REGENXBIO Inc.
Form 10-K
March 06, 2018
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2017

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number: 001-37553

REGENXBIO Inc.

(Exact name of registrant as specified in its charter)

Delaware	47-1851754
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

9600 Blackwell Road, Suite 210

Rockville, MD 20850

(Address of principal executive offices) (Zip Code)

(240) 552-8181

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Common Stock, $0.0001 par value per share	The Nasdaq Stock Market LLC
(Title of each class)	(Name of each exchange on which registered)

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

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

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

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

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

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

Large accelerated filer | Accelerated filer

Non-accelerated filer (Do not check if a smaller reporting company) | Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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

As of June 30, 2017, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates was approximately $505.0 million, based on the closing price of the registrant's common stock on The Nasdaq Global Select Market on June 30, 2017 of $19.75 per share. For purposes of this disclosure, shares of common stock held by each executive officer, director and stockholder known by the registrant to be affiliated with such individuals based on public filings and other information known to the registrant have been excluded since such persons may be deemed affiliates. This determination of executive officer or affiliate status is not necessarily a conclusive determination for other purposes.

As of March 2, 2018, there were 31,655,093 shares of the registrant's common stock, par value $0.0001 per share, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Specified portions of the registrant's proxy statement with respect to the registrant's 2018 Annual Meeting of Stockholders, which is to be filed pursuant to Regulation 14A within 120 days after the end of the registrant's fiscal year ended December 31, 2017, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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PART I

INFORMATION REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). These statements express a belief, expectation or intention and are generally accompanied by words that convey projected future events or outcomes such as "believe," "may," "will," "estimate," "continue "anticipate," "design," "intend," "expect," "could," "plan," "potential," "predict," "seek," "should," "would" or by variations o by similar expressions. We have based these forward-looking statements on our current expectations and assumptions and analyses made by us in light of our experience and our perception of historical trends, current conditions and expected future developments, as well as other factors we believe are appropriate under the circumstances. However, whether actual results and developments will conform with our expectations and predictions is subject to a number of risks, uncertainties, assumptions and other important factors, including, but not limited to:

- the timing of enrollment, commencement and completion of our clinical trials;
- the timing and success of preclinical studies and clinical trials conducted by us and our development partners;
- the timely development and launch of new products;
- the ability to obtain and maintain regulatory approval of our product candidates, and the labeling for any approved products;
- the scope, progress, expansion and costs of developing and commercializing our product candidates;
- our ability to obtain and maintain intellectual property protection for our product candidates and technology;
- our anticipated growth strategies;
- our expectations regarding competition;
- the anticipated trends and challenges in our business and the market in which we operate;
- our ability to attract or retain key personnel;
- the size and growth of the potential markets for our product candidates and the ability to serve those markets;
- the rate and degree of market acceptance of any of our product candidates;
- our ability to establish and maintain development partnerships;
- our expectations regarding our expenses and revenue;
- our expectations regarding regulatory developments in the United States and foreign countries; and
- the use or sufficiency of our cash and cash equivalents and needs for additional financing.

You should carefully read the factors discussed in the sections titled "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Annual Report on Form 10-K and in our other filings with the U.S. Securities and Exchange Commission (SEC) for additional discussion of the risks, uncertainties, assumptions and other important factors that could cause our actual results or developments to differ materially and adversely from those projected in the forward-looking statements. The actual results or developments anticipated may not be realized or, even if substantially realized, they may not have the expected consequences to or effects on us or our businesses or operations. Such statements are not guarantees of future performance and actual results or developments may differ materially and adversely from those projected in the forward-looking statements. These forward-looking statements speak only as of the date of this report. Except as required by law and the rules of the SEC, we do not undertake any obligation, and specifically decline any obligation, to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

As used in this Annual Report on Form 10-K, the terms "REGENXBIO," "we," "us," "our" or the "Company" mean REGENXBIO Inc. and its subsidiaries, on a consolidated basis, unless the context indicates otherwise.

NAV, REGENXBIO and the REGENXBIO logos are our registered trademarks. Any other trademarks appearing in this Annual Report on Form 10-K are the property of their respective holders.

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INDUSTRY AND MARKET DATA

We obtained the industry, market and competitive position data used throughout this Annual Report on Form 10-K from our own internal estimates and research, as well as from industry and general publications, in addition to research, surveys and studies conducted by third parties. Internal estimates are derived from publicly-available information released by industry analysts and third-party sources, our internal research and our industry experience, and are based on assumptions made by us based on such data and our knowledge of our industry and market, which we believe to be reasonable. We have not independently verified industry, market and competitive position data from third-party sources, but we believe the sources of such information to be reliable. While we believe the industry, market and competitive position data included in this Annual Report on Form 10-K is reliable and is based on reasonable assumptions, such data involves risks and uncertainties and are subject to change based on various factors, including those discussed in “Risk Factors.” These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

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ITEM 1. BUSINESS

Overview

We are a leading clinical-stage biotechnology company seeking to improve lives through the curative potential of gene therapy. Our gene therapy product candidates are designed to deliver genes to cells to address genetic defects or to enable cells in the body to produce therapeutic proteins or antibodies that are intended to impact disease. Through a single administration, our gene therapy product candidates are designed to provide long-lasting effects, potentially significantly altering the course of disease and delivering improved patient outcomes.

Our product candidate RGX-314 is for the treatment of wet age-related macular degeneration (wet AMD), a leading cause of total and partial vision loss in the United States, Europe and Japan. We began enrollment in the Phase I clinical trial for RGX-314 for the treatment of wet AMD in May 2017 and have completed dosing of three cohorts of six patients each, a total of 18 patients, in the Phase I clinical trial. We expect to present topline data from the Phase I clinical trial in late 2018.

Our product candidate RGX-501 is for the treatment of homozygous familial hypercholesterolemia (HoFH), a severe genetic disease characterized by premature and aggressive plaque buildup, life threatening coronary artery disease (CAD) and aortic valve disease predominantly due to abnormalities in the function or expression of the low-density lipoprotein receptor (LDLR) gene. We, together with trial sponsor the University of Pennsylvania (Penn), began enrollment in the Phase I/II clinical trial for RGX-501 in March 2017. We have completed dosing of the first cohort of three patients and have dosed two patients in the second cohort. We expect to present topline data from the Phase I/II clinical trial in late 2018.

We are also developing product candidates to address the neurological symptoms of two severe genetic lysosomal storage diseases, Mucopolysaccharidosis Type I (MPS I) and Mucopolysaccharidosis Type II (MPS II). MPS I is caused by deficiency of -l-iduronidase (IDUA) and MPS II is caused by deficiency of iduronate-2-sulfatase (IDS), both of which are enzymes that are responsible for breakdown of cellular waste products. Deficiencies in these enzymes lead to a number of physical symptoms and patients with severe forms of these diseases also exhibit significant cognitive decline. The investigational new drug applications (INDs) filed with the U.S. Food and Drug Administration (the FDA) for RGX-111 and RGX-121, our product candidates for MPS I and MPS II, respectively, are active. We expect to begin enrollment in a Phase I clinical trial for RGX-111 and a Phase I/II clinical trial for RGX-121 in mid-2018.

In addition to our lead product candidates, we have also funded, and plan to continue to fund, preclinical research on potential product candidate programs that may become part of our internal product development pipeline. We have partnered with a number of leading academic institutions and will continue to seek partnerships with innovative institutions to develop novel NAV gene therapy product candidates. We expect to announce an additional lead product candidate in the second half of 2018.

Our gene therapy product candidates deliver genes to cells using adeno-associated virus (AAV) vectors, which are non-replicating viral delivery vehicles that are not known to cause disease. Our product candidates all utilize viral vectors from our proprietary gene delivery platform, which we call our NAV Technology Platform. Our NAV Technology Platform consists of exclusive rights to AAV7, AAV8, AAV9, AAVrh10 and over 100 other novel AAV vectors (NAV Vectors). We currently have exclusive rights to over 100 patents and patent applications worldwide covering our NAV Vectors, including composition of matter claims for AAV7, AAV8, AAV9 and AAVrh10, as well as methods for their manufacture and therapeutic uses. We believe this patent portfolio forms a strong foundation for our current programs and with our ongoing research and development, we expect to continue to expand this robust

patent portfolio.

The foundation of our NAV Technology Platform was discovered in an effort to identify next generation AAV vectors that could overcome the limitations of earlier generation AAV vectors (AAV1 through AAV6). We believe the key benefits of NAV Vectors over earlier generation AAV vectors include:

- higher gene expression;
- longer-term gene expression;
- broad and novel tissue selectivity;
- lower immune response; and
- improved manufacturability.

In addition to our internal product development efforts, we also selectively sublicense our NAV Vectors to other biotechnology companies, which we refer to as NAV Technology Licensees. As of December 31, 2017, our NAV Technology Platform was being applied in the development of more than 20 partnered product candidates by 10 NAV Technology Licensees.

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Our internal and partnered product development program pipeline is shown below.

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Our partnered development pipeline benefits from the disease-specific expertise of our NAV Technology Licensees. Our partnering strategy provides us the flexibility to sublicense development of treatments designed to address significant unmet medical needs, while remaining focused on our core programs and therapeutic areas internally. We believe that the broad applicability of our NAV Technology Platform and any clinical successes of the treatments utilizing NAV Vectors will create new internal and partnered pipeline opportunities.

Our company was formed from a successful collaboration that began in February 2009 between FOXKISER LLP, Penn and James Wilson, M.D., Ph.D. As our team has grown, we have continued to build on our scientific foundation, adding depth in gene therapy and biotechnology leadership. Our management team includes leaders who are experienced in building and operating innovative healthcare ventures and have expert knowledge in the development of AAV gene therapy. We believe the strength of our team positions us to succeed in developing and bringing to market, independently or with our development partners, unique, best-in-class gene therapy treatments for a range of severe diseases with significant unmet medical needs.

Our Strategy

Our mission is to improve lives through the curative potential of gene therapy. We are seeking to develop, manufacture, commercialize and license product candidates across multiple therapeutic areas and target organs while continuing to expand our NAV Technology Platform. To achieve our mission, we are pursuing the following strategies:

- Apply our proprietary, next generation AAV vector technology to develop in vivo gene therapies for patients. We believe in vivo gene therapy is an ideal treatment paradigm for monogenic diseases with sub-optimal or non-existent therapies because of its potential to correct an underlying genetic defect, rather than just treating a patient's symptoms. In diseases not caused by a single gene defect, in vivo gene therapy has the potential to replace the need for frequent treatments by enabling the body to produce therapeutic proteins or antibodies consistently to impact the course of disease. We believe our NAV Technology Platform is proving to be a significant advancement over earlier AAV vectors in delivering these therapies. Based on data derived from third-party clinical studies and animal models using our NAV Vectors, we believe our NAV Technology Platform possesses unique, beneficial properties that are not seen in earlier generation AAVs. We believe that our NAV Technology Platform, which underpins our internal development programs and the programs of our NAV Technology Licensees, will enable us and our partners to develop best-in-class gene therapy candidates for a wide range of disease targets due to these unique properties.
- Focus on rapidly advancing our internal lead proprietary development programs in retinal, metabolic and neurodegenerative diseases. Both wet AMD and HoFH are diseases with high unmet clinical need and current treatments that are sub-optimal. We have enrolled 18 patients in a Phase I clinical trial for RGX-314 and we expect to present topline data from the Phase I clinical trial in late 2018. We have enrolled five patients in a Phase I/II clinical trial for RGX-501 and we expect to present topline data from the Phase I/II clinical trial in late 2018. The INDs for RGX-111 for the treatment of MPS I and RGX-121 for the treatment of MPS II are active. We expect to initiate a Phase I clinical trial for RGX-111 and a Phase I/II clinical trial for RGX-121 for the treatment of MPS II in mid-2018. If we are successful in achieving proof-of-concept in the Phase I or Phase I/II clinical trials for these diseases, we will pursue further development, including registration trials and commercialization of such product candidates.
- Establish gene therapy franchises in and beyond our current core therapeutic areas of retinal, metabolic and neurodegenerative diseases. After human proof-of-concept is achieved in a disease, we believe we will be able to apply what we have learned and use our NAV Technology Platform to more rapidly develop new product candidates for many similar diseases. Once an appropriate vector and route of administration for a particular disease type have been established, we believe a new gene can be inserted into the appropriate vector and the established route of

administration can be used for other similar diseases. To date, our strategy of focusing on retinal, metabolic and neurodegenerative diseases has been informed by significant animal, and in some cases human clinical, data that indicate specific NAV Vectors are particularly effective in the cells where these types of diseases manifest. Targeting tissues where diseases manifest is critical to impacting the course of diseases with our NAV gene therapy treatments (NAV Gene Therapy). This approach underpins our strategy for our neurodegenerative disease franchise, for example, where we applied knowledge from IND-enabling studies of RGX-111 for MPS I to enable a rapid follow-on IND filing for RGX-121, our MPS II program. We believe that this approach may also be applicable to metabolic and retinal diseases, as well as many other therapeutic areas, and will allow us to efficiently generate product candidates for diseases in and beyond our current areas of therapeutic focus, including the additional lead product candidate we expect to designate in the second half of 2018.

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- Further grow the potential of our NAV Technology Platform through strategic in-licensing and sublicensing of new programs. We plan to grow the potential of our NAV Technology Platform through licensing. For example, we are pursuing in-licensing for programs we deem to be the most promising research programs using our NAV Vectors. We intend to continue to selectively sublicense our NAV Technology Platform for specific vector and indication combinations to additional NAV Technology Licensees. Strategic sublicensing allows us to maintain our internal product development focus in our core disease indications and therapeutic areas while still expanding the NAV Gene Therapy pipeline, developing a greater breadth of treatments for patients, providing additional technological and potential clinical proof-of-concept for our NAV Technology Platform, and creating potential additional revenue.
- Leverage the NAV Technology Platform in the expression of therapeutic proteins, antibodies and gene editing. Our treatment for wet AMD involves the novel, one-time administration of our NAV AAV8 vector encoding a gene for a monoclonal antibody fragment, which has the potential to enable a patient's retinal cells to continuously produce therapeutic antibodies. To maintain efficacy, the current standard of care for the treatment of wet AMD requires repetitive and inconvenient intraocular injections of marketed therapeutic proteins or antibodies, typically ranging from every four to eight weeks in frequency. There are many diseases where the existing standard of care involves frequent administration of marketed therapeutic proteins or antibodies and we believe there are other patient populations that would benefit from NAV-based treatments designed to enable different cells in the body of patients to produce therapeutic proteins or antibodies. In addition, it has been demonstrated by several researchers that our NAV Technology Platform can be efficiently adapted to deliver different genome editing components to address the specific treatment needs of many disease targets. We may aim to invest in research and development in these areas or explore collaborations with strategic partners that have capabilities in the development of therapeutic antibodies, proteins and gene editing.
- Maintain and grow our extensive intellectual property portfolio. We plan to leverage our intellectual property rights and substantial expertise in AAV gene therapy in order to develop and commercialize NAV Gene Therapy. We have licensed exclusive rights to a broad portfolio of certain fundamental AAV gene therapy patents and patent applications. In securing these rights, we have focused on obtaining robust rights for those intellectual property assets we believe will be most important in providing us with a competitive advantage with respect to AAV gene therapy treatments. We plan to continue to seek to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business.

The Broad Potential and Application of Gene Therapy

The concept of developing human therapies involving the delivery of external genes has existed for decades, driven by the arrival of recombinant technology and the early demonstrations by scientists of the ability to deliver and drive expression of external gene sequences in mammalian cells.

We believe that gene therapy has the potential to become a new and important class of treatment because it may offer the following benefits:

- Ability to treat a broad range of diseases. Given the availability of the sequence of the entire human genome, it could be possible to design gene therapy to express or effect expression of any human protein whose presence, absence or activity causes disease. We believe gene therapy treatments can also be designed to enable the body to continuously produce therapeutic proteins or antibodies or be efficiently adapted to deliver different genome editing components to address the specific treatment needs of many disease targets.
- Ability to target mechanisms that cannot be targeted effectively by existing drug classes. Many proteins that play roles in disease cannot be targeted effectively with small molecules and therapeutic proteins. These limitations on small molecule and protein drugs may not apply to gene therapy, which we believe can be designed to target any gene in the genome.
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Ability to create convenient treatment profiles. Because gene therapies are designed to deliver a long-term effect with a single administration, a single gene delivered via gene therapy could potentially do the same work of administering conventional drugs for many years.

- Simplified discovery of treatment candidates. Identification of small molecule and protein drug candidates typically requires screening of a large number of potential candidates to find prospective leads. Identification of gene therapy candidates has the potential to be simpler and take considerably less time because it can involve relatively standard processes that can be applied in a similar fashion to many successive product candidates.

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Our NAV Gene Therapy Product Candidates

We have developed an internal pipeline of product candidates across the therapeutic areas of retinal, metabolic and neurodegenerative diseases. Below is a table summarizing our current internal development programs.

Retinal Diseases

We are developing applications of our NAV Technology Platform to treat acquired and inherited forms of retinal disease that can result in visual loss or complete blindness. The retina is the light-sensitive layer of cells that lines the inside of the eye and sends visual messages to the brain. The effects of retinal diseases are isolated to the eye, which we believe is an ideal target for gene therapy due to its relatively immunoprivileged state, small size and relative physical isolation from the rest of the body. We believe NAV Vectors can safely and effectively target a diverse set of retinal cells, including retinal pigment epithelium (RPE) cells and photoreceptors, enabling production of high levels of protein with the potential to impact a broad range of diseases. Additionally, the molecular basis of many retinal diseases is becoming well-understood and many retinal diseases are monogenic diseases whose complementary deoxyribonucleic acid (DNA) has already been successfully cloned. Diagnosis of many forms of inherited blindness is becoming quicker and simpler due to improved research and the application of technology to characterize the variable, unique patterns of different retinal diseases. We believe our NAV Gene Therapy may have improved profiles for achieving therapeutic efficacy where highly efficient gene delivery to the retina is required.

Third party studies have reported safety and efficacy of subretinal injection of AAV2 in clinical trials for a retinal disease called Leber congenital amaurosis type 2 (LCA2). Other programs have studied the safety and efficacy profile of AAV2 to treat neovascularization in wet AMD. For LCA2, retinal function was restored by reconstituting gene function in the RPE. However, for most retinal degeneration disorders, photoreceptor cells are the primary cell type involved and have historically been a more difficult cellular target in the retina for AAV gene therapy. We believe our NAV Technology Platform will be more efficient at gene delivery into many retinal cell types, particularly photoreceptor cells, than earlier generation AAV vectors such as AAV2. Data from mice, dogs and non-human primates suggests that, compared to other AAVs, NAV Vectors can safely and more effectively target a diverse set of retinal cells, including RPE cells and photoreceptors, when compared to other AAVs. For instance, in most retinal cells, NAV-mediated gene delivery reaches maximal levels of expression much sooner than AAV2-mediated delivery in these animal studies. Furthermore, in the same set of retinal cells, NAV Vectors achieve equivalent expression to AAV2 at a dose that is ten times less. Our NAV Technology Platform has been used successfully in a gene therapy approach in animal models of achromatopsia, LCA2, autosomal recessive retinitis pigmentosa, x-linked retinoschisis and wet AMD.

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We believe that retinal diseases are an ideal target for NAV Gene Therapy due to early evidence indicating efficiency at achieving gene delivery in a wide-array of cell types in the retina. We believe the first use of our NAV Technology Platform in a clinical trial for retinal diseases could result in robust safety and efficacy data but could also serve as a stepping stone for using NAV Gene Therapy in other human retinal diseases.

RGX-314 for the Treatment of Wet AMD

Overview of Wet AMD

Age-related macular degeneration (AMD) is a disease that results in diminution and eventual loss of central vision due to progressive damage to the macula, which is the functional center of the retina. A subset of AMD patients have wet AMD, which is characterized by loss of vision due to excess fluid accumulation from new blood vessel formation. Fluid leakage following this excess fluid accumulation can result in physical changes in the structure of the retina and adverse changes in vision. As this process progresses, blindness can result from atrophy and scar formation.

Wet AMD is a leading cause of total and partial vision loss in the United States, Europe and Japan. Wet AMD consists of approximately 10% of all cases of AMD, but accounts for approximately 90% of the vision loss associated with AMD. As indicated by the name, the risk for developing AMD increases with age and we anticipate the diagnosis rate will continue to increase as the population continues to trend towards an aging population. In the United States, the prevalence of wet AMD is estimated to be nearly 600,000 individuals and there may be over two million individuals living with wet AMD in the United States, Europe and Japan combined. In developed countries, an estimated two-thirds of people with AMD have been diagnosed, of whom about two-thirds are treated.

Current Therapies for Wet AMD

Anti-vascular endothelial growth factor (VEGF) therapies have significantly changed the landscape for treatment of wet AMD. They have quickly become the standard of care due to their ability to reduce fluid accumulation and, on average, improve vision in the majority of patients with wet AMD. Currently, there are three anti-VEGFs that are commonly used for the treatment of wet AMD. All of these therapies, however, require repetitive and inconvenient intraocular injections, typically ranging from every four to eight weeks in frequency, to maintain efficacy. Patients often experience vision loss with reduced frequency of treatment and due to a variety of factors, including inconvenience and discomfort associated with frequent injections in the eye, patient compliance is a significant concern with anti-VEGF therapies.

We are aware of multiple gene therapy product candidates developed previously to address the unmet medical need described above for wet AMD by targeting VEGF inhibition using AAV2 as the gene therapy vector. We believe published clinical trials for wet AMD gene therapy illustrate the safety of the subretinal delivery approach and the potential to reduce injection frequency using gene therapy. We also believe the data from these clinical trials may indicate that some patients may benefit from greater inhibition of VEGF activity and that utilizing NAV Technology could allow us to achieve better VEGF inhibition than our competitors using AAV2 to treat wet AMD.

RGX-314

RGX-314 is our product candidate for the treatment of wet AMD. RGX-314 is being developed as a novel, one-time subretinal treatment for wet AMD that includes the NAV AAV8 vector encoding a gene for a monoclonal antibody fragment. The expressed protein is designed to neutralize VEGF activity, modifying the pathway for formation of new leaky blood vessels and retinal fluid accumulation. After delivery of RGX-314, we believe retinal cells will continue

to produce the anti-VEGF protein.

Clinical Development of RGX-314

Enrollment in the Phase I clinical trial of subretinally administered RGX-314 in the United States in patients with wet AMD began in May 2017. The trial is an ascending dose design with a formal safety assessment of each dose group by an independent data safety monitoring board (DSMB) prior to dose escalation. The trial design allows for enrollment of up to 18 patients across three dose levels (3 × 10^9 genome copies (GC)/eye, 1 × 10^10 GC/eye, and 6 × 10^10 GC/eye). Each cohort consists of six patients who have a documented need and history of response to anti-VEGF therapies. Primary endpoints include adverse events (AEs), certain laboratory measures (including immunological parameters), evaluation of best-corrected visual acuity (BCVA), retinal fluid on spectral domain ocular coherence tomography (SD- OCT), presence of RGX-314 protein in aqueous fluid and other outcome measures. The primary purpose of the clinical trial is to evaluate the safety and tolerability of RGX-314 at 24 weeks after a single dose of RGX-314 administered by subretinal delivery. Following completion of the primary study period, it is expected that subjects will enter the follow-up period and will continue to be assessed until week 106 to assess long term safety and durability of effect.

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We have fully enrolled three dose cohorts, a total of 18 patients, in the Phase I clinical trial for RGX-314. Treatments have been administered at four sites in the United States. The procedure has been completed via automated delivery by trained retina surgeons using a vitrectomy machine within an hour or less in most cases. As we reported in January 2018, based on the first 12 patients dosed, we had observed RGX-314 to be generally well-tolerated by patients. At that time, we also shared an interim look at the RGX-314 protein expression data at the four-week timepoint on the first two cohorts of patients. In these first two cohorts, evidence of dose-dependent RGX-314 protein expression, as measured by enzyme-linked immunosorbent assay, or an ELISA, was observed.

We expect to present topline data from the RGX-314 Phase I clinical trial in late 2018, which will include both primary and secondary endpoint data.

Preclinical Proof of Concept for RGX-314

Our RGX-314 product candidate was designed to optimize a vector candidate to have the potential to express high levels of anti-VEGF. In order to evaluate the potential for RGX-314 for the treatment of wet AMD, the optimized RGX-314 product candidate was assessed in both mouse and non-human primate (NHP) models. Dose-dependent reduction of both the number of new retinal blood vessels and the incidence of retinal detachments related to exudation caused by vascular proliferation in the retina was also observed in two different VEGF-dependent animal models of wet AMD. In the study below, NHPs were injected subretinally with RGX-314 and expression of anti-VEGF was measured in the aqueous humor of treated animals. Ocular anti-VEGF protein expression was rapid in onset and levels remained consistent in all animals and doses tested, indicating the potential for consistent sustained expression of anti-VEGF after a one-time, subretinal administration of RGX-314.

(1) Wielechowski et al. 2016 Poster session presented at the meeting of the American Society of Gene & Cell Therapy, Washington, DC

Other Retinal Disease Programs

In addition to our RGX-314 program, we have also funded, and plan to continue to fund, preclinical research on potential retinal disease product candidate programs that may become part of our internal product development pipeline. Our goal is to develop a gene therapy franchise in retinal diseases, as well as explore further applications of NAV Technology. We have partnered with a number of leading academic institutions and will continue to seek partnerships with innovative institutions.

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Metabolic Diseases

Our product development pipeline includes treatment candidates for liver-targeted expression of genes. The selected candidates for our programs seek to leverage lessons learned from previous reports of preclinical and human proof-of-concept studies conducted by third-party investigators and our partners using our NAV Technology Platform. Based on these studies and our own research, we believe our NAV Technology Platform demonstrates promising properties for applications that involve gene delivery to liver cells that may result in long-term, high-level expression of protein.

Historically, a clinical trial for the treatment of hemophilia B using AAV2 vectors that were administered to achieve expression of genes in the liver did not produce evidence of efficacy. Reported data from this study generally did not show any measurable levels of expression sufficient to correct disease symptoms. In subjects where measurable expression levels were reported, gene expression faded over a short period of time. We believe selecting different AAV vectors will increase the levels and duration of expression.

The first clinical milestone of AAV-mediated liver gene therapy occurred in 2011 in a trial conducted at St. Jude Children's Research Hospital for the treatment of hemophilia B using AAV8 in which some patients were able to discontinue prophylactic FIX injections. In 2016, the same group reported in a study update that the treatment was shown to be durable for over five years and that long-lasting efficacy results were reported in the patients treated. Subsequently, two additional groups have reported human proof-of-concept using AAV8-mediated gene therapy to deliver and express a gene in the liver for the treatment of hemophilia B.

Our academic collaborators have also demonstrated in a MPS I feline model that liver-directed IDUA gene delivery using AAV8 resulted in persistent, normal levels of IDUA in the blood. In most cases, the treatment also resulted in cross-correction (cells that are transduced with vector can release enzyme, which is taken up by non-transduced cells) in most tissues including complete resolution of disease pathology in some tissues normally not responsive to enzyme replacement therapy (ERT).

We intend to advance a pipeline of programs in certain metabolic diseases that will be enhanced by the benefits of NAV-mediated liver gene therapy. Our initial focus is on a severe lipid disorder, HoFH.

RGX-501 for the Treatment of HoFH Caused by LDLR Mutations

Overview of HoFH

HoFH is a monogenic disorder caused predominantly by abnormalities in the function or expression of the LDLR gene. LDLR plays an important role in the regulation of cholesterol by facilitating uptake and degradation of low-density lipoprotein (LDL) in the liver. LDL is the primary carrier of cholesterol in the blood and has been implicated in the development of plaque buildup in the arteries. HoFH patients have very low levels or are completely deficient of LDLR, resulting in very high blood cholesterol levels which are typically greater than 500 milligrams per deciliter (mg/dl). This leads to premature and aggressive plaque buildup, life threatening CAD and aortic valve disease. Patients with HoFH develop progressive atherosclerosis, or narrowing and blockage of the arteries beginning at an early age, which leads to a high incidence of heart attacks in children and teenagers, among other severe symptoms. If untreated, HoFH patients usually die of causes related to CAD or aortic valve disease before the age of 30.

Published medical literature suggests that the worldwide prevalence of HoFH is estimated to be as high as 1 in 200,000. Based on disease severity and molecular characteristics, we estimate there are approximately 11,000 individuals globally who are primary candidates for gene therapy treatment of HoFH. Multiple studies have compared HoFH patients based on LDLR activity and have shown small differences in residual activity can lead to significant reductions in cholesterol levels and better long-term outcomes.

Current Therapies for HoFH

The current standard of care in HoFH focuses on early initiation of aggressive treatment because of the severe clinical effects of elevated LDL-C. Unfortunately, available treatment options are limited. Lipoprotein apheresis, a physical method of filtering the plasma of LDL-C, requires weekly or biweekly treatment in order to maintain effect. The procedure is laborious, requiring frequent intravenous access that can be challenging, expensive and not readily available. Other available treatments include statins, a class of pharmaceuticals commonly used to lower cholesterol levels, cholesterol absorption inhibitors and other cholesterol lowering medications. The FDA has approved two drugs as add-on therapy specifically for HoFH: lomitapide and mipomersen. Both result in a reduction of LDL-C, but their use is associated with an array of adverse events that may affect tolerance and long-term adherence. These therapies do not provide a cure for the disease and their use is limited due to tolerability and drug availability. Despite the implementation of an aggressive multi-drug therapy approach, the LDL-C levels of HoFH patients remain elevated and mean life expectancy remains at approximately 32 years. Other available treatments include PCSK9 inhibitors. PCSK9 inhibitors are designed to bind to a protein called PCSK9 and inhibit PCSK9 from binding to LDLR on the liver surface. In the absence of PCSK9, there is more LDLR on the surface of the liver to remove LDL-C from the blood. We believe that the emergence of PCSK9 inhibitors as therapy

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will increase the opportunity and awareness for the profile of RGX-501 by helping to identify more patients who may benefit from its product profile. A clinical trial evaluating a PCSK9 inhibitor demonstrated that its effectiveness relies on patients having functional LDLR. We believe that a substantial unmet medical need remains for the population of HoFH patients who are LDLR negative or severely deficient in LDLR function. We believe that RGX-501, by restoring or increasing LDLR function, may enhance the impact of PCSK9 inhibitors in the treatment of many patients with high cholesterol and as prescribers explore combination therapies. With all current therapies, even in combination, providing sub-optimal treatment for patients, a better solution is needed. We believe HoFH is a promising disease target for gene therapy.

RGX-501

RGX-501 is our product candidate for the treatment of HoFH, which is designed to use the AAV8 vector to deliver the human LDLR gene to liver cells. We believe that the liver is the preferred target organ for gene therapy of HoFH since LDLRs produced in the liver contribute to greater than 90% of the capture and breakdown of LDL, making the liver by far the most important LDLR producing organ. Additionally, the liver is also the only organ capable of excreting cholesterol from the body, a function that is critical to the maintenance of cholesterol balance. Finally, studies have shown that liver transplantation in HoFH patients corrects the disease, providing strong support that correction of hepatic LDL receptor activity by gene therapy is sufficient for metabolic correction of the disease.

We have received orphan drug product designation from the FDA for RGX-501.

Clinical Development of RGX-501

Enrollment in the Phase I/II clinical trial of intravenously administered RGX-501 in the United States in patients with HoFH began in March 2017. The trial is a single ascending dose design with a formal safety assessment by an independent DSMB prior to dose escalation. The trial design calls for enrollment of up to 12 subjects with dosing at a single center. Patient follow-up is being conducted at a number of sites globally. The primary endpoint is a safety assessment. The secondary endpoints are reduction in LDL-C and other outcome measures. Based on previous clinical trials and recent approvals in HoFH, we believe reduction in LDL-C is an endpoint that is an acceptable measure on which regulatory approval could be based.

We have enrolled five patients in the Phase I/II clinical trial for RGX-501, three in the first dose cohort and two in the second dose cohort. As we reported in January 2018, based on the first three patients dosed, we had observed RGX-501 to be generally well-tolerated by patients. One subject in the first cohort experienced a drug-related SAE within 24 hours of dosing of hypotension associated with a mild inflammatory response, which resolved within a few hours of onset. The nature and time frame of the SAE is distinct from expected and known immune responses to AAV therapy. The patient recovered quickly from the SAE without significant sequalae.

We expect to present topline data from the RGX-501 Phase I/II clinical trial in late 2018, which will include both primary and secondary endpoint data.

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Preclinical Proof of Concept for RGX-501

In order to evaluate the potential for RGX-501 for the treatment of HoFH, mouse LDLR liver-directed gene therapy with AAV8 was evaluated in mouse models of HoFH by our scientific collaborators at Penn. Mice were injected intravenously with the vector and followed for metabolic correction and reversal of pre-existing atherosclerotic lesions. Animals were also evaluated for gross clinical toxicity and abnormalities in serum transaminases, an indicator of liver damage. Animals in the Penn study receiving the vector showed a near complete normalization of hypercholesterolemia that remained stable for almost a year, as well as a substantial regression of atherosclerosis over two months as assessed by two independent methods of quantification at two different sites within the aorta. There was no vector induced toxicity of the liver based on histopathology and clinical chemistry.

(1) PLOS One: Gene Therapy in a Humanized Mouse Model of Familial Hypercholesterolemia Leads to Marked Regression of Atherosclerosis, Sadik H. Kassim and Hui Li, et al. (October 2010).

Other Metabolic Disease Programs

In addition to our RGX-501 program, we have also funded, and plan to continue to fund, preclinical research on potential metabolic disease product candidate programs and programs to address the systemic manifestations of a number of diseases that may become part of our internal product development pipeline. Our goal is to develop a gene therapy franchise in metabolic diseases, as well as explore further applications of NAV Technology. We have partnered with a number of leading academic institutions and will continue to seek partnerships with innovative institutions.

Neurodegenerative Diseases

We are focused on developing NAV Gene Therapy for diseases with significant unmet medical need that involve neurodegeneration in the brain and spinal cord—which together comprise the central nervous system (CNS). We believe our NAV Technology Platform has optimal features for gene delivery to the CNS. In addition, our programs involve novel strategies for improved delivery of NAV Gene Therapy to the CNS that enhance our candidate profiles.

For neurodegenerative disease, AAV2 vectors were historically applied via focal delivery in the brain by adopting existing direct injection techniques. In certain cases, investigators have attempted to use direct injection of vector into multiple sites of the brain to address neurodegenerative disorders that require gene delivery to larger areas. Although there are some examples in animal models in which focal delivery can be therapeutic, these techniques have not produced efficacy in humans.

For most neurodegenerative diseases, we believe that global delivery to the CNS will achieve optimal therapeutic efficacy. Widespread transduction of the CNS in animal models has been achieved by administration of NAV Vectors into the ventricles, cisterna magna, as well as lumbar puncture, which allows the vector to circulate through the cerebrospinal fluid (CSF). We are progressing similar delivery approaches through the CSF in humans to achieve global delivery to the CNS.

Additionally, one of our NAV Vectors, AAV9, has produced evidence of potentially unique and beneficial properties for gene delivery in the CNS by having the ability to cross the blood-brain barrier. As a result, treatments may be delivered via intravenous injection to target the CNS. One of our NAV Technology Licensees is currently using this approach in a clinical trial for the treatment of spinal muscular atrophy (SMA) Type I, which has shown evidence of lower motor neuron transduction.

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Based on these studies and our own research, we believe our NAV Technology Platform demonstrates promising properties for applications that involve gene delivery to the CNS that we believe will result in long-term, high-level expression of protein. We intend to advance a pipeline of programs in neurodegenerative diseases that will be enhanced by the benefits of using our NAV Technology Platform.

RGX-111 for the Treatment of MPS I Caused by Autosomal Recessive IDUA Mutations

Overview of MPS I

MPS I is a rare autosomal recessive, or non-sex-linked, genetic disease caused by deficiency of IDUA, an enzyme required for the breakdown of polysaccharides heparan sulfate and dermatan sulfate in lysosomes, which are intracellular structures that dispose of waste products inside cells. These polysaccharides, called glycosaminoglycans (GAGs), accumulate in tissues of MPS I patients, resulting in characteristic storage lesions and diverse clinical signs and symptoms. MPS I patients may exhibit short stature, bone and joint deformities, coarsened facial features, enlargement of both the liver and spleen (hepatosplenomegaly), cardiac valve disease, obstructive sleep apnea, recurrent upper respiratory infections, hearing impairment, carpal tunnel syndrome and vision impairment due to corneal clouding. In addition, many patients develop symptoms related to GAG storage in the CNS, which can include excessive accumulation of fluid in the brain, spinal cord compression and cognitive impairment. MPS I patients span a broad spectrum of disease severity and extent of CNS involvement. We believe this variability in severity correlates with residual IDUA expression. The severe form of MPS I is also referred to as Hurler syndrome. Hurler patients have two mutations of the IDUA gene, resulting in no active enzyme expression. These patients typically present with symptoms before two years of age and universally exhibit severe cognitive decline after an initial period of normal development. Patients with at least one mutation of the IDUA gene who are able to produce a small amount of active IDUA exhibit an attenuated, or less severe, phenotype. These phenotypes are referred to as Hurler-Scheie or Scheie syndrome. Hurler-Scheie represents an intermediate phenotype, with patients exhibiting some or all of the physical features of Hurler syndrome. Some Hurler-Scheie patients also experience neurological complications and cognitive decline.

MPS I is estimated to occur in 1 in 100,000 births. Based on global population, this equates to over 1,000 MPS I patients born each year worldwide. Studies suggest that severe forms of MPS I represent between one-half and two-thirds of all MPS I patients.

Current Therapies for MPS I

The current standard of care for patients with an attenuated form of MPS I is a recombinant form of human IDUA (Aldurazyme). Given as a weekly intravenous infusion, this ERT has demonstrated improvement in hepatosplenomegaly, growth, mobility and respiratory function. However, as the enzyme cannot cross the blood-brain barrier, ERT does not treat the CNS manifestations of MPS I.

The first disease modifying therapy developed for severe MPS I was bone marrow transplant (BMT). Though BMT has demonstrated improvements in survival, growth, cardiac and respiratory function, mobility and intellect, it is also associated with clinically relevant morbidity and an estimated 10% to 20% mortality. Accordingly, the procedure is reserved for patients with severe disease before two years of age because the risk-benefit ratio is thought to be more favorable in younger patients who have not yet experienced advanced cognitive decline. Another critical limitation of BMT is that cognitive decline continues for up to a year after transplant before stabilizing, leaving permanent cognitive deficits. In an effort to find approaches that treat the CNS manifestations of neurodegenerative diseases, clinical trials to evaluate direct administration of ERT into the spinal fluid (intrathecal administration) for the

treatment of MPS I and direct administration of ERT into the brain (intracerebroventricular administration) for Batten's Disease (a neurodegenerative disease) have been initiated. These approaches, however, do not address the underlying cause of these neurodegenerative diseases. Furthermore, we believe the need for frequent (bi-weekly or monthly) intrathecal or intracerebroventricular administration is likely to lead to patient compliance issues, further reducing the treatment potential of this method of ERT.

Overall, the limitations of BMT and ERT leave a significant unmet need for a method to safely achieve long-term IDUA reconstitution in the CNS for MPS I patients experiencing neurological complications.

RGX-111

RGX-111 is our product candidate for the treatment of MPS I which is designed to use the AAV9 vector to deliver the human IDUA gene to the CNS. Delivery of the enzyme that is deficient within cells in the CNS could provide a permanent source of secreted IDUA beyond the blood-brain barrier, allowing for long-term cross-correction of cells throughout the CNS. We believe this strategy could also provide rapid IDUA delivery to the brain, potentially preventing the progression of cognitive deficits that otherwise occurs in MPS I patients.

We have received orphan drug product designation and rare pediatric disease designation from the FDA for RGX-111.

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Planned Clinical Development of RGX-111

The IND for RGX-111 is active and we plan to initiate a Phase I clinical trial of RGX-111 based gene delivery via CNS administration in mid-2018 in subjects with MPS I. The clinical trial is a single ascending dose design and a formal safety assessment of the first dose group will be conducted by an independent DSMB prior to dose escalation. The trial design calls for enrollment of up to five subjects with MPS I. The first subject must be greater than 18 years of age, and all subsequent subjects will be greater than or equal to six years of age. All subjects must have documented evidence of early-stage neurocognitive deficits due to MPS I. The primary endpoint will be a safety assessment. The secondary endpoints include the effect of RGX-111 on biomarkers of IDUA activity in the CSF, serum and urine and the effect of RGX-111 on neurocognitive deficits, as well as other outcome measures.

We expect to present an interim update from the RGX-111 Phase I clinical trial in late 2018.

Preclinical Proof of Concept of RGX-111

To assess the feasibility of achieving widespread IDUA expression and correction of storage pathology throughout the brain of MPS I patients, we carried out proof-of-concept studies of intrathecal AAV9 delivery of IDUA using large animal models of MPS I. These studies demonstrated that AAV9 delivery can safely restore IDUA expression to levels equivalent to or greater than non-affected animals. As can be seen in the diagram below, animals treated with an intracisternal injection of an AAV9 vector expressing feline IDUA from a CB promoter (gray symbols) or CMV promoter (black symbols) showed IDUA expression levels above those of untreated animals and in some cases above those of wild-type animals (the dotted line represents mean CSF IDUA expression for two wild-type animals). Storage correction was observed throughout the CNS. Some animals had IDUA activity at lower levels than wild-type animals post-treatment but also achieved significant correction relative to diseased animals. The extent of CNS correction in our studies was substantially greater than that observed in a previous study of MPS I cats treated with BMT at similar ages, thus demonstrating that gene delivery can achieve rapid onset and high levels of IDUA delivery, and similar findings have also been observed in a canine model of MPS I. These findings provide proof of concept of AAV9 delivery of IDUA for treating the CNS pathology associated with MPS I.

IDUA Expression in Feline CSF Following IT AAV9 Delivery[(1)]

(1) Molecular Therapy: Intrathecal gene therapy corrects CNS pathology in a feline model of mucopolysaccharidosis I, Peter Bell, et al. (July 2014).

RGX-121 for the Treatment of MPS II Caused by X-Linked Recessive IDS Mutations

Overview of MPS II

MPS II, also known as Hunter syndrome, is a rare, X-linked recessive, or sex-linked, disease caused by a deficiency of IDS. IDS is another enzyme responsible for the breakdown of polysaccharides heparan sulfate and dermatan sulfate in the lysosomes of cells, resulting in a progressive, multisystem disorder with a similar phenotype to MPS I. In severe forms of the disease, early developmental milestones may be met, but developmental delay is readily apparent by 18

to 24 months. Developmental progression begins to plateau between three and five years of age, with regression reported to begin around six and a half years. By the time of death, most patients with CNS involvement are severely mentally handicapped and require constant care.

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MPS II is estimated to occur in approximately 1 in 100,000 to 1 in 170,000 births. Based on global population, this equates to approximately 500 to 1,000 MPS II patients born each year worldwide.

Current Therapies for MPS II

In 2006, recombinant IDS (Elaprase), an ERT, was approved by the FDA for the treatment of MPS II and has subsequently been approved for use internationally. However, ERT does not treat CNS manifestations of MPS II, since the enzyme cannot cross the blood-brain barrier. Specific treatment to address the neurological manifestations of MPS II and prevent or stabilize cognitive decline remains a significant unmet medical need. Overall, the limitations of ERT leave a significant unmet need for a method to safely achieve long-term IDS reconstitution in the CNS for MPS II patients experiencing neurological complications.

RGX-121

RGX-121 is our product candidate for the treatment of MPS II, which is designed to use the AAV9 vector to deliver the human IDS gene to the CNS. Delivery of the enzyme that is deficient within cells in the CNS could provide a permanent source of secreted IDS beyond the blood-brain barrier, allowing for long-term cross-correction of cells throughout the CNS. We believe this strategy could also provide rapid IDS delivery to the brain, potentially preventing the progression of cognitive deficits that otherwise occur in MPS II patients.

As noted above, this approach has been successfully used in the treatment of animal models of monogenic CNS diseases. Previously conducted studies of AAV9 directed gene therapy in the CNS with MPS I animal models have shown that AAV9 can successfully be used to achieve wide biodistribution within the CNS, robust expression of transgene product that benefits from cross-correction and overall acceptable safety profile. We believe these studies have validated the use of AAV9 in the development of CNS directed gene therapy products and that by using AAV9 for the development of both RGX-111 and RGX-121, we have been able to build upon the learnings and experience generated in our RGX-111 program to rapidly and efficiently focus our development efforts for RGX-121.

We have received orphan drug product designation and rare pediatric disease designation from the FDA for RGX-121.

Planned Clinical Development of RGX-121

The IND for RGX-121 is active and we plan to initiate a Phase I/II clinical trial of RGX-121 based gene delivery via CNS administration in mid-2018 in subjects with MPS II. The clinical trial is a single ascending dose design and a formal safety assessment of the first dose group will be conducted by an independent DSMB prior to dose escalation. The trial design calls for enrollment of up to six subjects with MPS II. Subjects in the study must be greater than or equal to four months of age and less than five years of age. All subjects must have documented evidence of neurocognitive deficits due to MPS II or have a relative diagnosed with severe MPS II who has the same IDS mutation as the subject. The primary endpoint will be a safety assessment. The secondary and exploratory endpoints include the effect of RGX-121 on biomarkers of IDS activity in the CSF, serum and urine and effect of RGX-121 on neurocognitive deficits, as well as other outcome measures.

We expect to present an interim update from the RGX-121 Phase I/II clinical trial in late 2018.

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Preclinical Development of RGX-121

To assess the feasibility of achieving widespread IDS expression and correction of storage pathology throughout the brain of MPS II patients, we carried out proof-of-concept studies of CNS AAV9 delivery using a mouse model of MPS II. There are no known large animal models of MPS II. MPS II mice were administered with AAV9 vector encoding a gene for IDS in the CNS, which resulted in higher levels of IDS enzyme activity in the brain. As shown in the diagram below, these higher levels of IDS enzyme activity resulted in a statistically significant reduction of neuronal storage lesions in the brains of treated mice as measured by cells positive for GM3, a ganglioside which accumulates in cells as a result of IDS deficiency. These results show the potential therapeutic benefit of AAV9-mediated IDS gene delivery to the CNS through the CSF to address neurological manifestations of MPS II.

GM3 Positive Cells in Mouse Tissue Following IT AAV9 Delivery[(1)]

(1) Human Gene Therapy: Delivery of an adeno-associated virus vector into cerebrospinal fluid attenuates central nervous system disease in mucopolysaccharidosis Type II mice, Christian Hinderer, et al. (August 2016).

Other Neurodegenerative Disease Programs

In addition to our RGX-111 and RGX-121 programs, we have also funded, and plan to continue to fund, preclinical research on potential neurodegenerative disease product candidate programs that may become part of our internal product development pipeline. Our goal is to develop a gene therapy franchise in neurodegenerative diseases, as well as explore further applications of NAV Technology, and we believe there are a number of neurodegenerative diseases that may be addressable using a similar approach to our RGX-111 and RGX-121 programs. We have partnered with a number of leading academic institutions and will continue to seek partnerships with innovative institutions to remain at the leading edge of the gene therapy field.

Commercial Licenses to NAV Technology Licensees

We sublicense our NAV Technology Platform to third parties in order to develop and bring to market NAV Gene Therapy for a range of severe diseases with significant unmet medical needs. Sublicensing allows us to maintain our internal product development focus on our core disease indications and therapeutic areas while still expanding the NAV Gene Therapy pipeline, developing a greater breadth of treatments for patients, providing additional technological and potential clinical proof-of-concept for our NAV Technology Platform, and creating potential additional revenue.

Each sublicense specifies the vector or vectors and disease indication or indications as well as whether the sublicense is exclusive or non-exclusive. In determining whether to sublicense, we first evaluate whether the disease indication is of interest to us in which case we may develop a therapeutic for the disease indication internally using our NAV Technology Platform. If it is not, we consider the size of the potential market and unmet need, competition, licensee development history and capabilities and licensee’s ability to pay in evaluating whether to enter into a license agreement. As of December 31, 2017, our NAV Technology Platform was being applied in the development of more than 20 partnered product candidates by 10 NAV Technology Licensees, most under a license to specific NAV Vectors for specific indications.

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Our license agreements include upfront fees, annual maintenance fees, milestone fees based on licensee candidate progression, and low-single to low-double digit royalties on sales. Such royalties are subject to customary reductions, such as if the licensee must obtain a license from a third party to avoid infringement of such third party's rights in order to exercise its rights under the license granted by us. We are obligated to make payments to our licensors with respect to the revenues we receive from our licensees for these sublicenses, in accordance with the terms of our agreements with our licensors.

As of December 31, 2017, our NAV Technology Licensees had eight clinical stage programs using NAV Vectors. The chart below provides an overview of the development status of the programs of our NAV Technology Licensees.

AveXis, Inc.

AveXis, Inc. License to Treat Spinal Muscular Atrophy, as Amended. In January 2018, we entered into an amendment to our 2014 license agreement with AveXis, Inc. (AveXis). Under the amendment, we granted AveXis an exclusive, worldwide commercial license, with rights to sublicense, to any recombinant AAV vector in our intellectual property portfolio during the term of the license agreement for the treatment of SMA in humans by in vivo gene therapy. Under the original AveXis license agreement, we had granted AveXis a license relating only to the NAV AAV9 vector.

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Additionally, the amendment modifies the terms and conditions of the license agreement relating to assignment. Under the amended assignment provision, AveXis is permitted to transfer the license agreement without our consent in connection with a change of control of AveXis, subject to the transferee or successor agreeing in writing to be bound by the terms of the license agreement and the payment to us of certain fees due upon such change of control, as described below. Under the original 2014 license agreement, any assignment by AveXis without our prior written consent had been prohibited. The amendment also provides that, solely upon the written request of AveXis, we may, in our sole discretion after receipt of such request, provide certain collaboration services to AveXis regarding the development and commercialization of gene therapy product candidates for the treatment of SMA.

Pursuant to the amendment, in consideration for the additional rights granted thereunder and in addition to the payments and royalties owed under the original 2014 license agreement, AveXis paid to us a fee of $80.0 million upon entry into the amendment. In addition, AveXis will pay to us (i) $30.0 million on the first anniversary of the effective date of the amendment, (ii) $30.0 million on the second anniversary of the effective date of the amendment and (iii) potential commercial milestone payments of up to $120.0 million. In the event of a change of control of AveXis, to the extent that any fee described in (i) or (ii) above, or the first $40.0 million of milestone payments described in (iii) above, has not yet been paid to us, AveXis will be obliged to pay any such unpaid fee to us upon the change of control. Additionally, for any product developed for the treatment of SMA using the NAV AAV9 vector, we will continue to receive mid-single to low double-digit royalties on net sales as defined in the original 2014 license agreement, and for any product developed for the treatment of SMA using a NAV vector other than NAV AAV9, we will receive a low double-digit royalty on net sales.

AveXis, Inc. License to Treat Rett Syndrome and Amyotrophic Lateral Sclerosis. In June 2017, we entered into an exclusive license agreement with AveXis for the development and commercialization of products to treat Rett Syndrome and amyotrophic lateral sclerosis (ALS) caused by mutations in the gene that produces the copper zinc superoxide dismutase 1 (SOD1) enzyme using AAV9. Under the license agreement, we granted AveXis an exclusive, sublicensable worldwide license under the licensed intellectual property to make, have made, use, import, sell and offer for sale licensed products in the treatment of Rett Syndrome and ALS caused by mutations in the SOD1 gene using AAV9. In consideration for the license, AveXis paid us an up-front fee of $6.0 million, and is required to pay annual maintenance fees, milestone fees of up to $36.0 million, a low double digit royalty percentage on net sales of licensed products, subject to reduction in specified circumstances, and a lower mid-double digit percentage of any sublicense fees AveXis receives from sublicensees for the licensed intellectual property rights.

Process Development and Manufacturing

We believe that we have the internal capabilities and access to the resources necessary to enable us to successfully commercialize NAV Gene Therapy products following regulatory approval, if any, by developing scalable processes to manufacture such products efficiently and at commercial quantity.

AAV Vector Production

We have invested significantly in our internal capabilities and infrastructure, including build out and opening of our advanced manufacturing and analytics lab, the first phase of which is complete. Our internal team possesses deep knowledge of AAV characterization and production, as well as significant experience and expertise in biologics process development (upstream, purification and formulation), scale-up and production at large scale. We believe our capabilities and infrastructure will enable us to continue to be leaders in development of scalable, proprietary production methods for NAV Gene Therapy products. We have established internal capability to produce NAV Vectors across multiple platforms and at a scale of up to 200 liters.

We have also entered into agreements with multiple leading biologics contract manufacturing organizations (CMOs) for production of material under current Good Manufacturing Practice (cGMP) requirements to support our current and future clinical trials, as well as potential future commercialization of our product development programs. We select our CMOs based on capability, capacity and expertise, and we believe our CMOs are capable of meeting global regulatory standards for clinical and commercial material supply. We believe partnering with multiple leading CMOs provides us with flexibility and diversity in suppliers, as well as access to potential future capacity to accommodate the scale that may be required for future clinical trials and commercialization.

We have entered into a strategic partnership with FUJIFILM Diosynth Biotechnologies (FUJIFILM) for the manufacture of our lead product candidates, which will support late-stage clinical development and early commercialization. Under the terms of the agreement with FUJIFILM, we gain guaranteed capacity for the supply of NAV AAV drug substance manufactured under cGMP at large scale—up to 2,000L—for three years, with the option to extend the agreement for an additional three years. FUJIFILM facilities are compliant with global regulatory standards in support of the initiation of worldwide clinical trials for our lead product candidates.

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In addition, we believe we have established a robust supply chain for our key raw materials to ensure both high quality standards and assurance of raw material supply as we advance our programs. We believe our management team retains significant expertise in managing a diverse network of CMOs and suppliers and that this expertise will enable us to execute on our manufacturing strategy in connection with our external partners.

Proprietary Methods

We have obtained rights to all of the proprietary technology underlying our NAV Technology Platform through our Platform Licenses (described below) and our sponsored research agreements (SRAs), under which we have exclusively licensed rights to certain manufacturing-related patents and non-exclusively licensed rights to certain know-how owned or developed by Penn. This intellectual property encompasses areas including scalable AAV production methods, methods of increasing the packaging yield of AAV and methods of purification of AAV vectors.

We have examined several methods of larger-scale manufacturing of AAV which have been optimized to yield high titer and quality vectors. However, further improvements to the efficiency and simplicity of the process may remain important to address future needs for commercial applications. Our production methods utilize linearly scalable unit operations which produce robust yield and purity of the target vector.

Scientists at Penn discovered that in contrast to earlier generation AAV2, most NAV Vectors were released primarily into the medium of production cultures and not retained in the cell. Because this distribution occurs in the absence of cell lysis, the production culture medium represents a relatively pure source of NAV Vectors and a lower level of cellular contaminants that reduces the need for complicated purification steps. This method, for which we have licensed from Penn the exclusive patent rights, is high-yielding and versatile for the production of different NAV Vectors and has been demonstrated to scale into a cGMP setting with comparable yields and product quality. Our future process development activities will build upon this platform to target higher yield of vector without impacting the product purity profile.

Other Capabilities

We have prepared and characterized a proprietary HEK293 master cell bank and other components (plasmid DNA banks) required for clinical vector production. Our master cell bank and other components are being used by us and certain of our NAV Technology Licensees for the production of NAV Vectors under cGMP for use in clinical trials.

Gene Therapy Overview and History of Earlier Generation AAV

Historically, the primary challenge for gene therapy has been the delivery of genes into cells. Genes are made of DNA, which is a large, highly charged molecule that is difficult to transport across a cell membrane and deliver to the nucleus, where it can be transcribed and translated into protein. The genetic material needs to be delivered efficiently and to the desired target tissues and cell types, which will vary depending on the disease to be treated. Based on this need, scientists have designed and developed a variety of gene vectors in order to facilitate gene delivery in cells.

To date, the study of gene vectors as treatments in humans has involved approaches with in vivo and ex vivo techniques using a variety of different gene vectors. Each approach presents different features and benefits for the treatment of a particular disease. Ex vivo gene therapy approaches generally are employed to target correction in blood and bone marrow. These methods typically involve harvesting and isolating a patient’s own cells. Both the patient and cells undergo several preparatory steps to allow for modification of the cells by gene vectors. Ultimately, the modified cells are re-administered to the patient. In vivo gene therapy approaches involve directly administering

(e.g., by infusion or injection) gene vectors into patients in order to reach desired cells in target tissues (e.g., liver, brain, eye, muscle, heart). These methods rely on a combination of the route of administration and the gene vectors themselves to facilitate the correction in the target tissues.

We focus on in vivo gene therapy. Among vectors available for in vivo gene therapy, viral vectors have been adopted with the greatest frequency because they have demonstrated the greatest efficiency in gene delivery to date. This efficiency exists because viral vectors are derived from naturally occurring viruses whose normal life-cycle relies on gene delivery of their own genomes. In other words, they are naturally optimized to deliver genes to cells. Many viral vectors have presented sub-optimal safety profiles for in vivo treatment in humans because the viruses from which they are derived are pathogenic (causing disease), immunogenic (causing immune response) or create genomic toxicity (delivering a gene to a place where it interrupts normal function). Vectors derived from adenovirus, herpes virus and retroviruses have been tested as in vivo viral vectors.

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Vectors derived from AAV have among the best safety profiles for gene therapy given that AAVs are not known to be associated with disease in humans. The earlier generation AAV vectors were designed by scientists in the mid-1980s and the first clinical trials using AAV began in the mid-1990s. There were only a handful of AAV vectors available to scientists at the time of the first clinical trials because AAV vectors were designed based on the capsid (the protein shell of a virus that encloses the genetic material of the virus) of AAV viruses known to be in existence and only six distinct serotypes (groups within a single species of microorganisms, such as bacteria or viruses, which share distinctive surface structures) had been discovered at that time. These earlier generation AAV vectors were shown to be limited in their application due to a variety of limitations and challenges, including:

- low or unmeasurable gene expression, meaning the delivered gene was enabling production of low or unmeasurable amounts of the therapeutic protein;
- short-term gene expression, meaning if gene expression was measurable, it was transient;
- limited tissue selectivity, meaning concentrated gene expression was not observed in the target organ; and
- high levels of immune response, meaning the body may neutralize the gene delivery vector with pre-existing antibodies or generate T-cells that inhibit the therapeutic effect.

Discovery of Next Generation AAV

In recognition of the limitations and challenges of earlier generation AAV vectors, an effort was undertaken in the early 2000s at Penn to discover other naturally occurring AAV sequences. The identification of such sequences was based on the observation that wild-type AAV (in contrast to recombinant AAV) can undergo a latent cycle in which the AAV genome stays within the cell, meaning the virus, including its capsid gene sequence, remains intact within the cell but does not reproduce. This allowed for identification of new sequences not by purifying viruses from tissues, but by searching for capsid gene sequences in a variety of tissues isolated from non-human primates and from humans, based on regions of the AAV capsid gene that did not vary between the known AAV vectors. By searching for capsid gene sequences in this manner, many more capsid protein sequences were discovered than would have been found by purifying viruses from tissues.

More than 100 new capsid sequences were identified by the process. The first few were initially designated AAV7, AAV8 and AAV9, after which, other sequences were identified by species from which it was isolated (e.g., “rh” indicating rhesus macaque) followed by a number (e.g., 10, for rh10). Early characterization of the initial discoveries of AAV7, AAV8, AAV9 and AAVrh10 suggested that these vectors may be significantly more efficient in various applications important for clinical translation than other previously known AAVs.

After patenting the next generation AAV vectors, Penn initiated a distribution program through a material-transfer process that enabled researchers to access the next generation AAV vectors for research use only, under specific restrictions. Thousands of custom reagents were sent to independent researchers, who began to characterize and validate the beneficial features of AAV vectors in animal models of disease. In 2010, the first clinical trials were conducted using the next generation AAV vectors and initial proof-of-concept and safety in humans was established from these trials. These clinical trials also produced longer-term efficacy results which reinforced our belief that these next generation vectors have beneficial properties not seen in the earlier generation AAV vectors.

We believe the next generation AAV vectors, which form the basis of our NAV Technology Platform, have many improved properties relative to earlier generation AAV vectors for development and commercialization of AAV treatments, including:

- higher gene expression;
- longer-term gene expression;

- broad and novel tissue selectivity;
- lower immune response; and
- improved manufacturability.

Our Proprietary NAV Technology Platform for Gene Delivery

Our NAV Technology Platform has been used in several clinical trials conducted by our partners and third-party investigators. In 2009, we licensed rights to the next generation AAV vectors discovered at Penn. Our NAV Vectors form the foundation of our NAV Technology Platform.

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We are developing therapeutics using NAV Vectors that contain genes which are synthesized to code for the expression of therapeutic proteins in target cells to correct the underlying causes of the diseases we seek to treat. Each product candidate is designed with a NAV Vector for a specific cell target and to express a specific protein. We incorporate proprietary modifications to both the AAV and the gene which enhance properties such as potency, stability and tissue distribution. Our proprietary technology, including the use of vectors derived from novel sequences of AAV such as AAV7, AAV8, AAV9 and AAVrh10, are protected by over 100 licensed patents and patent applications. The rights to our NAV Technology Platform provide our product candidates with what we believe to be a competitive advantage over product candidates developed with earlier generation AAV vectors due to the novel and beneficial properties of our NAV Vectors.

Key Potential Benefits of NAV Technology

The properties that make NAV Vectors unique from and potentially an improvement to earlier generation AAV vectors, as well as provide support that they are potentially best-in-class for development and commercialization of AAV treatments, are set forth in the pages that follow.

Higher Gene Expression

NAV Vectors have been shown to generate higher levels of gene expression in animals than earlier generation AAV vectors such as AAV2. In mice livers, one of our NAV Vectors, AAV8, produced levels of gene expression that were 10- to 100-fold higher than was achieved with AAV2. The figure below shows the contrast in the amount of gene expressed using the two vectors at the same dose.

AAV Transduction in Mouse Liver

In this experiment, the reporter gene LacZ, a gene which encodes a protein that turns a clear substrate blue in a specific medium, was included in the transgene sequence delivered by the vector so that cells expressing the transgene are stained blue, visually denoting expression level. It was possible to transduce the entire mouse liver and achieve long-term expression with AAV8. Higher gene expression creates the possibility of achieving therapeutic benefit in more diseases than was possible using earlier AAV vectors, as more therapeutic protein is generated with vectors that enable higher expression.

Longer-Term Gene Expression

We believe the longer-term gene expression seen using NAV Vectors is due to more stable genomic persistence and reduced cellular immunity, which are a function of novel capsid structure and lower dosing required using NAV Vectors due to the greater gene expression discussed earlier. NAV Vectors have demonstrated stable expression in animals for over eight years. Moreover, AAV8 vectors have demonstrated stable expression for over four years in clinical trials for hemophilia B patients.

Broad and Novel Tissue Selectivity

NAV Vectors also display high levels of tissue specificity. This property is important because it allows for development of therapeutics to target cells that earlier generation AAV vectors do not target or do not target well. In the CNS, AAV9 has emerged as a vector that enables efficient gene delivery when directly injected into the brain. This was aided by the ability of AAV9 to be transported throughout the brain, enabling broader delivery with a single injection.

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NAV Gene Therapy has demonstrated novel tissue selectivity for the CNS when delivered intravenously. Intravenous delivery of AAV9 resulted in efficient gene expression in the brain and spinal cord, and this route of administration produced results in both small and large animals, including non-human primates. This was the first time a gene therapy vector was demonstrated to cross the blood-brain barrier. This route of administration has recently been used clinically by one of our NAV Technology Licensees to treat SMA Type I.

NAV Vectors have also shown novel properties in the eye when investigated for the treatment of acquired disease and inherited retinal degenerations. AAV8 expressing a fluorescent protein was administered by subretinal injection in the non-human primate eye in order to show gene expression in the retina itself, which contains the cell types to be treated. As is depicted in the graphic below, a cross-section of the non-human primate retina below showed more efficient gene delivery (as demonstrated by the much greater amount of the fluorescent protein expressed) with AAV8 as compared to AAV2 in the retinal pigment epithelium (RPE) and to the photoreceptor (PR) layer. The majority of genes associated with retinal degeneration are located in the RPE and PR layer. These genes influence the cell's development or function and are therefore critical to most inherited retinal degenerations.

AAV Transduction of Layers in the Non-Human Primate Eye[(1)]

(1) Science Translational Medicine: Dosage Thresholds for AAV2 and AAV8 Photoreceptor Gene Therapy in Monkey, Luk H. Vandenberghe, et al. (2011). Reprinted with permission from the American Association for the Advancement of Science.

Lower Immune Response

Lower immune response to the gene therapy vector used to deliver the transgene is important for longer-term gene expression, higher expression and higher potency. Data indicate that more than 50% of certain human populations have a high level of neutralizing antibodies (NAbs) for the earlier generation vector AAV2. This represents a major obstacle to the effective use of these earlier generation AAV vectors due to the inhibition of gene delivery via particle neutralization in circulation, meaning pre-existing antibodies neutralize the vector with the transgene before it can reach the target cells. By contrast, frequency of neutralizing antibodies for AAV8 is consistently lower than for AAV2. In a French study, for example, AAV2 NAbs occurred at a frequency of 59% compared to 19% for AAV8. Thus, AAV8 is a candidate for liver-directed gene delivery in a higher proportion of the population than AAV2.

Additionally, reduced effect from the generation and reactivity of T-cells to NAV Vectors has been demonstrated, relative to earlier generation AAV vectors. Activation of T-cells to the capsid of AAV2 vectors has been implicated in liver toxicity in a clinical trial for the treatment of hemophilia B. A patient in this clinical trial developed an elevation of liver enzymes and subsequently lost expression. This led to a hypothesis that capsid protein antigens and memory T-cell activation may lead to clearance of AAV-transduced cells. To further investigate this kind of toxicity, scientists reported a study that evaluated T-cell responses to AAV vectors after administration to mice and nonhuman primates. In this study, high levels of T-cells specific to capsids of AAV2 were detected. AAV8, however, did not lead to activation of capsid-specific T-cells. In a more recent clinical trial for the treatment of hemophilia B, using AAV8, there was less of an effect from T-cells generated and reactive with AAV8. We believe this is likely a function of the lower doses that can be used as well as the structure of the vector itself.

Improved Manufacturability

The manufacturing process for NAV Vectors can be designed to reduce the number of difficult processing steps required for the earlier AAV vectors, improving overall yield at larger scale. NAV Vectors are derived from naturally "fit" viruses, which are stable structures that efficiently assemble, in contrast to the earlier generation AAV vectors. During production, NAV Vectors are secreted by AAV producer cells, eliminating the need for lysing (breaking down of the membrane of a cell, often by viral, enzymic or osmotic mechanisms that compromise the cells integrity) of cells, which can complicate purification and impact yield. This is a novel aspect of NAV Vectors that increases yield and efficiency in production.

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Platform License Agreements and Other Licenses

Platform Licenses

We have exclusively licensed many of our rights in our NAV Technology Platform from Penn and GlaxoSmithKline LLC (GSK), which together we refer to as our Platform Licenses. We currently use our NAV Technology Platform to develop treatments for retinal, metabolic and neurodegenerative diseases. We also sublicense our NAV Technology Platform to third parties in order to develop and bring to market NAV Gene Therapy for a range of severe diseases with significant unmet medical needs outside of our core disease indications and therapeutic areas. For further information regarding our commercial sublicenses, please see "Commercial Licenses to NAV Technology Licensees" located elsewhere in this Annual Report on Form 10-K.

The Trustees of the University of Pennsylvania. In February 2009, we entered into an exclusive, worldwide license agreement with Penn for patent and other intellectual property rights relating to a gene therapy technology platform based on AAVs discovered at Penn in the laboratory of James M. Wilson, M.D., Ph.D. This license was amended in September 2014 and April 2016. In February 2009, we also entered into an SRA with Penn (the 2009 SRA) under which we funded the nonclinical research of Dr. Wilson relating to AAV gene therapy and obtained an option to acquire an exclusive worldwide license in certain intellectual property created pursuant to such 2009 SRA. In December 2014, we entered into another SRA with Penn funding related nonclinical research of Dr. Wilson (the 2014 SRA). We entered into an additional SRA (the 2013 SRA) with Penn in November 2013 which was funded entirely by our NAV Technology Licensee, Dimension Therapeutics, Inc. (since acquired by Ultragenyx Pharmaceutical Inc.) (Dimension).

Our license agreement with Penn, as amended, provides us with an exclusive, worldwide license under certain patents and patent applications in order to make, have made, use, import, offer for sale and sell products covered by the claims of the licensed patents and patent applications as well as all patentable inventions (to the extent they are or become available for license) that:

- were discovered by Dr. Wilson or other Penn researchers working under his direct supervision at Penn prior to September 2014;
- are related to the AAV technology platform discovered by Dr. Wilson at Penn prior to February 2009 or pursuant to a sponsored research agreement or subsequent amendment to a sponsored research agreement; and
- are owned by Penn and available for licensing.

Prior to entering into the license agreement with us, Penn had previously entered into two license agreements with third parties with respect to certain of the licensed patents and patent applications. Our license from Penn is subject to those preexisting license grants. With respect to the first third party license granted by Penn, our license is non-exclusive with respect to the patents and patent applications licensed to the third party for so long as that preexisting license grant remains in effect and will become exclusive upon the expiration or termination of that existing license agreement. The pre-existing licenses also include a license agreement Penn entered into with GSK in May 2002 granting a license to certain patents and patent applications, of which we subsequently sublicensed certain rights to from GSK in March 2009. For further information regarding our GSK sublicense, please see "Platform License Agreements and Other Licenses—Platform Licenses—GlaxoSmithKline LLC" located elsewhere in this Annual Report on Form 10-K. Our license agreement with Penn provides that should the rights Penn licensed to GSK ever revert to Penn, such rights shall automatically be included in our license agreement with Penn.

The Penn license agreement, as amended, also provides us with a non-exclusive, worldwide license to use all data and information generated in the performance of clinical research relating to the RGX-501 clinical trial and all know-how

that:

- was developed by Dr. Wilson, or other Penn researchers working under his direct supervision at Penn; and
- is related to the AAV technology platform discovered by Dr. Wilson prior to September 2014; or
- is related to the AAV technology platform discovered by Dr. Wilson at Penn after September 2014 pursuant to the 2009 SRA, the 2014 SRA, the 2013 SRA or subsequent amendment to a sponsored research agreement; and
  - is owned by Penn;
    and
- is necessary or useful for the practice of the licensed patent rights.

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Under the terms of the Penn license agreement, we issued equity to Penn now represented by 213,150 shares of our common stock. We are also obligated to pay Penn:

- low- to mid-single digit royalties on net sales of licensed pharmaceutical products sold by us or our affiliates;
- low-single digit to low-double digit royalty percentages of net sales on products intended for research purposes only;
- low- to mid-double digit royalty percentage on royalties received from third parties on net sales of licensed pharmaceutical products by such third parties;
- low-double digit to mid-teen digit percentages of sublicense fees we receive for the licensed intellectual property rights from sublicensees; and
- reimbursements for ongoing patent prosecution and maintenance expenses.

As of December 31, 2017, we have incurred expenses of $3.3 million to Penn under the license agreement, excluding the equity interest issued to Penn as upfront consideration at the inception of the agreement. There are no future potential milestones to be paid under the license agreement. Our Penn license agreement, as amended, will terminate with respect to licensed products in a field of use other than the treatment of familial hypercholesterolemia (FH) on a product-by-product and country-by-country basis on the date each particular licensed product ceases to be covered by at least one valid claim, issued or pending, under the licensed patent rights. With respect to licensed products for treating FH, our Penn license agreement, as amended, will terminate on a product-by-product and country-by-country basis on the later of (i) the date the licensed product for treating FH ceases to be infringed or covered by a valid claim, issued or pending, under the licensed patent rights, and (ii) seven years following the first sale of such licensed product for treating FH. We can terminate this license agreement by giving Penn prior written notice. Penn has the right to terminate:

- with notice if we are late in paying money due under the license agreement;
- with notice if we fail to achieve a diligence event on or before the applicable completion date or otherwise breach the license agreement;
- if we or our affiliates experience insolvency; or
- if we commence any action against Penn to declare or render any claim of the licensed patent rights invalid or unenforceable.

Under the current 2014 SRA, as amended, we fund research at Penn and pay certain intellectual property legal and filing expenses and receive the rights to the research results, if any. Under the Penn license agreement, as amended, and the 2014 SRA, as amended, all patentable inventions conceived, created, or conceived and reduced to practice pursuant to the 2014 SRA, together with patent rights represented by or issuing from the U.S. patents and patent applications, including provisional patent applications, automatically become exclusively licensed to us and all research results are automatically licensed to us as know-how. Under the 2009 SRA, as amended, in consideration for our funding of research at Penn, we received an option to acquire a worldwide license on commercially reasonable terms to practice all patentable inventions conceived, created, or reduced to practice pursuant to the 2009 SRA, together with patent rights represented by or issuing from the U.S. patents and patent applications, including provisional patent applications. Under our 2014 SRA with Penn, as amended, we have agreed to fund research at Penn through 2020. We expect to continue to fund work at Penn and receive rights to the results of the research we fund.

GlaxoSmithKline LLC. In March 2009, we entered into a license agreement with GSK, which was amended in April 2009, in order to secure the exclusive rights to patents and patent applications covering NAV Technology that GSK had previously licensed from Penn (subject to certain rights retained by GSK and Penn). Under this GSK license agreement, we receive an exclusive, worldwide sublicense under the licensed patent rights to make, have made, use, import, sell and offer for sale products covered by the licensed patent rights anywhere in the world. Our rights under this GSK license agreement are subject to certain rights retained by GSK for the benefit of itself and other third parties, including rights relating to: domain antibodies; RNA interference and antisense drugs; internal research

purposes and GSK's discovery research efforts with non-profit organizations and GSK collaborators; AAV8 for the treatment of hemophilia B; AAV9 for the treatment of Muscular Dystrophy, congestive heart failure suffered by Muscular Dystrophy patients and cardiovascular diseases by delivery of certain genes; and non-commercial research in the areas of Muscular Dystrophy, hemophilia B, congestive heart failure suffered by Muscular Dystrophy patients, and other cardiovascular disease. Under the terms of the license agreement, we issued to GSK 1,085,824 shares of our common stock. We are obligated to pay GSK:

- up to $1.5 million in aggregate milestone payments, $0.5 million of which have been accrued or paid as of December 31, 2017;
- low- to mid-single digit royalty percentages on net sales of licensed products;

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- low- to mid-double digit percentages of any sublicense fees we receive from sublicensees for the licensed intellectual property rights; and
- reimbursements for certain patent prosecution and maintenance expenses.

As of December 31, 2017, we have incurred expenses of $7.1 million to GSK under the license agreement, excluding the equity interest issued to GSK as upfront consideration at the inception of the agreement. Under our GSK license agreement, we are required to use commercially reasonable efforts to develop and commercialize licensed products. Our GSK license agreement will terminate upon the expiration, lapse, abandonment or invalidation of the last licensed claim to expire, lapse, become abandoned or unenforceable in all the countries of the world where the licensed patent rights existed. However, if no patent ever issues from patent rights licensed from GSK, this license agreement will terminate a specified number of years after the first commercial sale of the first licensed product in any country. We may terminate this license agreement for any reason upon a specified number of days' written notice. GSK can terminate this license agreement if:

- we are late in paying GSK any money due under the agreement and do not pay in full within a specified number of days of GSK's written demand;
- we materially breach the agreement and fail to cure within a specified number of days; or
- we file for bankruptcy.

Other Licenses

Regents of the University of Minnesota. In November 2014, we entered into a license agreement with Regents of the University of Minnesota (Minnesota) for the exclusive rights to Minnesota's undivided interest in intellectual property jointly owned by Minnesota and us relating to the delivery of AAV vectors to the central nervous system for MPS I and MPS II. This license was amended in November 2016. Under this Minnesota license agreement, as amended, we receive an exclusive license under the licensed patent rights to make, have made, use, offer to sell or sell, offer to lease or lease, import or otherwise offer to dispose or dispose of products covered by the licensed patent rights in all fields of use in any country or territory in which a licensed patent has been issued and is unexpired or a licensed patent application is pending.

Under the terms of the Minnesota license agreement, as amended, we are obligated to pay Minnesota:

- an upfront payment of $0.1 million;
- up to $0.1 million in aggregate milestone payments per licensed product;
- low-single digit royalty percentages on net sales of licensed products;
- mid-single to low-double digit percentages of sublicense fees;
- annual maintenance fees; and
- patent-related maintenance expenses and fees.

We are obligated to achieve certain development performance milestones, each of which may be extended upon the payment of specified fees, related to our efforts to develop and commercialize products incorporating the licensed intellectual property.

As of December 31, 2017, we have incurred expenses of $0.3 million to Minnesota under the license agreement. This license agreement expires when there is no licensed patent or pending patent application in any country. Upon expiration, our license becomes a royalty-free, fully-paid up, perpetual, and irrevocable license. Minnesota may terminate the license agreement if we materially breach or materially fail to perform one or more of our obligations under the license agreement and we have not cured in full within a specified number of days after delivery of notice of default for payment or a specified number of days if the default relates to any other matter. Minnesota may terminate the license agreement if we become bankrupt or if we commence or maintain an action challenging any patent or

patent application licensed under the license agreement. We may terminate the agreement if Minnesota materially breaches or materially fails to perform one or more of its duties under this agreement. We may terminate for any reason upon a specified number of days' prior written notice but must pay an early termination fee.

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Intellectual Property

Our success depends in part on our ability to obtain and maintain intellectual property protection for our product candidates, core technologies and other know-how, to operate without infringing on the rights of others and to prevent others from infringing our rights. We strive to protect and enhance the proprietary technology, inventions, and improvements that are important to our business, including by seeking, maintaining and defending patent rights. We also rely on trade secrets relating to our technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our position in the field of gene therapy. Additionally, we intend to rely on regulatory protection afforded through orphan drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

We anticipate that our patent portfolio will continue to expand as a result of our SRAs with academic institutions, including the 2014 SRA with Penn, and our commercial licenses to NAV Technology Licensees. For further information regarding our commercial sublicenses, please see “Commercial Licenses to NAV Technology Licensees” located elsewhere in this Annual Report on Form 10-K.

Product Candidates

As of December 31, 2017, our patent portfolio included a total of two issued U.S. patents and eight pending International Patent applications filed pursuant to the Patent Cooperation Treaty (PCTs) relating to our product candidates, which are summarized below:

- RGX-314: Two PCTs for which any issued U.S. or European patent would expire in 2037;
- RGX-501: One issued U.S. patent that will expire in 2026, including patent term adjustment and one PCT, for which any issued U.S. or European patent would expire in 2036;
- RGX-111: One issued U.S. patent that will expire in 2034; and
- RGX-111/RGX-121: Five PCTs for which any issued U.S. or European patent would expire in 2034, 2036 or 2037.

NAV Technology

We have exclusively licensed rights relevant to our NAV Technology which includes novel recombinant AAV vectors AAV7, AAV8, AAV9, and AAVrh10, among others. Our licensed patent portfolio includes exclusive rights to more than 100 patents and patent applications worldwide relating to composition of matter patents and/or patent applications for our novel AAV vectors, as well as methods for their manufacture and therapeutic uses. We also possess substantial know-how and trade secrets relating to NAV Technology. As of December 31, 2017, our licensed patent portfolio included 10 issued U.S. patents and four European patents relating to the AAV7, AAV8, AAV9 and AAVrh10 vectors and uses thereof. These patents have terms that will expire as late as 2026.

Our licensed patent portfolio includes composition of matter claims for novel AAV vectors having certain other capsids and AAV capsids that have amino acid sequences that are at least 95% identical to such capsids.

Our patent portfolio also includes exclusive rights to patents and patent applications relating to:

- therapeutic compositions and methods involving the foregoing AAV vectors further comprising certain transgenes that encode therapeutic products, and their use in treating specified diseases;
- specific formulations or methods of delivery of the recombinant AAV vectors of interest for our in-house development programs;
-

technology related to engineering AAV therapeutics including recombinant AAV vectors engineered to target conducting airway cells, methods of altering the targeting and cellular uptake efficiency of an AAV viral vector having a capsid containing an AAV9 cell surface binding domain, the design of recombinant AAV viral vectors that confer passive immunization to airborne pathogens (the aforementioned gene therapy systems can include the use of certain gene expression regulation technology; we have exclusively licensed the patents and patent applications relating to this technology);

- methods of detecting an AAV nucleotide sequence useful in diagnostics; and
- methods of manufacture of recombinant AAV, including patents and applications directed to scalable AAV production methods; methods of increasing the packaging yield, transduction efficiency, and gene transfer efficiency of an AAV, and methods of purification of viral vectors, such as AAV vectors.

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Customers

Our revenue for the fiscal years ended December 31, 2017, 2016 and 2015 consisted of license revenue, reagent sales and grant revenue. One customer, which was based in the United States (AveXis), accounted for approximately 68% of our total revenue for the year ended December 31, 2017. No other customer accounted for more than 15% of revenue in 2017. Two customers, both of which were based in the United States, accounted for approximately 68% of our total revenue for the year ended December 31, 2016. No other customer accounted for more than 15% of revenue in 2016. Three customers, two of which were based in the United States and one of which was based in Ireland, accounted for approximately 79% of our total revenue for the year ended December 31, 2015. No other customer accounted for more than 15% of revenue in 2015. Future license revenue is uncertain due to the contingent nature of our licenses granted to third-parties and may fluctuate significantly from period to period. Refer to Note 2, “Summary of Significant Accounting Policies—Segment and Geographical Information,” in the Notes to Consolidated Financial Statements for financial data pertaining to our segment and geographic operations.

Research and Development

We are in the process of building a research and development organization that includes extensive expertise in AAV gene therapy and related scientific disciplines. We operate cross-functionally and are led by an experienced research and development management team. We use rigorous project management techniques to assist us in making disciplined strategic research and development program decisions and to help limit the risk profile of our product pipeline. We also access relevant market information and key opinion leaders in creating target product profiles when appropriate, as we advance our programs towards commercialization. We engage third parties to conduct portions of our preclinical research. In addition, we plan to utilize multiple clinical sites to conduct our clinical trials.

We incurred $57.2 million, $45.5 million and $17.3 million in research and development expenses in the years ended December 31, 2017, 2016 and 2015, respectively.

Competition

The biotechnology and pharmaceutical industries, including in the field of gene therapy, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property. While we believe that our NAV Technology Platform, strong intellectual property portfolio and scientific expertise in the gene therapy field provide us with competitive advantages, we face potential competition from many different sources, including larger and better-funded pharmaceutical and biotechnology companies, new market entrants and new technologies.

We are aware of several companies focused on developing gene therapies in various disease indications, including Abeona Therapeutics Inc., Applied Genetic Technologies Corporation, BioMarin Pharmaceutical Inc., bluebird bio, Inc., Sangamo Therapeutics, Inc., Sanofi Genzyme, Spark Therapeutics, Inc. and uniQure N.V. as well as several companies addressing other methods for modifying genes and regulating gene expression. Additionally, we have sublicensed our NAV Technology Platform for developing gene therapies in various disease indications to our NAV Technology Licensees. Not only must we compete with other companies that are focused on gene therapy products using earlier generation AAV technology and other gene therapy platforms, but any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future.

There are other organizations working to improve existing therapies or to develop new therapies for our initially selected disease indications. Depending on how successful these efforts are, it is possible they may increase the

barriers to adoption and success for our product candidates, if approved. These efforts include the following:

- Wet AMD. Marketed competition for wet AMD largely consists of anti-VEGF therapies developed by Roche/Genentech, Inc. (Lucentis, Avastin) and Regeneron Pharmaceuticals, Inc. (Eylea).
- HoFH. There are several companies with marketed products for the treatment of HoFH, including Aegerion Pharmaceuticals, Inc. (Juxtapid), Amgen Inc. (Repatha) and Kastle Therapeutics (Kynamro).
- MPS I. There is one principal competitor with a marketed product for the treatment of MPS I, Sanofi Genzyme (Aldurazyme).
- MPS II. The principal marketed competition for MPS II is a systemic enzyme replacement therapy, which is marketed by Shire plc (Elaprase).

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Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do. Our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Government Regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act (FD&C Act), and the Public Health Service Act (PHS Act) and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Applications to the FDA are required before conducting clinical testing of biological products, and each clinical study protocol for a gene therapy product is reviewed by the FDA and, in some instances, the U.S. National Institutes of Health (the NIH), through its Office of Biotechnology Activities' Recombinant DNA Advisory Committee (RAC). FDA approval also must be obtained before marketing biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates gene therapy products. CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

Ethical, scientific, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our

product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological Products Development Process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests, including evaluations of product chemistry, toxicity and formulation, and animal studies according to good laboratory practice (GLP) and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an IND, which must become effective before human clinical studies may begin;

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- performance of adequate and well-controlled human clinical studies according to the FDA's requirements for good clinical practice (GCP) and additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application (BLA) for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies, as well as information on the chemistry, manufacturing and controls to ensure product identity and quality, and proposed labeling;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with cGMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practice (GTP), for the use of human cellular and tissue products;
- potential FDA inspection of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation is submitted to and the study is registered with the NIH Office of Biotechnology Activities (OBA) pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, however many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee, which discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA web site and may be accessed by the public.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations imposing the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an independent institutional review board (IRB) at or servicing each institution at which the clinical study

will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed. Clinical studies generally also must be reviewed by an institutional biosafety committee (IBC), a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment. Some studies also employ a DSMB, which operates with independence from the study sponsor and has access to unblinded study data during the course of the study and may halt a study for ethical reasons such as undue safety risks.

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Human clinical studies are typically conducted in three sequential phases that may overlap or be combined:

- Phase I. The biological product is initially introduced into healthy human subjects and tested for safety. However, in the case of some products for rare, severe or life-threatening diseases, the initial human testing is often conducted in patients.
- Phase II. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- Phase III. Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product approval and labeling. Post-approval clinical studies, sometimes referred to as Phase IV clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. In some cases, Phase IV studies may be required by the FDA as a condition of approval. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for expedited reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase I, Phase II and Phase III clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its DSMB may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, our ability to recruit sufficient numbers of study subjects for any trial, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical studies, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must

develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

After the completion of clinical studies of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. Under the Prescription Drug User Fee Act (PDUFA), the BLA must be accompanied by a substantial user fee payment unless an exception or waiver applies. In addition, under the Pediatric Research Equity Act (PREA), a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant

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deferrals for submission of pediatric data or full or partial waivers of pediatric requirements. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, including whether it is effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality, potency and purity as those factors relate to the safety or effectiveness of the product. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary to assure the safe use of the biological product upon marketing. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with GTP. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products (HCT/Ps) which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure cGMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the

deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under PDUFA is to review 90% of standard BLAs in 10 months of the 60-day filing date and 90% of priority BLAs in six months of the 60-day filing date, whereupon a review decision is to be made. Two months are added to these time periods for new molecular entities. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information, or clarification regarding information already provided in the submission, constituting a major amendment to the BLA.

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Orphan Drug Designation

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

If a product that has orphan designation subsequently receives the first FDA approval for that product for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor’s product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Orphan drug products are also eligible for Rare Pediatric Disease Designation if greater than 50% of patients living with the disease are under age 18. A priority review voucher will be given to the sponsor of a product with a Rare Pediatric Disease Designation at the time of product approval that is transferable to another company.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products, including precision drugs or biological products, that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Also under the Fast Track program, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as Breakthrough Therapy designation, priority review, and accelerated approval. Under the Breakthrough Therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for additional benefits when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant

endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible. In addition, gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues, may be eligible for regenerative medicine advanced therapy (RMAT) designation. Products with an RMAT designation are eligible for the benefits of Breakthrough Therapy in addition to allowing the sponsor the ability to participate in meetings with the FDA to discuss whether accelerated approval would be appropriate based on surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a serious or life-threatening disease or condition compared to marketed products. Specific priority review programs exist for material threat medical countermeasures, rare pediatric diseases and tropical diseases. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review, in accordance with FDA guidance. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible

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morbidity. As a condition of approval, the FDA will require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies to confirm the clinical benefit of the medicine. In addition, the FDA currently requires as a condition for accelerated approval pre-submission of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, Breakthrough Therapy or RMAT designation, priority review and accelerated approval do not change the standards for approval. Rather, these programs are intended to expedite the development and approval process, but do not necessarily accomplish that intent.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to cGMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of cGMP deviations that may affect the identity, strength, quality, potency, or purity of a distributed product in a manner that may impact the safety or effectiveness of the product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion and related medical communication requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), the requirement to balance promotion information on efficacy with important safety information and limitations on use, industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and

quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product or conditions of approval, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

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U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted in the case of a biologic approved under a BLA, adds six months to existing exclusivity periods. This six-month exclusivity, which runs from the end of other exclusivity protection, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act (PPACA) signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic

Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations. Equivalent laws have been adopted in other countries that impose similar obligations.

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Other U.S. Healthcare Laws and Regulations

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and use of pharmaceutical products that are granted marketing approval. Arrangements with third-party payors, existing or potential customers and referral sources are subject to broadly applicable fraud and abuse and other healthcare laws and regulations, and these laws and regulations may constrain the business or financial arrangements and relationships through which manufacturers market, sell and distribute the products for which they obtain marketing approval. Such restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or kind, in exchange for, or to induce, either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers, on the one hand, and prescribers, patients, purchasers and formulary managers on the other. PPACA amends the intent requirement of the federal Anti-Kickback Statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;
- the federal False Claims Act (FCA), which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other federal healthcare programs that are false or fraudulent. Federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, also may implicate the FCA:
- federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- the federal Physician Payment Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services (CMS) information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members;
- the Health Insurance Portability and Accountability Act of 1996 (HIPAA) imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; and
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to: items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances. Many of these state and foreign laws differ from federal law and from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Violation of any of the laws described above or any other governmental laws and regulations may result in penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, the exclusion from participation in federal and state healthcare programs and imprisonment. Furthermore, efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly for manufacturers of branded prescription products.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. In the United States and markets in other countries, sales of any product candidates for which regulatory approval for commercial sale is obtained will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of FDA-approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved.

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Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. New metrics frequently are used as the basis for reimbursement rates, such as average sales price, average manufacturer price and actual acquisition cost. In order to obtain coverage and reimbursement for any product that might be approved for sale, it may be necessary to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the products, in addition to the costs required to obtain regulatory approvals. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. Health Technology Assessment which is intended to take account of medical, social, economic and ethical issues when determining the suitability of a medicinal product for reimbursement has increasingly become an element of the pricing and reimbursement decisions of the competent authorities in European Union Member States.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, PPACA contains provisions that may reduce the profitability of drug products, including, for example, increasing the minimum rebates owed by manufacturers under the Medicaid Drug Rebate Program, extending the rebate program to individuals enrolled in Medicaid managed care plans, addressing a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected and establishing annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act (FCPA), to which we are subject, prohibits corporations and individuals from engaging in bribery and corruption when dealing with foreign government officials. It is illegal to pay, offer to pay, promise or authorize the payment of money or anything of value, directly or indirectly, to any foreign government official, political party or political candidate in an attempt to secure an improper advantage in order to obtain or retain business or to otherwise influence a foreign official in his or her official capacity. Equivalent laws have been adopted in other countries that impose similar obligations.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Many countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the European Union, for example, an application for authorization of a clinical trial must be submitted to the competent regulatory authorities and a request for a related positive opinion must be submitted to the competent Ethics Committees in the European Union Member States in which the clinical trial takes place, much like the FDA and the IRB, respectively. Once the

clinical trial has been approved by the competent regulatory authorities and a positive opinion has been provided by the competent Ethics Committees in accordance with the European Union and the European Union Member State requirements, the corresponding clinical study may proceed.

To obtain regulatory approval of a biological medicinal product under European Union regulatory systems, we must submit a marketing authorization application. The grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing the European Medicines Agency (the EMA), commonly referred to as the EMA Regulation. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to the EMA which provides an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization after the EMA has delivered its opinion.

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Innovative medicinal products are authorized in the European Union on the basis of a full marketing authorization application (as opposed to an application for marketing authorization that relies, in whole or in part, on data in the marketing authorization dossier for another, previously approved medicinal product). Applications for marketing authorization for innovative medicinal products must contain the results of pharmaceutical tests, preclinical tests and clinical trials conducted with the medicinal product for which marketing authorization is sought. Innovative medicinal products for which marketing authorization is granted are entitled to eight years of data exclusivity. During this period, applicants for approval of generics or biosimilars of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product to support their application. Innovative medicinal products for which marketing authorization is granted are also entitled to ten years of market exclusivity. During these ten years' of market exclusivity, no generic or biosimilar medicinal product may be placed on the European Union market even if a marketing authorization for approval of a generic or biosimilar of the innovative product has been submitted to the EMA or to the competent regulatory authorities in the European Union Member States and marketing authorization has been granted. The ten years of market exclusivity will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product which is eligible for the relevant periods of data and market exclusivity.

Products authorized as "orphan medicinal products" in the European Union are entitled to benefits additional to those granted in relation to innovative medicinal products. In accordance with Article 3 of Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, a medicinal product may be designated as an orphan medicinal product if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the incentives derived from orphan medicinal product status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition. Further guidance on such criteria is provided in European Commission Regulation (EC) No. 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority". Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and following grant of a marketing authorization, the EMA and the European Union Member States' competent authorities are not permitted to accept another application for a marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication of a similar medicinal product for ten years following grant or authorization. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant may receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Products authorized in the European Union as orphan medicinal products are entitled to 10 years of data exclusivity. The products are, in parallel, entitled to 10 years of market exclusivity. The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product during the 10-year period of market exclusivity for the same therapeutic indication at any time if:

- The second applicant can establish in its application that its product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- The holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- The holder of the marketing authorization for the original orphan medicinal product cannot supply enough orphan medicinal product.

Similar to obligations imposed in the United States, medicinal products authorized in the European Union may be subject to post-authorization obligations, including the obligation to conduct Phase IV trials.

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Moreover, in the European Union, the sole legal instrument at the European Union level governing the pricing and reimbursement of medicinal products is Council Directive 89/105/EEC (the Price Transparency Directive). The aim of the Price Transparency Directive is to ensure that pricing and reimbursement mechanisms established in European Union Member States are transparent and objective, do not hinder the free movement and trade of medicinal products in the European Union and do not hinder, prevent or distort competition on the market. The Price Transparency Directive does not, however, provide any guidance concerning the specific criteria on the basis of which pricing and reimbursement decisions are to be made in individual European Union Member States. Neither does it have any direct consequence for pricing or levels of reimbursement in individual European Union Member States. The national authorities of the individual European Union Member States are free to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices and/or reimbursement of medicinal products for human use. Individual European Union Member States adopt policies according to which a specific price or level of reimbursement is approved for the medicinal product. Other European Union Member States adopt a system of reference pricing, basing the price or reimbursement level in their territory either, on the pricing and reimbursement levels in other countries, or on the pricing and reimbursement levels of medicinal products intended for the same therapeutic indication. Furthermore, some European Union Member States impose direct or indirect controls on the profitability of the company placing the medicinal product on the market.

Health Technology Assessment (HTA) of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some European Union Member States. These countries include the United Kingdom, France, Germany, Ireland, Italy, and Sweden. The HTA process in the European Union Member States is governed by the national laws of these countries. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of the use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the national healthcare system. Those elements of medicinal products are compared with other treatment options available on the market.

The outcome of HTA may influence the pricing and reimbursement status for specific medicinal products within individual European Union member states. The extent to which pricing and reimbursement decisions are influenced by the HTA of a specific medicinal product vary between the European Union Member States.

In 2011, Directive 2011/24/EU was adopted at the European Union level. This Directive concerns the application of patients' rights in cross-border healthcare. The Directive is intended to establish rules for facilitating access to safe and high-quality cross-border healthcare in the European Union. It also provides for the establishment of a voluntary network of national authorities or bodies responsible for HTA in the individual European Union Member States. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This could lead to harmonization of the criteria taken into account in the conduct of HTA between European Union Member States and in pricing and reimbursement decisions and negatively impact price in at least some European Union Member States.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and

criminal prosecution.

Employees

As of March 2, 2018, we employed 139 full-time employees, including 99 in research and development and 40 in executive, general and administrative functions. We have never had a work stoppage, and none of our employees are represented by a labor organization or under any collective bargaining arrangements. We consider our relationship with our employees to be good.

Corporate Information

We were originally formed on July 16, 2008 as ReGenX, LLC, a Delaware limited liability company, and we were subsequently renamed ReGenX Biosciences, LLC on December 22, 2009. On September 16, 2014, we underwent a corporate reorganization pursuant to which we were converted into a Delaware corporation under the name REGENXBIO Inc. Our principal offices are located at 9600 Blackwell Road, Suite 210, Rockville, MD 20850, and our telephone number is (240) 552-8181.

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Available Information

We file annual, quarterly, and current reports, proxy statements, and other documents with the SEC under the Exchange Act. The public may read and copy any materials that we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1 800 SEC 0330. Also, the SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers, including us, that file electronically with the SEC. The public can obtain any documents that we file with the SEC at www.sec.gov.

The public also may view and download copies of our SEC filings free of charge at our website, www.regenxbio.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this Annual Report on Form 10-K. Investors should also note that we use our website, as well as SEC filings, press releases, public conference calls and webcasts, to announce financial information and other material developments regarding our business. We use these channels, as well as the social media channels listed on our website, to communicate with investors and members of the public about our company. It is possible that the information that we post on these social media channels could be deemed material information. Therefore, we encourage investors, the media and others interested in our company to review the information that we post on these social media channels.

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ITEM 1A. RISK FACTORS

You should carefully consider the risk factors set forth below as well as the other information contained in this Annual Report on Form 10-K and in our other public filings in evaluating our business. Any of the following risks could materially and adversely affect our business, financial condition or results of operations. In addition, these risks could cause actual results and developments to differ materially and adversely from those projected in the forward-looking statements contained in this Annual Report on Form 10-K (please read the Information Regarding Forward-Looking Statements appearing at the beginning of this Form 10-K). The risks described below are not the only risks facing us. Additional risks and uncertainties not currently known to us or that we currently view to be immaterial may also materially adversely affect our business, financial condition or results of operations. In these circumstances, the market price of our common stock would likely decline and you could lose all or part of your investment.

Risks Related to our NAV Technology Platform and the Development of Our Product Candidates

Our gene therapy product candidates are based on a novel technology that makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval. Only a few gene therapy products have been approved in the United States, the European Union or elsewhere.

We have concentrated our research and development efforts on our proprietary adeno-associated virus (AAV) gene delivery platform (our NAV Technology Platform), and our future success depends on our and our licensees' successful development and commercialization of viable gene therapy product candidates. There can be no assurance that we or our licensees will not experience problems or delays in developing current or future product candidates or that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. We also may experience unanticipated problems or delays in expanding our manufacturing capacity, and this may prevent us from completing our clinical trials, meeting the obligations of our collaborations or commercializing our products on a timely or profitable basis, if at all. For example, we, a partner or another group may uncover one or more previously unknown risks associated with AAV or our NAV Technology Platform, and this may prolong the period of observation required for obtaining regulatory approval, necessitate additional clinical testing or invalidate our NAV Technology.

In addition, the clinical trial requirements of the U.S. Food and Drug Administration (the FDA), the European Medicines Agency (the EMA) and other regulatory authorities and the criteria these regulators use to determine the quality, safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be significantly more expensive and take longer than for other, better known or more extensively studied product candidates. Only a few gene therapy products have been approved in the United States, the European Union or elsewhere. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, the European Union or elsewhere, or how long it will take to commercialize our product candidates. Furthermore, approvals by one regulatory authority may not be indicative of what other regulatory authorities may require for approval, and approvals of ex vivo gene therapy products may not be indicative of what may be required for approval of in vivo gene therapy products.

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research (CBER), to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health (NIH), also are potentially subject to review by the NIH Office of Biotechnology Activities'

Recombinant DNA Advisory Committee (the RAC). However, according to NIH, the RAC will only publicly review clinical trials if the trials cannot be evaluated by standard oversight bodies and pose unusual risks. Although the FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if the FDA has reviewed the trial design and details and approved its initiation. Conversely, the FDA can put an investigational new drug application (IND) on a clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution to conduct a clinical trial, that institution's institutional biosafety committee as well as its institutional review board (IRB) would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates.

In the European Union, the EMA's Committee for Advanced Therapies (CAT) is responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products. The role of the CAT is to prepare a draft opinion on an application for marketing authorization for a gene therapy medicinal candidate that is submitted to the EMA. The development and evaluation of a gene therapy medicinal product must be considered in the context of the relevant European Union guidelines, and we may be required to comply with new guidelines concerning the development and marketing authorization for gene therapy medicinal products.

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Additionally, we may seek regulatory approval in territories outside the United States and the European Union, which may have their own regulatory authorities along with frequently changing requirements or guidelines. The regulatory review committees and advisory groups in the United States, the European Union and elsewhere, and any new guidelines they promulgate, may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate product revenue, and our business, financial condition, results of operations and prospects would be materially harmed.

Our business depends substantially on the success of our lead product candidates. If we are unable to obtain regulatory approval for, or successfully commercialize, our lead product candidates, our business will be materially harmed.

Our lead product candidates are in the early stages of development and will require substantial clinical development and testing, manufacturing bridging studies and process validation and regulatory approval prior to commercialization. Successful continued development and ultimate regulatory approval of our lead product candidates is critical for our future business success and our ability to generate product revenue. We have invested, and will continue to invest, a significant portion of our financial resources in the development of our lead product candidates. We will need to raise sufficient funds for, and successfully complete, our clinical trials of our lead product candidates in appropriate subjects. The future regulatory and commercial success of these product candidates is subject to a number of risks, including the following:

- we may not have sufficient financial and other resources or patient availability to complete the necessary clinical trials for our lead product candidates;
- we may not be able to provide evidence of quality, efficacy and safety for our lead product candidates;
- we do not know the degree to which our lead product candidates will be accepted by patients, the medical community and third-party payors as a therapy for the respective diseases to which they relate, even if approved;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA, EMA or comparable foreign regulatory bodies for marketing approval;
- subjects in our clinical trials, if any, may die or suffer other adverse effects for reasons that may or may not be related to our lead product candidates;
- subjects in clinical trials, if any, undertaken by licensees under a license we grant of certain intellectual property related to our NAV Technology Platform (our NAV Technology Licensees) may die or suffer other adverse effects for reasons that may or may not be related to our NAV Technology Platform;
- certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes;
- we may not successfully establish commercial manufacturing capabilities;
- if approved for treatment of the expected conditions, our lead product candidates will likely compete with other treatments then available, including the off-label use of products already approved for marketing and other therapies currently available or which may be developed;
- our products and products developed by our NAV Technology Licensees, if any, may not maintain a continued acceptable safety profile following regulatory approval;
    - we may not maintain compliance with post-approval regulation and other requirements; and

- we may not be able to obtain, maintain or enforce our rights under our licensed patents and other intellectual property rights.

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Of the large number of biologics and drugs in development in the biopharmaceutical industry, only a small percentage result in the submission of a Biologics License Application (BLA) to the FDA or marketing authorization application (MAA) to the EMA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market our lead product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure you that our lead product candidates will be successfully developed or commercialized. If we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize, our lead product candidates, we may not be able to generate sufficient revenue to continue our business.

We may not be successful in our efforts to identify or discover additional product candidates.

The success of our business depends in large part upon our ability to identify, develop and commercialize products based on our NAV Technology Platform. RGX-111, RGX-121, RGX-314 and RGX-501 are our only clinical programs and our research programs may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

If any of these events occur, we may be forced to abandon our development efforts for a program or for multiple programs, which would materially harm our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

We have tested only two of our product candidates in our own clinical trials.

Gene therapy development has inherent risks. Only two of our product candidates, RGX-314 and RGX-501, have ever been used in a clinical trial, our lead product candidates have limited preclinical results and we may experience unexpected results in the future. We or any of our future development partners will be required to demonstrate through adequate and well-controlled clinical trials that our product candidates containing our proprietary vectors are safe and effective, with a favorable benefit-risk profile, for use in their target indications before we can seek regulatory approvals for their commercial sale. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of development, including after commencement of any of our clinical trials.

The results of preclinical studies and early clinical trials are not always predictive of future results. Any product candidate we or any of our future development partners advance into clinical trials, including our lead product candidates, may not have favorable results in later clinical trials, if any, or receive regulatory approval. There is a high failure rate for drugs and biologic products proceeding through clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations that may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Any such delays could materially harm our business, financial condition, results of operations and prospects.

If our NAV vectors are not shown to be safe and effective, we may not realize the value of our investment in our technology. In addition, success in early clinical trials does not mean that later clinical trials will be successful, because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through initial clinical testing. Furthermore, our future trials will need to demonstrate sufficient

safety and efficacy for approval by regulatory authorities in larger patient populations. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. In addition, only a small percentage of drugs under development result in the submission of a BLA to the FDA or MAA to the EMA and even fewer are approved for commercialization.

We cannot be certain that any of our current or planned clinical trials will be successful, and any safety concerns observed in any one of our current or planned clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications. In addition, failure of one or more of our viral vectors, whether in our product candidates or those of our licensees, would impact the licensing of our NAV Technology Platform. Any such failure could materially harm our business, financial condition, results of operations and prospects.

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Because we are developing product candidates for the treatment of certain diseases in which there is little clinical experience and we are using new endpoints or methodologies, there is increased risk that the FDA, the EMA or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results and that these results may be difficult to analyze.

During the FDA review process, we will need to identify success criteria and endpoints such that the FDA will be able to determine the clinical efficacy and safety profile of our product candidates. As we are developing novel treatments for diseases in which there is little clinical experience with new endpoints and methodologies, there is heightened risk that the FDA, the EMA or other regulatory bodies may not consider the clinical trial endpoints to provide clinically meaningful results (reflecting a tangible benefit to patients). In addition, the resulting clinical data and results may be difficult to analyze. Even if the FDA does find our success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoints to a degree of statistical significance. Further, even if we do achieve the pre-specified criteria, we may produce results that are unpredictable or inconsistent with the results of the non-primary endpoints or other relevant data. The FDA also weighs the benefits of a product against its risks, and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. The EMA and other regulatory authorities in the European Union and other countries may make similar comments with respect to these endpoints and data.

The results from our preclinical studies or clinical trials for our product candidates may not support as broad a marketing approval as we seek, and the FDA, the EMA or other regulatory authorities may require us to conduct additional clinical trials or evaluate subjects for an additional follow-up period.

While we believe our product candidates should be applicable for the treatment of patients with certain conditions, the results from our preclinical and planned clinical trials may not support as broad of a marketing approval as we seek. Even if we obtain regulatory approval for our product candidates, we may be required by the FDA, the EMA or other regulatory bodies to conduct additional clinical trials to support approval of our product candidates for patients diagnosed with different mutations of the respective diseases to which our product candidates relate. This could result in our experiencing significant increases in costs and substantial delays in obtaining, or never obtaining, marketing approval for our product candidates to treat patients. The inability to market our product candidates to treat patients for the intended indications would materially harm our business, financial condition, results of operations and prospects.

We may find it difficult to enroll patients in clinical trials, and this could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as completion of required follow-up periods. If patients are unwilling to participate in our gene therapy studies because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in products employing our vectors or our platform, the need and length of time required to discontinue other treatment or for other reasons, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of our product candidates may be delayed, perhaps significantly. For example, due to the novel mechanism of our product candidates, we may implement a screening and clinical protocol that is innovative for gene therapy clinical trials, including requiring the discontinuation of some current therapies for a certain period of time before treatment administration. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our planned clinical trials in a timely manner. Patient enrollment and trial completion is affected by factors including:

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;

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- need and length of time required to discontinue other potential treatment options;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

Our current product candidates are being developed to treat a variety of conditions, many of which are rare. We plan to seek marketing approvals worldwide. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA, the EMA or other regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations (CROs) and physicians;
- different standards for the conduct of clinical trials;
- absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatments.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate then ongoing or planned clinical trials, any of which would harm our business, financial condition, results of operations and prospects.

We may encounter substantial delays in our planned clinical trials, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely commencement and completion of preclinical and clinical development include:

- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in opening clinical trial sites or obtaining required IRB or independent Ethics Committee approval at each clinical trial site;
- delays in recruiting suitable subjects to participate in our clinical trials;
- imposition of a clinical hold by regulatory authorities, including as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA good clinical practice (GCP), or applicable regulatory guidelines in the European Union and other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;

- delays in having subjects complete participation in a trial or return for post-treatment follow-up;
- clinical trial sites or subjects dropping out of a trial;

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- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events in trials of the same class of agents conducted by other sponsors; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete research studies, preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of our planned clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing or other requirements;
- have regulatory authorities withdraw, vary or suspend their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

Results from preclinical studies or early stage clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our product candidates and our NAV Technology Licensees' product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials. The clinical trial process may fail to demonstrate that any of our product candidates or our NAV Technology Licensees' product candidates are safe for humans and effective for indicated uses. This failure may cause us or the relevant NAV Technology Licensee to abandon the relevant product candidate, which could materially and adversely affect our business, financial condition, results of operations and prospects.

There is a high failure rate for drugs and biologic products proceeding through clinical trials. Many companies in the biotechnology and pharmaceutical industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. The design of a clinical trial can determine whether its

results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. Our company has limited experience in designing clinical trials and we may be unable to design and execute a clinical trial to support regulatory approval. Any of these factors could materially and adversely affect our business, financial condition, results of operations and prospects.

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Our NAV Technology Platform, our product candidates or NAV Technology Licensees' product candidates, and the process for administering such product candidates may cause undesirable side effects or have other properties that could delay or prevent regulatory approval of product candidates, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia in trials using lentivirus vectors and death seen in other trials using adenovirus vectors. While new recombinant vectors have been designed to reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration which could substantially limit the effectiveness of the treatment. In previous clinical trials involving AAV vectors for gene therapy, some subjects experienced the development of a T-cell response, whereby after the vector is within the target cell, the cellular immune response system triggers the removal of transduced cells by activated T-cells. If our vectors demonstrate a similar effect, we may decide or be required to halt or delay preclinical development or clinical development of our product candidates.

In addition to side effects caused by the product candidate, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur in our or third party trials, our clinical trials could be suspended or terminated.

As a result of these concerns, the FDA, the European Commission, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates and may harm our business, financial condition and prospects significantly.

Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy (REMS) and other regulatory authorities could impose other specific obligations as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which could delay approval of our product candidates. A REMS may include, among other things, a medication guide outlining the risks of the product for distribution to patients; a communication plan to health care practitioners or patients; and elements to assure safe use, which can severely restrict the distribution of a product by, for example, requiring that health care providers receive particular training and obtain special certification prior to prescribing and dispensing the product, limiting the healthcare settings in which the product may be dispensed, and subjecting patients to monitoring and enrollment in a registry. If the FDA requires us to adopt a REMS for our products and we are unable to comply with its requirements, the FDA may deem our products to be misbranded and we may be subject to civil money penalties. The European Commission, the EMA and other regulatory authorities may, following grant of marketing authorization in their territory, impose similar obligations.

Furthermore, if we or others later identify undesirable side effects caused by one of our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend, vary or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our NAV Technology Platform and our product candidates and could materially harm our business, prospects, financial condition and results of operations.

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We may be unable to obtain orphan drug designation or exclusivity for some product candidates. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is defined under the Food, Drug and Cosmetic Act as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, following the opinion of the EMA's Committee for Orphan Medicinal Products, the European Commission grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the United States can be extended by six months if the BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

If we request orphan drug designation for any of our product candidates, there can be no assurances that the FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize a product candidate and the approval may be for a narrower indication than we seek.

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based on additional government regulation from future legislation or administrative action or based on changes in regulatory authority policy during the period of product development, clinical trials and the review process.

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Regulatory authorities also may approve a product candidate for more limited indications than requested or they may impose significant limitations in the form of narrow indications, warnings or a REMS. These regulatory authorities may require precautions or contra-indications with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially harm our business, financial condition, results of operations and prospects.

Further, the regulatory authorities may require concurrent approval or the CE mark (a mandatory conformity assessment marking for certain products sold within the European Economic Area (the EEA)) of a companion diagnostic device, since it may be necessary to use FDA-cleared or FDA-approved, or CE-marked, diagnostic tests or diagnostic tests approved by other comparable foreign regulatory authorities to diagnose patients or to assure the safe and effective use of our product candidates in trial subjects. FDA refers to such tests as in vitro companion diagnostic devices. The FDA has articulated a policy position that, when safe and effective use of a therapeutic product depends on a diagnostic device, the FDA generally will require approval or clearance of the companion diagnostic device at the same time that FDA approves the therapeutic product. The FDA's guidance allows for two exceptions to the general rule of concurrent drug/device approval, namely, when the therapeutic product is intended to treat serious and life-threatening conditions for which no alternative exists, and when a serious safety issue arises for an approved therapeutic agent, and no FDA-cleared or FDA-approved companion diagnostic test is yet available. It is unclear how the FDA will apply this policy to our current or future gene therapy product candidates. Should the FDA deem genetic tests used for diagnosing patients for our therapies to be in vitro companion diagnostics requiring FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates.

In the European Union, companion diagnostics are subject to the European Union Directive on in vitro diagnostic medical devices and its implementation in the European Union Member States. Recently revised European Union laws on in vitro diagnostics will apply beginning in 2022 and provide stricter requirements for in vitro diagnostic medical devices and impose additional obligations on manufacturers of in vitro diagnostic medical devices that may impact the development and authorization of our product candidates in the European Union. For example, the new regulation extends the requirement for performance assessment procedures and requires greater involvement of notified bodies in the development of in vitro diagnostic medical devices. This may result in additional regulatory and premarket requirements to market new in vitro diagnostic medical devices. Companies producing in vitro diagnostic medical devices will be required to have a responsible person to oversee regulatory compliance. In addition, the new regulation modifies the risk classification of in vitro diagnostic medical devices in a manner that could increase the number of products classified in higher risk classes that are subject to stricter regulation.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.

Even if we obtain any regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, or obligations imposed as a condition for marketing authorization by other regulatory authorities, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, in the United States, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy

undergo follow-up observations for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with the FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In the European Union, the advertising and promotion of our product candidates may be subject to laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual European Union Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics (SmPC), as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the European Union. The applicable laws also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

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In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practice (cGMP) requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

In the European Union, marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual European Union Member States both before and after grant of the manufacturing and marketing authorizations. This includes control of compliance with cGMP rules. We and our third party manufacturers would be required to ensure that all of our processes, methods, and equipment are compliant with cGMP. Failure by us or by any of our third party partners, including suppliers, manufacturers and distributors, to comply with European Union laws and the related laws of individual European Union Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products and marketing of such products following authorization may result in administrative, civil or criminal penalties.

In addition, European Union legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that the EMA and the competent authorities of the European Union Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct ongoing assessments of the risks and benefits of marketed products, including the possible requirement to conduct additional clinical studies, which may be time-consuming and expensive and could materially decrease our profitability.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may take a variety of actions, including:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend, vary or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources to respond and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and harm our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of comparable foreign regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially harm our business, financial condition, results of operations and prospects.

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We face significant competition in an environment of rapid technological change and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer or more advanced or effective than ours, which may harm our financial condition and our ability to successfully market or commercialize our product candidates.

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

We are aware of several companies focused on developing gene therapies in various indications, as well as several companies addressing other methods for modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against any of our product candidates.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against those of competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

Even if we obtain and maintain approval for our product candidates from the FDA, we may never obtain approval for our product candidates outside of the United States, which would limit our market opportunities and harm our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit a marketing authorization application to EMA for approval of our product candidates by the European Commission in the European Union. However, obtaining such approval

from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be harmed.

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Risks Related to Our Financial Position

We have incurred substantial net losses since inception, and have only had one quarter since inception with profitability. We expect to normally incur losses for the foreseeable future and may never again achieve or maintain profitability.

Since inception, we have incurred substantial net losses. Our net losses for the years ended December 31, 2017, 2016 and 2015, were $73.2 million, $63.0 million and $22.8 million, respectively. As of December 31, 2017, we had an accumulated deficit of $187.8 million. We historically have financed our operations primarily through private and public offerings of our equity securities and sublicensing rights to our NAV Technology Platform. We have devoted substantially all of our efforts to licensing our NAV Technology Platform and to research and development, including preclinical and clinical development of our product candidates, as well as to building out our team. We expect that it could be several years, if ever, before we commercialize a product candidate. We license certain intellectual property related to our NAV Technology Platform to third parties. Our NAV Technology Licensees have multiple preclinical studies and clinical trials in progress. However, no NAV Technology Licensee has an approved or commercialized gene therapy product based on such licensing program. We expect to normally generate only limited revenue, if any, from our current NAV Technology Licensees and any future NAV Technology Licensees in the near term. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if, and as, we:

- further develop our sublicensing activities and NAV Technology Platform;
- continue our research studies and preclinical and clinical development of our product candidates, including our lead product candidates;
- initiate additional preclinical studies and clinical trials for our lead product candidates and future product candidates, if any;
- initiate additional activities relating to manufacturing, including building out additional laboratory and manufacturing capacity;
- seek to identify additional product candidates;
- prepare our BLA and MAA for our lead product candidates and seek marketing approvals for any of our other product candidates that successfully complete clinical trials, if any;
- expand our medical affairs efforts;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval, if any;
- operate as a public company;
- maintain, expand and protect our intellectual property portfolio; and
- acquire or in-license other product candidates and technologies.

For us to become profitable, we and our NAV Technology Licensees must develop and eventually commercialize product candidates with significant market potential. This will require us and our NAV Technology Licensees to be successful in a range of business challenges, including expansion of the licensing of our NAV Technology Platform, completing preclinical studies of product candidates, commencing and completing clinical trials of product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are sufficient to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our

operations. A decline in the value of our company also could cause you to lose all or part of your investment.

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We may need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our licensing activities, product development efforts or other operations.

We expect to require substantial future capital in order to complete research studies, preclinical and clinical development for our current product candidates and any future product candidates, and potentially commercialize these product candidates. We expect our spending levels to increase in connection with our preclinical and clinical trials of our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate certain of our licensing activities, our research and development programs or other operations.

Our operations have consumed significant amounts of cash since inception. As of December 31, 2017, our cash, cash equivalents and marketable securities were $176.4 million. We expect that our cash, cash equivalents and marketable securities as of December 31, 2017 will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 months from the date of this report, based on our current business plan.

Our future capital requirements will depend on many factors, including:

- the timing of enrollment, commencement and completion of our clinical trials;
- the results of our clinical trials;
- the results of our preclinical studies for our product candidates and any subsequent clinical trials;
- our planned expansion of the licensing of our NAV Technology Platform;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials, if any, for our product candidates;
- the costs associated with building out additional laboratory and manufacturing capacity, if any;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of future product sales, medical affairs, marketing, manufacturing and distribution activities for any of our product candidates for which we receive marketing approval;
- revenue, if any, received from commercial sale of our products, should any of our product candidates receive marketing approval;
    - the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- our current licensing agreements or collaborations remaining in effect;
- our ability to establish and maintain additional licensing agreements or collaborations on favorable terms, if at all;
- the extent to which we acquire or in-license other product candidates and technologies; and
- the costs associated with being a public company.

Many of these factors are outside of our control. Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory and marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our product revenues, if any, and any commercial milestones or royalty payments under our licensing agreements, will be derived from or based on sales of products that may not be commercially available for many years, if at all. In addition, revenue from our NAV Technology Platform sublicensing is dependent in part on the clinical and commercial success of our licensing partners, and no products have been commercialized by us or our NAV Technology Licensees using

our NAV Technology Platform to date. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

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To the extent that additional capital is raised through the sale of equity or equity-linked securities, the issuance of those securities could result in substantial dilution for our current stockholders and the terms may include liquidation or other preferences that adversely affect the rights of our current stockholders. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our common stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. Adequate additional financing may not be available to us on acceptable terms, or at all. We also could be required to seek funds through arrangements with partners or otherwise that may require us to relinquish rights to our intellectual property, our product candidates or otherwise agree to terms unfavorable to us.

We have generated limited revenue from our NAV Technology Platform sublicensing and may not successfully expand our licensing activities.

Our ability to generate revenue from our NAV Technology Platform sublicensing depends on the acceptance by third parties of our NAV Technology Platform as their primary gene therapy technology and our ability to market and license our technology platform. We do not anticipate generating revenues from product sales for the next several years, if ever, as described elsewhere in these risk factors and anticipate normally generating only limited revenue from our NAV Technology Platform sublicensing in the near future. To date, a significant portion of our revenues have been generated from the sublicensing of rights to our NAV Technology Platform. Our ability to generate future revenues from our NAV Technology Platform sublicensing depends on many factors, including:

- our NAV Technology Licensees successfully developing gene therapy products using our NAV Technology Platform;
- obtaining and maintaining market acceptance of our NAV Technology Platform as a primary gene therapy technology;
- maintaining our licensing agreements with our licensor partners, including GlaxoSmithKline LLC (GSK) and the University of Pennsylvania (Penn);
- addressing any competing technological and market developments;
    - implementing additional internal systems and infrastructure, as needed;
- negotiating favorable terms in any licensing or other arrangements into which we may enter and performing our obligations in such agreements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- avoiding and defending against third-party interference, infringement and other intellectual property related claims; and
- attracting, hiring and retaining qualified personnel.

We have never generated revenue from product candidate sales and have only generated limited revenue from reagent sales.

Our ability to generate revenue from product candidate sales depends on our ability, alone or with partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. All of our revenues to date have been from sublicensing our NAV Technology Platform, the sale of licensed reagents to third-parties for use in research and development and grant revenue generated through research and development grant programs offered by the U.S. federal government and the European Union. We expect grant revenue to be minimal in future periods, as we currently do not expect to receive any new grant awards. We do not dedicate resources to sales efforts for reagents. Accordingly, future revenue from reagent sales is uncertain and may fluctuate significantly from period to period. We do not anticipate generating revenues from our and our NAV

Technology Licensees' product candidate sales for the next several years, if ever. Our ability to generate future revenues from product candidate sales depends heavily on our, or our NAV Technology Licensees', success in:

- completing research studies and preclinical and clinical development of product candidates and identifying new gene therapy product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which clinical trials are completed;
- launching and commercializing product candidates for which regulatory and marketing approval is obtained by establishing a sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;

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- qualifying for adequate coverage and reimbursement by government and third-party payors for product candidates;
- maintaining and enhancing a sustainable, scalable, reproducible and transferable manufacturing process for our vectors and product candidates;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for product candidates, if approved;
- obtaining market acceptance of product candidates as a viable treatment option;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- avoiding and defending against third-party interference, infringement and other intellectual property related claims; and
- attracting, hiring and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, the EMA or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Our company was formed in July 2008. Our operations to date have predominantly focused on organizing and staffing our company, business planning, raising capital, acquiring our technology, administering and expanding our NAV Technology Platform sublicensing, identifying potential product candidates, undertaking research, preclinical studies and clinical trials of our product candidates and establishing licensing arrangements and collaborations. We have not yet fully demonstrated the ability to continue expansion of our NAV Technology Platform sublicensing efforts, complete and report clinical trials of our product candidates, obtain marketing approvals, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We have been transitioning from a company with a licensing and research focus to a company that is also capable of supporting clinical development activities and we may need to transition to supporting commercial activities in the future. We may not be successful in these transitions.

Changes in accounting standards and disagreements by the SEC, the Financial Accounting Standards Board (FASB) or various other bodies with respect to the interpretations, estimates and judgments required for the preparation of our financial statements could result in the restatement of our financial statements or other potential adverse effects.

We are subject to complex tax laws, regulations, accounting principles and interpretations thereof. The preparation of our financial statements requires us to interpret accounting principles and guidance and make estimates and judgments that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenue generated and expenses incurred during the reporting periods. Our interpretations, estimates and judgments are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for the preparation of our financial statements. U.S. generally accepted accounting principles are subject to interpretation by the SEC, FASB and various other bodies formed to interpret and create appropriate accounting principles and guidance. In the event that these rules change with respect to a matter that is or may become relevant to our business, such as revenue recognition, asset impairment and fair value determinations, inventories, business combinations and intangible asset

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valuations, leases and litigation, or in the event that one of these bodies disagrees with our accounting recognition, measurement or disclosure or any of our accounting interpretations, estimates or assumptions, it may have a significant effect on our reported results and may retroactively affect previously reported results. The need to restate our financial results could, among other potential adverse effects, result in us incurring substantial costs, affect our ability to timely file our periodic reports until such restatement is completed, divert the attention of our management and employees from managing our business, result in material changes to our historical and future financial results, result in investors losing confidence in our operating results, subject us to securities class action litigation, and cause our stock price to decline.

If we are unable to maintain effective internal control over financial reporting, investors may lose confidence in the accuracy of our financial reports.

As a public company, we are required to maintain internal control over financial reporting and to report any material weaknesses in such internal controls. Section 404 of the Sarbanes-Oxley Act (Section 404) requires that we evaluate and determine the effectiveness of our internal control over financial reporting and provide a management report on internal control over financial reporting. When we are no longer an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the JOBS Act), our management report on internal control over financial reporting will need to be attested to by our independent registered public accounting firm. We have not had, and do not expect to have, our independent registered public accounting firm attest to our management report on internal control over financial reporting while we are an emerging growth company. Had our independent registered public accounting firm performed an evaluation of the effectiveness of our internal control over financial reporting in accordance with Section 404, it is possible that material weaknesses may have been identified.

If we have, or fail to identify, a material weakness in our internal control over financial reporting, we may not detect errors on a timely basis, the accuracy and timing of our financial reporting may be adversely affected and our financial statements may be materially misstated. In addition, our internal control over financial reporting will not prevent or detect all errors and fraud. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If there are material weaknesses or failures in our ability to meet any of the requirements related to the maintenance and reporting of our internal controls, investors may lose confidence in the accuracy and completeness of our financial reports and that could cause the price of our common stock to decline. In addition, we could become subject to investigations by Nasdaq, the SEC or other regulatory authorities, which could require additional management attention and which could adversely affect our business.

Changes in U.S. federal, state and local or foreign tax laws, interpretations of existing tax laws, or adverse determinations by tax authorities, could increase our tax burden or otherwise adversely affect our financial condition or results of operations.

We are subject to taxation at the U.S. federal, state and local levels and in foreign jurisdictions. Our future tax rates and cash flows could be affected by changes in statutory rates and other legislative changes, changes in the valuation of our deferred tax assets and liabilities, changes in the composition of earnings in jurisdictions with differing tax rates, changes in determinations regarding the jurisdictions in which we are subject to taxation, and our ability to repatriate earnings from foreign jurisdictions. From time to time, governments may make substantive changes to their tax rules and the application thereof, which could result in materially higher corporate taxes than would be incurred under existing tax laws and could otherwise adversely affect our financial condition or results of operations.

We are subject to ongoing and periodic tax audits. An unfavorable outcome from any tax audit could result in higher tax costs, penalties or interest, or adjustments to our tax credits or net operating losses (NOLs), which could adversely affect our financial condition or results of operations.

We have incurred substantial net losses since inception and expect to normally incur losses for the foreseeable future. Under the Internal Revenue Code of 1986, as amended (the Code), we can carry forward our NOLs and other unused tax attributes, such as tax credits, to offset our future taxable income, if any, until such NOLs or other tax attributes are used or expire. If we undergo an “ownership change,” generally defined as a greater than 50% change by value in our equity ownership over a three-year period, the Code would limit our ability to use carryovers of our pre-ownership change NOLs, tax credits and certain other tax attributes to reduce our tax liability for periods after the ownership change. Therefore, an ownership change could result in increased U.S. tax liability for us if we generate taxable income in a future period.

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In December 2017, the Tax Cuts and Jobs Act of 2017 (the TCJA) was signed into law, which significantly reforms the Code. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for NOLs to 80% of current year taxable income, elimination of NOL carrybacks, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain significant exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modification or repeal of many business deductions and credits, including the orphan drug tax credit. The overall impact of the TCJA is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the TCJA. The impact of the TCJA on our securityholders is also uncertain and could be adverse. Prospective investors should consult with their legal and tax advisors with respect to the TCJA and the potential tax consequences of investing in or holding our securities.

Risks Related to Third Parties

We rely primarily on a sponsored research agreement with Penn for our nonclinical research and development activities and a loss of this relationship or of the principal investigator for that nonclinical research, James M. Wilson, M.D., Ph.D., could materially harm our business.

In February 2009, we entered into an exclusive worldwide license agreement with Penn for patent and other intellectual property rights relating to a gene therapy technology platform based on AAV vectors discovered at Penn in the laboratory of James M. Wilson. This license agreement has been amended from time to time. In February 2009, we also entered into a sponsored research agreement (the 2009 SRA with Penn, under which we funded the nonclinical research of Dr. Wilson relating to AAV gene therapy and obtained an option to acquire an exclusive worldwide license in certain intellectual property created pursuant to the 2009 SRA. In December 2014, we entered into another sponsored research agreement (the 2014 SRA) with Penn, under which we fund related nonclinical research of Dr. Wilson. The 2009 SRA and the 2014 SRA have each been amended from time to time.

Under the 2014 SRA, as amended, we fund nonclinical research at Penn and pay certain intellectual property legal and filing expenses and receive the rights to the research results. All patentable inventions conceived, created, or conceived and reduced to practice pursuant to the 2014 SRA, together with patent rights represented by or issuing from the U.S. patents and patent applications, including provisional patent applications, automatically become exclusively licensed to us under our existing licensing agreement with Penn and all research results are automatically licensed to us as know-how in our existing license agreement. Under our 2014 SRA with Penn, as amended, we have agreed to fund research at Penn through 2020. We expect to seek to amend the 2014 SRA in order to continue to fund work and receive rights to the results of the research we fund at Penn. Although we are currently developing our internal nonclinical research and development capabilities, a loss of our relationship with Penn or Dr. Wilson could materially harm our business.

We rely on third parties to conduct certain aspects of our clinical trials. If these third parties do not meet our deadlines or otherwise conduct the trials as required, our clinical development programs could be delayed or unsuccessful and we may not be able to obtain regulatory approval for or commercialize our product candidates when expected or at all.

We do not have the ability to conduct all aspects of our preclinical testing or clinical trials ourselves. We are dependent on third parties to conduct the clinical trials for RGX-501 and certain aspects of our clinical trials for other product candidates and, therefore, the timing of the initiation and completion of these trials may be controlled by such

third parties and may occur on substantially different timing from our estimates. Specifically, we rely on Penn to conduct our Phase I/II clinical trial for RGX-501 and we may also rely on CROs, medical institutions, clinical investigators, consultants or other third parties to conduct our trials in accordance with our clinical protocols and regulatory requirements.

There is no guarantee that Penn or any other third party on which we rely for administration and conduct of our clinical trials will devote adequate time and resources to such trials or perform as contractually required. If any such third party fails to meet expected deadlines, fails to adhere to our clinical protocols or otherwise performs in a substandard manner, our clinical trials may be extended, delayed, or terminated, which could materially harm our business. Additionally, if any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in our ongoing clinical trials unless we are able to transfer those subjects to another qualified clinical trial site. Furthermore, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, the integrity of the data generated at the applicable clinical trial site may be jeopardized, which could result in substantial delays in our clinical trials and materially harm our business.

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We have in the past, and in the future may, enter into licensing agreements or collaborations with third parties licensing parts of our NAV Technology Platform for the development of product candidates. If these licensing arrangements or collaborations are not successful, our business could be harmed.

We have entered into agreements involving the licensing of parts of our NAV Technology Platform and relating to the development and commercialization of certain product candidates and plan to enter into additional licensing agreements or collaborations in the future. We have limited control over the amount and timing of resources that our current and future licensees and collaborators, including our NAV Technology Licensees, dedicate to the development or commercialization of product candidates or of products utilizing licensed components of our NAV Technology Platform. Our ability to generate revenues from these arrangements will depend on our and our licensees' and collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. In addition, our licensees and collaborators have the ability to abandon research or development projects and terminate applicable agreements. Moreover, an unsuccessful outcome in any clinical trial for which our licensee or collaborator is responsible could be harmful to the public perception and prospects of our NAV Technology Platform or product candidates.

Any current or future licensing agreements or future collaborations we enter into may pose risks, including the following:

- licensees or collaborators have significant discretion in determining the efforts and resources that they will apply to these licensing agreements or collaborations;
- licensees or collaborators may not perform their obligations as expected;
- the clinical trials conducted as part of these licensing agreements or collaborations may not be successful;
- subjects in clinical trials undertaken by licensees or future collaborators, including our NAV Technology Licensees, may suffer adverse effects, including death;
- licensees or collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the licensees' or collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- licensees or collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates;
- licensees or collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the licensees or collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our licensees or collaborators as competitive with their own product candidates or products, which may cause licensees or collaborators to cease to devote resources to the commercialization of our product candidates;
- a licensee or collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- licensees or collaborators may breach their reporting, payment, intellectual property or other obligations to us, which could prevent us from complying with our contractual obligations to GSK and Penn;

- disagreements with licensees or collaborators, including disagreements over intellectual property and other proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- licensees or collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

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- disputes may arise with respect to the ownership of our other rights to intellectual property developed pursuant to our licensing agreements or collaborations;
- licensees or collaborators may infringe or otherwise violate the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- licensing agreements or collaborations may be terminated for the convenience of the licensee or collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our licensing agreements or collaborations do not result in the successful development and commercialization of products, or if one of our licensees or collaborators terminates its agreement with us, we may not receive any future milestone or royalty payments, as applicable, under the license agreement or collaboration. If we do not receive the payments we expect under these agreements, our development of product candidates could be delayed and we may need additional resources to develop our product candidates. In addition, if one of our licensees or collaborators terminates its agreement with us, we may find it more difficult to attract new licensees or collaborators and the perception of us in the business and financial communities could be harmed. Each of our licensees and collaborators is subject to similar risks with respect to product development, regulatory approval and commercialization, and any such risk could result in its business being harmed, which could adversely affect our collaboration.

We may in the future decide to partner or collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive licensing agreement or collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a variety of factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate the licensed product candidates with our existing operations.

We may not be successful in finding strategic collaborators for continuing development of certain of our product candidates or successfully commercializing our product candidates.

We may seek to establish strategic partnerships for developing and/or commercializing certain of our product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We may not be successful in our efforts to establish such a strategic partnership or other alternative arrangements for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy or market opportunity. In addition, we may be restricted under existing collaboration agreements from entering into future agreements with potential collaborators. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such transaction.

If we are unable to reach agreements with suitable licensees or collaborators on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have

sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates and our business, financial condition, results of operations and prospects may be materially harmed.

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Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties, including contractors, to research, develop and manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, these provisions may be breached, and the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's independent discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may materially harm our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we collaborate with, or may collaborate with in the future, will sometimes be granted rights to publish data arising out of such collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication. We may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and harm our business.

Risks Related to Manufacturing

Products intended for use in gene therapies are novel, complex and difficult to manufacture. We could experience production problems that result in delays in our development or commercialization programs, limit the supply of our products or otherwise harm our business.

We currently have development, manufacturing and testing agreements with third parties to manufacture supplies of our product candidates, in addition to our internal manufacturing laboratory. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of suppliers.

Our product candidates require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of biologics such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we employ multiple steps to control our manufacturing process to assure that the process works and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product

liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other applicable foreign standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA, the EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, the EMA or other foreign regulatory authorities may require that we not distribute a lot until the competent authority authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay clinical trials or product launches which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We also may encounter problems hiring and retaining the experienced scientific, quality control and manufacturing personnel needed to operate our manufacturing process which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements.

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Any problems in our manufacturing process or the facilities with which we contract could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in third-party manufacturing processes or facilities also could restrict our ability to meet market demand for our products. Additionally, should our manufacturing agreements with third parties be terminated for any reason, there may be a limited number of manufacturers who would be suitable replacements and it could take a significant amount of time to transition the manufacturing to a replacement.

Delays in obtaining regulatory approval of our manufacturing process or disruptions in our manufacturing process may delay or disrupt our commercialization efforts.

Before we can begin to commercially manufacture our product candidates in third-party or our own facilities, we must obtain regulatory approval from the FDA, which includes a review of the manufacturing process and facility. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities and may be required by other foreign regulatory authorities. The timeframe required to obtain such approval or authorization is uncertain. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors, contract laboratories or suppliers. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

We currently rely and expect to continue to rely on third parties to conduct our product manufacturing, and these third parties may not perform satisfactorily.

We do not currently plan to independently manufacture most of the material for our planned preclinical and clinical programs. We currently rely, and expect to continue to rely, on third parties for the production of our preclinical study and planned clinical trial materials and, therefore, we can control only certain aspects of their activities.

We rely on additional third parties to manufacture ingredients of our product candidates and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future product candidates. Some of these events could be the basis for FDA, EMA or other regulatory authority action, including injunction, recall, seizure or total or partial suspension of product manufacture or manufacturing authorization.

Failure to comply with ongoing manufacturing regulatory requirements could cause us to suspend production or put in place costly or time-consuming remedial measures.

Regulatory authorities may, at any time following approval of a product for sale, audit the manufacturing facilities for such product. If any such inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon us or any of our third-party manufacturers could materially harm our business, financial condition, results of operations and prospects.

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If we or any of our third party-manufacturers fail to comply with applicable cGMP regulations, regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be materially harmed.

Additionally, if supply from a manufacturing facility is interrupted, there could be a significant disruption in commercial supply of our products. An alternative manufacturer would need to be qualified, through a supplement to its regulatory filing, which could result in further delay. Regulatory authorities also may require additional trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our research studies, preclinical and clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of contamination during manufacturing. Any contamination could materially harm our ability to produce product candidates on schedule and could harm our results of operations and cause reputational damage.

Some of the raw materials and other components required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially harm our development timelines and our business, financial condition, results of operations and prospects.

Risks Related to the Commercialization of Our Product Candidates

If we are unable to establish sales, medical affairs and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, if approved, we may be unable to generate any product revenue.

We currently have no products to sell and therefore no product sales and marketing organization. To successfully commercialize any products that may result from our development programs, we will need to develop these capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any products we may develop will be expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may enter into collaborations regarding one or more of our product candidates with other entities to utilize their marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current licensees or future licensees or collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our potential products. If any of our product candidates is approved but fails to achieve market acceptance among physicians, patients or third-party payors, we will not be able to generate significant revenues from such product, which could materially harm our business, financial condition, results of operations and prospects.

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are and will be based on numerous assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, or at all, the commercialization of our products may be delayed or never achieved and, as a result, our stock price may decline.

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Our gene therapy approach utilizes vectors derived from viruses which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product candidates and harm our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with only a few gene therapy products approved to date in the United States, the European Union or elsewhere. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product candidates, prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are familiar and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would harm our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. Serious adverse events related to clinical trials we conduct, clinical trials involving our NAV Technology Platform conducted by others or any gene therapy products, even if such adverse events are not ultimately attributable to the relevant product candidates or products, may result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

Even if we receive regulatory approval, we still may not be able to successfully commercialize our lead product candidates or any future product candidate, and the revenue that we generate from any approved product's sales, if any, could be limited.

Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our products. From time to time, public sentiment may be more adverse to commercialization of gene therapy as a therapeutic technique. Even with the requisite approvals from the FDA, the EMA and other regulatory authorities, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidates in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of our product candidates will depend on a number of factors, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA, European Commission, or other comparable foreign regulatory authority-approved labeling;
- acceptance of a new formulation by health care providers and their patients;
- the prevalence and severity of any adverse effects;
- new procedures or methods of treatment that may be more effective in treating or may reduce the conditions which our products are intended to treat;
- pricing and cost-effectiveness;
- the effectiveness of our or any future collaborators' sales and marketing strategies;
- our ability to obtain and maintain sufficient third-party coverage and reimbursement from government health care programs, including Medicare and Medicaid, private health insurers and other third-party payors;
- unfavorable publicity relating to product candidates or gene therapy generally; and

- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or reimbursement.

Wood Products (b)	$	13,929		$	24,027		$	76,532		$	46,810
Building Materials Distribution		23,504			39,379			103,605			93,853
Total segment operating income		37,433			63,406			180,137			140,663
Unallocated corporate and other		(6,978)			(7,308)						

(23,822
)

(20,942
)
Income from operations
$
30,455

$
56,098

$
156,315

$
119,721

(a) Primarily represents intersegment sales from our Wood Products segment to our Building Materials Distribution segment.

(b) Wood Products segment operating income for the three and nine months ended September 30, 2018, includes an impairment loss of $10.4 million upon classifying certain Wood Products facilities in Northeast Oregon as held for sale. For additional information, see Note 6, Assets Held For Sale.

14. Commitments, Legal Proceedings and Contingencies, and Guarantees

Commitments

We are a party to a number of long-term log supply agreements that are discussed in Note 15, Commitments, Legal Proceedings and Contingencies, and Guarantees, of the Notes to Consolidated Financial Statements in "Item 8. Financial Statements and Supplementary Data" in our 2017 Form 10-K. In addition, we have purchase obligations for goods and services, capital expenditures, and raw materials entered into in the normal course of business. As of September 30, 2018, there have been no material changes to the above commitments disclosed in the 2017 Form 10-K.

Legal Proceedings and Contingencies

We are a party to legal proceedings that arise in the ordinary course of our business, including commercial liability claims, premises claims, environmental claims, and employment-related claims, among others. As of the date of this filing, we believe it is not reasonably possible that any of the legal actions against us will, individually or in the aggregate, have a material adverse effect on our financial position, results of operations, or cash flows.

Guarantees

We provide guarantees, indemnifications, and assurances to others. Note 15, Commitments, Legal Proceedings and Contingencies, and Guarantees, of the Notes to Consolidated Financial Statements in "Item 8. Financial Statements and Supplementary Data" in our 2017 Form 10-K describes the nature of our guarantees, including the approximate terms of the guarantees, how the guarantees arose, the events or circumstances that would require us to perform under the guarantees, and the maximum potential undiscounted amounts of future payments we could be required to make. As of September 30, 2018, there have been no material changes to the guarantees disclosed in the 2017 Form 10-K.

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15. Subsequent Events

On November 2, 2018, the Company made a decision to permanently curtail LVL production at our Roxboro, North Carolina facility by December 31, 2018. After extended efforts to improve the throughput and cost position of LVL production at Roxboro, we have concluded that we would be unable to reduce manufacturing costs to an acceptable level. Roxboro will continue to produce I-joists. We expect to record approximately $60 million of charges during fourth quarter 2018, substantially all of which will be to fully depreciate the curtailed LVL production assets.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Understanding Our Financial Information

This Management's Discussion and Analysis of Financial Condition and Results of Operations should be read in conjunction with our consolidated financial statements and related notes in "Item 1. Financial Statements" of this Form 10-Q, as well as our 2017 Form 10-K. The following discussion includes statements regarding our expectations with respect to our future performance, liquidity, and capital resources. Such statements, along with any other nonhistorical statements in the discussion, are forward-looking. These forward-looking statements include, without limitation, any statement that may predict, indicate, or imply future results, performance, or achievements and may contain the words "may," "will," "expect," "believe," "should," "plan," "anticipate," and other similar expressions. All of these forward-looking statements are based on estimates and assumptions made by our management that, although believed by us to be reasonable, are inherently uncertain. These forward-looking statements are subject to numerous risks and uncertainties, including, but not limited to, the risks and uncertainties described in "Item 1A. Risk Factors" in our 2017 Form 10-K, as well as those factors listed in other documents we file with the Securities and Exchange Commission (SEC). We do not assume an obligation to update any forward-looking statement. Our future actual results may differ materially from those contained in or implied by any of the forward-looking statements in this Form 10-Q.

Background

Boise Cascade Company is a building products company headquartered in Boise, Idaho. As used in this Form 10-Q, the terms "Boise Cascade," "we," and "our" refer to Boise Cascade Company and its consolidated subsidiaries. Boise Cascade is a large, vertically-integrated wood products manufacturer and building materials distributor. We have two reportable segments: (i) Wood Products, which manufactures engineered wood products (EWP), plywood, ponderosa pine lumber, and particleboard; and (ii) Building Materials Distribution (BMD), which is a wholesale distributor of building materials. For more information, see Note 13, Segment Information, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

Executive Overview

We recorded income from operations of $30.5 million during the three months ended September 30, 2018, compared with income from operations of $56.1 million during the three months ended September 30, 2017. In our Wood Products segment, income decreased $10.1 million to $13.9 million for the three months ended September 30, 2018, from $24.0 million for the three months ended September 30, 2017. The decrease in segment income was due primarily to an impairment loss as discussed below, as well as higher log costs, offset by higher sales prices of plywood and EWP. In our Building Materials Distribution segment, income decreased $15.9 million to $23.5 million for the three months ended September 30, 2018, from $39.4 million for the three months ended September 30, 2017, driven primarily by a gross margin decrease of $10.3 million resulting from a sharp decline in commodity prices

during third quarter 2018, as well as increased selling and distribution expenses of $5.7 million. These changes are discussed further in "Our Operating Results" below.

On September 10, 2018, Wood Products entered into an agreement to sell two lumber mills and a particleboard plant located in Northeast Oregon to Woodgrain Millwork. As a result, we recorded an impairment loss of $10.4 million in third quarter 2018 upon classifying the related assets as held for sale. For additional information, see Note 6, Assets Held For Sale, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

We ended third quarter 2018 with $181.3 million of cash and cash equivalents and $439.1 million of debt. At September 30, 2018, we had $395.4 million of unused committed bank line availability. We generated $4.2 million of cash

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during the nine months ended September 30, 2018, as cash provided by operations (net of $21.6 million in pension contributions) was offset partially by funding the Acquisitions, capital spending, dividends on our common stock, and tax withholding payments on stock-based awards. A further description of our cash sources and uses for the nine month comparative periods are discussed further in "Liquidity and Capital Resources" below.

Demand for the products we manufacture, as well as the products we purchase and distribute, is closely correlated with new residential construction in the U.S., which has historically been cyclical. To a lesser extent, demand for our products correlates with residential repair-and-remodeling activity and light commercial construction. As of October 2018, the Blue Chip Economic Indicators consensus forecast for 2018 and 2019 single- and multi-family housing starts in the U.S. were 1.28 million and 1.32 million units, respectively, compared with actual housing starts of 1.20 million in 2017, as reported by the U.S. Census Bureau. Single-family housing starts have represented approximately two-thirds of total housing starts in recent years and are the primary driver of our sales.

Although we believe U.S. demographics are supportive of further recovery in housing starts, we expect only modest residential construction growth due to constraints faced by builders, such as availability of labor and building lots. The pace of household formation rates and residential repair-and-remodeling activity will be affected by continued employment growth, wage growth, prospective home buyers' access to and cost of financing, housing affordability, improved consumer confidence, as well as other factors. Improved household formation rates in turn will help stimulate new construction.

Future commodity product pricing and commodity input costs could be volatile in response to industry operating rates, net import and export activity, transportation constraints or disruptions, inventory levels in various distribution channels, and seasonal demand patterns. Commodity product pricing was above historical levels in the first half of 2018; however, prices sharply declined during third quarter 2018 and continued to trend downward through October 2018. As a wholesale distributor of a broad mix of commodity products and a manufacturer of certain commodity products, we have sales and profitability exposure to declines in commodity product prices.

On November 2, 2018, the Company made a decision to permanently curtail laminated veneer lumber (LVL) production at our Roxboro, North Carolina facility by December 31, 2018. After extended efforts to improve the throughput and cost position of LVL production at Roxboro, we have concluded that we would be unable to reduce manufacturing costs to an acceptable level. Roxboro will continue to produce I-joists and we anticipate no impact on our customers from the laminated veneer lumber curtailment, as we have additional capacity and expansion opportunities at our Alexandria, Louisiana, and Thorsby, Alabama, EWP facilities that allow us to maintain our current service profile and also support future growth. We expect to record approximately $60 million of charges during fourth quarter 2018, substantially all of which will be to fully depreciate the curtailed LVL production assets.

Factors That Affect Our Operating Results and Trends

Our results of operations and financial performance are influenced by a variety of factors, including the following:

- the commodity nature of our products and their price movements, which are driven largely by industry capacity and operating rates, industry cycles that affect supply and demand, and net import and export activity;

- general economic conditions, including but not limited to housing starts, repair-and-remodeling activity, light commercial construction, inventory levels of new and existing homes for sale, foreclosure rates, interest rates, unemployment rates, household formation rates, and mortgage availability and pricing, as well as other consumer financing mechanisms, that ultimately affect demand for our products;

- the highly competitive nature of our industry;

- material disruptions and/or major equipment failure at our manufacturing facilities;
- our ability to successfully and efficiently complete and integrate acquisitions;
- impairment of our long-lived assets, goodwill, and/or intangible assets;
- labor disruptions, shortages of skilled and technical labor, or increased labor costs;
- the need to successfully formulate and implement succession plans for key members of our management team;

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- cost and availability of raw materials, including wood fiber and glues and resins;
- concentration of our sales among a relatively small group of customers, as well as the financial condition and creditworthiness of our customers;
- product shortages, loss of key suppliers, and our dependence on third-party suppliers and manufacturers;
- disruptions to information systems used to process and store customer, employee, and vendor information, as well as the technology that manages our operations and other business processes;
- substantial ongoing capital investment costs, including those associated with recent acquisitions, and the difficulty in offsetting fixed costs related to those investments;
- cost of compliance with government regulations, in particular environmental regulations;
- the cost and availability of third-party transportation services used to deliver the goods we manufacture and distribute, as well as our raw materials;
- exposure to product liability, product warranty, casualty, construction defect, and other claims;
- declines in demand for our products due to competing technologies or materials, as well as changes in building code provisions;
- the impact of actuarial assumptions, investment return on pension assets, and regulatory activity on pension costs and pension funding requirements;
- our indebtedness, including the possibility that we may not generate sufficient cash flows from operations or that future borrowings may not be available in amounts sufficient to fulfill our debt obligations and fund other liquidity needs;
- restrictive covenants contained in our debt agreements; and
- fluctuations in the market for our equity; and
- the other factors described in "Item 1A. Risk Factors" in our 2017 Form 10-K.

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Our Operating Results

The following tables set forth our operating results in dollars and as a percentage of sales for the three and nine months ended September 30, 2018 and 2017:

	Three Months Ended September 30		Nine Months Ended September 30	
	2018	2017	2018	2017
	(millions)			
Sales	$1,338.5	$1,226.6	$3,929.5	$3,340.0
Costs and expenses				
Materials, labor, and other operating expenses (excluding depreciation)	1,163.0	1,045.7	3,366.7	2,872.7
Depreciation and amortization	23.9	19.7	70.3	58.6
Selling and distribution expenses	93.4	87.5	273.6	243.5
General and administrative expenses	16.9	16.5	52.8	45.6
Other (income) expense, net	10.9	1.1	9.8	(0.1)
	1,308.1	1,170.5	3,773.2	3,220.3
Income from operations	$30.5	$56.1	$156.3	$119.7
	(percentage of sales)			
Sales	100.0 %	100.0 %	100.0 %	100.0 %
Costs and expenses				
Materials, labor, and other operating expenses (excluding depreciation)	86.9 %	85.3 %	85.7 %	86.0 %
Depreciation and amortization	1.8	1.6	1.8	1.8
Selling and distribution expenses	7.0	7.1	7.0	7.3
General and administrative expenses	1.3	1.3	1.3	1.4
Other (income) expense, net	0.8	0.1	0.2	—
	97.7 %	95.4 %	96.0 %	96.4 %
Income from operations	2.3 %	4.6 %	4.0 %	3.6 %

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Sales Volumes and Prices

Set forth below are historical U.S. housing starts data, segment sales volumes and average net selling prices for the principal products sold by our Wood Products segment, and sales mix and gross margin information for our Building Materials Distribution segment for the three and nine months ended September 30, 2018 and 2017.

	Three Months Ended September 30		Nine Months Ended September 30	
	2018	2017	2018	2017
	(thousands)			
U.S. Housing Starts (a)				
Single-family	235.6	230.0	687.7	649.0
Multi-family	95.0	89.3	284.5	265.0
	330.6	319.3	972.2	914.0
	(thousands)			
Segment Sales				
Wood Products	$402,672	$366,920	$1,226,146	$1,042,854
Building Materials Distribution	1,159,304	1,045,646	3,365,468	2,842,035
Intersegment eliminations	(223,464)	(185,922)	(662,129)	(544,863)
Total sales	$1,338,512	$1,226,644	$3,929,485	$3,340,026
	(millions)			
Wood Products				
Sales Volumes				
Laminated veneer lumber (LVL) (cubic feet)	4.5	4.1	14.1	13.3
I-joists (equivalent lineal feet)	61	57	192	183
Plywood (sq. ft.) (3/8" basis)	368	405	1,097	1,110
Lumber (board feet)	34	44	127	129
	(dollars per unit)			
Wood Products				
Average Net Selling Prices				
Laminated veneer lumber (LVL) (cubic foot)	$18.33	$17.22	$17.95	$16.82
I-joists (1,000 equivalent lineal feet)	1,261	1,157	1,220	1,120
Plywood (1,000 sq. ft.) (3/8" basis)	357	324	364	304
Lumber (1,000 board feet)	623	553	579	535
	(percentage of Building Materials Distribution sales)			
Building Materials Distribution				
Product Line Sales				
Commodity	47.9%	48.3%	49.0%	47.1%
General line	33.2%	33.9%	32.5%	34.2%
Engineered wood	18.9%	17.8%	18.5%	18.7%
Gross margin percentage (b)	10.3%	12.4%	11.4%	12.0%

(a) Actual U.S. housing starts data reported by the U.S. Census Bureau.

(b) We define gross margin as "Sales" less "Materials, labor, and other operating expenses (excluding depreciation)." Substantially all costs included in "Materials, labor, and other operating expenses (excluding depreciation)" for our Building Materials Distribution segment are for inventory purchased for resale. Gross margin percentage is gross margin as a percentage of segment sales.

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Sales

For the three months ended September 30, 2018, total sales increased $111.9 million, or 9%, to $1,338.5 million from $1,226.6 million during the three months ended September 30, 2017. For the nine months ended September 30, 2018, total sales increased by $589.5 million, or 18%, to $3,929.5 million from $3,340.0 million for the same period in the prior year. As described below, the improvement in sales was driven by the changes in sales volumes and prices for the products we manufacture and distribute with single-family residential construction activity being the key demand driver of our sales. In third quarter 2018, total U.S. housing starts increased 4%, with single-family starts up 2% from the same period in 2017. On a year-to-date basis through September 2018, total and single-family housing starts each increased 6% from the same period in 2017. Average composite lumber and average composite panel prices for the three months ended September 30, 2018, were 12% and 5% higher, respectively, than in the same period in the prior year, as reflected by Random Lengths composite lumber and panel pricing. For the nine months ended September 30, 2018, average composite lumber and average composite panel prices were up 23% and 22%, respectively, compared with the same period in the prior year. These improvements in composite commodity pricing resulted in improved sales in both of our segments, as noted below.

Wood Products. Sales, including sales to our BMD segment, increased $35.8 million, or 10%, to $402.7 million for the three months ended September 30, 2018, from $366.9 million for the three months ended September 30, 2017. The increase in sales was driven primarily by higher sales prices for plywood of 10%, resulting in increased sales of $12.2 million. In addition, sales prices for I-joists and LVL increased 9% and 6%, respectively, resulting in increased sales of $6.4 million and $5.0 million, respectively. Sales volumes for LVL and I-joists increased 9% and 8%, respectively, resulting in increased sales of $6.3 million and $5.2 million, respectively. An increase in lumber sales prices of 13% contributed $2.4 million to the improved sales. The increase in sales also includes the impact of adoption of the new revenue standard which resulted in increased "Sales" and "Materials, labor, and other operating expense (excluding depreciation)" of $6.1 million related to certain byproduct sales previously netted against costs. For information related to the new revenue standard, see Note 3, Revenues, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q. These increases were offset partially by decreases in plywood and lumber sales volumes of 9% and 23%, respectively, or $12.0 million and $5.6 million in sales, respectively.

For the nine months ended September 30, 2018, sales, including sales to our BMD segment, increased $183.3 million, or 18%, to $1,226.1 million from $1,042.9 million for the same period in the prior year. The increase in sales was driven primarily by higher sales prices for plywood of 20%, resulting in increased sales of $66.3 million. In addition, sales prices for I-joists and LVL increased 9% and 7%, respectively, resulting in increased sales of $19.2 million and $15.9 million, respectively. Sales volumes for LVL and I-joists increased 6% and 5%, respectively, resulting in increased sales of $13.1 million and $10.3 million, respectively. An increase in lumber sales prices of 8% contributed $5.7 million to the improved sales. The increase in sales also includes the impact of adoption of the new revenue standard which resulted in increased "Sales" and "Materials, labor, and other operating expense (excluding depreciation)" of $19.3 million related to certain byproduct sales previously netted against costs. These increases were offset partially by a decrease in plywood sales volumes of 1%, or $4.1 million in sales.

Building Materials Distribution. Sales increased $113.7 million, or 11%, to $1,159.3 million for the three months ended September 30, 2018, from $1,045.6 million for the three months ended September 30, 2017. Compared with the same quarter in the prior year, the overall increase in sales was driven by sales price and sales volume increases of 7% and 4%, respectively. By product line, commodity sales increased 10%, or $49.3 million; general line product sales increased 9%, or $31.4 million; and sales of EWP (substantially all of which are sourced through our Wood Products segment) increased 18%, or $33.0 million.

During the nine months ended September 30, 2018, sales increased $523.4 million, or 18%, to $3,365.5 million from $2,842.0 million for the same period in the prior year. Compared with the same period in the prior year, the overall increase in sales was driven by sales price and sales volume increases of 11% and 7%, respectively. By product line, commodity sales increased 23%, or $309.6 million; general line product sales increased 13%, or $122.2 million; and sales of EWP increased 17%, or $91.6 million.

Costs and Expenses

Materials, labor, and other operating expenses (excluding depreciation) increased $117.3 million, or 11%, to $1,163.0 million for the three months ended September 30, 2018, compared with $1,045.7 million during the same period in the prior year. In our Wood Products segment, the increase in materials, labor, and other operating expenses was primarily driven by higher per-unit costs of logs of 14%, compared with third quarter 2017. The increase in per-unit log costs was primarily due to an increase in the price of logs in the western U.S. However, materials, labor, and other operating expenses as a percentage of

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sales (MLO rate) in our Wood Products segment was flat compared with the first nine months of 2017. The MLO rate benefited from higher sales prices, resulting in improved leveraging of labor costs, offset by higher wood fiber costs. In BMD, the increase in materials, labor, and other operating expenses was driven by higher purchased materials costs as a result of higher sales volumes, as well as a 210 basis point increase in the MLO rate, compared with third quarter 2017. This increase in the MLO rate was driven primarily by a sharp decline in commodity prices during third quarter 2018, with average composite lumber prices and average composite panel prices declining 30% and 18% since early June 2018. In our Building Materials Distribution Segment, periods of increasing prices provide the opportunity for higher sales and increased margins, while declining price environments may result in declines in sales and profitability and lower of cost or net realizable value inventory write-downs, as we experienced during third quarter 2018.

For the nine months ended September 30, 2018, materials, labor, and other operating expenses (excluding depreciation), increased $494.0 million, or 17%, to $3,366.7 million, compared with $2,872.7 million in the same period in the prior year. In our Wood Products segment, the increase in materials, labor, and other operating expenses was primarily driven by higher sales volumes of EWP and higher per-unit costs of logs and OSB (used in the manufacture of I-joists) of 13% and 10%, respectively, compared with the first nine months of 2017. The increase in per-unit log costs was primarily due to an increase in the price of logs in the western U.S. However, the MLO rate in our Wood Products segment decreased by 280 basis points, which was primarily due to higher sales prices, resulting in improved leveraging of labor and wood fiber costs. In BMD, the increase in materials, labor, and other operating expenses was driven by higher purchased materials costs as a result of higher sales volumes, as well as a 70 basis point increase in the MLO rate, compared with the first nine months of 2017. Our MLO rate for the nine months ended September 30, 2018, was negatively impacted by the sharp decline in commodity prices during third quarter 2018.

Depreciation and amortization expenses increased $4.2 million, or 21%, to $23.9 million for the three months ended September 30, 2018, compared with $19.7 million during the same period in the prior year. For the nine months ended September 30, 2018, these expenses increased $11.7 million, or 20%, to $70.3 million, compared with $58.6 million in the same period in the prior year. The increase was due primarily to initiating depreciation on approximately $45 million of veneer and LVL related assets at our Roxboro, North Carolina EWP facility in fourth quarter 2017, as well as other capital expenditures.

Selling and distribution expenses increased $5.9 million, or 7%, to $93.4 million for the three months ended September 30, 2018, compared with $87.5 million during the same period in the prior year, due primarily to higher shipping and handling costs and employee-related expenses of $3.6 million and $1.0 million, respectively. During the nine months ended September 30, 2018, selling and distribution expenses increased $30.1 million, or 12%, to $273.6 million, compared with $243.5 million during the same period in 2017, due primarily to higher employee-related expenses and shipping and handling costs of $14.6 million and $9.9 million, respectively. For both the three and nine month periods, the cost increases were primarily a result of increased sales volumes in our BMD segment.

General and administrative expenses increased $0.4 million, or 3%, to $16.9 million for the three months ended September 30, 2018, compared with $16.5 million for the same period in the prior year. For the nine months ended September 30, 2018, general and administrative expenses increased $7.2 million, or 16%, to $52.8 million, compared with $45.6 million during the same period in 2017. For the nine month period, the cost increase was primarily a result of higher employee-related expenses due to base compensation increases and higher incentive costs from improved operating results.

Other (income) expense, net, was $10.9 million and $9.8 million, respectively, of expense for the three and nine months ended September 30, 2018, which included an impairment loss of $10.4 million (Impairment Loss) upon classifying certain Wood Products facilities in Northeast Oregon as held for sale. For additional information, see Note 6, Assets Held For Sale, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in

"Item 1. Financial Statements" of this Form 10-Q. Other (income) expense, net, was $1.1 million of expense for the three months ended September 30, 2017, which included a $1.0 million non-cash asset write-down in our Wood Products segment. For the nine months ended September 30, 2017, other (income) expense, net, was $0.1 million of income, which included a $1.2 million gain from the sale of machinery and equipment, offset by a $1.0 million non-cash asset write-down, in our Wood Products segment.

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Income From Operations

Income from operations decreased $25.6 million to $30.5 million for the three months ended September 30, 2018, compared with $56.1 million for the three months ended September 30, 2017. Income from operations increased $36.6 million to $156.3 million for the nine months ended September 30, 2018, compared with $119.7 million for the nine months ended September 30, 2017.

Wood Products. Segment income decreased $10.1 million to $13.9 million for the three months ended September 30, 2018, compared with $24.0 million for the three months ended September 30, 2017. The decrease in segment income was due primarily to the Impairment Loss and higher log costs, offset by higher sales prices of plywood and EWP. In addition, depreciation and amortization expense and general and administrative expenses increased $3.4 million and $1.6 million, respectively.

For the nine months ended September 30, 2018, segment income increased $29.7 million to $76.5 million from $46.8 million for the nine months ended September 30, 2017. The increase in segment income was due primarily to higher sales prices of plywood and EWP, offset partially by higher log and OSB costs, as well as the Impairment Loss. In addition, depreciation and amortization expense, selling and distribution expenses, and general and administrative expenses increased $10.0 million, $2.4 million, and $3.9 million, respectively.

Building Materials Distribution. Segment income decreased $15.9 million to $23.5 million for the three months ended September 30, 2018, from $39.4 million for the three months ended September 30, 2017. The decline in segment income was driven primarily by a gross margin decrease of $10.3 million, or a decline in gross margin percentage of 210 basis points, resulting from a sharp decline in commodity prices during third quarter 2018. In addition, selling and distribution expenses increased by $5.7 million.

For the nine months ended September 30, 2018, segment income increased $9.8 million to $103.6 million from $93.9 million for the nine months ended September 30, 2017. The improvement in segment income was driven primarily by a gross margin increase of $40.6 million generated from a sales increase of 18%, offset partially by increased selling and distribution expenses of $27.8 million.

Corporate and Other. Unallocated corporate expenses decreased $0.3 million to $7.0 million for the three months ended September 30, 2018, from $7.3 million for the three months ended September 30, 2017. For the nine months ended September 30, 2018, unallocated corporate expenses increased $2.9 million to $23.8 million from $20.9 million for the nine months ended September 30, 2017, primarily due to higher employee-related expenses, particularly incentive compensation, due to improved operating results.

Other

Pension expense (excluding service costs). On April 25, 2018, and August 10, 2018, we transferred $151.8 million and $124.8 million, respectively, of our pension plan assets to The Prudential Insurance Company of America (Prudential) for the purchase of group annuity contracts. Under the arrangements, Prudential assumed ongoing responsibility for administration and benefit payments for over 60% of our U.S. qualified pension plan projected benefit obligations. As a result of the transactions, we recognized non-cash pension settlement charges of $12.0 million and $11.3 million, respectively, in second and third quarters 2018. For additional information related to the transfer of pension plan assets, see Note 9, Retirement and Benefit Plans, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

Change in fair value of interest rate swaps. For information related to our interest rate swaps, see the discussion under "Interest Rate Risk and Interest Rate Swaps" of Note 2, Summary of Significant Accounting Policies, of

the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

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Income Tax Provision

On December 22, 2017, the Tax Act was enacted by the U.S. government. The most significant impact to our financial statements is the reduction of the corporate federal income tax rate from 35% to 21%. For the three months ended September 30, 2018, we recorded $0.8 million of income tax benefit on $13.0 million of income before income taxes, resulting in a negative effective rate of 6.2%. The primary reason for the difference between the federal statutory income tax rate of 21% and the effective tax rate was the 2017 return to provision true-up, including the remeasurement of deferred income taxes to the new federal statutory rate of 21%, offset partially by the effect of state taxes. The remeasurement of deferred income taxes includes a $3.8 million discrete tax benefit, which mostly relates to a $20.0 million discretionary pension contribution made during the current period, for which we received a tax deduction at the 2017 federal income tax rate. For the nine months ended September 30, 2018, we recorded $22.8 million of income tax expense and had an effective rate of 19.7%. The primary reason for the difference between the federal statutory income tax rate of 21% and the effective tax rate was the 2017 return to provision true-up on the remeasurement of deferred income taxes to the new federal statutory rate of 21% and the excess tax benefits of vested share-based payment awards, offset partially by the effect of state taxes. During the three and nine months ended September 30, 2017, we recorded $18.3 million and $36.5 million, respectively, of income tax expense and had an effective rate of 36.6% and 36.4%, respectively. The primary reason for the difference between the federal statutory income tax rate of 35% and the effective tax rate was the effect of state taxes. For additional information related to the Tax Act, see Note 4, Income Taxes, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

Liquidity and Capital Resources

We ended third quarter 2018 with $181.3 million of cash and cash equivalents and $439.1 million of debt. At September 30, 2018, we had $576.7 million of available liquidity (cash and cash equivalents and undrawn committed bank line availability). We generated $4.2 million of cash during the nine months ended September 30, 2018, as cash provided by operations (net of $21.6 million in pension contributions) was offset partially by funding the Acquisitions, capital spending, dividends on our common stock, and tax withholding payments on stock-based awards. Further descriptions of our cash sources and uses for the nine month comparative periods are noted below.

We believe that our cash flows from operations, combined with our current cash levels and available borrowing capacity, will be adequate to fund debt service requirements and provide cash, as required, to support our ongoing operations, capital expenditures, funding of acquisitions, lease obligations, working capital, pension contributions, and to pay cash dividends to holders of our common stock over the next 12 months. We expect to fund our seasonal and intra-month working capital requirements in the remainder of 2018 from cash on hand and, if necessary, borrowings under our revolving credit facility.

Sources and Uses of Cash

We generate cash primarily from sales of our products, as well as short-term and long-term borrowings. Our primary uses of cash are for expenses related to the manufacture and distribution of building products, including inventory purchased for resale, wood fiber, labor, energy, and glues and resins. In addition to paying for ongoing operating costs, we use cash to invest in our business, service our debt and pension obligations, pay dividends, repurchase our common stock, and meet our contractual obligations and commercial commitments. Below is a discussion of our sources and uses of cash for operating activities, investing activities, and financing activities.

	Nine Months Ended September 30	
	2018	2017
	(thousands)	

Net cash provided by operations	$119,821	$117,136
Net cash used for investment	(64,402)	(45,971)
Net cash used for financing	(51,217)	(2,958)

Operating Activities

For the nine months ended September 30, 2018, our operating activities generated $119.8 million of cash, compared with $117.1 million of cash generated in the same period in 2017. The $2.7 million increase in cash provided by operations was due primarily to an improvement in income from operations, offset by a $71.9 million increase in working capital during the

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nine months ended September 30, 2018, compared with a $31.3 million increase for the same period in the prior year, as well as an increase in pension contributions of $19.9 million. See "Our Operating Results" in this Management's Discussion and Analysis of Financial Condition and Results of Operations for more information related to factors affecting our operating results.

The change in working capital in both periods was primarily attributable to higher receivables and inventories, offset by an increase in accounts payable and accrued liabilities. The increases in receivables in both periods primarily reflect increased sales of approximately 17% and 47%, comparing sales for the months of September 2018 and 2017 with sales for the months of December 2017 and 2016, respectively. The increase in accounts payable and accrued liabilities provided $83.2 million of cash during the nine months ended September 30, 2018, compared with $108.1 million in the same period a year ago. During both periods, seasonal increases in inventory and extended terms offered by major vendors to our Building Materials Distribution segment led to the increase in accounts payable.

Investment Activities

During the nine months ended September 30, 2018 and 2017, we used $47.7 million and $48.1 million, respectively, of cash for purchases of property and equipment, including business improvement and quality/efficiency projects, replacement and expansion projects, and ongoing environmental compliance. During the nine months ended September 30, 2018, we used $17.5 million for the acquisitions of two distribution locations. These distribution locations add to our existing distribution business and strengthen our nationwide presence. In addition, we believe we will be able to broaden our product and service offerings within these markets following the acquisitions. Excluding acquisitions, we expect capital expenditures in 2018 to total approximately $75 million to $85 million. For the nine months ended September 30, 2017, we received asset sales proceeds of $2.3 million, primarily from the sale of machinery and equipment in our Wood Products segment. On October 11, 2018, BMD announced the planned acquisition of Arling Lumber, Inc., a wholesale building materials distributor in Cincinnati, Ohio, and expects to complete the transaction in the fourth quarter of 2018.

Financing Activities

During the nine months ended September 30, 2018, our financing activities used $51.2 million of cash, including $47.1 million for common stock dividend payments and $5.1 million of tax withholding payments on stock-based awards. During the nine months ended September 30, 2018, we also borrowed $7.5 million under our revolving credit facility to fund intra-month working capital needs, which were subsequently repaid during the same period with cash on hand. At September 30, 2018, we had no borrowings outstanding under the revolving credit facility.

During the nine months ended September 30, 2017, our financing activities used $3.0 million of cash, which primarily included $2.9 million of tax withholding payments on stock-based awards. We also borrowed $410.4 million under our revolving credit facility to fund intra-month working capital needs, which were subsequently repaid during the same period with cash on hand. At September 30, 2017, we had no borrowings outstanding under the revolving credit facility.

For more information related to our debt structure and dividend policy, see the discussion in Note 8, Debt, and Note 11, Stockholders' Equity, respectively, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this Form 10-Q.

Contractual Obligations

For information about contractual obligations, see Contractual Obligations in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2017 Form 10-K. There have been no material

changes in contractual obligations outside the ordinary course of business since December 31, 2017, except for two transfers of qualified defined benefit plan (Pension Plan) assets and related pension obligations to The Prudential Insurance Company during second and third quarters 2018 and a discretionary pension contribution of $20.0 million during third quarter 2018. As a result of these transactions, we remeasured our Pension Plan on April 25, 2018, and August 10, 2018. This resulted in a $38.5 million improvement in the funded status of our Pension Plan, thus reducing estimated future contributions to our Pension Plan. For more information, see Note 9, Retirement and Benefit Plans, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" of this form 10-Q.

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Off-Balance-Sheet Activities

At September 30, 2018, and December 31, 2017, we had no material off-balance-sheet arrangements with unconsolidated entities.

Guarantees

Note 7, Debt, and Note 15, Commitments, Legal Proceedings and Contingencies, and Guarantees, of the Notes to Consolidated Financial Statements in "Item 8. Financial Statements and Supplementary Data" in our 2017 Form 10-K describe the nature of our guarantees, including the approximate terms of the guarantees, how the guarantees arose, the events or circumstances that would require us to perform under the guarantees, and the maximum potential undiscounted amounts of future payments we could be required to make. As of September 30, 2018, there have been no material changes to the guarantees disclosed in our 2017 Form 10-K.

Seasonal and Inflationary Influences

We are exposed to fluctuations in quarterly sales volumes and expenses due to seasonal factors. These seasonal factors are common in the building products industry. Seasonal changes in levels of building activity affect our building products businesses, which are dependent on housing starts, repair-and-remodeling activities, and light commercial construction activities. We typically report lower sales in the first and fourth quarters due to the impact of poor weather on the construction market, and we generally have higher sales in the second and third quarters, reflecting an increase in construction due to more favorable weather conditions. We typically have higher working capital in the first and second quarters in preparation and response to the building season. Seasonally cold weather increases costs, especially energy consumption costs, at most of our manufacturing facilities.

Employees

As of October 21, 2018, we had approximately 6,490 employees. Approximately 21% of these employees work pursuant to collective bargaining agreements. As of October 21, 2018, we had nine collective bargaining agreements. The agreement covering approximately 99 employees at our Canadian EWP facility expired on December 31, 2017, but has been extended indefinitely pending negotiations. We may not be able to renew this agreement or may renew it on terms that are less favorable to us than the current agreement. We could also experience a material labor disruption, strike, or significantly increased labor costs at one or more of our facilities, either in the course of negotiations of a labor agreement or otherwise. In addition, the ongoing recovery in the U.S. economy and our industry, when coupled with low unemployment rates, has made it difficult to acquire and retain the skilled labor necessary to successfully operate our facilities. Labor disruptions or shortages could prevent us from meeting customer demands or result in increased costs, thereby reducing our sales and profitability.

Disclosures of Financial Market Risks

In the normal course of business, we are exposed to financial risks such as changes in interest rates, foreign currency exchange rates, and commodity prices. As of September 30, 2018, there have been no material changes to financial market risks disclosed in our 2017 Form 10-K.

Environmental

For additional information about environmental issues, see Environmental in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2017 Form 10-K.

Critical Accounting Estimates

Critical accounting estimates are those that are most important to the portrayal of our financial condition and results. These estimates require management's most difficult, subjective, or complex judgments, often as a result of the need to estimate matters that are inherently uncertain. We review the development, selection, and disclosure of our critical accounting estimates with the Audit Committee of our board of directors. For information about critical accounting estimates, see Critical Accounting Estimates in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2017 Form 10-K. At September 30, 2018, there have been no material changes to our critical accounting estimates from those disclosed in our 2017 Form 10-K.

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New and Recently Adopted Accounting Standards

For information related to new and recently adopted accounting standards, see "New and Recently Adopted Accounting Standards" in Note 2, Summary of Significant Accounting Policies, of the Condensed Notes to Unaudited Quarterly Consolidated Financial Statements in "Item 1. Financial Statements" in this Form 10-Q.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

For information relating to quantitative and qualitative disclosures about market risk, see the discussion under "Item 7A. Quantitative and Qualitative Disclosures About Market Risk" and under the headings "Disclosures of Financial Market Risks" and "Financial Instruments" in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2017 Form 10-K. As of September 30, 2018, there have been no material changes in our exposure to market risk from those disclosed in our 2017 Form 10-K.

ITEM 4. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

We maintain "disclosure controls and procedures," as defined in Rule 13a-15(e) under the Exchange Act. We have designed these controls and procedures to reasonably assure that information required to be disclosed in our reports filed or submitted under the Exchange Act, such as this Form 10-Q, is recorded, processed, summarized, and reported within the time periods specified in the Securities and Exchange Commission's rules and forms. We have also designed our disclosure controls to provide reasonable assurance that such information is accumulated and communicated to our senior management, including our chief executive officer (CEO) and our chief financial officer (CFO), as appropriate, to allow them to make timely decisions regarding our required disclosures. Based on an evaluation of our disclosure controls and procedures, our CEO and CFO have concluded that as of September 30, 2018, our disclosure controls and procedures were effective in meeting the objectives for which they were designed.

Limitations on the Effectiveness of Controls and Procedures

In designing and evaluating our disclosure and/or internal controls and procedures, we recognized that no matter how well conceived and well operated, a control system can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of its inherent limitations, a control system, no matter how well designed, may not prevent or detect misstatements due to error or fraud. Additionally, in designing a control system, our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. We have also designed our disclosure and internal controls and procedures based in part upon assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during the three months ended September 30, 2018, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

We are a party to legal proceedings that arise in the ordinary course of our business, including commercial liability claims, premises claims, environmental claims, and employment-related claims, among others. As of the date of this filing, we believe it is not reasonably possible that any of the legal actions against us will, individually or in the aggregate, have a material adverse effect on our financial position, results of operations, or cash flows.

ITEM 1A. RISK FACTORS

This report on Form 10-Q contains forward-looking statements. Statements that are not historical or current facts, including statements about our expectations, anticipated financial results, projected capital expenditures, and future business prospects, are forward-looking statements. You can identify these statements by our use of words such as "may," "will,"

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"expect," "believe," "should," "plan," "anticipate," and other similar expressions. You can find examples of these statements throughout this report, including "Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations." We cannot guarantee that our actual results will be consistent with the forward-looking statements we make in this report. You should review carefully the risk factors listed in "Item 1A. Risk Factors" in our 2017 Form 10-K, as well as those factors listed in other documents we file with the Securities and Exchange Commission and the risk factor below related to the impairment of long-lived assets. We do not assume an obligation to update any forward-looking statement.

Our long-lived assets, goodwill, and/or intangible assets may become impaired, which may require us to record noncash impairment charges that could have a material impact on our results of operations.

We review the carrying value of long-lived assets for impairment when events or changes in circumstances indicate that the carrying amount of the assets may not be recoverable. We also test goodwill in each of our reporting units and intangible assets with indefinite lives for impairment annually in the fourth quarter or sooner if events or changes in circumstances indicate that the carrying value of the asset may exceed fair value.

Factors such as lower than anticipated growth in single-family housing starts, loss of key customers, capacity additions by competitors, or changes in raw material or manufacturing costs that lead us to believe the long-lived asset will no longer provide a sufficient return on investment, could prompt decisions to invest capital differently than expected, sell facilities, or to curtail operations. Any of these factors, among others, could result in noncash impairment or accelerated depreciation charges in the future with respect to investments we have completed or expect to complete.

For example, in third quarter 2018, we entered into an agreement to sell two lumber mills and a particleboard plant located in Northeast Oregon to Woodgrain Millwork (the "Sale"). Upon classification as held for sale, we discontinued depreciation of the long-lived assets, and performed an assessment of impairment to identify and expense any excess of carrying value over fair value less costs to sell. As a result, we recorded a pre-tax impairment loss of $10.4 million during the three months ended September 30, 2018. Furthermore, on November 2, 2018, we made a decision to permanently curtail LVL production at our Roxboro, North Carolina facility by December 31, 2018. After extended efforts to improve the throughput and cost position of LVL production at Roxboro, we concluded that we would be unable to reduce manufacturing costs to an acceptable level. As a result, we expect to record approximately $60 million of charges during fourth quarter 2018, substantially all of which will be to fully depreciate the curtailed LVL production assets.

We continue to evaluate the operating performance, cost effectiveness, and strategic fit of our long-lived assets, including our Wood Products manufacturing facilities and Building Materials Distribution facilities. Long-lived assets, goodwill, and/or intangible assets may not provide the future economic benefit we expect and may become impaired, which could result in additional noncash impairment or accelerated depreciation charges. These noncash impairment or accelerated depreciation charges could have a material impact on our results of operations in the period in which these charges are recognized. For additional information and a discussion regarding the impact of impairment of long-lived assets on our results of operations and financial condition, see "Long-Lived Asset Impairment" included in "Critical Accounting Estimates" in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" of our 2017 Form 10-K.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

None.

ITEM 3. DEFAULTS UPON SENIOR SECURITIES

None.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

None.

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ITEM 6. EXHIBITS

Filed With the Quarterly Report on Form 10-Q for the Quarter Ended September 30, 2018

Number	Description
31.1	CEO Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	CFO Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1	CEO Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
32.2	CFO Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

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SIGNATURES

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

BOISE CASCADE COMPANY

/s/ Kelly E. Hibbs
Kelly E. Hibbs
Vice President and Controller
(As Duly Authorized Officer and Chief Accounting Officer)

Date: November 5, 2018