Dicerna Pharmaceuticals Inc
Form 424B4
January 30, 2014
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Filed Pursuant to Rule 424(b)(4)
Registration No. 333-193150

PROSPECTUS

6,000,000 Shares

Dicerna Pharmaceuticals, Inc.

Common Stock

We are offering 6,000,000 shares of our common stock. This is our initial public offering and no public market currently exists for our common stock.

Our common stock has been approved for listing 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 have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

Investing in our common stock involves a high degree of risk. Please read Risk Factors beginning on page 10 of this prospectus.

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

	PER SHARE	TOTAL
Public Offering Price	$ 15.00	$ 90,000,000
Underwriting Discounts and Commissions[(1)]	$ 1.05	$ 6,300,000
Proceeds to Dicerna Pharmaceuticals, Inc. before expenses	$ 13.95	$ 83,700,000

(1) The underwriters will also be reimbursed for certain expenses incurred in this offering. See Underwriting for details.
Certain of our existing stockholders, including certain affiliates of our directors, have agreed to purchase an aggregate of 3,400,000 shares of our common stock in this offering at the initial public offering price. The underwriters will receive the same underwriting discount on any shares purchased by these stockholders as they will on any other shares sold to the public in this offering.

Delivery of the shares of common stock is expected to be made on or about February 4, 2014. We have granted the underwriters an option for a period of 30 days to purchase an additional 900,000 shares of our common stock. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $7,245,000 and the total proceeds to us, before expenses, will be $96,255,000.

Joint Book-Running Managers

Jefferies **Leerink Partners** **Stifel**

Co-Lead Manager

Baird

Prospectus dated January 29, 2014

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We are responsible for the information contained in this prospectus. Neither we nor the underwriters have authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We do not, and the underwriters do not, take responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus is current only as of its date.

Through and including February 23, 2014 (25 days after the date of this prospectus), all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to the dealers obligation to deliver a prospectus when acting as an underwriter and with respect to their unsold allotments or subscriptions.

For investors outside the United States: Neither we nor the underwriters have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the United States. You are required to inform yourselves about and to observe any restrictions relating to this offering and the distribution of this prospectus outside of the United States.

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PROSPECTUS SUMMARY

This summary highlights selected information contained in greater detail elsewhere in this prospectus. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors and our historical financial statements and related notes included elsewhere in this prospectus, before making an investment decision.

Our Company

Overview

We are a biopharmaceutical company focused on the discovery and development of innovative treatments for rare inherited diseases involving the liver and for cancers that are genetically defined. We are using our proprietary RNA interference (RNAi) technology platform, which we believe improves on existing RNAi technologies, to build a broad pipeline in these therapeutic areas. We intend to discover, develop and commercialize novel therapeutics either on our own or in collaboration with pharmaceutical partners. In indications such as rare diseases in which a small sales force will suffice, we expect to retain substantially all commercial rights in key markets. In oncology and other more prevalent disease areas, we intend to partner our product candidates while seeking to retain significant portions of the commercial rights in North America. We have partnered two of our oncology development programs with the global pharmaceutical company Kyowa Hakko Kirin Co., Ltd. (KHK). We are eligible to receive royalties on worldwide net sales for these product candidates. We have an option to co-promote any product candidate targeting the oncogene KRAS, the more advanced of these two programs, in the U.S. for an equal share of the profits from U.S. net sales.

Our current development programs are as follows.

- **DCR-PH1 for Primary Hyperoxaluria 1 (PH1).** We are developing DCR-PH1 for the treatment of the rare and serious inherited disorder PH1 by targeting the liver metabolic enzyme glycolate oxidase. PH1 afflicts an estimated one to three people per million of population and may afflict as many as eight people per million of population and causes severe renal disease and early mortality. In the mouse genetic model of PH1, we have shown that by using our RNAi technology to inactivate the gene encoding glycolate oxidase we can significantly reduce the key pathology of PH1. We intend to begin clinical trials for DCR-PH1 in 2015. We expect to announce initial proof-of-concept clinical data in mid to late 2015.

- **Other rare inherited diseases involving the liver.** We are investigating a number of other rare diseases involving disease target genes expressed in the liver. These include maple syrup urine disease, familial amyloid polyneuropathy or cardiomyopathy, alpha-1 anti-trypsin hepatocyte inclusions, severe hemophilia A and B and paroxysmal nocturnal hemoglobinuria, among others. In each case, we are seeking to target a clear unmet medical need, a readily-identified patient population, favorable market dynamics, potential orphan drug designation and the possibility to use RNAi-based therapeutics to achieve an optimal combination of high efficacy and low toxicity. Based on the investigation results, we plan to select a specific disease or disorder to further research and develop. We expect to initiate clinical trials in 2015 for any program that we advance into development.

- **DCR-M1711 for MYC-related cancers.** We are developing DCR-M1711 for the treatment of various cancers by targeting the MYC oncogene, a gene that causes or promotes cancer when abnormally expressed or activated. The expression of MYC is increased in a wide variety of tumor types and this increased gene expression has been shown to be related to the presence and severity of cancer. Abundant genetic data implicates the MYC oncogene in promoting tumors and inhibition of MYC has exhibited strong anti-tumor effects in numerous animal models of human cancers. We expect to initiate clinical trials for DCR-M1711 in the first half of 2014 and expect to announce initial proof-of-concept clinical data in mid to late 2015. We intend to investigate DCR-M1711 in a variety of tumor types. Our initial focus is on hepatocellular carcinoma (HCC), which we believe represents 85 to 90 percent of primary liver cancer.

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- **Product candidate for KRAS-related cancers in collaboration with KHK.** We are developing a product candidate targeting the oncogene KRAS in collaboration with KHK. KRAS is frequently mutated in numerous major cancers including non-small cell lung cancer, colorectal cancer and pancreatic cancer. Such KRAS mutations are associated both with more aggressive disease as well as with resistance to current therapies.

All of our drug discovery and development efforts are based on the therapeutic modality of RNAi, a highly potent and specific mechanism for silencing the activity of a targeted gene. In this biological process certain double-stranded RNA molecules induce the potent and specific enzymatic destruction of the messenger RNAs (mRNAs) of target genes containing sequences that are complementary to one strand of the therapeutic double-stranded RNA molecule. Our discovery approach is based on double-stranded RNAs that we believe maximize RNAi potency in that they represent what we believe are optimal molecules for the RNAi initiating enzyme Dicer. We refer to these proprietary RNAi molecules as Dicer substrates, or DsiRNAs.

RNAi offers the potential to go beyond traditional therapeutic modalities, such as small molecules and monoclonal antibodies, and attack targets such as transcription factors, proteins lacking good small-molecule binding pockets and expressed exclusively inside cells that control which genes are turned on or off in the genome. Some of these targets have been known for decades and are considered to be highly attractive targets for drug development. Targets such as MYC and KRAS have been shown to be oncogenes that are critical drivers of cancer formation in both animal models and humans.

We believe that DsiRNAs provide the following qualities and advantages for triggering RNAi compared to other types of double-stranded RNAs used to induce RNAi.

- **We initiate RNAi through the Dicer enzyme.** DsiRNAs are structured to be ideal for processing by the enzyme Dicer, the initiation point for RNAi in the human cell cytoplasm. Unlike earlier generation RNAi molecules, which mimic the output product of a Dicer enzyme processing event, DsiRNAs enter the RNAi pathway at this natural initiation point. This benefit increases the potency of our DsiRNA molecules relative to other molecules used to induce RNAi.

- **We use a proprietary delivery system.** We have developed EnCore lipid nanoparticles, a proprietary and effective system for the delivery of our DsiRNAs to liver tissue and to solid tumors. Our delivery particles are highly potent, have low toxicity and are amenable to manufacturing in large scale. We have found that, even at doses as low as 13.1μg/kg, we can induce silencing of gene expression at the 50 percent level, which we believe is 100-fold to 1,000-fold below the dose level at which we would expect to see dose-limiting toxicity. Other RNAi molecules in development are delivered by a variety of methods, including other types of lipid nanoparticles, nanoparticle systems that use polymers instead of lipids, and non-nanoparticle methods involving conjugation of the RNAi molecules to molecular targeting agents.

- **Our molecules have two conjugation points, which are cleaved off by the Dicer enzyme, allowing for direct delivery.** Due to the way that the Dicer enzyme processes our DsiRNAs, we believe our molecules provide advantages for targeted delivery methods that do not use lipid nanoparticles. Our DsiRNAs have two distinct conjugation points at the blunt end of the double-stranded RNA. At this blunt end the two strands of the DsiRNA can be conjugated to a targeting agent and an endosomal escape agent, respectively. These agents allow the DsiRNA to be targeted to specific cell types and to enter the cytoplasm of the cell. The targeting agent mediates cell binding and internalization, and the endosomal escape agent mediates cytoplasmic release. After delivery to the cytoplasm, the Dicer enzyme cleaves the molecule just as with an unconjugated DsiRNA. Because of this quality, our targeted delivery methods are able to use covalent chemical linkers that we believe are more easily synthesized directly into the RNA strand, facilitating delivery and enhancing the drug-like properties of the molecules. RNAi molecules that are not cleaved by Dicer may require the use of cleavable linkers, which are less stable and may be more challenging to synthesize into the RNA strands. We have shown that both conjugation points on our DsiRNAs can be used simultaneously without

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inhibiting processing by the Dicer enzyme. We anticipate that our future product candidates will utilize these conjugation points to improve further the delivery of our DsiRNAs. We are currently developing delivery technologies using this approach to deliver directly our DsiRNAs subcutaneously to liver tissues and ultimately to solid tumors.

The key elements of our strategy are:

- **Validate our product candidates and our platform in clinical proof-of-concept studies.** Beginning in early 2014, we plan to conduct clinical trials that we believe will generate human proof-of-concept data. We intend to maximize the likelihood of success in those trials by: (1) using genetic analysis to identify a target population that is likely to respond to our therapeutics and (2) observing biomarkers and other markers as indications of efficacy at an early stage. Based on precedents in the RNAi field, we anticipate that our strong data showing the destruction or knockdown of target mRNA molecules induced by double-stranded RNA molecules at preclinical dose levels will translate into clinical results. We expect to initiate clinical trials for DCR-M1711 in the first half of 2014 and for DCR-PH1 in 2015. We expect to announce initial proof-of-concept clinical data for DCR-M1711 and DCR-PH1 in mid to late 2015.

- **Identify new indication areas with high unmet medical need.** We intend to continue to use our DsiRNA molecules and our drug delivery technology platform to create new, high value pharmaceutical development programs. Our primary focus will remain: (1) rare inherited diseases involving the liver and (2) genetically-defined oncogene targets in oncology.

- **Continue to develop product candidates for rare diseases and oncology while retaining meaningful commercial rights.** We seek to maintain significant commercial rights to our key development programs. In the rare disease area, such as PH1, we seek to retain full commercial rights in key markets. In oncology, we seek to partner our product candidates while retaining meaningful commercial rights in North America.

- **Enter into additional partnerships with pharmaceutical companies either on our RNAi technology platform or specific indications outside of our core therapeutic areas.** We may choose to establish platform partnerships with pharmaceutical companies across multiple indication areas or in therapeutic areas outside of rare diseases and oncology depending on the attractiveness of the opportunities. These partnerships will provide us with validation of our technology platform, funding to advance our proprietary product candidates and access to development, manufacturing and commercial expertise and capabilities.

- **Continue to invest in our RNAi technology platform.** We will continue to invest in expanding and improving our DsiRNA molecules and our EnCore and other delivery technologies in order to develop new product candidates in indications that we are currently exploring and that we intend to explore in the future. Building on what we believe are our advantages in potency and delivery, we seek to develop product candidates that will have a dramatic impact on the RNAi field.

Risks related to our business

Our ability to implement our current business strategy is subject to numerous risks, as more fully described in the section titled Risk Factors immediately following this prospectus summary. These risks include, among others, the following.

- We have no source of predictable revenue, have incurred significant losses since inception, may never become profitable and may incur substantial and increasing net losses for the foreseeable future as we continue development of, and seek regulatory approvals for, our product candidates.

- Our success is primarily dependent on the successful development, regulatory approval and commercialization of our product candidates, all of which are in early development.

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

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- If clinical trials of our product candidates fail to demonstrate safety and efficacy, we may be unable to obtain regulatory approvals and commercialize our product candidates.

- We are subject to regulatory approval processes that are lengthy, time-consuming and unpredictable. We may not obtain approval for any of our product candidates from the U.S. Food and Drug Administration (FDA) or foreign regulatory authorities.

- Even if we obtain regulatory approval, the market may not be receptive to our product candidates based on a novel therapeutic modality or we may be unable to market any of our product candidates to achieve acceptance and use by the medical community.

- We may encounter difficulties satisfying the requirements of clinical trial protocols, including patient enrollment.

- We may never receive milestone payments under our research collaboration and license agreement with KHK or establish and maintain other licenses, collaborations and strategic relationships with terms and timing favorable to us.

- It is difficult and costly to protect our intellectual property rights.

- We may face competition from other companies in our field or claims from third parties alleging infringement of their intellectual property.

- We may be unable to recruit or retain key employees, including our senior management team.

- We depend on the performance of third parties, including contract research organizations and third-party manufacturers.

- We will likely need to obtain additional funding on acceptable terms to continue operations.

We are a preclinical stage biopharmaceutical company with a limited operating history. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We do not currently have any product candidates in clinical trials or approved for sale, and we continue to incur significant research and development and general and administrative expenses related to our operations. We are not profitable and have incurred losses in each year since our founding in October 2006. Our net loss for the years ended December 31, 2011 and 2012 was $8.6 million and $10.1 million, respectively. Our net loss for the nine months ended September 30, 2013 was $11.8 million. As of September 30, 2013, we had an accumulated deficit of $78.7 million. We expect to continue to incur significant losses for the foreseeable future. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods.

Neither we nor our collaborator KHK will be permitted to market our product candidates in the U.S. until we receive regulatory approval from the FDA, and approval by foreign regulatory agencies will be required to market our product candidates in other countries. Neither we nor our collaborator have submitted an application for or received marketing approval for any of our product candidates. Regulatory approval of our product candidates is not guaranteed, and the approval process is expensive and may take several years.

Corporate information

We were incorporated in Delaware in October 2006. We maintain our executive offices at 480 Arsenal Street, Building 1, Suite 120, Watertown, Massachusetts 02472, and our main telephone number is (617) 621-8097. We maintain a website at www.dicerna.com, which contains information about us. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated into, this prospectus and should not be considered part of this prospectus.

As used in this prospectus, unless otherwise noted, we, us, our and the Company refer to Dicerna Pharmaceuticals, Inc. and, where appropriate, its consolidated subsidiary.

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.

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Emerging growth company

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

As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise generally applicable to public companies. These provisions include:

- only two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced Management s Discussion and Analysis of Financial Condition and Results of Operations disclosure;
- reduced disclosure about our executive compensation arrangements;
- no requirement that we hold non-binding advisory votes on executive compensation or golden parachute arrangements; and
- exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We have taken advantage of some of these reduced burdens, and thus the information we provide stockholders may be different than you might get from other public companies in which you hold shares.

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THE OFFERING

Issuer	Dicerna Pharmaceuticals, Inc.
Shares of common stock offered by us	6,000,000 shares.
Shares of common stock to be outstanding immediately after this offering	16,627,660 shares (17,527,660 if the underwriters exercise in full their option to purchase additional shares of common stock).
Underwriters option to purchase additional shares of common stock in this offering	We have granted the underwriters a 30-day option to purchase up to 900,000 additional shares at the public offering price less underwriting discounts and commissions.
Dividend policy	We have never paid cash dividends on our common stock and we do not anticipate paying any cash dividends in the foreseeable future. See Dividend Policy.
Use of proceeds	We estimate that the net proceeds from this offering will be approximately $80.4 million (approximately $92.9 million if the underwriters exercise in full their option to purchase additional shares of common stock) after deducting the underwriting discounts and commissions and our estimated offering expenses. We expect to use the net proceeds from this offering to fund preclinical and clinical trials of proprietary product candidates, continued technology platform development, working capital and general corporate purposes, as well as potential acquisition or in-licensing activities. See Use of Proceeds.
Proposed NASDAQ symbol	DRNA.
Risk factors	You should carefully read and consider the information set forth under Risk Factors and all other information included in this prospectus for a discussion of factors that you should consider before deciding to invest in shares of our common stock.

Certain of our existing stockholders, including affiliates of our directors, have agreed to purchase an aggregate of 3,400,000 shares of our common stock in this offering at the initial public offering price.

The number of shares of common stock to be outstanding after this offering excludes, as of December 31, 2013:

- 5,950 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2013 under our 2007 Employee, Director and Consultant Stock Plan, as amended;
- 1,615,728 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2013 under our 2010 Employee, Director and Consultant Equity Incentive Plan, as amended (2010 Plan);

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- 115,351 shares of common stock reserved for issuance pursuant to future awards under our 2010 Plan as of December 31, 2013;
- 1,900,000 shares of common stock reserved for issuance pursuant to future awards under our 2014 Performance Incentive Plan, which will become effective upon the effectiveness of the registration statement to which this prospectus relates;
- 1,000,000 shares of common stock reserved for issuance pursuant to future awards under our 2014 Employee Stock Purchase Plan, which will become effective upon the effectiveness of the registration statement to which this prospectus relates; and
- 135,301 shares of common stock issuable upon exercise of warrants outstanding as of December 31, 2013 to purchase shares of common stock, Series A preferred stock, Series B preferred stock or Series C preferred stock, assuming the conversion of all outstanding shares of preferred stock immediately prior to completion of this offering.

Unless otherwise expressly stated or the context otherwise requires, the information in this prospectus accounts for the one-for-250 reverse split of our common stock and the one-for-25 reverse split of our Series A and Series B preferred stock, both of which occurred on July 25, 2013, and assumes or reflects that:

- the underwriters do not exercise their option to purchase up to 900,000 additional shares of common stock within 30 days from the date of this prospectus;
- the number of our authorized shares of capital stock has been increased to 150,000,000 shares of common stock and 5,000,000 shares of preferred stock;
- the amendments to our charter documents and bylaws, which are expected to occur prior to the closing of this offering, have occurred; and
- the conversion of each share of Series A, Series B and Series C preferred stock into one share of common stock immediately prior to the completion of this offering has occurred.

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SUMMARY FINANCIAL AND OTHER DATA

The following table sets forth summary financial data for us for the years ended December 31, 2011 and 2012 and for the nine months ended September 30, 2012 and 2013. The summary financial statements of operations data for the fiscal years ended December 31, 2011 and 2012 and the summary balance sheet data as of December 31, 2011 and 2012 are derived from our audited financial statements included elsewhere in this prospectus. The summary financial statements of operations data for the nine months ended September 30, 2012 and 2013 and the summary balance sheet data as of the nine months ended September 30, 2013 are derived from our unaudited condensed financial statements included elsewhere in this prospectus. Our unaudited financial statements are prepared on the same basis as our audited financial statements. We have included, in our opinion, all adjustments, consisting only of normal recurring adjustments, that we consider necessary for a fair presentation of the financial information set forth in those statements. Our historical results are not necessarily indicative of our results to be expected for any future interim financial period, and the results for the nine months ended September 30, 2013 are not necessarily indicative of results to be expected for the full year ending December 31, 2013.

The following summary financial data should be read in conjunction with, and is qualified in its entirety by reference to, Selected Historical Financial Information and Other Data, Management s Discussion and Analysis of Financial Condition and Results of Operations and our historical financial statements and related notes appearing elsewhere in this prospectus.

Summary Financial Data (in thousands except share and per share data)

	YEAR ENDED DECEMBER 31,		NINE MONTHS ENDED SEPTEMBER 30,	
	2011	2012	2012	2013
			(Unaudited)	
Revenue	$ 7,908	$ 7,015	$ 762	$
Operating expenses:				
Research and development	10,705	11,565	8,078	7,364
General and administrative	4,816	4,700	3,631	3,577
Total operating expenses	15,521	16,265	11,709	10,941
Loss from operations	(7,613)	(9,250)	(10,947)	(10,941)
Other income (expense):				
Preferred stock warrant remeasurement	51	469	352	219
Interest income	3	2	1	1
Loss on extinguishment of debt				(318)
Interest expense	(997)	(1,342)	(1,040)	(760)
Total other income (expense)	(943)	(871)	(687)	(858)
Net loss	$ (8,556)	$ (10,121)	$ (11,634)	$ (11,799)
Less: Accretion and dividends on redeemable convertible preferred stock	(4,099)	(4,097)	(3,068)	(2,379)
Net loss attributable to common stockholders	$ (12,655)	$ (14,218)	$ (14,702)	$ (14,178)
Net loss per share attributable to common stockholders Basic and diluted	$ (492.76)	$ (516.00)	$ (533.86)	$ (505.45)
Weighted average shares outstanding Basic and diluted	25,682	27,554	27,539	28,050
		$ (4.95)		$ (2.65)

Pro forma net loss per share attributable to common stockholders (unaudited)	Basic and diluted		
Pro forma weighted average shares outstanding (unaudited)	Basic and diluted	2,045,571	4,444,333

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	AS OF SEPTEMBER 30, 2013		
	ACTUAL	PRO FORMA [1] *(Unaudited)*	PRO FORMA AS ADJUSTED [2]
Balance Sheet Data:			
Cash and cash equivalents	$ 54,712	$ 54,712	$ 135,062
Current assets	55,125	55,125	135,475
Current liabilities	6,560	6,560	6,560
Total assets	56,072	56,072	136,442
Long-term debt net of current portion	1,407	1,407	1,407
Preferred stock warrant liability	436		
Redeemable convertible preferred stock	110,237		
Additional paid-in capital	16,177	126,849	207,199
Accumulated deficit	(78,746)	(78,746)	(78,746)
Total stockholders' equity (deficit)	(62,568)	48,105	128,455

(1) Pro forma balance sheet data give effect to (i) the automatic conversion of all outstanding shares of preferred stock into an aggregate of 10,589,434 shares of common stock upon the closing of this offering and (ii) reclassification of our preferred stock warrants as a component of equity in connection with the conversion of preferred stock warrants into common stock warrants upon the closing of this offering.

(2) Pro forma as adjusted balance sheet data give effect to the automatic conversion of all outstanding shares of preferred stock into an aggregage of 10,589,434 shares of common stock upon the closing of this offering and the sale of 6,000,000 shares of common stock by us in this offering at the initial public offering price of $15.00 per share, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us and the filing of our amended and restated certificate of incorporation, which will occur immediately prior to the closing of this offering.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the following risk factors and all other information contained in this prospectus before purchasing our common stock. If any of the following risks, as well as other risks and uncertainties occur, our business, financial condition, results of operations and prospects could be materially and adversely affected. In that case, the market price of our common stock could decline and you could lose some or all of your investment.

Risks Related to Our Business

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

We are a preclinical stage biopharmaceutical company with a limited operating history, focused on the discovery and development of treatments based on the emerging therapeutic modality RNA interference (RNAi), a biological process in which ribonucleic acid (RNA) molecules inhibit gene expression. Since our inception in October 2006, we have devoted our resources to the development of Dicer substrate RNA (DsiRNA) molecules and delivery technologies. We have had significant operating losses since our inception. As of September 30, 2013, we had an accumulated deficit of $78.7 million. For the twelve months ended December 31, 2011 and 2012 and the nine months ended September 30, 2013, our net loss was $8.6 million, $10.1 million and $11.8 million, respectively. Substantially all of our losses have resulted from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations. Our technologies and product candidates are in early stages of development, and we are subject to the risks of failure inherent in the development of product candidates based on novel technologies.

To date, we have generated revenue primarily from the receipt of upfront research funding, license and option exercise fees and preclinical payments under our research collaboration and license agreement with Kyowa Hakko Kirin Co., Ltd. (KHK). We have not generated, and do not expect to generate, any product revenue 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 collaborator, 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 collaborator, 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.

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

In December 2009, we entered into a research collaboration and license agreement with KHK for the research, development and commercialization of DsiRNA molecules and drug delivery technologies for therapeutic targets, primarily in oncology. Under the research collaboration and license agreement with KHK, KHK has paid us a total of $17.5 million as of September 30, 2013. During the first two years of the collaboration, we worked together with KHK to optimize KHK s lipid nanoparticles for tumor delivery and to identify DsiRNAs optimized against oncology and KRAS targets. Based on the results of this research, KHK exercised options to advance two separate DsiRNAs into the development stage, including one with a KRAS target. For each product candidate under the research collaboration and license agreement, we have the potential to receive clinical, regulatory and commercialization milestone payments of up to $110.0 million and royalties on net sales of such product candidate. The success of our collaboration programs with KHK depends entirely upon the efforts of KHK. Except for certain co-promotion and profit sharing rights we retain with respect to the KRAS product candidate if it is approved for marketing and commercialization in the U.S., KHK has sole discretion in determining and directing the efforts and resources, including the ability to discontinue all efforts and resources, it applies to the development and, if approval is

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obtained, commercialization and marketing of the product candidates covered by the collaboration. KHK may not be effective in obtaining approvals for the product candidates developed under the collaboration arrangement or in marketing, or arranging for necessary supply, manufacturing or distribution relationships for, any approved products. Under the research collaboration and license agreement, KHK may change its strategic focus or pursue alternative technologies in a manner that results in reduced, delayed or no revenue to us. KHK has a variety of marketed products and product candidates under collaboration with other companies, including some of our competitors, and its own corporate objectives may not be consistent with our best interests. If KHK fails to develop, obtain regulatory approval for or ultimately commercialize any product candidate under our collaboration or if KHK terminates our collaboration, our business, financial condition, results of operations and prospects could be materially and adversely affected. In addition, any dispute or litigation proceedings we may have with KHK in the future could delay development programs, create uncertainty as to ownership of intellectual property rights, distract management from other business activities and generate substantial expense.

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

If our product candidates enter and advance through preclinical studies and clinical trials, we will need substantial additional funds to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. We have used substantial funds to develop our product candidates and delivery technologies and will require significant funds to conduct further research and development and preclinical testing and clinical trials of our product candidates, to seek regulatory approvals for our product candidates and to manufacture and market products, if any, that are approved for commercial sale. As of September 30, 2013, we had $54.7 million in cash, cash equivalents and short-term investments. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments, the net proceeds from this offering and available borrowings under our credit facility, will be sufficient to fund our anticipated level of operations through 2015. Our future capital requirements and the period for which we expect our existing resources to support our operations may vary significantly from what we expect. Our monthly spending levels vary based on new and ongoing development and corporate activities. Because the length of time and activities associated with successful development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. To execute our business plan, we will need, among other things:

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

- to market our products to achieve acceptance and use by the medical community in general.

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

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

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 collaborator or any future collaborator or licensing partner;
- the timing of the release of results from any clinical trials conducted by us or our collaborator KHK;
- our execution of any collaboration, licensing or similar arrangement, and the timing of payments we may make or receive under such existing or future arrangements or the termination or modification of any such existing or future arrangements;
- any intellectual property infringement lawsuit or opposition, interference or cancellation proceeding in which we may become involved;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- if any of our product candidates receives regulatory approval, market acceptance and demand for such product candidates;
- regulatory developments affecting our product candidates or those of our competitors; and
- changes in general market and economic conditions.

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

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

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

Relatively few product candidates based on RNAi have been tested in animals or humans, and a number of clinical trials conducted by other companies using RNAi technologies have not been successful. We may discover that DsiRNA does not possess certain properties required for a drug to be effective, such as the ability to remain stable in

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the human body for the period of time required for the drug to reach the target tissue or the ability to cross the cell wall and enter into cells within the target tissue for effective delivery. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these necessary drug-like properties into DsiRNA. We may spend substantial funds attempting to introduce these properties and may never succeed in doing so. In addition, product candidates based on DsiRNA may demonstrate different chemical and pharmacological properties in patients than they do in laboratory studies. Even if product candidates, such as DCR-PH1 and DCR-M1711, have successful results in animal studies, they may not demonstrate the same chemical and pharmacological properties in humans and may interact with human biological systems in unforeseen, ineffective or harmful ways. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

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

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

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

- the timing of our receipt of any marketing and commercialization approvals;
- the terms of any approvals and the countries in which approvals are obtained;
- the safety and efficacy of our product candidates;
- the prevalence and severity of any adverse side effects associated with our product candidates;
- limitations or warnings contained in any labeling approved by the FDA or other regulatory authority;
- relative convenience and ease of administration of our product candidates;
- the willingness of patients to accept any new methods of administration;
- the success of our physician education programs;

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

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

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

With our focus on the emerging therapeutic modality RNAi, these risks may increase to the extent the space becomes more competitive or less favored in the commercial marketplace. Additional risks apply in relation to any disease indications we pursue which are classified as rare diseases and allow for orphan drug designation by regulatory agencies in major commercial markets, such as the U.S., Europe and Japan. For instance, we are in the preliminary stages of developing a treatment for the rare genetic disorder Primary Hyperoxaluria 1 (PH1) with the

liver metabolic enzyme glycolate oxidase as our target. Because of the small patient population for a rare disease, if pricing is not approved or accepted in the market at an appropriate level for an approved product with orphan drug designation, such drug may not generate enough revenue to offset costs of development, manufacturing, marketing and commercialization despite any benefits received from the orphan drug designation, such as market exclusivity, assistance in clinical trial design or a reduction in user fees or tax credits related to development expense. Market size is also a variable in disease indications not classified as rare. Our estimates regarding potential market size for any indication may be materially different from what we discover to exist at the time we commence commercialization, if any, for a product, which could result in significant changes in our business plan and have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We have no products on the market and all of our product candidates are in early stages of development. Our ability to achieve and sustain profitability depends on obtaining regulatory approvals, including institutional review board (IRB) approval, for and successfully commercializing our product candidates, either alone or with third parties, such as our collaborator KHK. Before obtaining regulatory approval for the commercial distribution of our product candidates, we or a collaborator must conduct extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Preclinical testing and clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. The start or end of a clinical study is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparative drug or required prior therapy, clinical outcomes or financial constraints. For instance, delays or difficulties in patient enrollment or difficulties in retaining trial participants can result in increased costs, longer development times or termination of a clinical trial. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the eligibility criteria for the clinical trial, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites and the availability of effective treatments for the relevant disease.

A product candidate can unexpectedly fail at any stage of preclinical and clinical development. The historical failure rate for product candidates is high due to scientific feasibility, safety, efficacy, changing standards of medical care and other variables. The results from preclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. We, the FDA or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects participating in such trials are being exposed to unacceptable health risks or adverse side effects. 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 Investigational New Drug applications (INDs) or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators 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 regarding the scope or design of our clinical trials;
- delays in enrolling research subjects in clinical trials;

- high drop-out rates of research subjects;

- inadequate supply or quality of product candidate components or materials or other supplies necessary for the conduct of our clinical trials;

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- greater than anticipated clinical trial costs;
- poor effectiveness of our product candidates during clinical trials;
- unfavorable FDA or other regulatory agency inspection and review of a clinical trial site;
- failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;
- delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or
- varying interpretations of data by the FDA and similar foreign regulatory agencies.

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

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

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA requires clinical trials to be conducted in accordance with good clinical practices, including 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 and clinical development materials may become limited or interrupted or may not be of satisfactory quantity or quality.

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

The manufacturing process for a product candidate is subject to FDA and foreign regulatory authority review. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities in order

to comply with regulatory standards, such as current Good Manufacturing Practices (cGMP). In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of

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components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. 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 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 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 arrangement with KHK, 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 not be able to maintain any new or existing collaboration if, for example, development or approval of a product candidate is delayed, sales of an approved product candidate do not meet expectations or the collaborator terminates the collaboration. Any such collaboration, or other strategic transaction, may require us to incur non-recurring or other charges, increase our near- and long-term expenditures and pose significant integration or implementation challenges or disrupt our management or business. These transactions would entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of our business and diversion of our management s time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected collaboration, acquisition or integration costs, write-downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the collaboration or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and have a

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

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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 will develop product candidates and processes competitive with our product candidates. Competitive therapeutic treatments include those that have already been approved and accepted by the medical community and any new treatments that enter the market. We 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 are aware of multiple companies that are working in the field of RNAi therapeutics, including major pharmaceutical companies such as Novartis International AG, Takeda Pharmaceutical Company Limited and Merck & Co., Inc., which has entered into an agreement with Alnylam Pharmaceuticals, Inc. (Alnylam) to sell Sirna Therapeutics, Inc., its wholly owned subsidiary, to Alnylam in a pending transaction announced in January 2014, subject to satisfaction of closing conditions, including the requirements under the Hart-Scott-Rodino Antitrust Improvements Act, and biopharmaceutical companies such as Alnylam, Tekmira Pharmaceuticals Corporation (Tekmira), Arrowhead Research Corporation (Arrowhead), Silence Therapeutics plc, RXi Pharmaceuticals Corporation, Quark Pharmaceuticals, Inc. and Marina Biotech, Inc. In particular, Arrowhead holds a non-exclusive license to the same patent rights of City of Hope (COH) and Integrated Data Technologies, Inc. (IDT) as we are licensed under our license agreement with COH. As a result, we cannot rely on those patent rights to prevent Arrowhead or third parties working with Arrowhead from developing, marketing and selling products that compete directly with our product candidates.

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

If our lead product candidates are approved for the indications we are currently pursuing, they will compete with a range of therapeutic treatments that are either in development or currently marketed. For example, Nexavar, marketed by Amgen Inc. and Bayer AG, is currently in use for the treatment of HCC. In addition, Tekmira has announced that it expects to initiate a multicenter, single arm, open label dose escalation Phase 1/2 study for TKM-PLK1 in HCC in the first half of 2014. There are also a number of pharmaceuticals and biologics that are marketed or in clinical development for the treatment of solid tumors. The most common treatments for solid tumors are various chemotherapeutic agents, radiation therapy and certain targeted therapies, including monoclonal antibodies such as Avastin, Erbitux, Herceptin and Vectibix. Small molecules, such as Nexavar, Sutent and Tarceva, are also indicated for the treatment of solid tumors. In addition, we believe that Kadmon Corporation, LLC is evaluating salirasib (KD032) in clinical trials for the treatment of KRAS-specific non-small cell lung cancer, pancreatic cancer and other solid tumors.

Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we have. If we successfully obtain approval for any product candidate, we will face competition based on many different factors, including the safety and effectiveness of our products, the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration, the timing and scope of regulatory approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. 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. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan.

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

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

We have limited experience in drug development and have not begun clinical trials for any of our 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 or partners, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

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

We currently have no sales, marketing or distribution capabilities or experience. If any of our product candidates is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or enter into collaborations with third parties to perform these services. If we decide to market our products directly, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our 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 terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition, results of operations and prospects could be materially adversely affected.

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

Even if we receive marketing and commercialization approval of a product candidate, we will be 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 has 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

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also has the authority to require a risk evaluation and mitigation strategies (REMS) plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. The 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 letters, holds on clinical trials, refusal by the FDA to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, injunction, civil penalties and criminal prosecution.

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

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

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

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to 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 and regulations

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intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and 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 or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

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

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

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

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

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

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

Our current operations are located in our facilities situated in Watertown, Massachusetts. 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 result in us being unable to fully utilize the facilities, may have a material adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. Loss of access to these

facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption may have a material adverse effect on our business, financial position, results of operations and prospects.

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

We have incurred substantial losses during our history, do not expect to become profitable for the foreseeable future and may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. We may be unable to use these losses to offset income before such unused losses expire. Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an ownership change, which is generally defined as a greater than 50 percentage point change by value in its equity ownership over a three-year period, the corporation s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be further limited. We have not performed an analysis on whether we have experienced any ownership changes in the past. It is possible that we have experienced an ownership change and our net operating losses are subject to such limitation. In addition, additional changes in our stock ownership, including pursuant to this offering, could result in an ownership change. As of December 31, 2012, we had U.S. federal and Massachusetts net operating loss carryforwards of $47.3 million and $47.0 million, respectively. Any limit on these loss carryforwards if we have or do experience an ownership change could have an adverse effect on our business, financial position, results of operations and prospects.

The investment of our cash, cash equivalents and fixed income marketable securities is subject to risks which may cause losses and affect the liquidity of these investments.

As of September 30, 2013, we had $54.7 million in cash, cash equivalents and fixed income marketable securities. 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. Pending use in our business, we expect to invest the net proceeds of this offering in substantially the same manner. These investments are subject to general credit, liquidity, market and interest rate risks, including the impact of U.S. sub-prime mortgage defaults that have affected various sectors of the financial markets and caused credit and liquidity issues. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our condensed 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 relevant accounting authorities, including the Securities and Exchange Commission. Changes to accounting methods or policies, or interpretations thereof, may require us to reclassify, restate or otherwise change or revise our financial statements, including those contained in this prospectus.

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

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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 December 31, 2013, our patent estate, including the patents and patent applications that we have licensed from COH included approximately 16 issued patents and approximately 67 pending patent applications for research and development of our DsiRNA molecules and delivery technologies. We may not be able to apply for patents on certain aspects of our product candidates or delivery technologies in a timely fashion or at all. Our existing issued and granted patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technology. There is no guarantee that any of our pending patent applications will result in issued or granted patents, that any of our issued or granted patents will not later be found to be invalid or unenforceable or that any issued or granted patents will include claims that are sufficiently broad to cover our product candidates or delivery technologies or to provide meaningful protection from our competitors. Moreover, the patent position of biotechnology and pharmaceutical companies can be highly uncertain because it involves complex legal and factual questions. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our current and future proprietary technology and product candidates are covered by valid and enforceable patents or are effectively maintained as trade secrets. If third parties disclose or misappropriate our proprietary rights, it may materially and adversely impact our position in the market.

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

In addition, there are numerous recent changes to the patent laws and proposed changes to the rules of the USPTO which may have a significant impact on our ability to protect our technology and enforce our intellectual property rights. For example, the America Invents Act (AIA) enacted within the last several years involves significant changes in patent legislation. The 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 recent decision by the 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 which contain modifications that we believe 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 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 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. In addition, there can be no assurance that:

- Others will not or may not 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 are the first to make the inventions covered by each of our issued patents and pending patent applications that we own or license.

- We or our licensors, collaborators or any future collaborators are the first to file patent applications covering certain aspects of our inventions.

- Others will not independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.

- A third party may not challenge our patents and, if challenged, a court may not hold that our patents are valid, enforceable and infringed.

- Any issued patents that we own or have licensed will provide us with any competitive advantages, or will not be challenged by third parties.

- We may develop additional proprietary technologies that are patentable.

- The patents of others will not have an adverse effect on our business.

- Our competitors do not conduct research and development activities in countries where we do 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.

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

We do, and will continue to, rely on intellectual property rights licensed from third parties to protect our technology. We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have a license from COH (on behalf of itself and IDT) to certain patent rights, which provide platform intellectual property for research and development of our DsiRNA molecules. 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. See Business-Strategic Partnerships and Collaborations City of Hope license agreement. We also intend to license additional third-party intellectual property in the future. Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue litigation less aggressively than we would. Further, we may not obtain exclusive rights, which would allow for third parties to develop competing products. Without protection for, or exclusive right to, the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. In addition, we sublicense our rights under our third-party licenses to KHK and may sublicense such rights to current or future collaborators or any future strategic partners. Any impairment of these sublicensed rights could result in reduced revenue under our collaboration agreement with KHK or result in termination of an agreement by one or more of our collaborators or any future strategic partners.

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

To the extent that we do not have exclusive rights in the patents covered by the license granted to us by COH, we cannot prevent third parties from developing DsiRNA based product candidates in competition with ours. Prior to entering into the license with us, COH had entered into a non-exclusive license with a third party with respect to such patent rights to manufacture, use, import, offer for sale and sell products covered by

the licensed patent rights for the treatment or prevention of disease in humans (excluding viruses and delivery of products into the eye or ear). While we believe that such non-exclusive license has been terminated, COH has informed us that a sublicensee to that non-exclusive license was permitted to enter into an equivalent non-exclusive license which, to our knowledge, is subsisting with Arrowhead Research Corporation (Arrowhead), as successor to the non-exclusive license holder. As successor to the non-exclusive license holder, we believe that Arrowhead has substantially similar access to the same patent rights related to DsiRNA granted to us under our license with COH. Arrowhead is developing RNA-based

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therapeutics for the treatment of diseases of the liver, which may directly compete with our product candidates. In addition, the U.S. government has certain rights to the inventions covered by the patent rights and COH, as an academic research and medical center, has the right to practice the licensed patent rights for educational, research and clinical uses. If Arrowhead or another party develops, manufactures, markets and sells any product covered by the same patent rights and technologies that compete with ours, it could significantly undercut the value of any of our product candidates, which would materially adversely affect our revenue, financial condition and results of operations.

Other companies or organizations may challenge our or our licensors patent rights or may assert patent rights that prevent us from developing and commercializing our products.

RNAi therapeutics are relatively new scientific fields, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi, RNAi therapeutic and DsiRNA patents and have licensed many of these patents from third parties on an exclusive or non-exclusive basis. The issued patents and pending patent applications in the U.S. and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics and DsiRNA therapeutics. Specifically, we own and have licensed a portfolio of patents, patent applications and other intellectual property covering: (1) certain aspects of the structure and uses of DsiRNAs, including their manufacture and use as therapeutics, and DsiRNA-related mechanisms, (2) chemical modifications to DsiRNAs that improve their suitability for therapeutic uses, (3) DsiRNAs directed to specific gene sequences and drug targets as treatments for particular diseases and (4) delivery technologies, such as in the field of lipid chemistry, lipid nanoparticles and lipid nanoparticle formulation.

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

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need to apply to our DsiRNA therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for DsiRNA drugs we wish to develop. Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may not be able to market products or perform research and development or other activities covered by these patents.

We may not be able to protect our intellectual property rights throughout the world.

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

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patents or marketing of competing products in violation of our proprietary rights generally in certain jurisdictions. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

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

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws in the U.S., and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition from others in those jurisdictions. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position in the relevant jurisdiction may be impaired and our business and results of operations may be adversely affected.

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

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

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our products or our technology, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity

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

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 or licenses could be costly or not available on commercially reasonable terms.

Because the RNAi intellectual property landscape is still evolving, it is difficult to conclusively assess our freedom to operate without infringing on third party rights. There are numerous companies that have pending patent applications and issued patents broadly directed to RNAi generally and to RNAi delivery technologies. Our competitive position may suffer if patents issued to third parties or other third party intellectual property rights cover our products or elements thereof, or our manufacture or uses relevant to our development plans. In such cases, we may not be in a position to develop or commercialize products or product candidates unless we successfully pursue litigation to nullify or invalidate the third party intellectual property right concerned, or enter into a license agreement with the intellectual property right holder, if available on commercially reasonable terms. For instance, we received a letter from Alnylam in March 2010, claiming that we require access to certain patent and patent applications owned or controlled by Alnylam and demanding that we cease and desist from alleged infringing activities unless and until we obtain a license from Alnylam for the necessary intellectual property. We have disputed Alnylam s claims and engaged in several discussions with Alnylam. We have not received any further correspondence from Alnylam since 2010 regarding this claim. However, there can be no assurance that Alnylam will not continue to pursue this or other claims against us. We are aware of issued patents, and there may be others of which we are not aware, held by third parties that, if found to be valid and enforceable, could be alleged to be infringed by our DsiRNA molecules. We are also aware of pending patent applications, and there may be others of which we are not aware, that if they result in issued patents, could be alleged to be infringed by our DsiRNA molecules. If such an infringement claim should be brought and be successful, we may be required to pay substantial damages, be forced to abandon our product candidates or seek a license from any patent holders. No assurances can be given that a license will be available on commercially reasonable terms, if at all.

For example, we are aware of a European patent, granted in 2006, and assigned to Alnylam (EP 1 352 061 B1) (EP 061 patent), that broadly covers various RNAi constructs, including potentially our DsiRNA molecules. The EP 061 patent has been validated and is currently in force in Austria, Germany, Ireland, Liechtenstein, Switzerland, and the United Kingdom. It has not yet been validated in any other European countries. Another third party, Sirna Therapeutics, Inc. (acquired by Merck & Co., Inc. in 2006), filed an opposition seeking to revoke the EP 061 patent as invalid. In August 2009, the Opposition Division of the European Patent Office (EPO) rejected the opposition and upheld all of the claims of the EP 061 patent as originally granted. That decision is currently on appeal by Sirna Therapeutics. We are currently not a party to the opposition. In January 2014, Alnylam announced that it had entered into an agreement to acquire Sirna Therapeutics, subject to satisfaction of closing conditions, including the requirements under the Hart-Scott-Rodino Antitrust Improvements Act. If Alnylam completes its acquisition of Sirna Therapeutics or assets related to Sirna Therapeutics RNAi intellectual property, we expect that the appeal would likely be terminated, in which case we would not be able to join or continue the opposition in the EPO, though we could seek to challenge this patent in the individual European countries where it has been validated. If the EP 061 patent is upheld on appeal and remains in force in each validated European country, we could be prevented from commercializing our DsiRNA products in each of those countries and we could be sued for patent infringement in such countries. We are aware that others are pursuing patent applications directed to similar subject matter in the U.S. and other jurisdictions and reinstatement of a revoked European patent broadly covering various RNA constructs. If any one of these applications were ultimately to issue as patents or the revoked patent were reinstated

with claims that cover our DsiRNA molecules, their methods of use or methods of delivery, we could be sued for patent infringement in each of those countries as well. If we were unsuccessful in defending ourselves in any of these actions, we may be required to pay substantial damages, be forced to abandon our product candidates or seek a license from any patent holders, in each case, in such countries. We believe that the expected expiration date of the EP 061 patent and any foreign counterparts that might issue is early 2022.

It is also possible that we have failed to identify relevant third party patents or applications. For example, U.S. applications filed before November 29, 2000 and certain U.S. applications filed after that date that will not be filed outside the U.S. remain confidential until patents issue. Patent applications in the U.S. and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our products or platform technology could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our products or the use of our products. Third party intellectual property right holders may also actively bring infringement claims against us. We cannot guarantee that we will be able to successfully settle or otherwise resolve such 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, if possible, 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.

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

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

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

In addition to seeking patent protection for certain aspects of our product candidates and delivery technologies, we also consider trade secrets, including confidential and unpatented know-how important to the maintenance of our competitive position. We protect trade secrets and confidential and unpatented know-how, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants that obligate them to maintain confidentiality and assign their inventions to us. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts in the U.S. and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently

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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 may be 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 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. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail in defending such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of 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. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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

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

Risks Related to Government Regulation

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

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

We have very limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to obtain FDA and other 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 FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Because the drugs we are developing may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. While we believe the product candidates that we are currently developing are regulated as new drugs under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any

regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

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

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

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

We and our collaborators are subject to federal, state, and foreign healthcare laws and regulations pertaining to fraud and abuse and patients rights. These laws and regulations include:

- the U.S. federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for a healthcare item or service, or the purchasing or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid;

- the U.S. federal false claims law, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government funded programs 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 U.S. federal Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) Act, which prohibit executing a scheme to defraud healthcare programs, impose requirements relating to the privacy, security, and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;

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

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

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

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

- adverse regulatory inspection findings;
- warning letters;
- voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on, or prohibitions against, importation or exportation of our products;
- suspension of review or refusal to approve pending applications or supplements to approved applications;
- exclusion from participation in government-funded healthcare programs;
- exclusion from eligibility for the award of government contracts for our products;
- suspension or withdrawal of product approvals;
- product seizures;
- injunctions; and
- civil and criminal penalties and fines.

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

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

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Because our programs are in the early stages of development, we are unable at this time to determine their cost effectiveness or the likely level or method of reimbursement. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for pharmaceutical products. If the price we are able to charge for any products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

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

- they are 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; and
- they have been approved by the FDA and meet other requirements of the statute.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net 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. 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 in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the U.S. in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act (ACA), a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending and enhance remedies against fraud and abuse. The ACA also contains provisions that will affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following.

- Mandatory rebates for drugs sold into 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 under the Public Health Services Act has been extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities.
- 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 products 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 health program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

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

The full effects of the U.S. healthcare reform legislation cannot be known until the new law is fully implemented through regulations or guidance issued by the Centers for Medicare & Medicaid Services and other federal and state healthcare agencies. The financial impact of the U.S. healthcare reform legislation over the next few years will depend on a number of factors, including but not limited to, the policies reflected in implementing regulations and guidance and changes in sales volumes for products affected by the new system of rebates, discounts and fees. The new legislation may also have a positive impact on our future net sales, if any, by increasing the aggregate number of persons with healthcare coverage in the U.S., but such increases are unlikely to be realized until approximately 2014 at the earliest.

Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the U.S. to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

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

U.S. federal government agencies currently face potentially significant spending reductions. Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts would include aggregate reductions to Medicare payments to providers of up to two percent per fiscal year, starting in 2013. Under the American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, the imposition of these automatic cuts was delayed until March 1, 2013. Certain of these automatic cuts have been implemented. The full impact on our business of these automatic cuts is uncertain. If federal spending is reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

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

In the event that any of our product candidates receive regulatory approval and we or others identify undesirable side effects 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 be required to recall the product or change the way the product is administered to patients;
- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a black box warning or a contraindication;

- 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 and This Offering

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

We are an emerging growth company as defined in the 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 of the Sarbanes-Oxley Act of 2002 (Sarbanes-Oxley Act), (2) reduced disclosure obligations regarding executive compensation in this prospectus and 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. In addition, as an emerging growth company, we are only required to provide two years of audited financial statements and two years of selected financial data in this prospectus. We could be an emerging growth company for up to five years, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31, or if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, in which case we would no longer be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

Our stock price is likely to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the initial public offering price. The market price for our common stock may be influenced by many factors, including the other risks described in this section of the prospectus titled Risk Factors and the following:

- the success of competitive products or technologies;
- results of preclinical and clinical studies of our product candidates, or those of our competitors, our existing collaborator or any future collaborators;
- regulatory or legal developments in the U.S. and other countries, especially changes in laws or regulations applicable to our products;
- introductions and announcements of new products by us, our commercialization partners, or our competitors, and the timing of these introductions or announcements;
- actions taken by regulatory agencies with respect to our products, clinical studies, manufacturing process or sales and marketing terms;

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

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

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

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

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- developments or disputes concerning patents or other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our products;
- our ability or inability to raise additional capital and the terms on which we raise it;
- the recruitment or departure of key personnel;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- actual or anticipated changes in earnings estimates or changes in stock market analyst recommendations regarding our common stock, other comparable companies or our industry generally;
- our failure or the failure of our competitors to meet analysts projections or guidance that we or our competitors may give to the market;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- announcement and expectation of additional financing efforts;
- speculation in the press or investment community;
- trading volume of our common stock;
- sales of our common stock by us or our stockholders;
- the absence of lock-up agreements in connection with this offering with the holders of substantially all of our outstanding shares;
- the concentrated ownership of our common stock;
- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;

- natural disasters and other calamities; and

- general economic, industry and market conditions.

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

You will experience immediate and substantial dilution as a result of this offering and may experience additional dilution in the future.

If you purchase common stock in this offering, you will incur immediate and substantial dilution of $7.27 per share, representing the difference between the initial public offering price of $15.00 per share and our pro forma net tangible book value per share as of September 30, 2013 after giving effect to this offering and the conversion of all outstanding shares of our preferred stock upon the closing of this offering. Moreover, we issued warrants and options in the past to acquire common stock at prices significantly below the initial public offering price. As of December 31, 2013, there were 135,301 shares subject to outstanding warrants and 1,621,678 shares subject to outstanding options. To the extent that these outstanding warrants or options are ultimately exercised, you will incur further dilution.

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. No prediction can be made as to 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.

Substantially all of our outstanding shares will not be subject to lock-up agreements in connection with this offering. The sale of a significant number of our shares may cause the market price of our common stock to drop significantly.

Our executive officers have entered into lock-up agreements with the underwriters under which they have agreed, subject to specific exceptions, not to sell shares of our common stock or securities exchangeable or exercisable therefor owned by

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them for a period of 180 days following the date of this prospectus. However, the holders of substantially all of our shares of common stock and securities convertible or exercisable into shares of our common stock outstanding at the time of this offering have not entered into any lock-up agreements in connection with this offering. As a result, a substantial number of shares of our common stock will be available for sale in the public market after the completion of this offering. The sale of a significant number of shares of our comment stock in the public market or the perception that such sale may occur could significantly reduce the market price of our common stock. In addition, if a significant number of shares of our common stock were to be sold immediately after the completion of this offering, this would decrease the likelihood that the underwriters would exercise all or part of their over-allotment option and, consequently, decrease the likelihood that we will receive the additional net proceeds from such an exercise.

Based on shares of our capital stock outstanding as of December 31, 2013 and assuming the underwriters do not exercise their option to purchase up to 900,000 additional shares of common stock, we will have 16,627,660 shares of common stock outstanding after the completion of this offering, including the 6,000,000 shares of common stock that we are selling in this offering which may be resold in the public market immediately. Based on 10,627,660 shares of common stock outstanding as of December 31, 2013 assuming the conversion of our preferred stock, the shares of our common stock (excluding the shares sold in this offering) that will be available for sale in the public market, subject to any applicable volume limitations under federal securities laws with respect to affiliate sales, either immediately after the completion of this offering or in the near future are as follows:

- beginning on the date of this prospectus, approximately 701,085 shares of our common stock, or 6.6 percent of such total outstanding shares of our common stock as of December 31, 2013, will be immediately available for sale in the public market;

- beginning 90 days after the date of this prospectus, an additional approximately 9,913,442 shares of our common stock, or 93.3 percent of such total outstanding shares of our common stock as of December 31, 2013, will be eligible for sale in the public market from time to time thereafter, subject in some cases to the volume and other restrictions of Rule 144 of the Securities Act of 1933, as amended; and

- beginning 180 days after the date of this prospectus, the remainder of the shares of our common stock will be eligible for sale in the public market due to the expiration of the lock-up agreements between our executive officers and the underwriters, unless the representatives of the underwriters waive the provisions of these lock-up agreements and allow these stockholders to sell their shares earlier.

In addition, as of December 31, 2013, there were 135,301 shares subject to outstanding warrants, 1,621,678 shares subject to outstanding options and an additional 115,351 shares reserved for future issuance under our employee benefit plans that will become eligible for sale in the public market to the extent permitted by any applicable vesting requirements, the lock-up agreements and Rules 144 and 701 under the Securities Act of 1933, as amended.

Moreover, immediately after this offering, holders of an aggregate of up to 10,593,858 shares of our common stock and holders of warrants to purchase 135,301 shares of our common stock will have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If such holders, by exercising their registration rights, cause a large number of securities to be registered and sold into the public market, these sales could have an adverse effect on the market price for our common stock. We also intend to register all shares of common stock that we may issue under our equity incentive plans. Once we register these shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates under Rule 144 and the lock-up agreements. For more information, see Shares Eligible for Future Sale.

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

Our executive officers are parties to employment agreements providing, in the event of a termination of employment in connection with a change of control of us, for aggregate cash payments of up to approximately $1.5 million 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 harm 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.

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An active trading market for our common stock may not develop.

Prior to this offering, there has been no public market for our common stock. The initial public offering price for our common stock was determined through negotiations with the underwriters. Although our common stock has been approved for listing on The NASDAQ Global Select Market, an active trading market for our shares may never develop or be sustained following this offering. If an active market for our common stock does not develop, it may be difficult for you to sell shares you purchase in this offering without depressing the market price for the shares or at all.

Because our management will have broad discretion over the use of the net proceeds from this offering, you may not agree with how we use them and the proceeds may not be invested successfully.

We intend to use the net proceeds to us from this offering to fund research and development and clinical trial expenses and potential in-licensing of intellectual property and technology, and other general corporate purposes, including funding the costs of operating as a public company, and therefore, our management will have broad discretion as to the use of the offering proceeds. Accordingly, you will be relying on the judgment of our management with regard to the use of these 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 proceeds will be invested in a way that does not yield a favorable, or any, return for our company.

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. We do not currently have and may never obtain research coverage by securities and industry analysts. If no or few securities or industry analysts commence coverage of us, the trading price for our stock would be negatively impacted. In the event we obtain securities or industry analyst coverage, 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.

Based on the beneficial ownership of our common stock as of December 31, 2013, after this offering, our executive officers and directors, together with holders of five percent or more of our outstanding common stock before this offering and their respective affiliates, will beneficially own approximately 37.1 percent of our outstanding common stock (assuming no exercise of the underwriters option to purchase additional shares of common stock). After giving effect to purchases by certain of our existing stockholders, including certain affiliates of our directors, in this offering, our directors, executive officers and principal stockholders, together with their affiliates, will beneficially own, in the aggregate, approximately 57.5 percent of our outstanding common stock, or 54.6 percent of our outstanding common stock if the underwriters exercise their overallotment option in full, upon the completion of this offering, based on shares of our capital stock outstanding as of December 31, 2013. 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 your interests. 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 certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace

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or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

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

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

We will incur increased costs as a result of opera