all of the information that you should consider before investing in any of our securities. You should carefully read this prospectus together with the more detailed information incorporated by reference in this prospectus.*

**Overview**

We are a biopharmaceutical company focused on the discovery and development of innovative subcutaneously delivered RNA Interference (RNAi)-based pharmaceuticals using our GalXC RNAi platform for the treatment of rare diseases involving the liver and for other therapeutic areas involving the liver such as chronic liver diseases, cardiovascular diseases, and viral infectious diseases. Within these therapeutic areas, we believe our GalXC RNAi platform will allow us to build a broad pipeline with commercially attractive pharmaceutical properties, including a subcutaneous route of administration, infrequent dosing (e.g, dosing that is monthly or quarterly, and potentially even less frequent), high therapeutic index, and specificity to a single target gene. Within our therapeutic areas, we seek to focus our drug discovery and development efforts on target genes where the connection between that target gene and the disease is well understood and documented.

The GalXC RNAi platform supports Dicerna's long-term strategy to retain a full or substantial ownership stake and invest internally for diseases with focused patient populations, such as certain rare diseases, as we see such diseases as representing opportunities that carry high probabilities of success, have easily identifiable patient populations and a limited number of Centers of Excellence to facilitate reaching these patients, and have the potential for more rapid clinical development programs. For more complex diseases with multiple gene dysfunctions and larger patient populations, we plan to pursue partnerships that can provide the enhanced scale, resources and commercial infrastructure required to maximize these prospects.

**Our Corporate Information**

We were incorporated in Delaware in October 2006. Additional information concerning the Company is contained in the documents we file with the SEC, as described above. We maintain our executive offices at 87 Cambridgepark Drive, Cambridge, MA 02140, and our main telephone number is (617) 621-8097. We maintain a website at [dicerna.com](http://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 into, this prospectus and should not be considered part of this prospectus.

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**RISK FACTORS**

An investment in our securities is speculative in nature and involves a high degree of risk. Before deciding whether to invest in our securities, you should carefully consider the discussion of the material risks of investing in our securities contained in our filings with the SEC, as well as in the applicable prospectus supplement, in evaluating us and our business and prospects before you decide to purchase any of our securities. You should also be aware that this document and other public statements we make may contain statements that do not relate strictly to historical fact, any of which may be forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, and should take into account the considerations relating to such statements discussed under Risk Factors or any similar heading in the applicable prospectus supplement and in our filings we make with the SEC. Any of the risks and uncertainties set forth therein could materially and adversely affect our business, results of operations, cash flow and financial condition, which in turn could materially and adversely affect the trading price or value of our securities. As a result, you could lose all or part of your investment.

The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations.



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**USE OF PROCEEDS**

Unless otherwise described in the applicable prospectus supplement, we intend to use the net proceeds from the sale of any securities described in this prospectus for preclinical studies and clinical trials, with the remainder of any net proceeds from sales of securities being used for continued technology platform development, working capital and general corporate purposes.

We may set forth additional information concerning our expected use of net proceeds from sales of securities in the applicable prospectus supplement relating to the specific offering. Pending use of net proceeds as described above, we may invest net proceeds in interest-bearing, investment-grade securities.

The applicable prospectus supplement may not identify precisely the amounts we plan to spend on each of the uses of proceeds listed above or any other uses of proceeds that we may identify in that applicable prospectus supplement. In addition, the amounts actually expended for each purpose may vary significantly depending upon numerous factors, including:

the costs and results of research, development and product candidate testing, including clinical trials;

costs and results of the regulatory approval process;

costs and structure of potential acquisitions, collaborations or other transactions;

the structure of and changes in our relationships with licensors, licensees and collaborators;

the costs of filing, prosecuting, defending and enforcing patent claims;

manufacturing, marketing and other costs associated with commercialization of products; and

changes in the focus and direction of our research and development programs.

**DIVIDEND POLICY**

We have never declared or paid any cash dividends on our capital stock and do not anticipate paying any cash dividends in the foreseeable future. Payment of cash dividends, if any, in the future will solely be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

**RATIO OF EARNINGS TO FIXED CHARGES**

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The following table sets forth, for each of the periods presented, our ratio of earnings to fixed charges and our coverage deficiency. You should read this table in conjunction with the financial statements and notes incorporated by reference in this prospectus.

| <b>(in thousands)</b>                             | <b>Six Months</b>     | <b>For the Year Ended December 31,</b> |             |             |
|---|-----------------------|--|-------------|-------------|
|   | <b>Ended June 30,</b> | <b>2015</b>                            | <b>2014</b> | <b>2013</b> |
|   | <b>2016</b>           |  |             |             |
| Net loss  | (\$ 31,315)           | (\$ 62,839)                            | (\$ 47,939) | (\$ 18,518) |
| Ratio of earnings to fixed charges <sup>(1)</sup> | N/A                   | N/A                                    | N/A         | N/A         |
| Coverage deficiency                               | (\$ 31,315)           | (\$ 62,839)                            | (\$ 47,939) | (\$ 18,518) |

- <sup>(1)</sup> We did not record earnings for the years ended December 31, 2015, 2014 and 2013, or for the six months ended June 30, 2016. Accordingly, our earnings were insufficient to cover fixed charges for such periods and we are unable to disclose a ratio of earnings to fixed charges.

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**GENERAL DESCRIPTION OF SECURITIES**

We may offer shares of common or preferred stock, various series of senior or subordinated debt securities, warrants, other rights to purchase securities, or units consisting of combinations of the foregoing, in each case from time to time under this prospectus, together with the applicable prospectus supplement, at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. At the time we offer a particular type or series of securities, we will provide an applicable prospectus supplement describing the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

designation or classification;

aggregate principal amount or aggregate offering price;

voting or other rights;

rates and times of payment of interest, dividends or other payments;

liquidation preference;

original issue discount;

maturity;

ranking;

restrictive covenants;

redemption, conversion, exercise, exchange, settlement or sinking fund terms, including prices or rates, and any provisions for changes to or adjustments in such prices or rates and in the securities or other property receivable upon conversion, exercise, exchange or settlement;

any securities exchange or market listing arrangements; and

important U.S. federal income tax considerations.

This prospectus may not be used to offer or sell securities unless accompanied by an applicable prospectus supplement. The applicable prospectus supplement may add, update or change information contained in this prospectus or in documents incorporated by reference in this prospectus. You should read the prospectus supplement related to any securities being offered.

We may sell the securities directly to or through underwriters, dealers or agents. We and our underwriters, dealers or agents reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through underwriters or agents, we will include in the applicable prospectus supplement (i) the names of the underwriters or agents and applicable fees, discounts and commissions to be paid to them; (ii) details regarding over-allotment options, if any; and (iii) net proceeds to us.

The following descriptions are not complete and may not contain all the information you should consider before investing in any securities we may offer hereunder; they are summarized from, and qualified by reference to, our amended and restated certificate of incorporation, bylaws and the other documents referred to in the descriptions, all of which are or will be publicly filed with the SEC, as applicable. See [Where You Can Find More Information](#).

### **DESCRIPTION OF CAPITAL STOCK**

Our authorized capital stock consists of 150 million shares of common stock, par value \$0.0001 per share, and 5 million shares of preferred stock, par value \$0.0001 per share. As of September 30, 2016, there were 20,753,001 shares of common stock outstanding, none held as treasury stock, 87,901 subject to outstanding warrants to purchase common stock (including outstanding warrants to purchase preferred stock that became

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exercisable for shares of common stock upon the closing of our initial public offering), and 5,135,854 reserved for issuance upon exercise of outstanding stock options granted under Company incentive plans, and 616,215 available for future issuance pursuant to our existing stock incentive plans. No shares of preferred stock are issued and outstanding.

**Common Stock.** Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. In the election of directors, a majority of the votes cast at a meeting of stockholders is sufficient to elect a director, except that if the number of nominees exceeds the number of directors to be elected, then a plurality of the votes cast at a meeting of stockholders is sufficient to elect a director. Our stockholders do not have cumulative voting rights in the election of directors. Accordingly, holders of a majority of the voting shares are able to elect all of the directors. Except as noted below under Anti-takeover effects of Delaware law, our certificate of incorporation and our bylaws, a majority vote of common stockholders is generally required to take action under our certificate of incorporation and bylaws. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription or conversion rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. All outstanding shares of common stock are fully paid and non-assessable. American Stock Transfer and Trust Company, LLC is the transfer agent and registrar for our common stock.

**Preferred Stock.** Our board of directors has the authority, without further vote or action by the stockholders, to designate and issue shares of preferred stock in one or more series and to designate the rights, preferences and privileges of each series, which may be greater than the rights of the common stock. We will fix in a certificate of designation the number of shares, the designation and the rights, preferences and privileges, including any dividend, conversion, voting or preemptive rights, terms of redemption or repurchase, liquidation preferences and sinking fund terms, auction and remarketing procedures, and any transfer or other restrictions or limitations of or relating to any series of preferred stock that we sell under this prospectus and applicable prospectus supplements. The Delaware General Corporation Law (DGCL) provides that in addition to any voting rights that may be provided in the applicable certificate of designation, preferred stock holders have the right to vote separately as a class on a proposed amendment to our charter involving certain fundamental changes in their rights. Preferred stock terms could adversely affect the voting power or other rights of common stock holders and the likelihood that they would receive dividend or liquidation payments, and could have the effect of delaying, deferring or preventing a change in control. You should read the applicable prospectus or prospectus supplement and the certificate of designation relating to any series of preferred stock we may offer.

**Outstanding Warrants.** As of September 30, 2016, we had outstanding warrants as follows:

five warrants to purchase an aggregate of 2,198 shares of our common stock with an exercise price of \$250 per share, each exercisable at any time on or before June 17, 2020; and

seven warrants to purchase an aggregate of 85,703 shares of our common stock with an exercise price of \$7.00, each exercisable at any time on or before June 26, 2018.

**Registration Rights**

We are party to an amended and restated registration rights agreement dated as of July 30, 2013, pursuant to which certain of our stockholders are entitled to demand, Form S-3 and piggyback registration rights. The shares of common stock that they may cause to be registered are referred to as registrable securities .

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### ***Demand registration rights***

Subject to certain limitations, the holders of at least a majority of the registrable securities, which majority includes the holders of at least 74% of our shares of Series C Preferred Stock which have since been converted to common shares, have the right to demand we file, no more than two times, a registration statement on Form S-1 to register all or a portion of their registrable securities.

### ***Form S-3 registration rights***

Subject to certain limitations, the holders of at least 25 percent of the registrable securities have the right to demand we file an unlimited number of registration statements on Form S-3, provided that the anticipated aggregate offering price of the registrable securities to be sold under the registration statement on Form S-3 exceeds \$3.0 million, net of underwriting discounts and commissions.

### ***Piggyback registration rights***

Subject to certain conditions, if we propose to register any of our securities under the Securities Act, for sale to the public, the holders of registrable securities are entitled to receive written notice of such registration and to request that we include some or all of their registrable securities for resale in the registration statement. Under certain conditions, the managing underwriter of the offering will have the right to limit the number of shares of selling stockholders to be included in such registration.

### ***Expenses of registration; indemnification***

Other than underwriting fees, commissions and discounts on the shares sold by any holder of registrable securities, we are generally required to bear all registration expenses incurred in connection with the demand, Form S-3 and piggyback registrations described above, except that we are not obligated to pay for more than two registrations in the case of demand and Form S-3 registrations. The amended and restated registration rights agreement contains customary indemnification provisions with respect to registration rights.

### ***Termination of registration rights***

The demand, Form S-3 and piggyback registration rights described above will terminate on the date five years after the closing of our initial public offering which is February 4, 2019. In addition, the registration rights of a holder of registrable securities will expire if (i) the holder holds one percent or less of our outstanding common stock and all of the holder's registrable securities may be sold in a three-month period under Rule 144 of the Securities Act or (ii) the holder can sell all shares of common stock held by it in compliance with Rule 144(b)(1)(i) of the Securities Act.

### **Anti-Takeover Effects of Provisions of Delaware Law and Our Charter Documents**

Our certificate of incorporation and bylaws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

### ***Removal of directors***

Our certificate of incorporation and bylaws provide that subject to any limitations imposed by law and the rights of the holders of any series of our preferred stock, the board of directors or any individual director may be removed from

office at any time without cause by the affirmative vote of the holders of a majority of the voting power of all the then-outstanding shares of voting stock of the Company, entitled to vote at an election of directors.



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### ***No written consent of stockholders***

Our certificate of incorporation and bylaws provide that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting.

### ***Meetings of stockholders***

Our certificate of incorporation and bylaws provide that special meetings of stockholders, which the Company is not obligated to call more than once per calendar year, may only be called 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). In addition, our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

### ***Advance notice requirements***

Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than the close of business on the ninetieth (90<sup>th</sup>) day nor earlier than the close of business on the one hundred twentieth (120<sup>th</sup>) day prior to the first anniversary of the annual meeting for the preceding year. The notice must contain certain information specified in the bylaws. These provisions may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

### ***Amendment to certificate of incorporation and bylaws***

Our certificate of incorporation provides that the affirmative votes of the holders of at least a majority of the voting power of all of the then-outstanding shares of our voting stock will be required to amend certain provisions of our certificate of incorporation, including provisions relating to the size of our board of directors, removal of directors, special meeting of stockholders and actions by written consent. The affirmative votes of the holders of at least a majority of the voting power of all of the then-outstanding shares of our voting stock will be required to amend or repeal our bylaws. In addition, our bylaws may be amended or repealed by our board of directors, subject to any limitations set forth in the bylaws.

### ***Blank check preferred stock***

Our certificate of incorporation provides for 5,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute

the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred

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stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

### ***Delaware Law***

We are subject to the provisions of Section 203 of the DGCL, which, subject to certain exceptions, prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the interested stockholder attained such status with the approval of the board of directors or the business combination is approved in a prescribed manner. A business combination includes a merger or asset sale involving or other transaction resulting in a financial benefit to the interested stockholder. Subject to various exceptions, an interested stockholder is a person who, together with affiliates and associates, owns, or within the past three years did own, 15% or more of a corporation's voting stock. This statute could prohibit or delay the accomplishment of mergers or other takeover or change in control attempts and, accordingly, may discourage attempts to acquire the Company.

### ***Delaware as sole and exclusive forum***

Our bylaws provide, that unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware shall, to the fullest extent permitted by law, be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of us, (ii) 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, (iii) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, as amended, or our certificate of incorporation or bylaws, (iv) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws, or (v) any action asserting a claim governed by the internal affairs doctrine.

### ***Charter Documents***

Our bylaws provide that we will indemnify our directors and executive officers to the fullest extent permitted by Delaware law and that we may indemnify our other officers, employees and other agents. We may enter into indemnification contracts with our directors and officers and purchase insurance on behalf of any person whom we are required or permitted to indemnify. In addition, our charter provides that the liability of our directors for monetary damages shall be eliminated, except for (i) breach of the directors duty of loyalty to the Company or its stockholders, (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) violating Section 174 of the DGCL, or (iv) any transaction from which the director derived an improper personal benefit. Pursuant to Delaware law and subject to the foregoing exceptions, our directors shall not be liable for monetary damages for breach of the directors' fiduciary duty of care to the Company and its stockholders. This provision does not eliminate the duty of care: in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief remain available under Delaware law, and it does not affect a director's responsibilities under any other law, such as U.S. federal securities laws or state or federal environmental or other laws.

## **DESCRIPTION OF DEBT SECURITIES**

We may issue debt securities from time to time, in one or more series, as senior, subordinated or junior subordinated, convertible or non-convertible and secured or unsecured debt. Any senior debt securities will rank equally with any unsubordinated debt. Subordinated debt securities will rank equally with any other subordinated debt of the same ranking we may issue. Convertible debt securities will be convertible into or exchangeable for our common stock or

other securities at predetermined conversion rates, and conversion may be mandatory or at the holder's option.

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Debt securities will be issued under one or more indentures, which are instruments between us and a national banking association or other eligible party acting as trustee on behalf of holders of debt securities. Following is a summary of certain general features of debt securities we may offer; we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement, which may differ in certain respects from the terms we describe below. You should read the applicable prospectus supplement, any free writing prospectus we may authorize and the indentures, supplemental indentures and forms of debt securities relating to any series of debt securities we may offer.

**General.** Except as we may otherwise provide in the applicable prospectus supplement, the relevant indenture will provide that debt securities may be issued from time to time in one or more series. The indenture will not limit the amount of debt securities that may be issued thereunder, and will provide that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution, an officers certificate or a supplemental indenture, if any, relating to such series.

We will describe in each applicable prospectus supplement the following terms relating to any series of debt securities, including, to the extent applicable:

the title or designation;

whether the debt securities will be secured or unsecured, and the terms of any security;

whether the debt securities will be subject to subordination, and any terms thereof;

any limit upon the aggregate principal amount;

the date or dates on which the debt securities may be issued and on which we will pay the principal;

the interest rate, which may be fixed or variable, or the method for determining the rate, the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining them;

the manner in which the amounts of payment of principal of, premium (if any) or interest on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;

the currency of denomination;

if payments of principal of, premium (if any) or interest will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;

the place or places where the principal of, premium (if any) and interest will be payable, where debt securities of any series may be presented for registration of transfer, exchange or conversion, and where notices and demands to or upon the Company in respect of the debt securities may be made;

the form of consideration in which principal of, premium (if any) or interest will be paid;

the terms and conditions upon which we may redeem the debt securities;

any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund, amortization or analogous provisions or at the option of a holder;

the dates on which and the price or prices at which we will repurchase the debt securities at the option of holders and other detailed terms and provisions of these obligations;

the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;

the portion of principal amount payable upon declaration of acceleration of the maturity date, if other than the principal amount;

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whether the debt securities are to be issued at any original issuance discount and the amount of discount with which the debt securities may be issued;

whether the debt securities will be issued in certificated or global form and, in such case, the depositary and the terms and conditions, if any, upon which interests in such global security or securities may be exchanged in whole or in part for the individual securities represented thereby;

provisions, if any, for defeasance in whole or in part and any addition or change to provisions related to satisfaction and discharge;

the form of the debt securities;

the terms and conditions upon which convertible debt securities will be convertible or exchangeable into our securities or property or those of another person, if at all, and any additions or changes, if any, to permit or facilitate the same;

any provisions granting special rights to holders upon the occurrence of specified events;

any restriction or condition on transferability;

any addition or change in the provisions related to compensation and reimbursement of the trustee;

any addition to or change in the events of default described in this prospectus or in the indenture and any change in the acceleration provisions so described;

whether the debt securities will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;

whether we will be restricted from incurring any additional indebtedness;

any addition to or change in the covenants described in this prospectus or in the indenture, including terms of any restrictive covenants; and

any other terms which may modify or delete any provision of the indenture.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with

information on the U.S. federal income tax considerations and other special considerations applicable to any debt securities in the applicable prospectus supplement.

***Conversion or Exchange Rights.*** We will set forth in the applicable prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or other securities. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or other securities that the holders of debt securities receive would be subject to adjustment.

***Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction.*** Except as we may otherwise provide in the applicable prospectus supplement, the indenture will provide that we may not merge or consolidate with or into another entity, or sell other than for cash or lease all or substantially all our assets to another entity, or purchase all or substantially all the assets of another entity unless we are the surviving entity or, if we are not the surviving entity, the successor, transferee or lessee entity expressly assumes all of our obligations under the indenture or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders additional protection in the event we experience a change of control or in the event of a highly-leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect them.



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***Events of Default Under the Indenture.*** Except as we may otherwise provide in the applicable prospectus supplement, the following will be events of default under the indenture with respect to any series of debt securities that we may issue:

if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;

if we fail to pay the principal, or premium, if any, when due whether by maturity or called for redemption;

if we fail to pay a sinking fund installment, if any, when due and our failure continues for 30 days;

if we fail to observe or perform any other covenant relating to the debt securities, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the trustee or holders of not less than a majority in aggregate principal amount of the outstanding series; and

if specified events of bankruptcy, insolvency or reorganization occur as to the Company.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) will necessarily constitute an event of default with respect to any other series. The occurrence of an event of default may constitute an event of default under any credit or similar agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

Except as we may otherwise provide in the applicable prospectus supplement, if an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities are discount securities, that portion of the principal amount as may be specified in the terms of such securities) of and premium and accrued and unpaid interest, if any, on all such debt securities. Before a judgment or decree for payment of the money due has been obtained with respect to any series, the holders of a majority in principal amount of that series (or, at a meeting of holders at which a quorum is present, the holders of a majority in principal amount represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration) and the Company has deposited with the trustee or paying agent a sum sufficient to pay all amounts owed to the trustee under the indenture, all arrears of interest, if any, and the principal and premium, if any, on the debt securities that have become due other than by such acceleration. We refer you to the applicable prospectus supplement relating to any discount securities for the particular provisions relating to acceleration of a portion of the principal amount thereof upon the occurrence of an event of default.

Subject to the terms of the indenture, and except as we may otherwise provide in a prospectus supplement, if an event of default under the indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of

its rights or powers under such indenture at the request or direction of any of the holders of the applicable series, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to that series, provided that, subject to the terms of the indenture, the trustee need not take any action that it believes, upon the advice of counsel, might involve it in personal liability or might be unduly prejudicial to holders not involved in the proceeding.

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Except as we may otherwise provide in the applicable prospectus supplement, a holder of the debt securities of any series will only have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies if:

the holder previously has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least a majority in aggregate principal amount outstanding of that series have made written request, and such holders have offered reasonable indemnity to the trustee to institute the proceeding as trustee; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount outstanding of that series (or at a meeting of holders at which a quorum is present, the holders of a majority in principal amount of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

Except as we may otherwise provide in the applicable prospectus supplement, these limitations will not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, them.

We will periodically file statements with the applicable trustee regarding our compliance with specified covenants in the applicable indenture.

***Modification of Indenture; Waiver.*** Except as we may otherwise provide in the applicable prospectus supplement, we and the trustee may, without the consent of any holders of any series, execute a supplemental indenture to change the indenture with respect to specific matters, including, among other things:

to surrender any right or power conferred upon us;

to provide, change or eliminate any restrictions on payment of principal of or premium, if any; provided that any such action shall not adversely affect the interests of the holders of debt securities of any series in any material respect;

to change or eliminate any of the provisions of the indenture; provided that any such change or elimination shall become effective only when there is no outstanding debt security created prior to the execution of such supplemental indenture that is entitled to the benefit of such provision and as to which such supplemental indenture would apply;

to evidence any successor entity to us;

to evidence and provide for the acceptance of appointment by a successor trustee with respect to one or more series of debt securities and to add or change provisions of the indenture to facilitate the administration thereof by more than one trustee;

to cure any ambiguity, mistake, manifest error, omission, defect or inconsistency in the indenture or to conform the text of any provision in the indenture or in any supplemental indenture to any description thereof in the applicable section of a prospectus, prospectus supplement or other offering document that was intended to be a verbatim recitation of a provision of the indenture or of any supplemental indenture;

to add to or change or eliminate any provision of the indenture as shall be necessary or desirable in accordance with any amendments to the U.S. Trust Indenture Act of 1939;

to make any change in any series of debt securities that does not adversely affect in any material respect the interests of the holders thereof; and

to supplement any of the provisions of the indenture to such extent as shall be necessary to permit or facilitate the defeasance and discharge of any series of debt securities; provided that any such action shall not adversely affect the interests of holders of any debt securities.

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In addition, and except as we may otherwise provide in the applicable prospectus supplement, under the indenture the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount outstanding (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount represented at such meeting) that is affected. We and the trustee may, however, make the following changes only with the consent of each holder of any outstanding debt securities affected:

extending the fixed maturity;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon redemption;

reducing the principal amount of discount securities payable upon acceleration of maturity;

making the principal of or premium or interest payable in currency other than that stated;

impairing the right to institute suit for the enforcement of any payment on or after the fixed maturity date;

materially adversely affecting the economic terms of any right to convert or exchange; and

reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver; or modifying, without the written consent of the trustee, the rights, duties or immunities of the trustee.

Except for certain specified provisions, and except as we may otherwise provide in the applicable prospectus supplement, the holders of at least a majority in principal amount of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount represented at such meeting) may, on behalf of the holders of all debt securities of that series, waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may, on behalf of all such holders, waive any past default under the indenture with respect to that series and its consequences, other than a default in the payment of the principal of, premium or any interest; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

***Discharge.*** Except as we may otherwise provide in the applicable prospectus supplement, the indenture will provide that we can elect to be discharged from our obligations with respect to one or more series of debt securities. In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, the premium, if any, and interest on, the debt securities of the affected series on the dates payments are due.

***Form, Exchange and Transfer.*** Except as we may otherwise provide in the applicable prospectus supplement, we will issue debt securities only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. Except as we may otherwise provide in the applicable prospectus supplement, the indenture will provide that we may issue debt securities in temporary or permanent global form and as book-entry securities that will be deposited with a depository named by us and identified in a prospectus supplement with respect to that series.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities or the indenture, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

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We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

Except as we may otherwise provide in a prospectus supplement, if we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

***Information Concerning the Trustee.*** The trustee, other than during the occurrence and continuance of an event of default under the indenture, will undertake to perform only those duties as are specifically set forth in the indenture. Upon an event of default, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee will be under no obligation to exercise any of the powers given it by the indenture at the request of any holder unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

***Payment and Paying Agents.*** Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of interest on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

Unless we otherwise indicate in the applicable prospectus supplement, we will pay principal of and any premium and interest at the office of the trustee or, at the option of the Company, by check payable to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the trustee our sole paying agent for payments. We will name in the applicable prospectus supplement any other paying agents that we initially designate. We will maintain a paying agent in each place of payment.

All money we pay to a paying agent or the trustee for the payment of principal or any premium or interest which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the security thereafter may look only to us for payment thereof.

***Governing Law.*** The indenture and the debt securities will be governed and construed in accordance with the laws of the State of New York.

***No Personal Liability of Directors, Officers, Employees and Stockholders.*** No incorporator, stockholder, employee, agent, officer, director or subsidiary of ours will have any liability for any obligations of ours or, due to the creation of any indebtedness under the debt securities, the indentures or supplemental indentures. The indenture provides that all such liability is expressly waived and released as a condition of, and as consideration for, the execution of such indentures and the issuance of the debt securities.

**DESCRIPTION OF WARRANTS, OTHER RIGHTS AND UNITS**

We may from time to time issue warrants or other rights (together, Rights), in one or more series, for the purchase of shares of our common stock or preferred stock. We may issue Rights independently or together with



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such securities, and such Rights may be attached to or separate from them. Rights will be evidenced by a Rights certificate issued under one or more Rights agreements between us and a Rights agent which will act solely as our agent in connection with the Rights and will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of Rights.

We may issue securities in Units, each consisting of two or more types of securities. For example, we might issue Units consisting of a combination of shares of our common stock and warrants to purchase shares of our common stock. If we issue Units, the applicable prospectus supplement will contain information with regard to each of the securities that is a component of the Units. In addition, the applicable prospectus supplement will describe the terms of any Units we issue. The forms of any certificates and agreements relating to such Units will be filed as exhibits to the registration statement of which this prospectus forms a part by amendment thereof or as exhibits to a Current Report on Form 8-K incorporated herein by reference.

The applicable prospectus supplement and such forms may add, update or change the terms and conditions of the Rights or Units described in this prospectus. You should read the prospectus supplements, Rights agreements and Rights certificates that contain the terms of the Rights in their entirety.

The particular terms of each issue of Rights or Units will be described in the applicable prospectus supplement, including, to the extent applicable:

the title of the Rights or Units;

any initial offering price;

the title, aggregate principal amount or number and terms of the securities purchasable upon exercise of the Rights;

the principal amount or number of securities purchasable upon exercise of each Right and the price at which that principal amount or number may be purchased upon exercise of each Right;

the currency or currency units in which any offering price and any exercise price are payable;

the title and terms of any related securities with which the Rights are issued and the number of the Rights issued with each security;

any date on and after which the Rights or Units and the related securities will be separately transferable;

any minimum or maximum number of Rights that may be exercised at any one time;

the date on which the right to exercise the Rights will commence and the date on which the right will expire;

a discussion of U.S. federal income tax, accounting or other considerations applicable to the Rights or Units;

whether the Rights represented by the Rights certificates, if applicable, will be issued in registered or bearer form and, if registered, where they may be transferred and registered;

any anti-dilution provisions of the Rights or Units;

any redemption or call provisions applicable to the Rights;

any provisions for changes to or adjustments in the exercise price of any Rights; and

any additional terms of the Rights or Units, including terms, procedures and limitations relating to exchange and exercise of the Rights or Units.

Rights certificates will be exchangeable for new Rights certificates of different denominations and, if in registered form, may be presented for registration of transfer, and Rights may be exercised, at the corporate trust

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office of the Rights agent or any other office indicated in the applicable prospectus supplement. Before the exercise of Rights, holders of Rights will not be entitled to payments of any dividends, principal, premium or interest on securities purchasable upon exercise of the Rights, to vote, consent or receive any notice as a holder of and in respect of any such securities or to enforce any covenants in any indenture, or to exercise any other rights whatsoever as a holder of securities purchasable upon exercise of the Rights.

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**PLAN OF DISTRIBUTION**

We may sell the offered securities in and outside the United States (1) through underwriters or dealers, (2) directly to one or more purchasers, including to a limited number of institutional purchasers, to a single purchaser or to our affiliates and stockholders, (3) through agents or (4) through a combination of any of these methods.

If underwriters or dealers are used in the sale, the securities will be acquired by the underwriters or dealers for their own account and may be resold from time to time in one or more transactions, including:

in one or more transactions at a fixed price or prices, which may be changed from time to time;

in at-the-market offerings, within the meaning of Rule 415(a)(4) of the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise;

through a market maker or into an existing trading market on an exchange or otherwise;

at prices related to those prevailing market prices; or

at negotiated prices.

The applicable prospectus supplement will set forth the following information to the extent applicable:

the terms of the offering;

the names of any underwriters, dealers or agents;

the name or names of any managing underwriter or underwriters;

the purchase price of the securities;

the net proceeds from the sale of the securities;

any delayed delivery arrangements;

any underwriting discounts, commissions and other items constituting underwriters' compensation;

any initial public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any commissions paid to agents.

**Sale through Underwriters or Dealers**

If any securities are offered through underwriters, the underwriters will acquire the securities for their own account and may resell them from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer and sell securities to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. Unless otherwise provided in the applicable prospectus supplement, the obligations of the underwriters to purchase the securities will be subject to certain conditions, and the underwriters will be obligated to purchase all of the offered securities if they purchase any of them. In connection with the sale of securities, underwriters may be deemed to have received compensation from us in the form of underwriting discounts or commissions and dealers may receive compensation from the underwriters in the form of discounts or concessions. The underwriters may change from time to time any initial public offering price and any discounts or concessions allowed or reallocated or paid to dealers.

In order to facilitate the offering of securities, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. Specifically, the underwriters may overallocate in connection

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with the offering, creating a short position in the securities for their account. In addition, to cover overallocments or to stabilize the price of the shares, the underwriters may bid for, and purchase, shares in the open market. Finally, an underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed shares in transactions to cover syndicate short positions, in stabilization transactions, or otherwise. Any of these activities may stabilize or maintain the market price of the offered securities above independent market levels. The underwriters are not required to engage in these activities, and may discontinue any of these activities at any time.

Some or all of the securities that we offer through this prospectus may be new issues of securities with no established trading market. Any underwriters to whom we sell securities for public offering and sale may make a market in those securities, but they will not be obligated to do so and they may discontinue any market making at any time without notice. Accordingly, we cannot assure you of the liquidity of, or continued trading markets for, any securities offered pursuant to this prospectus.

If any securities are offered through dealers, we will sell the securities to them as principals. They may then resell those securities to the public at varying prices determined by the dealers at the time of resale.

## **Direct Sales and Sales through Agents**

We may sell the securities directly to purchasers. If the securities are sold directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities, we will describe the terms of any such sales in the applicable prospectus supplement. We may also sell the securities through agents designated from time to time. Sales may be made by means of ordinary brokers' transactions on the NASDAQ Global Select Market at market prices, in block transactions and such other transactions as agreed by us and any agent. In the applicable prospectus supplement, we will name any agent involved in the offer or sale of the offered securities, and we will describe any commissions payable to the agent. Unless otherwise provided in the applicable prospectus supplement, any agent will agree to use its reasonable best efforts to solicit purchases for the period of its appointment.

## **At-the-Market Offerings**

To the extent that we make sales through one or more underwriters or agents in at-the-market offerings, we will do so pursuant to the terms of a sales agency financing agreement or other at-the-market offering arrangement between us, on one hand, and the underwriters or agents, on the other. If we engage in at-the-market sales pursuant to any such agreement, we will issue and sell our securities through one or more underwriters or agents, which may act on an agency basis or a principal basis. During the term of any such agreement, we may sell securities on a daily basis in exchange transactions or otherwise as we agree with the underwriters or agents. Any such agreement will provide that any securities sold will be sold at prices related to the then prevailing market prices for our securities. Therefore, exact figures regarding proceeds that will be raised or commissions to be paid cannot be determined at this time. Pursuant to the terms of the agreement, we may agree to sell, and the relevant underwriters or agents may agree to solicit offers to purchase blocks of our common stock or other securities. The terms of any such agreement will be set forth in more detail in the applicable prospectus supplement.

## **Remarketing Arrangements**

Offered securities may also be offered and sold, if we so indicate in the applicable prospectus supplement, in connection with a remarketing upon their purchase, in accordance with a redemption or repayment pursuant to their terms, or otherwise, by one or more remarketing firms, acting as principals for their own accounts or as our agents.

Any remarketing firm will be identified and the terms of its agreements, if any, with us and its compensation will be described in the applicable prospectus supplement. Remarketing firms may be deemed to be underwriters of the offered securities under the Securities Act.

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**Delayed Delivery Contracts**

If we so indicate in the applicable prospectus supplement, we may authorize agents, underwriters or dealers to solicit offers by certain institutions to purchase securities from us pursuant to contracts providing for payment and delivery on a specified future date. The applicable prospectus supplement will describe the conditions to those contracts and the commission payable for solicitation of those contracts.

**General Information**

We may have agreements with the agents, dealers, underwriters and remarketing firms to indemnify them against certain civil liabilities, including liabilities under the Securities Act, or to contribute with respect to payments that the agents, dealers or underwriters may be required to make. Agents, dealers, underwriters and remarketing firms may be customers of, engage in transactions with or perform services for us in the ordinary course of their businesses.

Each underwriter, dealer and agent participating in the distribution of any of the securities that are issuable in bearer form will agree that it will not offer, sell or deliver, directly or indirectly, securities in bearer form in the United States or to United States persons, other than qualifying financial institutions, during the restricted period, as defined in United States Treasury Regulations Section 1.163-5(c)(2)(i)(D)(7).



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**LEGAL MATTERS**

Sidley Austin LLP, Palo Alto, California will issue an opinion regarding the legality of certain of the offered securities. Any underwriters will be advised about other issues relating to any offering by their own legal counsel.

**EXPERTS**

The consolidated financial statements incorporated in this prospectus by reference from the Company's Annual Report on Form 10-K, have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

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**5,714,286 Shares**

**Common Stock**

**PROSPECTUS SUPPLEMENT**

***Joint Book-Running Managers***

**Stifel**

**Evercore ISI**

***Co-Lead Managers***

**H.C. Wainwright & Co.**

**SunTrust Robinson Humphrey**

**December 14, 2017**

