APPLIED GENETIC TECHNOLOGIES CORP
Form 10-K
September 10, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the Fiscal Year Ended June 30, 2015

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
Commission File Number: 001-36370

APPLIED GENETIC TECHNOLOGIES CORPORATION

(Exact Name of Registrant as Specified in Its Charter)

Delaware	59-3553710
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

11801 Research Drive

Suite D

Alachua, Florida 32615

(Address of Principal Executive Offices, Including Zip Code)

(386) 462-2204

(Registrant’s Telephone Number, Including Area Code)

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

Title of class	Name of exchange on which registered
Common Stock, $.001 par value	NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act: None

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

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

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

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

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. x

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

Large accelerated filer o Accelerated filer x

Non-accelerated filer o Smaller reporting company o

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

The aggregate market value of the voting common shares held by non-affiliates of the registrant was approximately $83.4 million, computed by reference to the closing sale price of the common stock as reported by The NASDAQ Global Market on December 31, 2014, the last trading day of the registrant's most recently completed second fiscal quarter. The Company has no non-voting common shares.

As of August 31, 2015, a total of 17,953,531 shares of the registrant's common stock, $0.001 par value per share, were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the registrant's Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission on or before October 28, 2015 are incorporated by reference in Part III of this Annual Report on Form 10-K.

APPLIED GENETIC TECHNOLOGIES CORPORATION

ANNUAL REPORT ON FORM 10-K

FOR FISCAL YEAR ENDED JUNE 30, 2015

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, including the sections entitled “Business,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” contains forward-looking statements. These statements may relate to, but are not limited to, expectations of our future results of operations, business strategies and operations, financing plans, potential growth opportunities, potential market opportunities and the effects of competition, as well as assumptions relating to the foregoing. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. These risks and other factors include, but are not limited to, those listed under “Risk Factors.” In some cases, you can identify forward-looking statements by terminology such as “may,” “will,” “should,” “could,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “pre “potential,” “might,” “would,” “continue” or the negative of these terms or other comparable terminology. These statements are only predictions. Actual events or results may differ materially.

There may be events in the future that we are not able to accurately predict or control and that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements. Except as required by applicable law, including the securities laws of the United States and the rules and regulations of the SEC, we do not plan to publicly update or revise any forward-looking statements contained in this Annual Report on Form 10-K after we file it, whether as a result of any new information, future events or otherwise. Before you invest in our common stock, you should be aware that the occurrence of any of the events described in the “Risk Factors” section and elsewhere in this Annual Report on Form 10-K could harm our business, prospects, operating results and financial condition. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements.

Except as otherwise indicated, all share and per share information referenced in this report has been adjusted to reflect the 1-for-35 reverse split with respect to our common stock effected on March 4, 2014.

As used herein, except as otherwise indicated by context, references to “we,” “us,” “our,” or the “Company” refer to Applied Genetic Technologies Corporation.

PART I

ITEM 1. BUSINESS

Overview

We are a clinical-stage biotechnology company developing gene therapy products designed to transform the lives of patients with severe diseases in ophthalmology. We believe our proprietary gene therapy platform and our expertise in viral vector selection, design, delivery and manufacturing will facilitate the rapid clinical advancement and regulatory approval of our product candidates and enhance their therapeutic and commercial potential.

Our lead product candidates include treatments for X-linked retinoschisis, or XLRS, two forms of achromatopsia, or ACHM, and X-linked retinitis pigmentosa, or XLRP. These four orphan diseases of the eye are caused by mutations in single genes, significantly affect visual function and currently lack effective medical treatments.

- XLRS is characterized by abnormal splitting of the layers of the retina, resulting in poor visual acuity in young boys, which can progress to legal blindness in adult men. We currently are enrolling patients in a Phase 1/2 clinical trial with our XLRS product candidate and anticipate having initial clinical data from early cohorts around the end of calendar year 2015.

- ACHM is characterized by the absence of cone photoreceptor function, resulting in extremely poor visual acuity, light sensitivity, day blindness and complete loss of color discrimination. We expect to file an IND for our first ACHM product candidate in late 2015, and thereafter to initiate a Phase 1/2 clinical trial in the United States. We expect development of our second ACHM product candidate to follow shortly behind this timeline.
- We have also begun preclinical studies for our product candidate addressing XLRP, a disease characterized by progressive degeneration of the retina, which can lead to total blindness in adult men. For our XLRP product candidate, we expect to file an IND in late 2016, and thereafter to initiate a Phase 1/2 clinical trial in the United States.
- Finally, we are utilizing our previous experience in wet AMD to evaluate new potential product candidates. We expect to announce one or more product candidates for AMD in late 2015.

On July 1, 2015, we entered into a broad collaboration and license agreement with Biogen MA Inc., a wholly owned subsidiary of Biogen Inc. (“Biogen”), to develop gene-based therapies for multiple ophthalmic diseases including the XLRS and XLRP programs and three discovery programs. We will be responsible for the clinical development programs of XLRS through product approval and

of XLRP through the completion of first-in-human trials. Biogen will support the clinical development costs, subject to certain conditions, following the first-in-human study for XLRS and IND-enabling studies for XLRP.

Our gene therapy platform is based on viral vectors that utilize a modified version of the non-replicating adeno-associated virus, or AAV, to deliver a functional copy of a gene to the patient's own cells through a variety of delivery methods, and we have obtained preliminary indications of safety and efficacy in clinical trials. These vectors deliver the functional genetic material to the nucleus of the cell, providing safe, sustained expression of the therapeutic protein to treat the disease without modifying the existing DNA of the patient.

We have developed extensive internal expertise in the selection and design of viral vectors - including capsids, promoters, expression cassettes, formulation, delivery and manufacturing that is supported by a broad intellectual property estate. Our proprietary AAV vector manufacturing process is both reproducible and scaleable with a favorable cost of goods. We have assembled an experienced management team and a world-class group of scientific advisors, and we have strong collaborative relationships with key opinion leaders in the field of gene therapy. Combining these attributes, we have built a gene therapy platform that we believe will provide patients with treatments that may have life-long clinical benefits, potentially based on a one-time therapeutic administration.

We and our scientific collaborators have generated human proof-of-concept data that we believe provide preliminary evidence of the safety and efficacy of our gene therapy approach through preclinical studies and clinical trials in two other eye diseases: Leber congenital amaurosis (type 2), or LCA2, a form of early onset retinal degeneration caused by mutations in the RPE65 gene, and the wet form of age-related macular degeneration, or wet AMD, an eye disease affecting a large patient population.

Our strategy is to leverage the capabilities of our gene therapy platform to address diseases in ophthalmology where there is significant unmet medical need. We have concentrated initially on underserved orphan indications that are small enough to allow for clinical trials on a manageable scale but prevalent by orphan disease standards and that provide markets that we believe we can serve using a small, targeted commercial infrastructure. The eye diseases we are targeting are well understood with highly predictive animal models and clearly defined clinical endpoints, characteristics that we believe will facilitate clinical development and regulatory approval of our product candidates. We believe our initial focus on these orphan eye diseases will provide us with an attractive business opportunity and position us to drive the advancement of gene therapy technology. We plan to leverage our experience in orphan ophthalmology to develop new treatments for eye diseases with larger patient populations, such as wet AMD. We will also evaluate opportunities to extend the commercial application of our gene therapy platform in other underserved indications beyond ophthalmology.

Our AAV vectors can be used to introduce functional genes into many different cell types by a variety of delivery methods and can carry genes of up to 4,000 base pairs in length, a payload capacity sufficient to accommodate more than 90% of the individual genes in the human genome. We have developed a proprietary manufacturing process that we believe will enable our vectors to be manufactured reliably, and at high quality, on a commercial scale. Our gene therapy platform therefore has the potential to provide treatments for many other diseases outside of our current focus on orphan ophthalmology, including those with large dosing requirements or in larger markets. We have already conducted preclinical proof-of-concept studies and Phase 1 and Phase 2 clinical trials of a treatment for alpha-1 antitrypsin deficiency, or AAT deficiency, an inherited orphan lung disease. We expect to explore other therapeutic areas selectively, either alone or through partnerships.

The chart below summarizes our current gene therapy programs:

Our initial focus on orphan ophthalmology

Many chronically debilitating diseases for which there are currently no effective treatments have patient populations too small to attract the interest of large commercial entities. We believe that such orphan diseases can provide us with an attractive business opportunity. We are concentrating initially on several underserved diseases that are prevalent by orphan disease standards but small enough to allow for clinical trials on a manageable scale and to provide markets that we believe we can serve using a small, targeted commercial infrastructure.

We have focused on orphan ophthalmology because we believe there is a significant unmet medical need in eye diseases. The diseases we are targeting are also of interest to us due to a number of factors that, in combination, have enabled us to screen and more accurately predict the potential safety and efficacy of products at an early stage of development:

- Well-understood disease mechanisms. Because sight is the most important sense to humans—many people fear blindness more than premature death—even very rare diseases that cause vision loss have been studied extensively and are well-understood down to the molecular mechanism of action.
- Monogenic diseases. We are initially pursuing eye diseases where the genetic abnormality is known and is caused by mutations in a single gene, known as monogenic diseases. We therefore know exactly what gene sequence to insert into the patient's cells, thus mitigating the uncertainty of disease biology.
- Highly predictive animal models. For many eye diseases there are highly predictive animal models in which the disease is caused by the same underlying genetic defect and has clinical outcomes that are similar to those in humans.
    - Local delivery of therapeutic agent. Direct delivery to the eye of a therapeutic agent, via methods already widely used in ophthalmology, allows us to use lower doses, with reduced risk of unintended effects.
- Short time to clinical data. In XLRS and ACHM, we expect to obtain meaningful clinical data within six months after a one-time administration of the product candidate to a patient, which we believe will facilitate the clinical development of our product candidates.

Ophthalmology is also attractive to us as a clinical stage company because treatments for diseases affecting vision have clearly defined, objective clinical endpoints with validated measurement tools that are accepted by the FDA. Other orphan drug companies have spent considerable time and resources working with the FDA to identify acceptable clinical endpoints and develop measurement tools in sometimes ill-defined diseases. In ophthalmology the four accepted endpoints—visual acuity, visual fields, contrast sensitivity and color vision—are well understood, routinely measured by clinicians, and the FDA consistently applies them and provides guidance on how much improvement is required for clinical relevancy. We believe these clearly defined endpoints will help accelerate the process of clinical study and regulatory approval for our ophthalmic products.

Finally, through our internal research work and in collaboration with partners, we have obtained preliminary safety data in clinical trials with the two major delivery routes used in ophthalmology: intravitreal and subretinal injection. In clinical trials conducted by our licensee Genzyme, 19 patients with wet AMD were treated by intravitreal injection of an AAV vector, and in other trials conducted by us and others more than 50 patients with LCA2 have been treated with subretinal injections of AAV vectors, in both cases without reports of serious adverse events attributed to the vector, and with promising indications of efficacy for LCA2 patients.

Our strategy

Our objective is to become the world leader in developing and commercializing gene therapy treatments for eye diseases, and thereby to provide a better life for patients with these diseases, for which in some cases there are no currently available treatments. Our strategy to accomplish this goal is to:

- Develop and commercialize drugs in orphan ophthalmology. Our lead product candidates are treatments for the severe orphan eye diseases XLRS, ACHM, and XLRP. Given the severity of these diseases and the current lack of treatment options, a one-time-treatment alternative that corrects the underlying genetic defect would provide superior long-term value for patients, their families and the healthcare system more broadly.
- Expand our position in ophthalmology.
- Continue our leadership position in orphan ophthalmology. We have developed significant experience in the orphan ophthalmology space through our work on XLRS, ACHM, XLRP and LCA2. We have strong relationships with key opinion leaders in the field and with leading patient advocacy groups. We have received grants aggregating $8.9 million from the Foundation Fighting Blindness, or FFB, the National Institutes of Health, or NIH, the National Eye Institute, or NEI, and the FDA. Our scientific advisory board is comprised of leaders in the fields of ophthalmology and genetics, including one of our scientific founders, William W. Hauswirth, Ph.D., the Rybaczki-Bullard Professor of Ophthalmology and Molecular Genetics at the University of Florida College of Medicine.
- Expand our product offerings to wet AMD. We plan to develop new treatments for wet AMD by leveraging our experience developing products in orphan ophthalmology and our work with Genzyme on a first generation product for wet AMD. Advances have been made in understanding of the disease etiology and the number of known potential targets has increased since the first anti-VEGF gene therapy programs were designed. We plan to use our resources and access to experts in this field to evaluate these new targets and rapidly move a product candidate into the clinic.
- Seek opportunities for strategic partnerships and acquisitions in ophthalmology gene therapy. On July 1, 2015, we entered into a broad collaboration and license agreement with Biogen to develop gene-based therapies for multiple ophthalmic diseases including the XLRS and XLRP programs and three discovery programs. We believe there may be additional opportunities for us to partner with newly commercial companies and academic groups. We expect that our breadth of experience in research, manufacturing, clinical and regulatory matters will help us to identify and execute in- licensing, co-development arrangements, intellectual property acquisitions or manufacturing agreements that would further extend our leadership position in ophthalmology gene therapy.
- Extend our expertise in AAV vector design, delivery and manufacturing. We believe that our understanding of our target indications and our robust internal expertise in viral vector design, physical vector delivery, vector manufacturing, clinical trial design and clinical trial conduct are significant competitive advantages. We intend to continue to devote substantial resources to developing the science underlying successful AAV vector design and delivery including external research collaborations with companies such as 4D Molecular Therapeutics to deploy its proprietary AAV vector discovery platform to identify and optimize novel next-generation vectors to target specific cell populations within the human retina that can be used in future product development, as well as to expand the capabilities of our reproducible, scalable manufacturing process.. We also intend to enhance our discovery capabilities and reduce our reliance on external research at academic organizations by expanding our basic research capabilities for target identification, vector design and candidate therapeutic screening.
- Expand our manufacturing capabilities and create a pilot manufacturing group. We will seek to decrease our dependence on contract manufacturers by acquiring capital equipment and staffing a facility capable of process development and non-cGMP manufacturing at a scale of up to 100 liter, or 100 L, batches, for indications beyond

orphan ophthalmology. Such a facility would enable us to complete process development at a final manufacturing scale appropriate for many indications prior to transfer of manufacturing to a cGMP facility, as well as allowing us the flexibility to produce all non-cGMP batches for early research work and GLP toxicology and biodistribution studies, giving us better control of our future manufacturing requirements. We believe these investments will facilitate the more rapid advancement of our products through regulatory approval and enhance the therapeutic and commercial potential of our gene therapy platform.

- Pursue orphan indications with high unmet medical need and greater probability of clinical, regulatory and commercial success. We will continue to focus on diseases for which the underlying genetic defect is well characterized and can be addressed by correcting or inserting a single gene, for which predictive animal models exist and for which clinical endpoints are objective and have been validated by the FDA. We believe that focusing on these types of indications will enable us to obtain data more rapidly and accelerate the process of clinical study and regulatory approval of our products. Given the relatively low prevalence of orphan diseases and the strong key opinion leader communities and patient advocacy groups around them, we also believe we will be able to serve these markets independently with a small, targeted commercial infrastructure.
- Evaluate opportunities to leverage our gene therapy platform to address indications outside of ophthalmology. We intend to develop and partner selectively to expand the scope of our pipeline and the utilization of our gene therapy platform. The adaptability of our platform also presents an opportunity for us to selectively form collaborative alliances to expand our capabilities and product offerings into a range of genetically defined diseases and potentially to accelerate the development and commercialization of gene therapy products more broadly. We recently completed a partnership with Biogen that provides us with significant resources to expand our product development activities as well as access to significant development and commercialization expertise.

Gene therapy background

Genes enable production of proteins that perform a vast array of functions within all living organisms. Many diseases have a genetic aspect whereby a mutated gene is passed down from generation to generation. Mutated genes can cause production of abnormal proteins, which can cause disease.

Gene therapy involves the introduction of a functional copy of the gene into a patient's own cells using a delivery system most commonly based on a viral vector to treat the genetic defect. Gene therapy has the potential to change the way these patients are treated, by correcting the underlying genetic defect that is the cause of their disease rather than offering treatments that only address symptoms. We believe that by correcting the underlying genetic defect, gene therapy can provide transformative disease modifying effects—potentially with life-long clinical benefits based on a one-time therapeutic administration.

The promise of gene therapy has evolved over the last decade, with a growing body of clinical data that we believe has provided evidence of efficacy and safety in a variety of disease areas, improvements in vector design and manufacturing processes by us and others and the establishment of regulatory guidelines for the development and approval of gene therapy products. These advances have led to increased investment from the biopharmaceutical industry and supported the emergence of gene therapy as an important therapeutic modality for patients with significant unmet medical needs.

Our gene therapy platform

Our approach to gene therapy product development is conceptually straightforward. We design an AAV vector that will carry the functional gene necessary to express the desired protein, produce the vector using our proprietary production methods, and then deliver the product directly to the appropriate cells in a patient by a suitable physical delivery method. Although the concept of gene transfer is simple, the process of developing and manufacturing AAV vectors capable of delivering the genetic material safely into a patient's own cells is highly technical and demands significant expertise, experience and know-how.

Our gene therapy platform is built on our core competencies in three key areas:

- vector selection and design;
- vector manufacturing; and
- vector delivery.

Our vector selection and design process

AAV vectors. The success of a gene therapy platform is highly dependent on the vector selected. Our platform is based on the use of a modified version of the non-replicating adeno-associated virus to deliver the correct DNA directly to the nucleus of the cells affected by the disease. We believe that AAV vectors are particularly well suited for treating our target diseases and have advantages over other viral vectors, such as adenovirus, herpes virus and lentivirus. These advantages include:

Simplicity —AAV is a small, simple non-enveloped virus with only two native genes. This makes the virus straightforward to work with from a vector engineering standpoint.

Stability —AAV is extremely stable: it is resistant to degradation by shear, solvents and enzymes, facilitating purification and final formulation. AAV stability could also enable development of a freeze-dried formulation, should this become necessary for larger markets where shipping and distribution of the current frozen formulation would be challenging.

Sustained expression —Unlike vectors based on other viruses, our AAV vectors are capable of inserting the functional gene into the patient's cells as an extra-chromosomal episome, which is a stable, circular form of DNA in the nucleus of cells. Inserting the functional gene as an episome supports long-term production of the protein, leading to sustained therapeutic effect, without altering the patient's existing DNA. Sustained expression is a powerful advantage of using AAV as a vector: a one-time therapeutic administration of a functional gene into a cell can potentially support protein production for the life of the cell, which, in the cell types we are currently focused on treating, may approximate the duration of the patient's lifetime.

Safety —We believe AAV vectors are the safest for use in human gene therapy. In contrast, clinical trials using other vectors, such as lentivirus, adenovirus and herpes virus, have reported serious adverse events. The safety advantages of AAV vectors include the following:

- AAV elicits a low immune response, reducing the risk of adverse inflammatory reactions. In contrast, trials with adenoviral vectors have reported severe inflammatory reactions.
- AAV vectors, while they provide sustained expression, do not alter the patient's existing DNA, and safety is therefore improved over vectors that alter the patient's DNA. Trials using early versions of lentiviral vectors, which insert genes directly into, and thereby alter, the patients' DNA, resulted in several well-publicized adverse events, including reported cases of leukemia.
- AAV has never been linked to human disease, unlike most other viruses used as gene delivery vectors such as adenovirus, herpes virus and lentivirus.
- AAV vectors have no viral genes remaining, eliminating the possibility that any viral genes will cause an adverse event.

AAV vectors have been used in more than 100 human clinical trials, by us and others, with no serious adverse events traced to the use of AAV as the gene delivery vector. In our direct experience with human clinical trials for LCA2, AAT deficiency and wet AMD, over 100 patients were treated using AAV vectors, with no serious adverse events attributed to the vector. In a Phase 2 trial of our AAT deficiency product candidate, patients were treated with doses more than 1,000-fold higher than those planned for use in any of our ophthalmic indications, with no serious adverse events reported.

Carrying capacity —AAV vectors have the capacity to carry therapeutic gene sequences up to 4,000 base pairs in length into a patient's cell. As more than 90% of human genes have coding sequences less than 3,000 base pairs in length, we expect to be able to pursue a wide variety of indications with our AAV vectors.

Vector design. After the selection of the vector type, there are many other critical factors to be considered when designing a gene therapy product. These include selecting the appropriate:

- therapeutic gene,
- promoter and related gene regulatory elements,
- AAV sequences needed to signal replication and packaging, and
- AAV capsid (the protein shell) in which these elements are packaged.

The first step in vector design is to identify the therapeutic protein that we want the patient's own cells to produce, and many times optimize the gene for efficient therapeutic protein expression in patient's own cells, and then insert that efficient gene into an AAV vector. Production of the protein requires a promoter, which is a genetic element to drive expression. Certain promoters function well only in certain cell types, whereas other promoters function well in almost any cell type. We make our selection by comparing different promoters in the specific type of cells that are affected in each disease target, ideally in an animal whose physiology is close to that of humans, to find the promoter that best enables production of therapeutic levels of protein in that cell type.

After the promoter and gene of interest are selected, we insert these elements between AAV viral sequences that are needed for replication and packaging of the vector into the AAV capsid. There are hundreds of variations of AAV capsids with different efficiencies in their ability to bind to and enter varying cell types. We select the capsid for a specific product candidate after comparing different capsids in the type of cells that are affected by the targeted disease.

One of our key capabilities is our depth of understanding of the complex interplay between the clinical disease, the cells in the patient's body that need treatment, the selection of a capsid and a promoter, the design of the gene construct and the physical administration method. We have spent years conducting research on the best combinations of these elements with the aim of developing safe and effective gene therapy treatments.

Vector manufacturing: our H.A.V.E. method

We have developed a proprietary, high-yield vector manufacturing process using scalable technologies for herpes-assisted vector expansion, which we refer to as our H.A.V.E. manufacturing method. While the H.A.V.E. manufacturing method uses the herpes virus as a helper in the first step of a four-step AAV vector manufacturing process, there is no herpes virus in the final product. Our H.A.V.E. manufacturing method addresses problems of low productivity and low efficacy that have historically plagued efforts to manufacture AAV vectors and enables us to produce vectors with improved potency, efficiency and safety over processes previously used by us and others. It also enables us to produce a more purified and concentrated end product, as evidenced by an approximately 25- to 30-fold reduction in non-infectious viral contaminants as compared to vectors used in previous clinical trials.

Our manufacturing process has been reviewed by both the FDA and the European Medicines Agency, or EMA, and has been authorized for production of product candidates for use in clinical trials in the United States and Europe. Our manufacturing process is also reproducible and scalable. It has been transferred successfully to Genzyme and to SAFC Pharma, our contract manufacturing organization, where it is used in manufacturing clinical materials pursuant to the FDA's current good manufacturing practices, or GMP, requirements.

We and SAFC Pharma have successfully produced the necessary material for the clinical trials we have conducted to date, and have more than enough manufacturing capacity to meet the requirements of our planned future trials. We are currently investing in the development of mid- to large-scale manufacturing processes with a view towards supporting our product candidates, if approved, at commercial scale. We are developing a pilot manufacturing group to decrease our dependence on contract manufacturers by securing capital equipment and staffing a facility capable of process development and non-cGMP manufacturing at up to 200 L scale.

We hold or have licensed 26 issued and 6 pending patents covering our manufacturing technology. We believe that our core competency and intellectual property estate in vector manufacturing differentiate us competitively and provide a key element of our gene therapy platform.

Vector delivery

Our gene therapy platform allows for vector delivery by a variety of methods, and we select the method that is most beneficial for the disease we are targeting. The method used depends on the type of cells we are targeting for

treatment.

In ophthalmology, the product candidate can best be delivered to cells in the eye by intravitreal or subretinal injection.

Intravitreal injection into the vitreous humor, which is the clear gel that fills the space between the lens and the retina of the eye, is best for delivering the product candidate to the retinal neurons in the inner retina (the portion of the retina closest to the lens), to photoreceptors located in the fovea (the very center of the macula, which is the central part of the retina that is required for fine visual acuity), and other cells in the lateral portions of the eye. This routine procedure can be carried out in an ophthalmologist's office.

Subretinal injection between the photoreceptors in the outer retina and the retinal pigment epithelium just below the retina are best for delivering the product candidate to the outer retina, farthest from the lens, where the AAV vector can readily enter photoreceptor cells and retinal pigment epithelium cells. This is a short, outpatient surgical procedure that is frequently performed by retinal surgeons.

We expect to use intravitreal injection as the method of delivery for our XLRS product candidate, and we plan to evaluate both subretinal injection and intravitreal injection as methods of delivery for our ACHM and XLRP product candidates.

For other indications, such as the orphan lung disease AAT deficiency, where secretion of a therapeutic protein into the bloodstream is the goal, we plan to administer the product candidate to muscle cells. There are large numbers of muscle cells in the body, providing the ability to produce a large amount of protein for systemic circulation. This can be accomplished by several methods, including:

- intramuscular injection , in which the product candidate is directly injected into muscle cells, and
- vascular delivery, in which the product candidate is administered to the muscle cells of an entire leg, using infusion methods similar to those currently employed in cardiac catheterization, oncology and anesthesiology. In preclinical animal studies of our product candidate for AAT deficiency, using a vascular delivery method was shown to achieve much higher serum levels and lower immune responses compared to direct intramuscular injection.

These methods of administration of our product candidates are well established for the safe and effective delivery of other drugs and protein products. AAV vectors can be delivered by these and other methods to a wide array of other cells, such as heart muscle cells in certain cardiac diseases or directly into the brain in certain neurologic diseases.

Our approach can potentially arrest, correct or treat a disease with a one-time therapeutic administration, as many of the cells to which the product candidate is delivered will survive for the life of the patient and treatment of those cells thereby has the potential to deliver life-long effects. For example, cells in the retina, important in XLRS and ACHM, mature shortly after birth and in the absence

of disease exist unchanged for the life of the patient. Once treated with our gene therapy products, these cells have the potential to express the therapeutic protein for the remaining life of the cell. This approach potentially provides significant value to patients, families, providers and payors.

Our product programs

Our lead programs address XLRS, ACHM, and XLRP, which are orphan diseases of the eye that are caused by mutations in single genes, significantly affect visual function starting at birth and currently lack effective medical treatments.

We initially developed our gene therapy platform and obtained clinical evidence of its safety and efficacy in proof-of-concept programs involving two other eye diseases: LCA2 and wet AMD. We obtained clinical evidence of safety and tolerability with both programs as well as encouraging signs of biologic activity. We chose to not continue the development of the LCA2 product for a number of reasons but most importantly because we believed the disease characteristics and market opportunity for our current lead programs were more attractive. In the case of wet AMD, our partnership with Genzyme was terminated and we now have freedom to operate and are pursuing product development independently.

We are also developing a product candidate for treatment of the inherited orphan lung disease AAT deficiency for which we have conducted preclinical proof-of-concept studies and Phase 1 and Phase 2 clinical trials. We believe our AAT deficiency program provides proof of concept for the use of our gene therapy platform in indications outside our focus area of orphan ophthalmology.

Our lead programs

X-linked retinoschisis

XLRS is an inherited retinal disease caused by mutations in the RS1 gene, which is located on the X chromosome and encodes the retinoschisin, or RS1, protein. Retinoschisin is expressed and secreted primarily from photoreceptor cells and binds strongly and specifically to the surface of photoreceptor and bipolar cells in the retina. Mutated forms of retinoschisin are unable to bind properly, resulting in schisis, or splitting of the nerve fiber layers of the retina, primarily in the macula. The disease begins early in childhood, and affected boys typically have best-corrected visual acuity of 20/60 to 20/120 at initial diagnosis. Complications such as retinal hemorrhage or retinal detachment occur in up to 40% of patients, especially in older patients. According to Molecular Genetics of Inherited Eye Diseases (1988), the incidence rate for XLRS is between one in 5,000 and one in 20,000 males. Using an incidence rate of 1 in 11,500 and assuming half the population is male, we estimate that there are about 13,000 persons in the United States and about 22,000 persons in Europe with XLRS, or 35,000 persons in the United States and Europe combined.

The diagnosis of XLRS is made based on clinical findings and results of imaging studies and ERG. Clinical findings include reduced visual acuity and a characteristic spoke-wheel appearance of the macula when viewed by an ophthalmoscope, which is the instrument commonly used by ophthalmologists and optometrists to view the retina. Images obtained by optical coherence tomography, or OCT, a method of viewing layers of the eye somewhat like a sonogram, show spaces between the layers of the retina within the macula and fovea in most school-age boys with XLRS. These spaces mean that electrical signals cannot move from the photoreceptors to other retinal neurons and on to the brain, resulting in poor vision. When this is measured by ERG testing it can be detected by a markedly abnormal ERG response.

The figure below shows an OCT image from a normal individual (top) and from a patient with XLRS (bottom). The black spaces indicated by the arrows in the bottom portion of the figure demonstrate splitting of the layers of the retina leaving spaces that interfere with the movement of electrical signals.

There is currently no approved treatment for XLRS. Management of disease manifestations includes low vision aids such as large-print textbooks, preferential seating in the front of the classroom and use of handouts with high contrast. Surgery may be required to address complications of vitreous hemorrhage or full-thickness retinal detachment. Anecdotal reports suggest that topical carbonic anhydrase inhibitors may provide some reduction in the degree of schisis detected by OCT and improvement in visual acuity in some but not all patients, but the absence of controlled clinical trials makes interpretation of these reports difficult. In addition, treatment with carbonic anhydrase inhibitors does not address the fundamental genetic defect in persons affected by XLRS. Neither carbonic anhydrase inhibitors nor any other medicinal products have been approved by regulatory agencies for treatment of XLRS.

Our XLRS product candidate

Our gene therapy approach involves using an AAV vector to insert a functional copy of the RS1 gene into the patient's retinal cells, thereby inducing those cells to produce the normal retinoschisin protein. Our XLRS product candidate contains the RS1 gene and a promoter that has been shown to work well in primate retinal cells, and is packaged in an AAV capsid that is able to efficiently enter cells in the inner layers of the retina after intravitreal injection.

After the vector containing a functional copy of the RS1 gene enters a retinal cell, the gene is processed by normal biochemical processes into a stable DNA episome in the nucleus of the cell. This stable form of the gene allows production of the normal retinoschisin protein which is then secreted from the retinal cells and binds to the surfaces of photoreceptor and bipolar cells in the retina, pulling them together and eliminating any splitting between the layers of the cells. Upon light stimulation of the photoreceptor cells, the presence of the retinoschisin allows normal transmission of electrical signals from the photoreceptor cells to the bipolar cells and then to other retinal neurons that transmit the signals to the visual cortex in the brain. Production of normal retinoschisin continues as long as the episome persists in the cell, which may be for many years or even life-long, thereby providing long-term potential benefit after a one-time therapeutic administration.

Preclinical proof of concept for our XLRS product candidate

In mouse models of XLRS, our gene therapy approach restores to normal the abnormal ERG characteristic that is present in XLRS. Mouse models of XLRS have been developed by deactivating, or knocking out, the RS1 gene in mice. These "knockout" mice have clinical features similar to humans with XLRS, including reduced visual acuity, schisis cavities detected by OCT, and a markedly abnormal ERG response.

The figure below shows staining for retinoschisin (top row) and for nuclei in retinal cells (bottom row) in a normal mouse (left), a RS1 knockout mouse in the absence of treatment (middle) and a RS1 knockout mouse treated with an AAV-RS1 vector (right). The knockout mouse retina has no expression of retinoschisin and has splitting and disorganization of the layers of the retina, indicated by the arrowheads in the middle panel of the nuclear staining. After treatment, RS1 staining is present in a normal fashion and the nuclear staining shows restoration of the organization of the cell layers in the retina (right).

Based on data from Min et al. Molecular Therapy (2005)

Treatment by injection of an AAV vector expressing either mouse or human RS1 in these knockout mice improved visual function as measured by increased ERG b-wave responses.

The figure below shows improved ERG responses in RS1 knockout mice at various times after treatment with an AAV-RS1 vector compared to ERG responses in untreated control RS1 knockout mice. The figure shows a progressive decrease in the ERG response in the untreated mice but a slower decrease and eventual increase in the ERG response in the treated mice.

Based on data from Min et al. Molecular Therapy (2005)

We have concluded that intravitreal injection is the preferred route of administration for an AAV-RS1 vector. We therefore evaluated intravitreal injection of an AAV vector expressing a marker protein packaged in several different AAV capsids in monkeys and demonstrated that a vector packaged in an engineered capsid was able to target expression to the macula, which is the primary area in which retinoschisis occurs.

The figure below shows expression of a marker protein (white areas) in the macula, fovea and nerve fibers of a monkey retina after intravitreal injection of a vector contained in the engineered capsid. We believe that intravitreal injection of a vector containing the RS1 gene in the same engineered capsid would show expression of retinoschisin in the same areas.

Based on AGTC animal study data

Planned clinical development of our XLRS product candidate

We are currently enrolling patients in a Phase 1/2 clinical trial in which we expect to enroll a total of 27 XLRS patients at 4 clinical sites. The study design is illustrated below:

We are also currently conducting a natural history study in persons affected by XLRS. This study will document the progression of the disease in the absence of treatment, and its results will provide important information about the best methods for measuring visual function in these patients and will guide us in the design of subsequent clinical trials in which our product candidate will be tested for safety and efficacy. The study is being conducted at three clinical sites that specialize in inherited retinal diseases: the Casey

Eye Institute in Portland, Oregon, the Retina Foundation of the Southwest in Dallas, Texas, and the Kellogg Eye Center in Ann Arbor, Michigan.

Completion of the Phase 1/2 clinical study and the natural history study will guide us in finalizing the design of a pivotal Phase 3 clinical trial. In the planned pivotal Phase 3 trial, we would expect to enroll 40 - 75 patients who will be evaluated for changes in visual function over a 12-month period. If successful, we believe the results of this second trial could support submission of a Biologics License Application, or BLA, to the FDA in the United States and a Marketing Authorization Application, or MAA, to the EMA in Europe for our XLRS product candidate.

As a part of our collaboration, Biogen has obtained worldwide commercialization rights for the XLRS program. AGTC will be responsible for the clinical development program through product approval. Biogen will support the clinical development costs, subject to certain conditions, following the first-in-human study. We have an option to share development costs and profits after the initial clinical trial data are available, and an option to co-promote the second of these products (XLRS and XLRP) to be approved in the United States.

Congenital achromatopsia

ACHM is an inherited retinal disease characterized by the lack of cone photoreceptor function. Cone photoreceptors are concentrated in the macula and the fovea. ACHM is present from birth and throughout life. Individuals with this condition have no cone photoreceptor function, markedly reduced visual acuity, photophobia, or light sensitivity, and complete loss of color discrimination. Their only functioning photoreceptors are rod photoreceptors, which respond to low intensity light conditions and mediate night vision but cannot achieve fine visual acuity. Best-corrected visual acuity in persons affected by ACHM, even under subdued light conditions, is usually about 20/200, a level at which people are considered legally blind. They also experience extreme light sensitivity resulting in even worse visual acuity under normal daylight conditions, or day blindness.

ACHM can be caused by mutations in any of at least five genes that are required for normal cone photoreceptor function. The most common causes are mutations in the CNGB3 gene (about half of all cases) or CNGA3 gene (about one-fourth of all cases). These genes encode the CNGB3 and CNGA3 proteins, which combine to form a channel in the photoreceptor membrane that is required for phototransduction, the process whereby a light signal is converted to an electrical signal that is then transmitted to the brain. According to Retinal Dystrophies and Degenerations (1988), the incidence rate for ACHM is approximately one in 30,000 people, and we therefore estimate that there are about 10,000 people in the United States and about 17,000 people in Europe with ACHM. Of these, about half, or a total of 13,500 in the United States and Europe combined, have the form of the disease caused by mutations in the CNGB3 gene.

There is currently no specific treatment for ACHM. Symptoms are managed by the use of dark lenses to reduce discomfort from ambient light, and low vision aids such as high-powered magnifiers for reading. Children with ACHM are provided preferential seating in the front of classrooms to benefit maximally from their magnifying devices.

Our ACHM product candidates

Our gene therapy approach to treatment of ACHM involves using an AAV vector to insert a functional copy of the CNGB3 or CNGA3 gene into the patient’s own photoreceptor cells. Our first ACHM product candidate contains the CNGB3 gene and a promoter, the PR1.7 promoter, that has been shown in preclinical studies to drive efficient gene expression in primate cone photoreceptors and restores cone photoreceptor function in dog and mouse models of achromatopsia. We have identified an AAV capsid that works well for subretinal delivery and are evaluating additional AAV capsids to identify those that work well for intravitreal delivery that could be used in follow-on products.

After our ACHM product candidate containing the functional CNGB3 gene enters a photoreceptor cell, the gene is processed by normal biochemical processes into a stable DNA episome in the nucleus of the cell. The stable form of the gene allows production of the normal CNGB3 protein, which combines with the normal CNGA3 protein already being produced in the cell, to form a channel in the photoreceptor membrane that is required for phototransduction. Restoration of phototransduction enables cone photoreceptors to convert light entering the eye into an electrical signal that is transmitted to other retinal neurons and then to the visual cortex in the brain. Production of normal CNGB3 protein continues as long as the episome persists in the cell, which may be for many years or even life-long, thereby providing long-term potential benefit after a one-time therapeutic administration.

There are several other genes in which mutations are known to cause ACHM, with signs and symptoms that are the same as in ACHM caused by CNGB3 mutations. AAV vectors expressing these genes would be additional potential product candidates for treatment of ACHM caused by mutations in these genes, and we believe they would have the potential for rapid regulatory approval, if our product candidate for ACHM caused by CNGB3 mutations were already approved. Mutations in the CNGA3 gene are responsible for about 25% of ACHM cases in the US and Europe but are responsible for almost all cases in patients from the Middle East. Proof-

of-concept efficacy after subretinal injection of AAV vectors expressing CNGA3 has also been demonstrated in mouse and sheep models of CNGA3-related ACHM.

Preclinical proof of concept for our ACHM product candidates

In mouse and dog models of ACHM, our product candidate was able to restore photoreceptor function, improve visual acuity and mitigate photophobia and day blindness.

ACHM occurs in two breeds of dogs, Alaskan malamutes and German shorthaired pointers, due to mutations in the CNGB3 gene that either produce an abnormal protein or completely prevent production of the protein. Both breeds have clinical characteristics similar to human ACHM patients, with day blindness and absence of retinal cone function as measured by ERG. Treatment by subretinal injection of an AAV vector expressing human CNGB3 restored cone function in dogs with either mutation. Cone-specific ERG responses were undetectable in these dogs before treatment but were clearly detected after treatment. Day blindness was demonstrated before treatment by testing the ability of the dogs to navigate a maze under progressively brighter conditions. Before treatment, it took the ACHM dogs progressively longer to navigate the maze as the ambient light increased from dim light to normal room lighting and even longer with normal outdoor daytime lighting. After treatment, the day blindness was substantially eliminated, and the treated ACHM dogs were able to navigate the maze under bright light conditions at almost the same speed as normal dogs.

The figure below shows the average time taken to navigate a maze as the ambient light intensity was increased for three groups of dogs: normal dogs, dogs with ACHM that were untreated and dogs with ACHM that were treated with our ACHM product candidate. The figure shows that under low light conductions (0.2 lux, equivalent to the light conditions on a moonlit night), when vision is normally mediated only by rod photoreceptors, all three groups navigated the maze rapidly. As the light intensity was progressively increased (to 646 lux, equivalent to the light conditions in a business office), and vision became mediated by cone photoreceptors, the untreated ACHM dogs took progressively longer to navigate the maze, as they bumped into walls in the maze and had to advance by trial and error. In contrast, as the light intensity was progressively increased, the time taken to navigate the maze did not change for normal dogs and increased only slightly for the treated ACHM dogs.

Based on Komaromy et al. Human Molecular Genetics (2010)

Untreated ACHM dogs also demonstrated photophobia and day blindness when outdoors in daylight, which severely limited their ability to interact with people and objects in their environment. After treatment there was a dramatic improvement in this important clinical manifestation of ACHM. The restored function persisted for more than 2.5 years (the longest duration tested).

In addition, a mouse model of ACHM was developed by knocking out the CNGB3 gene in mice. These knockout mice have markedly impaired cone photoreceptor function, as measured by ERG and visual acuity testing. Treatment by subretinal injection of an AAV vector expressing human CNGB3 in the knockout mice improved cone-specific ERG responses to nearly normal levels and improved visual acuity, as measured by their ability to follow a rotating pattern of vertical stripes of varying thickness.

In conjunction with scientists based in Israel, we have initiated a preclinical study involving a product candidate for CNGA3-related ACHM, which uses the same promoter and capsid used in our CNGB3 product candidate, to evaluate its safety and efficacy in the sheep model of the disease. We have also initiated an international natural history study in patients with CNGA3-related ACHM.

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Planned clinical development of our CNGB3-related ACHM product candidate

We are currently conducting a natural history study in persons affected by ACHM caused by CNGB3 mutations. Results of this study will provide important information about the best methods for measuring visual function in these patients and will guide us in the design of subsequent clinical trials in which our product candidate will be tested for safety and efficacy. This study is being conducted at multiple clinical sites that specialize in inherited retinal diseases.

We are in the final stages of preparing the IND for our ACHM CNGB3 product candidate. Once the IND has cleared the FDA, we anticipate enrolling18 achromatopsia CNGB3 patients in a Phase1/2 clinical trial. The anticipated study design is illustrated below:

Completion of the Phase 1/2 clinical study and the natural history study will guide us in finalizing the design of a pivotal Phase 3 clinical trial. In the planned pivotal Phase 3 trial, we expect that between 40 and 75 patients will be enrolled and evaluated for changes in visual function over a 12-month period following treatment. If successful, we believe the results of this pivotal Phase 3 trial could support our submission of a BLA to the FDA and of an MAA to the EMA for our ACHM product candidate.

X-linked retinitis pigmentosa

Retinitis pigmentosa is an inherited retinal dystrophy with progressive loss of vision. It is commonly first observed in boys and young men who notice problems with vision under low light conditions, or night blindness, followed by a restriction of peripheral visual fields, or tunnel vision, leading to poor central vision and eventual total blindness.

The incidence rate for retinitis pigmentosa is about one in 4,000 people, according to Retinitis Pigmentosa (1988), and we estimate that there are about 75,000 people in the United States and 125,000 people in Europe with retinitis pigmentosa, or 200,000 people in the United States and Europe combined. According to a paper by Dr. Marianne Haim published in Acta Ophthalmologica (1992), about 10% of cases of retinitis pigmentosa are caused by mutations in a gene on the X chromosome and are referred to as X-linked retinitis pigmentosa, or XLRP, from which we therefore estimate that there are about 20,000 persons with XLRP in the United States and Europe combined.

A preclinical study in a dog model of XLRP caused by mutations in the RPGR gene demonstrated a delay in the rate of disease progression in eyes that received a subretinal injection of an AAV vector expressing RPGR. We have inserted a stable form of the RPGR cDNA into an HSV helper to produce our XLRP product candidate and are currently conducting preclinical studies to further evaluate the ability of this product candidate to delay disease progression in animal models of XLRP. If these studies are successful, we will conduct additional preclinical studies required for submission of an IND to the FDA. These studies will include single-dose toxicology studies in animals that will evaluate the safety and distribution within the animals after our XLRP product candidate is delivered by both subretinal and intravitreal injection.

As a part of our collaboration, Biogen obtains worldwide commercialization rights for the XLRP program. The Company will lead the clinical development program through the completion of first-in-human trials. Biogen will support the clinical development costs, subject to certain conditions, following the IND-enabling studies. The Company has an option to share development costs and profits after the initial clinical trial data are available, and an option to co-promote the second of these products (XLRS and XLRP) to be approved in the United States.

Other opportunities in ophthalmology

We believe our current gene therapy platform will enable us to develop and test new AAV vectors that carry different gene sequences for other inherited diseases in ophthalmology, reducing the need for early research work. In this way, we anticipate being

able to move products rapidly through preclinical studies and into clinical development. We also believe that there are large market ophthalmology diseases where AAV vectors may provide benefit, such as wet AMD.

Wet AMD

Age-related macular degeneration, or AMD, is a retinal disease that affects older adults and results in a loss of vision in the center of the visual field (the macula). It is a major cause of blindness and visual impairment and occurs in neovascular ("wet") or nonneovascular ("dry") forms. In the wet form, abnormal growth of blood vessels in the retina is stimulated by a protein called vascular endothelial growth factor, or VEGF. The abnormal blood vessel growth, or neovascularization, causes vision loss due to blood and protein leakage in the macula. A paper by Friedman et al. published in Archives of Ophthalmology (2004) estimated the total number of persons with wet AMD in the United States to be 1.2 million, from which we estimate there are about 3.2 million persons with wet AMD in the United States and Europe combined.

Wet AMD is currently treated with intravitreal injections of anti-VEGF agents delivered every one to two months, for an indefinite period. While these VEGF-targeted therapies have proven efficacious for many patients, there is an urgent medical need to improve on the approximately 35% success rate for existing therapies by targeting other critical factors, and to reduce the burdensome injection frequency for patients and physicians.

Based on our proof-of-concept studies, we believe that gene therapy offers a potential long-term solution to treat wet AMD with a single injection. Additionally, as in the case of "cocktail" treatment paradigms in oncology, there is a strong rationale for combination therapy to become the standard of care in wet AMD. For instance, we are aware that others are conducting Phase 3 trials of an anti-platelet-derived growth factor, or PDGF, agent in combination with anti-VEGF agents for wet AMD. We believe that, while the predictability of targeting VEGF itself would mitigate development risk, the most compelling gene therapy approach would offer not only sustained expression but also pathway synergy with existing anti-VEGF options. We have defined our preferred target profile and are proceeding with a comprehensive review of possible targets.

The development pathway for wet AMD therapies has been well-established. Preclinical CROs offer predictive animal models that reproduce the neovascularization typical of wet AMD in humans and yield results within a few months. In the clinic, physicians can readily detect therapeutic effects by measuring visual function with an eye chart and anatomical biomarkers using widely available imaging devices. We intend to test several lead targets head-to-head in animal models. If sufficient rationale exists for more than one target, we will investigate deploying one viral vector to address multiple targets. Given our experience gained from our prior partnership with Genzyme, our already-established manufacturing infrastructure and our planned regulatory path, we expect to be able to file an IND for a wet AMD product candidate efficiently.

Other autosomal recessive retinal diseases

It is estimated that approximately 220 genes causing inherited retinal disease have been identified, of which 146 are autosomal recessive and therefore most amenable to treatment by gene replacement therapy. Among the 42 most common autosomal recessive forms of retinitis pigmentosa, LCA and cone or cone-rod dystrophy, 38 have gene coding regions of less than 3,760 nucleotides and can therefore be readily accommodated within our AAV vectors. We are continuing to evaluate indications having these characteristics to select those most appropriate for addition to our longer-term product development pipeline.

Manufacturing

Until recently, there has been a lack of manufacturing infrastructure to enable the production of gene therapies in a reliable and reproducible manner at a commercially viable scale. The historical challenges for gene therapy manufacturing relate to the difficulty of developing constructs that provide the necessary helper functions, and in

having systems that provide adequate yield, scalability and potency. We have made significant investments in developing improved manufacturing processes, which include the following:

- We have developed proprietary AAV vector manufacturing processes and techniques that produce a more purified and concentrated product candidate, as evidenced by the approximately 25- to 30-fold reduction in non-infectious viral contaminants as compared to vectors used in many previous clinical trials.
- We do not need a specially cloned and isolated cell line for each of our disease targets; we instead use specially engineered replication-incompetent herpes simplex helpers, or HSV helpers, which are stable and straightforward to clone.
- We have developed over 30 assays to accurately characterize our process and the HSV and AAV vectors we produce.

- We have developed a purification system applicable to multiple AAV capsids.
- We are investing in the development of mid- to large-scale manufacturing processes to enable the manufacture of our product candidates at commercial scale.

We believe these improvements and our continued investment in our manufacturing platform will enable us to develop best-in-class, next generation gene therapy products.

Our viral vector production platform for AAV-based gene therapeutics, which we call the herpes-assisted vector expansion, or H.A.V.E. method, offers significant benefits in comparison with the methods used by others to manufacture AAV vectors, as summarized in the following table.

AAV production method	Straightforward cloning	High efficiency	High yield	Scalable
Transfection	Yes	No	No	No
Baculovirus	No	No	Yes	Yes
Adenovirus	No	Yes	Yes	Yes
Our H.A.V.E. method	Yes	Yes	Yes	Yes

The four key steps involved in our proprietary H.A.V.E. manufacturing method are as follows:

- First, the therapeutic gene and the appropriate AAV capsid genes are inserted into individual HSV helpers, and these helpers are individually grown in a complementing cell line called V27. The complementing cell line is required to provide critical functions that allow the replication-incompetent HSV helpers to grow; the same cell line is used to produce HSV helpers for all disease targets. This step occurs in disposable culture vessels of increasing size, up to and including disposable stirred tank bioreactors. The HSV helpers are harvested, minimally processed and concentrated to prepare them for use in producing our AAV vectors. These HSV helpers can be stored frozen for years before use.
- Next, the two HSV helpers are used together to infect a cell line called sBHK, allowing for packaging of the therapeutic gene into the AAV capsid and to produce our AAV vectors. The sBHK cell line does not provide the critical functions that would allow for growth of the HSV helpers, which provides an added layer of safety. The same sBHK cell line is used to produce AAV vectors for all disease targets. This step occurs in disposable culture vessels of increasing size depending on the amount of AAV vector that is required. The AAV vector is recovered by using a detergent solution to break open the sBHK cells and release the AAV vectors. This step also destroys any residual HSV helpers that were used to infect the sBHK cells.
- The third step is to purify the harvested AAV vector using two chromatography columns. The exact method used to column-purify our AAV vectors varies depending on the AAV capsid used in the product candidate; we have developed purification methods for multiple AAV capsids. We have shown in formal clearance studies that the combination of detergent treatment and two chromatography columns can remove up to 10^{14} (100 trillion) units of HSV. This step also helps to eliminate any remaining parts, such as proteins or DNA, of the HSV helpers and sBHK production cells.
- The final step is to formulate, filter and fill the AAV vector in appropriate containers for use in animal or human studies. This filled AAV vector drug product can be stored frozen for years before use.

H.A.V.E. Production of our AAV Vectors for Gene Therapy

The H.A.V.E. method is inherently flexible, allowing the manufacture of a wide range of AAV vectors without the need to modify the manufacturing steps used to produce the HSV helpers or AAV vectors. We have already demonstrated our manufacturing knowledge through multiple successful production batches of both HSV helpers and AAV vectors at SAFC Pharma, our contract manufacturing organization, under current good manufacturing practices, or GMP.

Research is already underway to meet our future manufacturing needs. Projects include scale-up to larger batch production for use in our AAT deficiency program, continued modifications of the purification step to accommodate new AAV capsids, complete removal of animal-derived products from the V27 cell growth step, and formulations that allow for higher AAV vector concentrations.

We are also in the process of acquiring capital equipment and staffing a facility capable of process development and non-cGMP manufacturing at 100 L scale. Such a facility would enable us to complete all process development at final manufacturing scale appropriate for many indications prior to transfer of manufacturing to a cGMP facility, giving us better control of our future manufacturing requirements.

Strategic collaborations and acquisitions

We have formed strategic alliances where both parties contribute expertise to enable the discovery and development of potential gene therapy product candidates. To access the substantial funding and other resources required to develop and commercialize gene therapy products, we intend to seek other opportunities to form strategic alliances with collaborators who can augment our industry-leading gene therapy expertise.

On July 1, 2015, we entered into a broad collaboration and license agreement with Biogen to develop gene-based therapies for multiple ophthalmic diseases. Biogen has made an upfront payment to us in the amount of $124.0 million, which includes a $30.0 million equity investment and certain prepaid research and development expenditures. Biogen will be granted a license to the XLRS and XLRP programs and the option to license discovery programs for two additional ophthalmic indications and one non-ophthalmic indication at the time of clinical candidate selection. Under the collaboration, we are eligible to receive upfront and milestone payments exceeding $1 billion. This includes up to $472.5 million collectively for the two lead programs, which also will carry royalties in the high single digit to mid-teen percentages of annual net sales. In addition, Biogen may make payments up to $592.5 million across the discovery programs, along with royalties in the mid-single digits to low teen percentages of annual net sales.

Biogen will also receive an exclusive license to use our proprietary manufacturing technology platform to make AAV vectors for up to six genes, three of which are at our discretion, in exchange for payment of milestones and royalties.

We have also entered into an agreement with SAFC Pharma, which also is our current contract manufacturing organization, for cGMP manufacture of clinical grade material for third parties. This arrangement allows us to approach other gene therapy companies that might benefit from our manufacturing and vector design capabilities. Under such an arrangement, we could potentially license our manufacturing technology and receive upfront payments, milestones and royalties. SAFC Pharma would do the manufacturing of commercial grade material.

Our plan to bring in-house a pilot manufacturing facility will further support these efforts. Such a facility will allow us to manufacture small amounts of non-clinical grade material for other gene therapy companies as they perform their pre-clinical experiments. It will also enable us to develop additional expertise in viral vector design as we look to forge partnerships and alliances within the gene therapy space.

We also plan to continue to in-license additional intellectual property to support our current programs, to establish new development programs and to support our manufacturing technology. Additionally we will seek to partner with both new commercial gene therapy companies and academic institutions to leverage our expertise in vector design, research, manufacturing and the regulatory process. The goal of these collaborations would be to forge strategic partnerships around technologies and programs that would fit with our current development pipeline. In general, we would seek new intellectual property, development programs in rare diseases, pipeline products where the regulatory pathway is understood, partners with strong scientific, clinical and management expertise, and programs that have synergy with our current knowledge base and product pipeline that would add to our industry leadership. We would also be looking at programs where the disease being treated has a large enough patient population that there would be adequate financial returns for the investment of resources.

We will also evaluate opportunities to add products, technology and talent in areas consistent with our strategy through selective acquisitions.

Our relationship with the University of Florida

All of our scientific founders spent part of their careers at the University of Florida, or UF, and three are still UF faculty members. Since our inception we have licensed significant technology from and funded research at multiple labs at UF. Pursuant to four agreements, we have licensed three U.S. patents and multiple pending applications covering inventions made at UF. UF has multiple capabilities in genetic cloning, gene therapy manufacturing, animal model development and facilities for both small and large animal testing, and in certain instances we have benefited from the ability to conduct important research at UF without having to expand in-house facilities and personnel. We interact frequently with the Powell Gene Therapy Center at UF and have an excellent working relationship with the UF Office of Technology Licensing.

In May 2013, we and UF were jointly awarded an $8.3 million dollar grant from the NEI to support development of our ACHM product candidate, with Dr. William Hauswirth, one of our scientific founders and Professor and holder of the Rybaczki-Bullard Chair in the Department of Ophthalmology at UF, as principal investigator. As a sub-awardee, we expect to receive approximately $3.8 million over four years under this grant.

Our relationships with patient advocacy groups and academic centers

We have long believed that when developing products to treat orphan indications it is important to form strong relationships with patient advocacy groups, and we have done this successfully with both the Foundation Fighting Blindness, or FFB, and the Alpha-1 Foundation. Both organizations are well known for their advocacy of patients' interests in obtaining diagnosis, developing treatments and providing for reimbursement. Both actively support research into treatment, and we have been awarded three research grants totaling $1.6 million from the FFB and one grant of $0.3 million from the Alpha-1 Foundation. More importantly, both organizations have been instrumental in assisting us in forming ties with disease experts, recruiting patients into clinical trials and helping us to understand the needs, wants and concerns of patients.

We also have formed strong relationships with key academic centers across the United States that have core competencies in gene therapy, orphan ophthalmology and AAT deficiency. These centers conduct sponsored research, act as advisors and collaborate with us on grant proposals. Since our inception, we have been awarded grant funding, either independently or with our collaborators. This funding has provided peer-reviewed scientific validation of our programs and has facilitated critical early stage research for our leading product candidates.

Intellectual property

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing

technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have developed or in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of gene therapy products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, certain genes, methods of transferring genetic material into cells, processes to manufacture our AAV-based product candidates and other proprietary technologies and processes related to our lead product candidates.

As of August 24, 2015, our patent portfolio included approximately 56 patents and patent applications that we own and approximately 64 patents and patent applications that we have licensed. More specifically, we own five U.S. patents, six pending U.S. applications, 32 foreign patents and 13 foreign patent applications. We have licensed 22 U.S. patents, four pending U.S. applications, 35 foreign patents and three pending foreign patent applications. Of the patents and patent applications that we own or license, 32 cover methods to manufacture AAV vectors, the longest lived and most significant of which is expected to expire in 2025. Ten of the patent applications that we own are directed to small cone promoters and uses thereof. A patent issuing from this group could have an expiration date in 2034.

Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our gene therapy product candidates and AAV manufacturing process. Our owned and licensed patent portfolio includes patents and patent applications directed to our AAT deficiency, XLRS and ACHM programs, as well as our foundational AAV platform. See also “—License agreements.”

In addition to the above, we have established expertise and development capabilities focused in the areas of preclinical research and development, manufacturing and manufacturing process scale-up, quality control, quality assurance, regulatory affairs and clinical trial design and implementation. We believe that our focus and expertise will help us develop products based on our proprietary intellectual property and to expand our intellectual property.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent’s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the United States Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent. The issued patents that we own and license are expected to expire on various dates from 2016 to 2029.

The term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the

patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent per approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a new drug application, or NDA, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be

breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

License agreements

We have rights to use and exploit multiple issued and pending patents under licenses from other entities. We consider the commercial terms of these licenses, which provide for modest milestone and royalty payments, and their provisions regarding diligence, insurance, indemnification and other similar matters, to be reasonable and customary for our industry.

Information about our principal licenses is set forth below.