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Initiation of Coverage

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Biotechnology: Initiating Coverage

An Investor's Guide to Understanding Gene Therapy: A Paradigm Shift Whose Time Has Come

Initiating Coverage of Spark Therapeutics, REGENXBIO, Voyager Therapeutics, and Adverum Biotechnologies at Outperform; Audentes Therapeutics at Market Perform

Please read domestic and foreign disclosure/risk information beginning on page 234 and Analyst Certification on page 234.

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Executive Summary

The Gene Therapy Era Has Arrived

What started off as a clinical off-shoot of molecular biology in the 1970s has moved from a therapeutic concept to a viable therapy to address various rare and not so rare genetic diseases. While the gene therapy field has gone through nearly three decades of ups and downs, in our opinion, we are at the cusp of ushering in a new era of therapies that can address the underlying biology of many inherited disorders. Two therapies have already been approved for commercialization in Europe, although calling either a commercial success is a stretch. UniQure's Glybera, the first approved in Europe in 2012, experienced extremely limited usage in the commercial setting and was withdrawn from the market early this year. GlaxoSmithKline's Strimvelis, approved in 2016 at a price tag of $594,000 euros (about $665,000 USD), is currently treating patients with ADA deficiency, although given the size of the patient population, we see this platform more as a good will gesture as compared to a robust money generating machine.

That said, we view these two products largely as proof of concept therapeutics whereby clinical trials were able to show efficacy and long-term safety, both of which helped clear regulatory hurdles with flying colors. While the pessimist might view the turbulent history of the gene therapy space as more of what's to come, we view this field as a potential revolution. In short, within the next few years, we expect multiple U.S. approvals of gene therapy products, with Spark's LUXTURNA leading the pack in January 2018 (PDUFA). In addition, bluebird bio's LentiGlobin appears to have achieved durable RBC (red blood cell) transfusion independence in patients with β-thalassemia, with Phase III studies underway. Last but not the least, promising clinical results have also been generated in Hemophilia A and B (e.g., Spark and BioMarin), spinal muscular atrophy (AveXis), and Parkinson's disease (Voyager).

What Started Out as a Cottage Industry Has Grown Substantially

By our count, there are at least 33 public and 27 private companies developing gene therapy products either by themselves or through partnerships (Exhibits 2 and 3). Collectively, these players are working on one-time solutions for at least 59 diseases, addressing $100+ billion market opportunities, according to our estimates. Given the number of players, the compelling clinical results achieved to date, and the partnerships/deals done in the space, we believe gene therapy is poised to become the next-wave therapeutic category. If we are correct, the current setup of this space is very similar to that seen in the CAR T space, where we just witnessed one of the largest acquisitions of a pre-commercial company (Gilead's acquisition of Kite for $12 billion) ever.

More Partnerships and Acquisitions Are Likely to Occur in the Future

Given the market opportunity as well as the clinical successes to date, it is not surprising that a number of partnership or acquisition transactions have already taken place (Exhibits 23 and 24). Interestingly, we view these transactions in two distinct categories: 1) acquisition of a novel platform for a premium, and 2) acquisition of a company with a failed clinical trial but a promising platform and intellectual property, for a premium. For example, there was recently a bidding war between Ultragenyx and REGENXBIO for the acquisition of Dimension Therapeutics (shares of Dimension moved from $33 million in market cap to ~$150 million). In addition, Pfizer acquired Bamboo Therapeutics for an upfront payment of approximately $200 million in addition to milestone payments of up to $495 million. Partnership examples in the space include the Pfizer/Sangamo licensing agreement, which gave Pfizer worldwide rights to Sangamo's hemophilia A program, and a slew of partnerships signed between REGENXBIO and multiple other gene therapy players (e.g., AveXis and Biogen), which granted these companies access to REGENXBIO's AAV vectors. While some big pharma companies like Pfizer have an established presence in the gene therapy

arena, there are still many large-cap pharmaceutical or biotechnology companies who have not subscribed to the gene therapy model – and therein lies the opportunity, in our opinion. Based on the progress made in the gene therapy space, we believe more big pharma or large-cap biotech companies are likely to enter the gene therapy battlefield, resulting in increased potential partnership and M&A activities.

IPOs, Secondary Offerings, and Reverse Mergers Have Helped Access Public Funds

The IPO activity in the gene therapy space started to pick up in early 2015, with 12 companies having gone public since then. Collectively, these IPOs raised total gross proceeds of more than $1 billion, with Spark leading the largest IPO so far in the space (Exhibit 25). Since their respective IPOs, many of these companies have also been able to continue to access funds through secondary public offerings, delivering total gross proceeds of $3.6 billion since 2013 (Exhibit 26). Notable secondary offerings include this year's raises for Spark (gross proceeds of ~$403 million), bluebird (~$400 million), and AveXis (~$288 million). Besides IPOs and secondary offerings, revere mergers have also become an option to tap the financial markets. Recently, a private gene therapy company (Rocket Pharmaceuticals) announced its intent to merge with a public company (Inotek Pharmaceuticals). Moving forward, we continue to believe that most gene therapy companies should not have trouble accessing financing as long as they continue to deliver promising results in the clinic.

Gene Therapy Valuation

Arguably, the entire gene therapy space has taken off like a rocket, with the total market capitalization of the companies in our gene therapy index growing from $9.7 billion as of January 1, 2017, to $20.3 billion as of October 6, 2017. Specifically, the gene therapy group generated an average return of approximately 90% year-to-date, outperforming both the NBI (28%) and the S&P500 (14%) (Exhibit 27). Sangamo Therapeutics achieved the highest return of 423%, while Applied Genetic Technologies Corporation (AGTC) was the worst performer so far.

Upcoming Events in the Gene Therapy Space

Moving forward, a slew of catalysts could further drive the valuation of the gene therapy space. In the hemophilia A world, we expect additional updates on BioMarin's BMN270 on October 18 and Spark's SPK-8011 at the American Society of Hematology (ASH) meeting. In addition, we expect the first clinical readouts from Sangamo's hemophilia A program (SB-525) by YE17 or early 2018 and Shire's SHP654 in 2018. With respect to other products, key events include: 1) the FDA's decision on Spark's LUXTURNA on/before the PDUFA date of January 12, 2018; 2) additional data updates on AveXis' SMA (2018/2019) and Voyager's Parkinson's disease programs (1Q18), and 3) the first readouts from REGENXBIO's wet AMD and HoFH trials (YE17), Audentes Therapeutics' two rare disease programs (4Q17/1Q18), and Adverum's A1AT deficiency study (2018).

Blue Sky Scenario Does Not Preclude Some Dark Clouds

Like many other breakthrough technologies, gene therapy has experienced its share of significant setbacks, including deaths seen in the clinical trials, and disappointing results observed in wet AMD (Avalanche and Genzyme), as well as Alpha-1 antitrypsin (A1AT) deficiency (Applied Genetic Technologies

Corporation) and Hemophilia B (Dimension Therapeutics). Furthermore, many challenges remain – unforeseen near-term and long-term safety issues could appear; efficacy, in particular, the degree of persistence remains an open-ended question for many of the therapies in development; the translation of mouse models to human conditions remains challenging; the ability to redose, which currently does not exist, if the therapeutic affect wears off; the pricing of once and done therapies in a multi-payor system; and last but not least, the viability of a business model in some ultra-rare/orphan disease indications where the patient numbers are so small, one would either need to give it away or charge prices >$5 million. That said, we believe all these challenges can be overcome in time.

Are All Gene Therapies Created the Same? The Answer Is, "No"

The concept of gene therapy sounds easy. After all, it is "simply" the use of a "recombinant nucleic acid used to regulate, repair, replace, enhance or delete a defective or missing genetic component within a host cell." However, in reality, there are several important pieces that must all come together, including the selection of the correct vector, development of an optimal transgene, and the most expedient route of administration, which is very much dependent on the indication. Therefore, in our view, the success or failure of one product in one indication does not necessarily mean that other products are slated to the same fate. For example, Spark's product for hemophilia B has delivered promising products, whereas Dimension's solution for the same indication was disappointing in the clinic.

Once and Done? For Now, "Yes"

While the field currently does not have an answer regarding the ultimate therapeutic durability in patients, in our opinion, long-lasting treatment effects could be maintained in tissues/organs (such as the eye and the liver) that have a relatively low cellular turnover rate. As a matter of fact, some patients with a genetic retinal disorder treated by Spark's LUXTURNA have maintained the vision improvements out to four years. In the hemophilia world, meaningful improvements in factor level activity achieved by either Spark's or BioMarin's products are still observed at 12+ months. Finally, bluebird bio's therapeutic for patients suffering from cerebral adrenoleukodystrophy (Lorenzo's oil disease) recently provided an update stating that most treated patients were alive and free of complications at a median follow-up of 29.4 months. In a best case scenario, the clinical outcomes achieved by a one-time administration of a gene therapy should last the lifetime of the patient. Given that the majority of current gene therapy products are not designed to purposely integrate the transgene into a recipient's own genome, we believe the effects of these products are likely to diminish over time.

What's the Impact of Pre-Existing Neutralizing Antibodies and Is Re-Dosing Possible in the Future?

Neutralizing antibodies against the AAV vectors utilized in most of the gene therapy products exist in many people, with a prevalence rate ranging from 38% (AAV8) to 72% (AAV2) for wild type AAV vectors. Patients with high titers of these antibodies against a certain vector are usually not eligible for the treatment of a gene therapy based on this vector. Due to immune responses induced by the vectors after administration, re-dosing of a gene therapy is not possible at the present time. That said, we believe the industry is likely to figure out ways to tackle this problem. In fact, Selecta Biosciences' platform technology, which may be able to mitigate the formation of anti-drug antibodies, could potentially allow for re-dosing of a gene therapy. Of note, Spark and Selecta Biosciences have an ongoing collaboration for this cause.

Are There Long-Term Safety Concerns?

So far, AAV based products appear to be well tolerated, without the associated deaths or insertional mutagenesis observed with other vectors. That said, the long-term safety profile remains to be established. Although the regulatory requirements for many gene therapies require a minimum follow-up of 15 years (after product approval), many replication negative vectors do not have such stringent guidelines. Nevertheless, we believe that many of these patients will be followed for considerable time out of an over-abundance of caution.

How Are Gene Therapy Products Going to Be Reimbursed?

A new generation of therapeutics will require a new way to think about pricing. Based on the CMS payment model established for the first CAR T product, Novartis' Kymriah, as well as GSK's money-back guarantee for Strimvelis, clearly, evidence-based pricing is here to stay. Going forward, we see payment models encompassing not only evidence-based pricing, but also annuity-based models and one-time pricing models. As we evaluated the market opportunities and spoke with a variety of management teams, we began to design our models to account for two main types of scenarios: 1) a one-time upfront payment model for ultra-rare diseases – regardless of how long the therapy might work; given the rare patient populations and lack of therapeutic options, the healthcare system would be able to bear the price tag; and 2) an outcomes-based annuity model with an annual payment that is in line with, or at a slight premium to, currently available therapies. For example, in the case of hemophilia A, we have modeled that the first movers charge close to $400,000/year, as compared to on average $300,000/year charged for the administration of factors for severe patients (does not include the price of inhibitors). Regardless of the ultimate price, what we like about this model is that payors reimburse the company on a yearly basis, as long as the therapy works and regardless of the patient switching insurance carriers.

Can Gene Therapy Be a Business?

While the first two gene therapy products approved in Europe have yet to deliver on the promise of gene therapy, we believe the future remains bright. Although UniQure's Glybera was pulled off the market due to lackluster sales, and GSK's Strimvelis has only treated two patients as of July 2017 (about a year after approval), in our opinion, the lack of commercial adoption is largely due to the ultra-rare nature of the indications pursued, and not a reflection of the efficacy and safety of the therapies. That said, gene therapy product candidates currently in development could face similar problems, especially if the targeted patient population is small. In addition, patient indications for some rare diseases could face initial commercial challenges if the group as a whole is under-diagnosed. The flip side? Other indications such as hemophilia, Parkinson's disease, and wet age-related macular degeneration (AMD) should not have patient identification issues, but rather, the competition to displace existing therapies. Regardless, we believe each of these scenarios can result in profitable businesses over time.

Initiating Coverage on the Gene Therapy Space

We are initiating coverage of: 1) Spark Therapeutics with an Outperform rating and a price target of $96 given an approval expected in the near future, encouraging clinical data seen with the hemophilia A program, a marquee partner (Pfizer) driving development in hemophilia B, a platform technology to address large areas of unmet need; 2) REGENXBIO with an Outperform rating and a price target of $39 given a powerful AAV technology platform that has generated 10 partnerships with leading biotech/gene therapy companies (e.g., Biogen, Shire, and AveXis), resulting in over 25 partnered and unpartnered assets; 3) Voyager Therapeutics with an Outperform rating and a price target of $35 given the clinically meaningful improvements on multiple efficacy endpoints among patients with Parkinson's disease (PD); 4) Adverum Biotechnologies with an Outperform rating and a price target of $6 given a negative enterprise value and multiple product candidates slated to enter the clinic in the near future; and 5) Audentes Therapeutics with a Market Perform rating since, in our opinion, the company's current market capitalization adequately reflects the solid preclinical results seen to date.

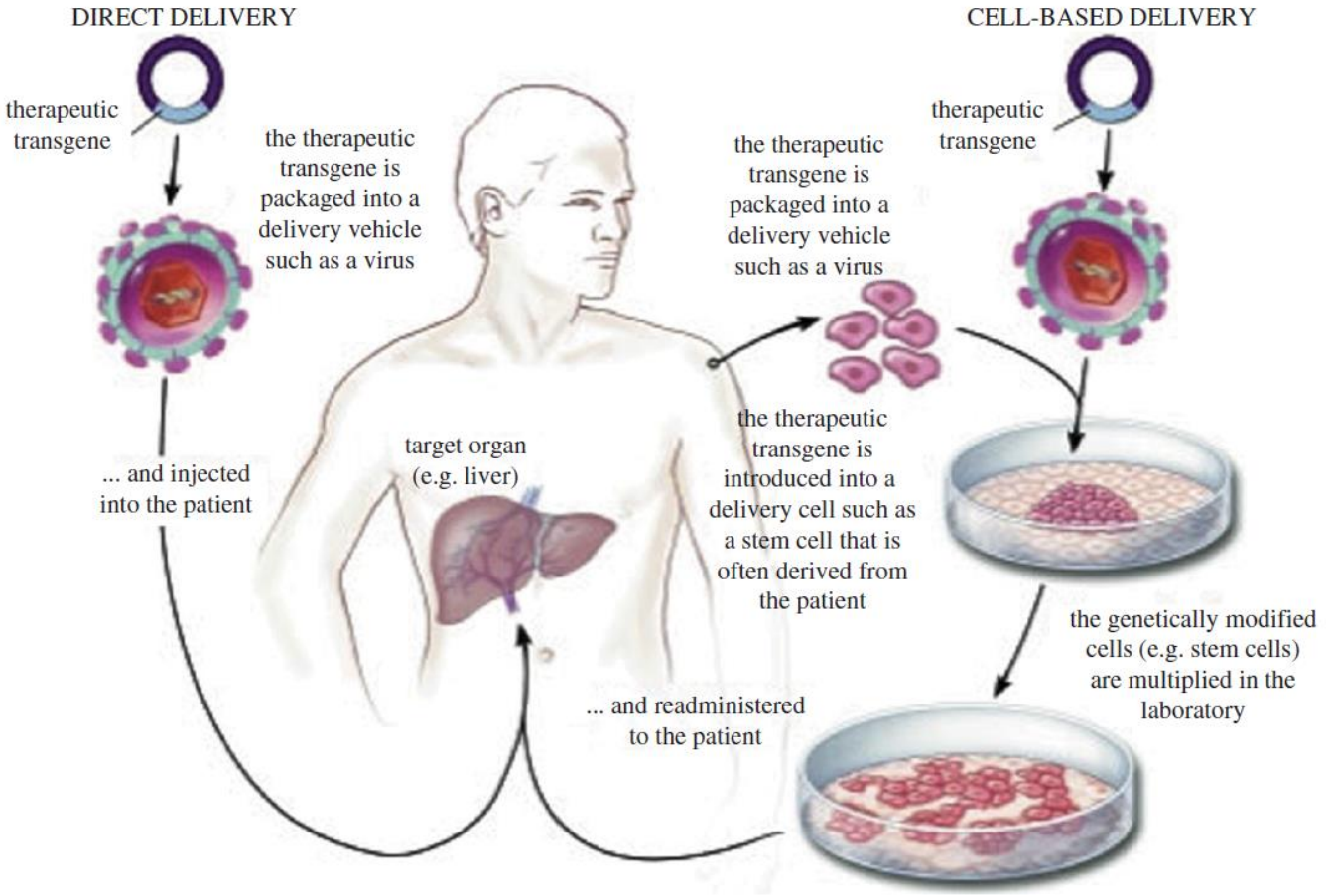
Gene Therapy 101

The human genome is comprised of nucleic acid sequences, which are the building blocks of approximately 20,000 protein coding genes. Every protein coding gene stores information for the synthesis of a specific protein that in turn controls a variety of biological functions in the human body. Any defect in a gene, therefore, results in an aberrant protein, which affects the natural physiology of the body, resulting in the development of a genetic disorder or illness. The underlying concept of gene therapy is simple: one or more therapeutic genes are introduced into a patient's cells to replace or correct the defective gene, leading to the rescue of the aberrant protein. Therefore, a gene therapy is any therapeutic agent that consists of recombinant nucleic acid used to regulate, repair, replace, enhance, or delete a defective or missing genetic component within a host cell.

Broadly, gene therapy consists of a two-step process: 1) a therapeutic gene coding for a functional protein is encapsulated into a non-viral carrier or inserted into the genome of a viral vector (typically an attenuated virus); and 2) the delivery of the modified vector to the target cells results in the construct either incorporating within the host genome, or existing as an episome outside the host genome, and transcribing the therapeutic gene of interest. Depending on the delivery method, gene therapy can be accomplished by transferring the engineered gene of interest into extracted cells, transfected, and subsequently redelivered (ex vivo gene transfer, e.g. chimeric antigen receptor or (CAR T) therapies). Alternatively, the viral vector carrying the functional gene copy is systematically or locally injected into the body, allowing the virus to engage with the cells of interest and infiltrate the cell (in vivo gene transfer) (Exhibit 1).

Theoretically, if the gene is transcribed or switched "on," the cells harboring the new gene should be able to synthesize the functional protein, thereby leading to the prevention, attenuation or even a cure of the underlying disease. Of note, our guide is focused on a discussion of gene therapy which aims to achieve a functional gain or loss of particular proteins and thereby could potentially result in the correction of an associated disease (recessive or dominant), with a focus on the in vivo gene transfer for hereditary diseases.

Exhibit 1: **What Is a Gene Therapy?**



Source: Proceedings. Biological Sciences; 2015 Dec 22; 282(1821): 20143003; Mary Collins, Adrian Thrasher; Gene therapy: progress and predictions; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707739/

Gene Therapy Players

Given the profound market opportunity and significant clinical progress, many companies have entered the gene therapy arena through internal efforts, partnerships, or acquisitions. By our count, there are a total of 31 public and 29 private companies developing gene therapy products (Exhibits 2 and 3). Of note, CAR T therapies, which are also a type of gene therapy, are not included in this report. We note that multiple big pharma and large-cap biotech companies including Novartis, Pfizer, Bristol Myers Squibb, Bayer, Sanofi, Biogen, Regeneron, and Shire have already established a presence in the gene therapy arena via acquisitions or partnerships. That said, many other large-cap companies have not entered the space. Interestingly, excluding these companies as well as Vertex, BioMarin, and Bioverativ, the total market capitalization of other pure gene therapy players is approximately $21 billion, with bluebird bio, Spark, and AveXis collectively making up nearly 60% of the total value.

Exhibit 2: **Select Public Companies Developing Gene Therapies**

Company	Product type	Pure gene therapy play?	Key Partner (s)	Market Cap ($ million)
Novartis	Genome editing	No	Intellia	224,882
Pfizer	AAV, genome editing	No	Spark, Sangamo, 4D Molecular Therapeutics	214,402
Bayer	AAV	No	Dimension Therapeutics	113,709
Sanofi	AAV, lentiviral	No	REGENXBIO, Voyager, Oxford BioMedica	108,664
Bristol-Myers Squibb	AAV	No	uniQure	106,284
Biogen	AAV	No	REGENXBIO, AGTC	69,240
Regeneron	AAV, genome editing	No	Adverum, Intellia	49,458
Shire Plc	AAV	No	Sangamo, REGENXBIO	45,814
Vertex	Genome editing	No	CRISPR Therapeutics	39,104
BioMarin Pharmaceutical Inc.	AAV	No		16,617
Bioverativ Inc	Genome editing, lentiviral	No	Sangamo	6,374
bluebird bio	Lentiviral, genome editing	No		5,824
AveXis, Inc.	AAV	Yes	REGENXBIO	3,311
Spark Therapeutics	AAV	Yes	Pfizer	3,196
Sangamo Therapeutics Inc	AAV, genome editing	Yes	Pfizer, Shire, Bioverativ	1,334
Intellia Therapeutics	Genome editing	Yes	Novartis, Regeneron	1,117
Editas Medicine	Genome editing	Yes		1,053
REGENXBIO	AAV	Yes	Biogen, Sanofi Genzyme, Shire, AveXis, Audentes, Voyager, Adverum, Dimension, Esteve, Lysogene	1,041
CRISPR Therapeutics	Genome editing	Yes	Vertex, Casebia	783
Audentes Therapeutics, Inc.	AAV	Yes	REGENXBIO	721
Abeona Therapeutics Inc.	AAV	Yes		713
Voyager Therapeutics	AAV	Yes	Sanofi Genzyme, REGENXBIO	556
Nightstar Therapeutics	AAV	Yes		471
Selecta Biosciences Inc	AAV	No	Spark	436
Oxford BioMedica	Lentiviral	Yes	Sanofi	380
UniQure N.V.	AAV	Yes	Chiesi, BMS	274
Adverum Biotechnologies	AAV	Yes	REGENXBIO, Regeneron	154
Dimension Therapeutics, Inc.	AAV	Yes	Bayer	151
GenSight Biologics SA	AAV	Yes		142
Krystal Biotech	Modified HSV-1	Yes		96
Lysogene SAS	AAV	Yes	REGENXBIO	74
Applied Genetic Technologies Corporation	AAV	Yes	Biogen	72
Fibrocell Science Inc.	Lentiviral	Yes	Intrexon	43

Source: Company reports, Raymond James research

Exhibit 3: **Select Private Companies Developing Gene Therapies**

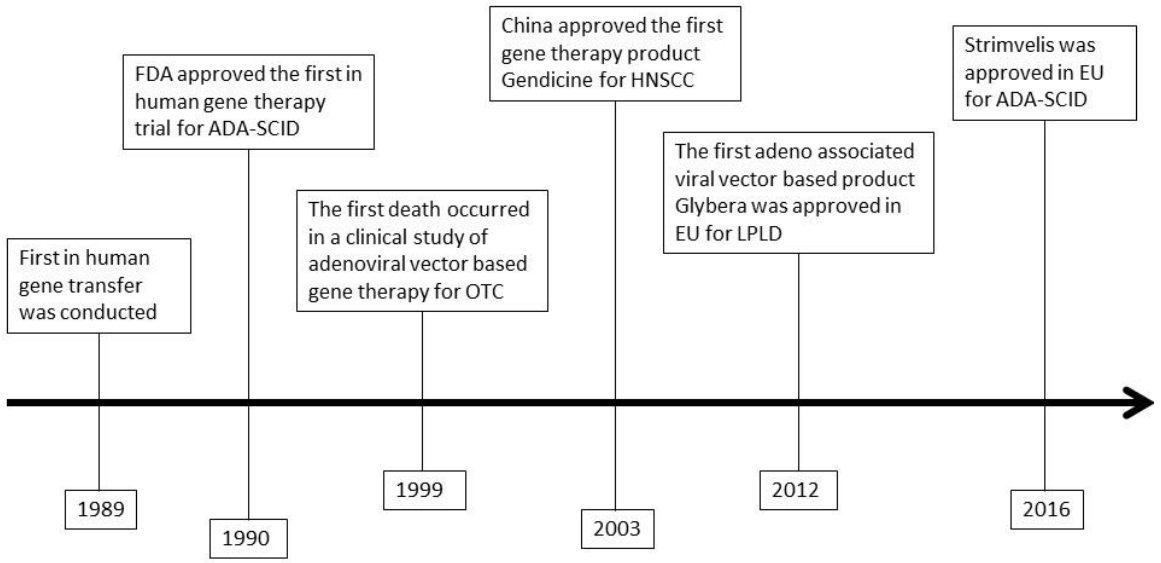
Company	Product type	Key Partner (s)
Agilis Biotherapeutics	AAV	Intrexon
American Gene Technologies International Inc.	Lentiviral	
Asklepios BioPharmaceutical, Inc.	AAV	
AVROBIO	Lentiviral	Baxter, Pfizer
B-MoGen	Transposon	
Calimmune, Inc.	Lentiviral, nonviral	
Caribou Biosciences	Genome editing	Intellia, Novartis
Casebia Therapeutics	Genome editing	Bayer, CRISPR Therapeutics
Errant Gene Therapeutics	Lentiviral	
Freeline Therapeutics	AAV	
Généthon	AAV, lentiviral	Audentes
Hemera Biosciences	AAV	
Homology medicines	AAV	
Horama SAS	AAV	
Juventas Therapeutics	Nonviral	
MeiraGTx Limited	AAV	
Milo Biotechnology	AAV	
Orchard Therapeutics	Lentiviral	Oxford BioMedica
Poseida Therapeutics	Transposon	
Precision Biosciences	Genome editing	
Rocket Pharmaceuticals Ltd	AAV, lentiviral	MolMed
Solid Biosciences	AAV	
Synpromics	Promoter optimization	GE Healthcare, AGTC, uniQure, Adverum
Transposagen Biopharmaceuticals, Inc.	Transposon, genome editing	
Universal Cells Inc.	AAV, genome editing	
Vivet therapeutics	AAV	
4D Molecular Therapeutics	AAV	Pfizer, Roche, AGTC, uniQure, Benitec

Source: Company reports, Raymond James research

A Brief History of Gene Therapy: More Than Two Decades of Ups and Downs

Mounting evidence from animal models suggests that gene therapy can be used to prevent, alleviate, or cure underlying diseases including certain cancers, infectious diseases, and genetic and autoimmune disorders. However, its translation into humans has been met with a mixture of encouraging and disappointing results, as well as some major setbacks (Exhibit 4).

Exhibit 4: **Key Landmarks of Gene Therapy**



Source: Raymond James research

The first in human clinical studies of gene therapy were conducted in 1990, in which ex vivo gene transfer to umbilical cord blood cells or to autologous T lymphocytes were evaluated in children with severe combined immune deficiency (SCID) caused by mutations in the adenosine deaminase (ADA) gene. At the time, only limited efficiency of transduction and durability were observed due to the inherent drawbacks associated with a murine retroviral vector based delivery system.

In the late 1990s, better gene transfer protocols and vectors were developed, and numerous successful treatments in small and large animal models of human diseases were reported. However, immune responses and insertional mutagenesis issues emerged as the main hurdles for gene therapy. In 1999, a Phase I dose-escalating study of a second generation adenoviral vector containing the ornithine transcarbamylase (OTC) gene was conducted. A boy with partial OTC developed a rapid and severe immune response to the intravenously delivered adenoviral vector and died two days after the treatment. The death of 18-year-old Jesse Gelsinger overshadowed the progress in the field for close to a decade, although in the background, academic groups continued to make advances.

In 2000, studies of ex vivo retroviral gene transfer of the γc-chain (common to several cytokine receptors) to autologous hematopoietic stem cells (HSCs) demonstrated two (10%) partial and 17 (85%) complete cures of 20 treated patients with X-linked SCID, a significantly better clinical outcome than that achieved by the standard treatment of allogeneic bone marrow transplantation. Unfortunately, five (25%) patients developed leukemia and one death occurred due to a subsequent oncogene activation as a result of non-specific viral integration.

Despite the setbacks, the field continued to advance with the development of even newer vectors and gene transfer methods. A significant milestone was achieved in 2003 when the first gene therapy product, Gendicine, was approved by the Chinese FDA (CFDA) for the treatment of head and neck squamous-cell carcinoma (HNSCC) in combination with radiotherapy (Exhibit 5). Gendicine, a replication-defective recombinant adenovirus vector containing the human p53 tumor suppressor gene, was evaluated in a Phase II and a Phase III study demonstrating that Gendicine combined with radiotherapy achieved a 64% complete response (CR) rate (n=56) as compared to a 19% CR rate in the radiotherapy arm (n=63) in patients with late-stage HNSCC. Since its commercial launch in 2004, Gendicine has treated more than 5,000 HNSCC patients (by 2007) as well as been used in off-label settings for liver, lung, gastric, and other cancers with late or terminal stage. To our knowledge, this product is not approved anywhere else in the world.

Subsequently, the first approval of an AAV (adeno-associated virus) based gene therapy was marked by Glybera (developed by UniQure and approved in the EU in 2012), an adeno-associated virus 1 (AAV1) encoding a functional lipoprotein lipase (LPL) gene, for the treatment of familial lipoprotein lipase deficiency (LPLD), an inherited genetic disease. The efficacy and safety of Glybera were evaluated in three studies, in which Glybera demonstrated clinically meaningful benefits for patients with LPLD. Moreover, in a retrospective study of the 22 LPLD patients treated with Glybera, a decreased incidence of pancreatitis was achieved (17/22 or 77% of patients). However, since its commercial launch, only one patient has been treated by Glybera. Due to the lackluster sales and the ultra-rare prevalence of LPLD (approximately one in a million), UniQure recently withdrew Glybera in Europe.

Another gene therapy product, Strimvelis (GSK2696273), was recently approved in the EU (May 2016) for the treatment of ADA-SCID, an ultra-rare disease that affects approximately 15 newborns in Europe each year. Strimvelis is an ex vivo gene therapy based on a retroviral vector mediated gene transfer of ADA into autologous HSCs. The approval of Strimvelis was based on multiple studies including a Phase I/II pivotal study conducted between 2002 and 2012, in which 18 patients with ADA-SCID were treated. Results show that 100% of patients survived during a median seven-year follow-up period. In addition, the ADA transgene was found to be expressed in multiple hematopoietic lineages, including lymphocytes and red blood cells, thereby leading to a systemic restoration of immune function. Importantly, among the 19 evaluable patients who received Strimvelis in all studies combined, 15 of them no longer required ADA enzyme replacement therapy (ERT), which translated into a 79% intervention-free survival rate during a four-year follow-up period. While Strimvelis, which has a one-time price tag of $665,000, is efficacious, this gene therapy is still in the early stage of its commercial launch. According to Reuters (link), the first commercial patient was treated in March 2017, with a second patient treated later and two more lined up for the treatment as of July 2017.

Exhibit 5: **Approved Gene Therapy Products**

Product	Company	MOA	Indication	Year of Approval	Region of Approval
Gendicine	Sibiono GeneTech	Delivery of P53 by adenovirus	HNSCC	2003	China
Glybera	UniQure	In vivo AAV gene therapy	LPLD	2012	EU
Strimvelis	GSK	Ex vivo stem cell gene therapy	ADA-SCID	2016	EU

Source: Raymond James research

Recent Clinical Successes/Setbacks

Besides these approvals, compelling clinical data has also been generated in multiple other indications. Notable clinical results seen to date are discussed below.

RPE-65 Mediated IRDs: The First U.S. Gene Therapy Is on the Horizon
(see our Spark IOC on page 135 for more detail)

Spark's LUXTURNA (voretigene neparvovec), which utilizes a recombinant AAV2 vector to deliver a functional RPE65 gene, has been evaluated in three clinical trials for RPE65 mediated IRDs, with all demonstrating compelling results. Notably, the registration-directed, controlled Phase III study met the primary endpoint among the intent to treat (ITT) population, a statistically significant vision improvement seen in the treatment group as compared to the control group (p = 0.001). Given the clinical results, in our opinion, LUXTURNA is likely to be approved, with a PDUFA date of January 12, 2018.

Hemophilia: Multiple Gene Therapy Companies Love This Space and Have Generated Compelling Hemophilia Results (see our Spark IOC on page 135 for more detail)

With respect to hemophilia A, both BioMarin's BMN-270 and Spark's SPK-8011 have generated promising clinical data. In July 2017, BioMarin reported updated 52-week data for the first seven patients who received BMN-270 ($6x10^{13}$ vg/kg) as well as the initial 24-week data for patients who received a lower dose ($4x10^{13}$ vg/kg). As of the data cutoff in May 2017, BMN-270 ($6x10^{13}$ vg/kg) achieved a 97% reduction in annualized bleeding rate (ABR) in six patients who received prophylaxis factor treatment before the study. More importantly, mean factor VIII (FVIII) levels among treated patients were 104%, with most patients in the normal range (50-150%) and one patient at 218%. To put the data into context, the normal FVIII activity levels range from 50% to 150%, and when the factor VIII activity level is ≥ 12%, the number of annual joint bleeds is nearly zero. In August 2017, the company provided updated data from the $4x10^{13}$ vg/kg dose cohort, which demonstrated that the factor VIII activity levels continued to increase over time, with the mean value changing from 5% at four weeks to 31% at 20 weeks and to 51% at 32 weeks.

While early, Spark's SPK-8011 has also generated intriguing results. In early August, 2017, Spark provided the first results from the ongoing Phase I/II dose-escalation study evaluating SPK-8011. As of the August 1, 2017, data cutoff, three patients had received a single injection of the gene therapy, with the first two treated at an initial dose level of 5×10^{11} vg/kg and the third at a second dose level of 1×10^{12} vg/kg. Notably, the first two patients had been followed for 23 and 12 weeks, with both achieving stable factor VIII activity of 11% and 14% of the normal levels (both appeared to have plateaued), respectively. While the third patient had not been followed long enough, management indicated that this patient's factor activity level was tracking proportionally higher but had plateaued. Specifically, the factor activity for the third patient at the early stage was slightly higher than 2x of that seen for the first two patients at the same time period. Therefore, we believe the third patient could eventually achieve stable factor VIII activity of approximately 22-30%.

In the hemophilia B world, Spark's 9001, which is licensed to Pfizer, has also delivered promising results. In a Phase I/II study, 10 hemophilia B patients were treated with one single IV injection of SPK-9001. Notably, all treated patients achieved a steady-state factor IX (FIX) level 12 weeks after treatment, with a mean factor IX (FIX) level of 33% (14% to 81%), which translated into a 96% and 99% decrease in ABR and AIR, respectively. More importantly, these improvements were maintained at a longer follow-up (five patients had been followed for ≥ 12 months).

Parkinson's Disease: A Unique Option Is in the Making

(see our Voyage IOC on page 182 for more detail)

Voyager's VY-AADC01, which utilizes an AAV2 vector to deliver a functional copy of the aromatic amino acid decarboxylase (AADC) gene, has generated promising results in patients with advanced Parkinson's disease. Based on our analysis of the clinical results, we believe VY-AADC01 appears to be an active drug with a good safety profile, having achieved dose and time dependent improvements on multiple endpoints including the diary on- and off-time, the Unified Parkinson Disease Rating Scale (UPDRS) scores, and the reductions in the doses of oral medications (e.g., levodopa). For example, the average increase in diary on-time without troublesome dyskinesia achieved in one dose cohort (n=5) was 2.2 hours at six months and 3.3 hours at 12 months, both of which were greater than those seen in a lower dose cohort at the same time points. In addition, an approximately 55% reduction (reduction is improvement) in the UPDRS-III on-medication scores were seen in two high-dose cohorts at either six months or 12 months, whereas there were no improvements over the course of 24 months seen in lower dose cohort. The activities of daily living as measured by the UPDRS-II scores also improved in both high dose cohorts at either six months or 12 months.

Spinal Muscular Atrophy: A Better Choice May Be Coming

Spinal muscular atrophy (SMA) is a hereditary orphan disease caused by mutations in the SMN1 gene leading to motor neuron loss, progressive weakness, and infant death. Type I SMA is the most severe form of the disease, with onset within six months of age, as well as a 75%, 50%, 25% and <10% survival rate at 8.1, 10.5, 13.6 and 24 months, respectively. In addition, babies with Type I SMA will never be able to sit, crawl, and walk without support, and usually have difficulty in breathing and swallowing (thus most likely will require a ventilator).

AveXis is developing a gene therapy product (AVXS-101) that consists of a functional copy of the SMN1 gene and a recombinant AAV9 vector delivered through an intravenous injection into a peripheral limb vein. In a Phase I study of AVXS-101 in 12 patients with Type I SMA, all treated patients were alive and event-free at an age of 20 months. By way of comparison, Biogen's SPINRAZA, which has been approved for SMA, demonstrated a survival rate of 77% at six months among 52 patients in a pivotal study. In terms of the manifestation of motor neuron functions, 92% (11/12) of patients achieved head control and sitting with support, and 83% (10/12) were able to sit unassisted (75% (9/12) being able to sit unassisted for more than 30 seconds). In addition, 67% of these babies were able to speak. In terms of safety, AVXS-101 appeared to be well tolerated, with clinically asymptomatic liver enzyme elevation seen, which was able to be managed with an immunosuppression regimen (prednisolone).

β-thalassemia and Sickle Cell Disease: Killing Two Birds With One Stone?

β-thalassemia is a hereditary blood disease caused by mutations in the β-globin gene, leading to the production of defective red blood cells (RBCs) that are lacking hemoglobin A. Specifically, mutations in the β-globin gene can result in either a non (β0) or decreased (β+) functional β-globin. For patients with transfusion dependent thalassemia (TDT) who require constant transfusions to correct their severe anemia status, most have the β0/β0 genotype. Similar to the etiology of β-thalassemia, sickle cell disease (SCD) is a hereditary blood disorder resulting from a mutation in the β-globin gene, which leads to an abnormal red blood cell function.

bluebird bio is developing an ex vivo gene therapy (LentiGlobin) where a functional copy of the β-globin gene is introduced to a patient's own hematopoietic stem cells (HSCs) through a lentiviral vector mediated gene transduction. Currently, the company is conducting four clinical trials (Northstar/HGB-204, HGB-205, HGB-206, and Northstar-2/HGB-207) evaluating the safety and efficacy profile of LentiGlobin in patients with TDT and SCD.

TDT

The Northstar study (fully enrolled) is a single-dose, open-label, non-randomized, multi-center Phase I/II trial of LentiGlobin in patients with TDT (eight with a β0/β0 genotype, 10 with a non- β0/β0 genotype). As of the data cutoff in September 2016, no transfusion was needed in five patients with a non β0/β0 genotype who had been followed for 12 months. In addition, the median βA-T87Q (the therapeutic β globin) level was 11.7 g/dL, which was higher than 2.0 g/dL as the pre-specified efficacy endpoint. In regard to patients with a β0/β0 genotype who had been followed for at least 12 months, a median reduction of 63% and 65% in annualized transfusion volume and frequency were achieved, respectively. Finally, a correlation between the viral copy number (VCN) and βA-T87Q production was observed. On the safety front, LentiGlobin demonstrated a comparable safety profile to autologous transplantation, with no drug related >=G3 adverse events seen to date.

The HGB-205 study is a single-dose, open-label, non-randomized, Phase I/II trial assessing the safety and efficacy of LentiGlobin in up to seven patients with TDT or severe SCD. As of the data cut-off in September 2016, four TDT patients treated with LentiGlobin were followed between 11.6 and 33.5 months, with none of them requiring a transfusion for 33.1, 29.9, 11.5, and 11.6 months, respectively. In terms of safety, LentiGlobin was well tolerated with no observed drug related adverse events.

Given the favorable safety and efficacy profile seen to date with LentiGlobin in patients with TDT, the company is conducting a single-dose, open-label, non-randomized, multi-center Phase III (Northstar-2) trial to evaluate this gene therapy in patients with non-β0/β0 TDT. As of June 2017, the study has treated three patients, for whom a comparable or better level of VCN and βA-T87Q were achieved than those seen in the Northstar study. In terms of safety, no LentiGlobin-related AEs were reported during a two- to six-month follow-up period. In addition to the ongoing Northstar-2 study, bluebird bio plans to initiate a Phase III study (Nightstar-3) of LentiGlobin in patients with β0/β0 TDT by YE17.

SCD

As of the data cutoff in September 2016, one patient with severe SCD was treated with LentiGlobin and followed for 22.9 months in the HGB-205 Phase I/II study. Efficacy-wise, over 48% of anti-sickling hemoglobin was achieved among all hemoglobin production at 21 months after treatment, which was higher than the 30% disease modifying threshold level. Additionally, no blood transfusion was needed for more than 18 months as well as no hospitalization or SCD-related events recorded. On the safety front, LentiGlobin was well tolerated with no drug related AEs.

In another a single-dose, open-label, non-randomized, multi-center Phase I clinical study of LentiGlobin in patients with severe SCD, seven patients were treated as of the data cutoff in September 2016. A range of 0.1 – 2.0 g/dL of βA-T87Q globin was seen among these treated patients. The safety profile in the infused subjects in the HGB-206 study is consistent with autologous transplantation. As of the data cutoff date, 10 Grade 3 bone marrow harvest-related AEs were seen in three patients, including one severe AE. In addition, at least one SAE was seen in six patients after LentiGlobin infusion. There were no drug related AEs.

Cerebral Adrenoleukodystrophy (CALD): Another bluebird bio Goal

CALD is an ultra-orphan, monogenic, neurological disease caused by mutations in the ABCD1 gene, which result in an accumulation of long chain fatty acids that leads to cerebral inflammation and demyelination. bluebird bio is developing an ex vivo gene therapy (Lenti-D) where a functional copy of the ABCD1 gene is introduced to a patient's own hematopoietic stem cells (HSCs) through a lentiviral vector mediated gene transduction.

In a single-dose, open-label, non-randomized, multi-center Phase II/III study (Starbeam/ALD-102) evaluating the safety and efficacy of Lenti-D in patients with CALD, Lenti-D demonstrated a promising efficacy profile as evidenced by a stabilization or improvement in a range of neurological measurements. As of the data cutoff in March 2016, 94% (16/17) of patients achieved a stabilization in the neurologic function score (NFS, change of <3 points and an absolute NFS≤4), while 82% (14/17) of patients had a stable Loes score (a measure of the extent of demyelination). In addition, 94% (16/17) of patients achieved a resolution of gadolinium enhancement by six months after treatment, with reemergence of diffuse contrast enhancement seen in 30% (5/17) of patients. On the safety front, the safety profile of Lenti-D appeared to be consistent with myeloablative conditioning with one possibly drug-related SAE (Grade 3 BK-mediated viral cystitis) as well as one possibly drug-related AE (Grade 1 tachycardia), both of which resolved with standard measures. As of the most recent update, 88% (15/17) of treated patients were alive and with no major functional disabilities (MFD) at a 24-months follow-up period, which compares favorably with a pre-determined efficacy benchmark of a 76% MFD-free survival rate.

Recent Clinical Failures

Like many other breakthrough technologies, gene therapy has also experienced its share of significant setbacks, including the aforementioned deaths seen in the clinical trials conducted in the late 1990s as well as disappointing results in recent clinical efforts.

Wet AMD Was Not Easy

Two companies have previously tried to develop gene therapy for wet AMD, including Avalanche (Annapurna reverse-merged into Avalanche, forming Adverum) and Genzyme (acquired by Sanofi). Unfortunately, both Avalanche's and Genzyme's product candidates failed to demonstrate a statistically significant benefit.

Avalanche's AVA-101, made of a wild type AAV2 vector that contained a gene expressing soluble Flt-1 (a naturally occurring anti-VEGF protein), was once evaluated in a single-center (Australia), open-label Phase I/IIa study (NCT01494805). While AVA-101 was safe without related SAEs, the gene therapy did not achieve encouraging efficacy results. Over the course of 52 weeks, the mean BCVA change from baseline for the treatment group (n=21) was 2.2 letters vs. -9.3 letters for the control group (n=11). While the difference in the mean BCVA changes from the baseline between the two groups was statistically significant, the BCVA improvements achieved by AVA-101 appear to be relatively inferior to what have been reported for the monthly treatment of Lucentis in many other studies (12-month mean BCVA change: 2.2 letters vs 6.3-11.0 letter). In addition, it did not appear that the gene therapy significantly reduced the number of Lucentis rescue injections, with the median number of rescue injections being two (range: one to six) for the treatment group and four (range: three to five) for the control group. In terms of the impact on central retinal thickness, the treatment group performed worse than the control group, as evidenced by an increase of 25 mm in retinal thickness from baseline in the treatment group vs. a reduction of 56 mm in the control group. Avalanche eventually concluded that there was no evidence of a complete and/or durable anti-VEGF response in the majority of patients treated with AVA-101, leading to an ultimate decision not to initiate the planned Phase IIb trial to further evaluate this gene therapy for wet AMD.

Genzyme's GZ402663 (AAV2-sFLT-01), which utilized an AAV-2 vector that expresses a modified soluble Flt1 receptor, originated from the collaboration established between Genzyme and Applied Genetic Technologies (AGTC) in December 2004. Following the acquisition of Genzyme, Sanofi took over the development of this gene therapy for wet AMD. Due to a lack of efficacy, in April 2015, Sanofi decided not to further develop GZ402663. GZ402663 was once evaluated in an open-label, dose-escalating Phase I study (NCT01024998) at four outpatient retinal clinics in the U.S. A total of 19 wet AMD patients were enrolled into five cohorts and received a single intravitreal injection of GZ402663 into one eye at different doses: cohort 1 - $2x10^8$ vg (n=3), cohort 2 - $2x10^9$ vg (n=3), cohort 3 - $6x10^9$ vg (n=3), cohort 4 - $2x10^{10}$ vg

(n=3), and cohort 5 - $2x10^{10}$ vg (n=7). On the safety front, GZ402663 appeared to be safe and well tolerated, with no systemic adverse events associated with the injection of the gene therapy. In terms of efficacy, overall, the gene therapy even at the highest dose did not improve the BCVA score significantly, although improvements were seen in some patients during certain time periods. For example, the 10 patients in cohorts 4 and 5 achieved a slight improvement in the mean BCVA from baseline to week 8, which declined afterwards, resulting in an eventual reduction in the mean BCVA score at week 52.

Alpha-1 Antitrypsin (A1AT) Deficiency Was Also Tough

Applied Genetic Technologies Corporation (AGTC) once evaluated a gene therapy product (rAAV1-CB-hAAT, or AGTC-0106), which utilized a recombinant AAV1 vector to deliver the human A1AT gene, for A1AT deficiency. AGTC conducted a Phase II study (NCT01054339) evaluating rAAV1-CB-hAAT in three dosing cohorts (6×10^{11}, 1.9×10^{12}, or 6×10^{12} vg /kg, n=3 for each). Of note, these patients received multiple intramuscular injections distributed across a single or multiple muscle sites on a single occasion. Dose-dependent expression of serum A1AT was observed, with the highest dose cohort achieving a mean expression level of 0.572 µM on day 30, which then declined to 0.24 µM on day 90 with little change thereafter. None of these patients had serum A1AT levels of >1 µM over the course of study. Recall, the therapeutic threshold of serum A1AT levels is 11 µM, which is far from being reached by this gene therapy. While no one developed antibodies against the A1AT proteins, all patients developed anti-AAV antibodies as well as interferon-ɣ enzyme-linked immunospot responses to the AAV peptides. On the safety front, AGTC-0106 appeared to be safe, with no serious adverse events reported.

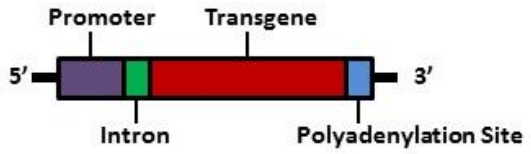
The Bottom Line: Not All Gene Therapy Products Are Created the Same

While the concept of gene therapy sounds easy, in reality, there are several important pieces that must all come together including the vector, the transgene, and the route of administration. Therefore, in our view, the success or failure of one product in one indication does not necessarily mean that other products are slated to the same fate. Specifically, the failures in wet AMD and A1AT deficiency do not preclude the possibility that the newer generation products developed by other companies may eventually generate significantly better clinical results.

Let's Get Technical: A Closer Look at the Backbone of Gene Therapy

Gene therapy can be classified into three broad categories: 1) gene addition; 2) gene correction/alteration; and 3) gene knockdown. Most of the time, the gene of interest is administered within an expression cassette that consists of a cDNA or genomic DNA (where introns are included) flanked by a promoter on the 5' side and a transcription stop codon on the 3' polyadenylation side (Exhibit 6). Importantly, choosing the appropriate promoter to drive the expression of the transgene could have an impact on the efficiency of the therapeutic response. For example, disease or tissue specific promoters are usually preferred over universal (such as CMV) promoters in order to obtain targeted transcription of the therapeutic gene. Moreover, expression levels of the therapeutic gene can be further improved by fusing an enhancer into the tissue-specific promoter sequence, resulting in more powerful hybrid promoters.

Exhibit 6: **General Format of an Expression Cassette**



Source: Raymond James research

In order for the gene to express at the proper site, the expression cassette needs to reach the relevant cells within the targeted organ and traffic through the plasma membrane and cytoplasm before entering the nucleus. To accomplish this, a slew of vectors capable of packaging and delivering the expression cassette have been created, with significant improvement of clinical results observed due to the continuous advances in vector technologies.

That said, four main technical hurdles emerged as clinical studies have proceeded (Exhibit 7):

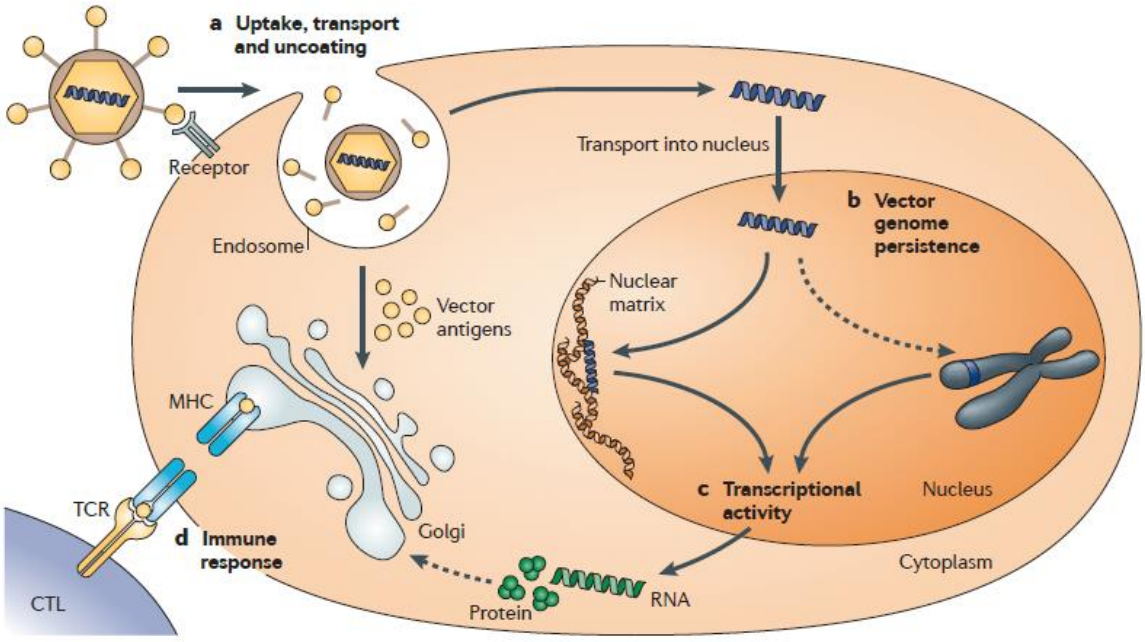
1) Vector uptake, transport, and uncoating when administered into the human body. The interaction between the vector and a variety of host specific factors such as the cell receptor, endothelial barrier, and nuclear membrane all impact the final destination of the vector;

2) Vector persistence. Whether the transgene is integrated into the host chromosome or not (e.g., episomal form) as well as the turnover of the target tissues (quiescent or active) all appear to contribute to vector persistence (see Exhibit 8 for the turnover rate of different tissues);

3) Sustained transcriptional expression. Epigenetic modification to the vector genome appears to be the main culprit for the silencing of transgene expression once integrated in the host genome; and

4) Host immune response. Activation of host immune response against either the vector particle or transgene product remains a major reason for the lack of efficacy of gene therapy.

Exhibit 7: **The Four Barriers to Successful Gene Therapy**



Source: Nature Reviews Genetics; 2011 May;12(5):316-28; State-of-the-art gene-based therapies: the road ahead; Kay MA; https://www.ncbi.nlm.nih.gov/pubmed/21468099

Exhibit 8: **Tissue Turnover Rate**

Cell type	Turnover time
Small intestine epithelium	2 - 4 days
Stomach	2 - 9 days
Blood neutrophils	1 - 5 days
White blood cells eosinophils	2 - 5 days
Gastrointestinal colon crypt cells	3 - 4 days
Cervis	6 days
Lungs alveoli	8 days
Tongue taste buds (rat)	10 days
Platelets	10 days
Bone osteoclasts	2 weeks
Intestine paneth cells	20 days
Skin epidermis cells	10 - 30 days
Pancreas beta cells (rat)	20 - 50 days
B cells (mouse)	4 - 7 weeks
Trachea	1 - 2 months
Hematopoietic stem cells	2 months
Sperm	2 months
Bone osteoblasts	3 months
Red blood cells	4 months
Liver hepatocyte cells	0.5 - 1 year
Fat cells	8 years
Cardiomyocytes	0.5-10% per year
Skeleton	10% per year
Central nervous system	Life time
Lens cells	Life time
Oocytes	Life time

Source: Raymond James research

Therefore, the characteristics of an ideal vector which are able to confer the potential to overcome these hurdles include high specificity, low virulence and immunogenicity, high genome persistence, and its ability to completely unload the functional human gene into the host cells. To accomplish this, non-viral and viral gene-transfer vectors have been developed (Exhibit 9).

While viral vectors are more efficient in transferring the engineered gene of interest, they carry a risk of causing toxicities associated with the host's immune defense mechanism or insertional mutagenesis into the host genome. To overcome this issue, a viral vector that could achieve a persistent expression while minimizing the incidence of insertional mutagenesis was evaluated - the adeno-associated virus (AAV) vector. AAV vectors deliver the expression cassette with the therapeutic gene of interest to the nucleus where the transgene functions in an episomal form (outside the host genome). This strategy is effective as long as the target cell does not proliferate, therefore avoiding the potential dilution of the construct over time.

To completely avoid the insertional mutagenesis and potential for immune toxicity, non-viral vectors have been developed with the hopes of being cheaper, safer, and capable of delivering large amounts of DNA into host cells. Nonetheless, one drawback of non-viral vectors is the low rate of transfection due to a variety of the aforementioned host barriers.

Exhibit 9: **Major Attributes of Gene Transfer Vectors**

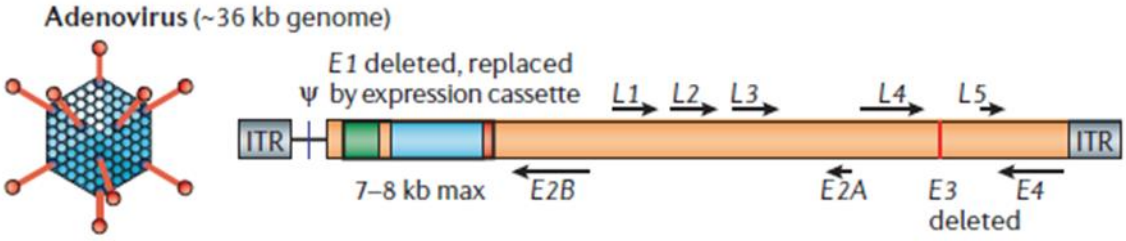
	Non-viral	Adenovirus	AAV	Retrovirus	lentivirus
Genome integration	No	No	Mostly no	Yes	Yes
Insertional mutagenesis	No	No	No	Yes	Yes
Immunogenicity	None/low	High	Low	Low	Low
Capacity	Flexible	8 – 36 kb	4.5 kb	Up to 10 kb	Up to 10 kb
Expression persistency	Days or weeks	Days	Months to Life-long	Life-long	Life-long

Source: Raymond James research

Adenoviral Vector

Adenoviral vectors were the first gene-transfer vectors used in the in vivo setting to treat hereditary disorders. The building block of an adenoviral vector is the double-stranded DNA (dsDNA) adenovirus, which consists of a 34–36 kb genome encoding the early (E1, E2, E3, E4, and E5) and late (L1, L2, L3, L4, and L5) genes flanked by two inverted terminal repeats (ITRs) (Exhibit 10). There are more than 51 different serotypes of adenovirus found in humans, among which adenovirus 5 (AD5 or serotype 5) is the most prevalent form, with 45–80% of the population have neutralizing antibodies against this serotype. Each adenovirus binds to target cells through epitopes in its penton and fibre bases. Therefore, modifications of vector specificity and improvement of transfer efficiency can be achieved through changing the sequences of these epitopes. Importantly, once getting into the nucleus, the adenovirus genome largely remains in an episomal form, which minimizes the risk of insertional mutagenesis.

Exhibit 10: **Adenoviral Vector Construct**



Source: Nature Reviews Genetics; 2006 Apr;7(4):261-76; O'Connor TP, Crystal RG; Genetic medicines: treatment strategies for hereditary disorders; https://www.ncbi.nlm.nih.gov/pubmed/16543931

The first-generation adenoviral vector retained many wild-type viral genes, with only the E3 master gene being deleted and E1 unit replaced with a transgene construct of up to 7.5 kb (Exhibit 10). However, this type of vector resulted in significant toxicity given the expression of other adenoviral associated genes that remained. As the field advanced, an adenoviral vector with both the E1 and E4 genes being

selectively deleted resulted in lower immune responses against the virus. In addition, so called "gutless" adenoviral vectors have been created by deleting all the viral genes, which enables a large carrying capacity of more than 30 kb.

Although adenoviral vectors were the first to achieve high levels of systemic gene transfer into many tissues in animal models, the therapeutic benefit was mostly transient (days to weeks). In addition, when delivered systemically in humans, adenoviral vectors induced severe toxicity at dose levels that were required for efficacy. Toxicities induced by adenoviral vectors were largely derived from an immediate innate immune response and an adaptive (specifically, antigen-dependent) response. As mentioned earlier, the first death from a gene therapy procedure was found largely due to the host immune responses against the intravenously administered adenovirus vectors. Separately, in a Phase I study for patients with severe hemophilia A, the intravenous delivery of an adenovirus vector encoding the Factor VIII (FVIII) protein caused transient thrombocytopenia and transaminase elevation, which led to the trial being halted. Net-net, due to the highly immunogenic nature and associated high risks to induce toxicities, adenoviral vectors have largely been substituted by adeno-associated viral vectors for the development of in vivo gene therapies.

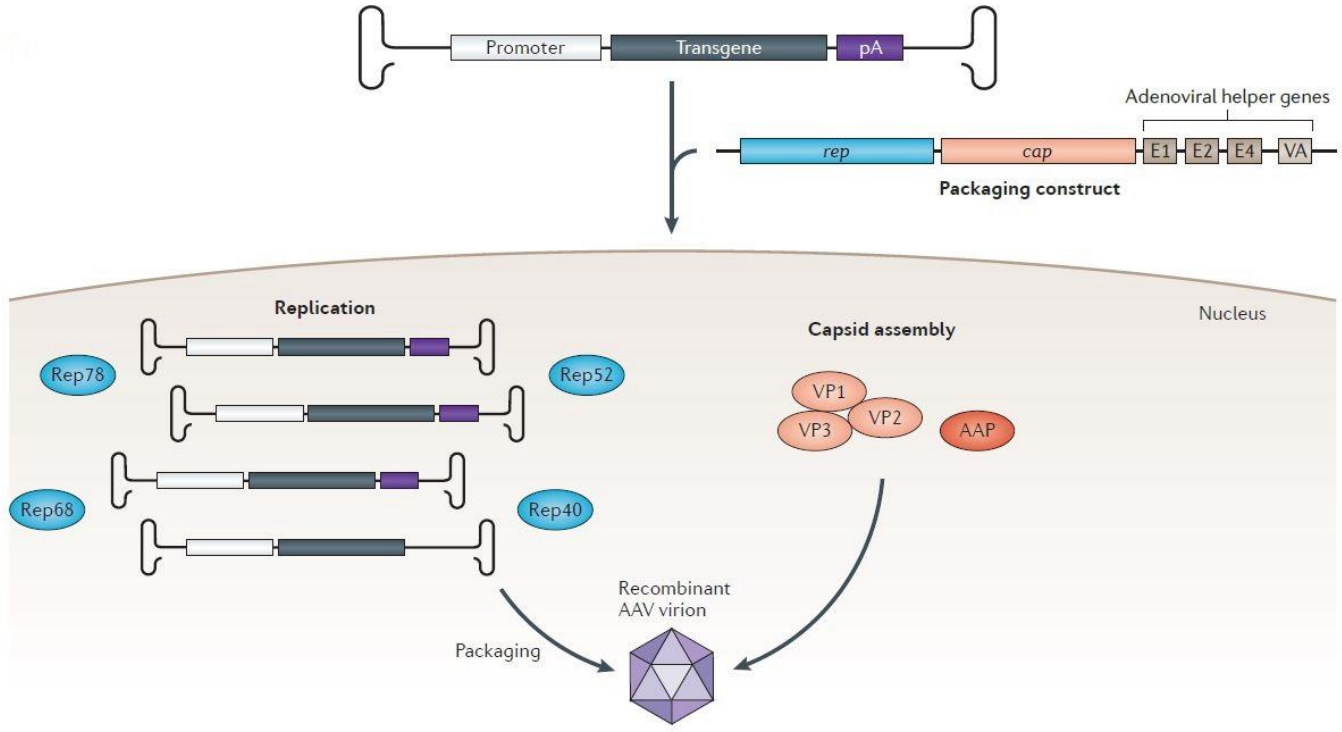
That said, targeted delivery of adenoviral vectors could potentially minimize immune responses due to a limited exposure of viral antigens relative to systemic delivery. For example, Generx (alferminogene tadenovec), originally developed by Cardium Therapeutics, is a replication-deficient human adenovirus serotype 5 (Ad5) that encodes the human FGF4, an angiogenic protein capable of enhancing the formation of new blood vessels. In four Phase I-III studies (AGENT-1, 2, 3, and 4) in over 650 patients with refractory angina, Generx administered through antegrade intracoronary delivery demonstrated a favorable safety profile in a follow-up period between 23 and 50 months. More importantly, in a pooled analysis of the two Phase IIb/III studies (AGENT 3/4) in 532 patients, Generx achieved a statistically significant improvement in treadmill exercise capacity in female patients as compared to the placebo, although a high placebo response occurred in male patients, which resulted in no significant improvement in terms of cardiac functional status in the whole patient population. On the back of a favorable safety and efficacy profile of Generx seen to date, a randomized, placebo-controlled Phase III study to evaluate Generx for refractory Angina caused by myocardial ischemia is expected to start at the end of 2017.

AAV Vector

Adeno-associated virus (AAV) is a helper dependent parvovirus composed of a 4.7 kb single-stranded DNA (ssDNA) genome with two open reading frames (ORFs), which function as the viral origin of replication and a packaging signal, flanked by ITRs (Exhibit 11). It is usually quiescent inside the cells (nonpathogenic) in the absence of a helper virus (such as the adenovirus). While the replication (Rep) ORF encodes non-structural proteins involved in viral replication, transcriptional regulation and genomic integration, the packaging (Cap) ORF encodes structural proteins that mediate and contribute to the assembly of the viral capsid. To generate a recombinant AAV vector, the therapeutic gene of interest is inserted between the ITRs to replace the Rep and Cap ORFs. In addition, the Rep and Cap are provided in trans (in separate constructs) along with helper viral genes to facilitate the vector production.

The resulting AAV vector is able to transduce both dividing and non-dividing cells, with the advantage to persistently express the transgene (episomal form) in organs where cells normally have a low turnover, including the liver, retina, brain, and heart. AAV vectors are one of the most favorable delivery vehicles for gene therapy largely due to two reasons: 1) the AAV genome contains no expressed genes; therefore, induction of host immunity against the vector is less problematic as compared to adenoviral vectors, except for induction of antibodies that are directed against the AAV capsid (as it flows through the blood stream); and 2) the genomic integration of recombinant AAV vectors occurs at a very low background frequency (0.1 - 0.5%), therefore minimizing the insertional mutagenesis risk with no reported genotoxicity to date. That said, in our opinion, the long-term risk of AAV vector based gene therapy for tumorigenesis in humans is still unknown.

Exhibit 11: **AAV Genome and Construct of AAV Vector**



Source: Nature Reviews Genetics; 2014 Jul;15(7):445-51; Kotterman MA, Schaffer DV; Engineering adeno-associated viruses for clinical gene therapy; https://www.ncbi.nlm.nih.gov/pubmed/24840552

There are more than 100 variants of AAV, with 13 characterized human or non-human primate serotypes. In regard to the practice of gene therapy, the serotype 2 genome (AAV2) is often used as the prototype for the design of viral vectors. Notably, some serotypes have considerable differences in tropism (tissue preference) relative to AAV2. Therefore, targeted delivery and improved transduction efficiency have been achieved by using AAV with different tropisms (Exhibit 12). That said, based on accumulating evidence seen to date, it appears that tropism of AAV vectors demonstrated in animal studies only has a limited correlation with the tropism observed in humans.

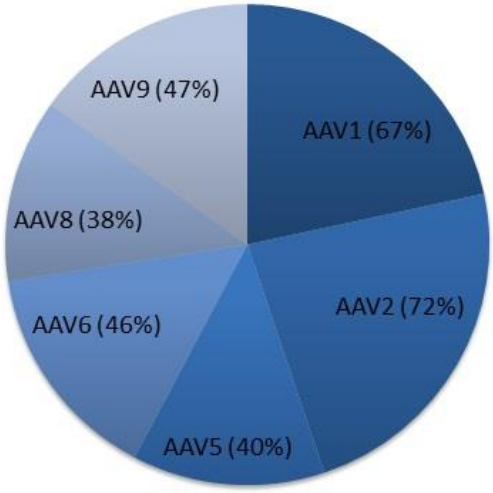
Exhibit 12: **The Origin and Tissue Tropism of AAV Isolates**

Viral serotype	Origin of species	Tissue tropism validation								
		Skeletal muscle	CNS	Retina	Airway	Liver	Heart	Pancreas	Kidney	Lung
AAV1	Human/NHP	murine, NHP, canine	murine, NHP	murine	murine, NHP	murine	murine, pig (cardiac)	murine		
AAV2	Human	murine	murine, monkey	human, NHP, murine canine		murine			murine	
AAV3	Human	murine								
AAV4	NHP		murine	murine, canine					murine	murine, NHP
AAV5	Human	murine	murine, canine	murine	murine	human				
AAV6	Human	murine, dog			murine, dog, NHP		murine, dog, sheep, pig			
AAV7	NHP	murine	murine	murine		murine				
AAV8	NHP	murine, canine, NHP	murine, canine, NHP	murine, canine		human, murine, NHP, canine	murine	murine	murine	
AAV9	Human	murine, canine	murine, NHP	murine, NHP		murine	murine, NHP, porcine, NHP	murine	murine	murine
AAVrh10	NHP	murine canine	murine, rat	murine		murine	murine	murine	murine	murine

Source: Raymond James research

That said, challenges of gene delivery using AAV vectors remain, including low packaging capacity (up to approximately 4.5 kb), limited tropism for certain cell types (such as neurons) and pre-existing (Exhibit 13) or acquired immunity toward viral vectors. To overcome these hurdles, vector engineering methods such as rational design and directed evolution were developed to help AAV break the constraints from natural phenotypes, potentially enabling them to acquire novel properties in terms of avoiding or minimizing immune responses and improving transduction efficiency.

Exhibit 13: **Prevalence of Pre-Existing Neutralizing Antibodies to Different AAV**



Source: Raymond James research

The first clinical application of AAV vectors for gene therapy occurred evaluating an AAV2 vector with a cDNA encoding the cystic fibrosis transmembrane-conductance regulator (CFTR) protein in patients with cystic fibrosis (CF). However, this study failed to achieve a clinically meaningful level of CFTR in the target cells for two main reasons: 1) to accommodate the 4.5 kb CFTR cDNA, which is the maximum size that can fit into AAV vectors, a short and weak promoter was used, which led to poor transcription efficiency; and 2) the limited specificity of AAV2 for human airway epithelium resulted in poor vector transduction to the targeted cells. As more clinical studies have been conducted, accumulating experience on AAV vectors have led to the better vector design, more rational selection of disease target, and thereby better clinical results. As summarized in Exhibit 14, currently numerous gene therapy trials are ongoing, with the majority targeting monogenic diseases, especially those that originate in the liver or eyes.

Exhibit 14: **Companies With AAV Vector Based *in vivo* Gene Therapy in Clinical Development**

Company	Product	Target/Transgene	AAV Vector	Promoter (specificity)	Indication	Current Status
Spark	LUXTURNA	RPE65	AAV2	CB (non-specific)	IRD with RPE65 mutation	PDUFA at 01/12/2018
	SPK-7001	CHM/REP-1			Choroideremia	Phase I/II
	SPK-9001	FIX Padua	rAAVx		Hemophilia B	Phase I/II
	SPK-8011	FVIII			Hemophilia A	Phase I/II
Abeona	ABO-102	SGSH	rAAV9	U1a	MPS IIIA	Phase I/II
	ABO-101	NAGLU	rAAV9		MPS IIIB	Phase I/II to start
Applied Genetic Technologies	rAAV2tYF-CB-hRS1	RS1	rAAV2	CB	XLRS	Phase I/II
	rAAV2tYF-PR1.7-hCNGB3	CNGB3	rAAV2	PR1.7 (cone)	ACHM	Phase I/II
Adverum	ADVM-043	M-type A1AT	AAVrh10		A1AT Deficiency	Phase I/II (4Q17)
Audentes	AT132	MTM1	AAV8	CB (non-specific)	XLMTM	Phase I/II
AveXis	AVXS-101	SMN1	AAV9		SMA Type 1	Phase III
Dimension	DTX301	OTC	AAV8		OTC Deficiency	Phase I/II
Regenxbio	RGX-314	Anti-VEGF Ab fragment	rAAV8		Wet AMD	Phase I
	RGX-501	LDLR	AAV8		HoFH	Phase I/II
Voyager	VY-AADC01	AADC	AAV2		Parkinson's Disease	Phase I
UniQure	AMT-060	FIX	AAV5		Hemophilia B	Phase I/II (completed)
Milo	AAV1-FS344	Follistatin	AAV1	CMV (non-specific	BMD and sIBM	Phase I
Nightstar Therapeutics	AAV2-REP1	REP1	AAV2		choroideremia	Phase II
	AAV-RPGR	RPGR			XLRP	Phase I/II
BioMarin	BMN 270	BDD-FVIII	AAV5		Hemophilia A	Phase III (4Q17)
Sangamo	SB-525*	FVIII			Hemophilia A	Phase I/II
Baxalta/Shire	BAX335	FIX Padua	AAV8		Hemophilia B	Phase I/II (completed)
GenSight	GS010	ND4	AAV2	Mitochondrial targeting sequence	LHON	Phase III
MeiraGTx	A00X	Aquaporin-1			Xerostomia	Phase I
	A001	RPE65			LCA	Phase I/II
	A002	CNGB3	AAV2/8		ACHM	Phase I/II
	A004	RPGR	AAV2/5		XLRP	Phase I/II
Hemera Biosciences	AAVCAGsCD59	sCD59	AAV2		Dry AMD	Phase I

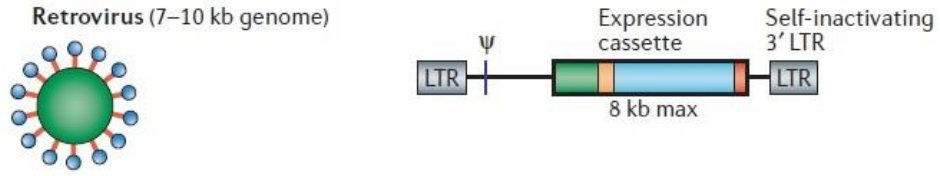
FVIII: factor VIII; FIX: factor IX. *Pfizer collaboration

Source: BiomedTracker, ClinicalTrials.gov, company reports, Raymond James research

Retroviral Vector

The genome of a retrovirus contains a 7 – 12 kb, single-stranded RNA which is transcribed into a DNA intermediate by an enzyme called reverse transcriptase upon host cell infection (Exhibit 15). The DNA intermediate functions as a provirus, which is subsequently incorporated into the host's genome by the integrase. Simple retroviruses, such as the onco-retrovirus, has a genome consisting of two long terminal repeats (LTRs) that flank four genes – gag, pro, pol, and env – which encode proteins that determine viral particle structures, particle maturation, provirus' host genome integration, and viral tropism, respectively. With regard to the design of a retroviral vector, viral protein-coding sequences in the RNA genome are replaced with an expression cassette of up to 8 kb. In general, retroviral vectors are designed to be self-inactivating by deletion of the enhancer and promoter regions in the 3' LTR to prevent LTR-driven transcription. In addition, the vectors are produced in packaging cells that provide the missing components (like viral particles) in trans.

Exhibit 15: **Retroviral Vector Construct**

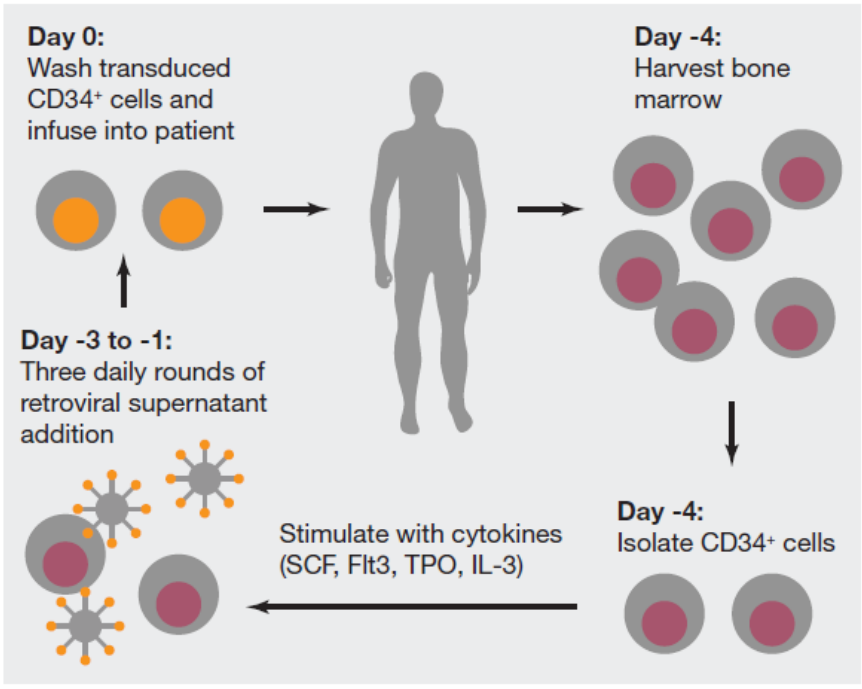


Source: Nature Reviews Genetics; 2006 Apr;7(4):261-76; O'Connor TP, Crystal RG; Genetic medicines: treatment strategies for hereditary disorders; https://www.ncbi.nlm.nih.gov/pubmed/16543931

One of the most extensively studied onco-retroviral vectors is derived from the moloney murine leukemia retrovirus (MMLV). MMLV vectors are the first vectors used in FDA approved clinical trials, which have undergone multiple modifications and are now collectively referred to as the retroviral vectors. Two inherent attributes render MMLV vectors the preferred choice of retroviral vectors: 1) the ease to replace the viral protein-coding sequence with the transgene cassette; and 2) the feasibility and convenience to pseudotype the envelope protein (with foreign viral envelop proteins), which allows for a vector entry into target cells. One key advantage of using retroviral vectors for gene delivery is their ability to integrate into host genome, therefore potentially targeting genetic diseases that require a permanent gene modification of target cells. However, a permanent genome integration can also lead to insertional mutagenesis, which in turn could lead to the development of a neoplasm. In addition, when delivered in vivo, retroviral vectors are difficult to concentrate in high titers due the vulnerability to complement activation (innate immunity).

Consequently, most clinical studies using retroviral vectors to treat hereditary disorders employ an ex vivo strategy to transfect either white blood cells or autologous hematopoietic stem cells (HSCs) to target hematological diseases. Importantly, a selective advantage of genetically modified, transplanted cells over the endogenous cells that express the abnormal genes is often required in most situations. One example is the aforementioned Strimvelis, which has been approved in the EU (2016) for the treatment of ADA-SCID. Strimvelis consists of a human ADA cDNA sequence loaded onto a retroviral vector with components from both the MMLV and moloney murine sarcoma virus (MMSV). CD34+ HSCs from patients with ADA-SCID are harvested and transduced with Strimvelis ex vivo, which are injected back to patients after vector transduction (Exhibit 16). As mentioned earlier, patients treated with Strimvelis achieved a 100% survival during a median follow up of seven years, with the vast majority of them not requiring enzyme replacement therapy (ERT) after the gene transfer treatment. Of note, patients with ADA-SCID only need as little as 5% of the ADA activity to reach a normal phenotype with genetically corrected cells likely bearing a selective advantage over the abnormal cells.

Exhibit 16: **Gene Therapy for "Bubble Boy" Disease**



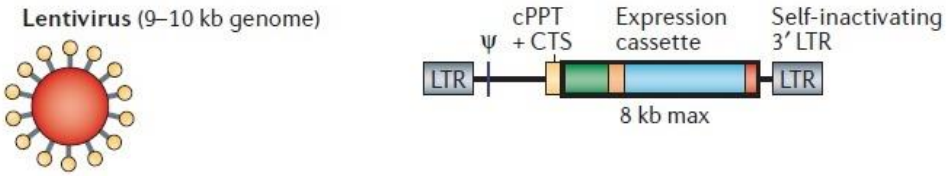
Source: Cell; 2016 Jul 14;166(2):263; Hoggatt J; Gene Therapy for "Bubble Boy" Disease; https://www.ncbi.nlm.nih.gov/pubmed/27419862

Lentiviral Vector

Lentivirus is a genus of retrovirus whose genome consists of an additional set of accessory genes (vif, vpr, vpu, nef), which are largely involved in viral replication and infection. The design of lentiviral vectors is similar to retroviral vectors, for which all viral protein-coding sequences are replaced with an expression cassette. Additionally, lentiviral vectors harbor two unique elements, the central polypurine tract (cPPT) and central termination sequence (CTS), whose function is to improve the nuclear import of proviral DNAs, which allows for a more efficient viral transduction as compared to retroviral vectors (Exhibit 17). Moreover, two additional properties render lentiviral vectors more efficient than retroviral vectors in terms of gene transfer, including: 1) the ability to transduce non-dividing cells; and 2) relative ease to be pseudotyped with the VSV-G (vesicular stomatitis virus G) envelope protein, which allows for a high concentrated titer. That said, similar to retroviral vectors, the risk of inducing insertional mutagenesis by lentiviral vectors has limited their clinical applications largely in the ex vivo setting.

One of the most prominent examples of the clinical application of lentiviral vectors is the creation of chimeric antigen receptor (CAR) through an ex vivo delivery of engineered gene constructs to human T cells. The resulting CAR-T cell resembles a hybrid of an antibody and T cell, which is able to directly recognize tumor cell surface antigens including proteins, glycoproteins, and glycolipids. To date, the most clinically validated and advanced CAR-T cell product candidate is the anti-CD19 CAR-T cells, which have demonstrated an impressive efficacy and safety profile in a variety of hematological malignancies, particularly in the hard to treat ALL and NHL.

Exhibit 17: **Retroviral Vector Construct**



Source: Nature Reviews Genetics; 2006 Apr;7(4):261-76; O'Connor TP, Crystal RG; Genetic medicines: treatment strategies for hereditary disorders; https://www.ncbi.nlm.nih.gov/pubmed/16543931

Genome Editing

With recent developments in whole-genome sequencing technologies, scientists are poised to deliver upon the promises of the genomic revolution. Editing, regulating, and targeting genomes using engineered nucleases has rapidly evolved from a powerful tool in biological research to something that could be used to treat illnesses in humans. In short, genome editing by nucleases enables investigators to manipulate virtually any gene in a wide variety of cell types and organisms. Although these nuclease technologies are yet to be fully characterized, targeted changes to genome sequences have the potential to transform research and stimulate the development of novel therapies for human genetic diseases. Currently, there are three public companies, including Intellia Therapeutics, Editas Medicine, and CRISPR Therapeutics, which are primarily focusing on the development of potentially curative genome editing treatments with early stage product candidates in their pipeline.

The core technology utilized in genome editing is based on the use of engineered nucleases, that is, artificial proteins composed of sequence-specific DNA-binding domains fused to a nuclease that non-specifically cleaves DNA. At its core, genome editing is a two-step process. The first crucial step for performing targeted editing is induction of DNA double strand-breaks (DSBs) into specific DNA sites. After the desired cut or cuts are made, the cellular DNA repair machinery responds to complete the edit through one of two possible mechanisms—non-homologous end joining (NHEJ) or homology-directed repair (HDR) pathways.

NHEJ

NHEJ-mediated repair of nuclease-induced DSBs occurs in the absence of a DNA template as it repairs a cleavage site. This repair pathway is highly error prone and leads to efficient introduction of insertion and deletion mutations (indels) at the original site of the break. The NHEJ mechanism can be used to either revise a target region or to “cut-out” and “remove” a segment of DNA, depending on how many cuts are made. In the “cut and revise” model, a single cut is made, which disrupts binding at the reading frame of coding sequences or binding sites in promoters and enhancers, thus causing frameshift mutations that can lead to knockout of gene function. In the “cut and remove” process, two cuts are made, which results in the removal of the sandwiched gene segment.

HDR

The second mechanism, homology-directed repair of nuclease-induced double-strand breaks, occurs if a double-stranded DNA “donor template” is supplied. HDR is considered a more accurate mechanism for DSB repair. The cell can use the donor template to replace defective sequences with correct ones. This system can be used both to introduce specific point mutations and to inject desired sequences. This can be thought of as a “cut and replace” process allowing scientists to “cut out” and remodel specific disease-causing genes, much like a transplant surgeon is able to remove a damaged organ and replace it with a healthy counterpart.

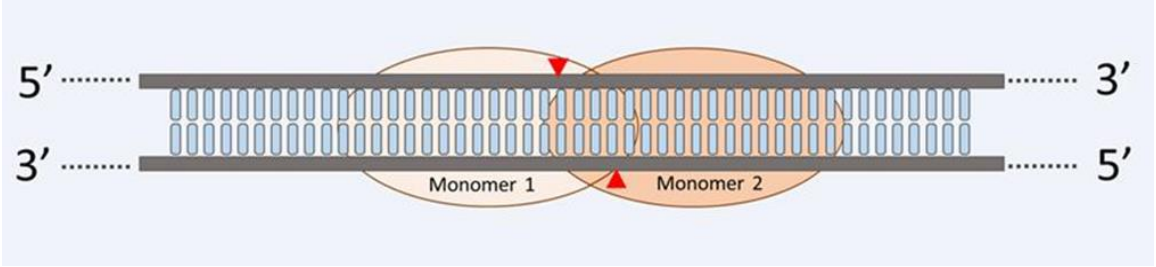
New Generation Genome Editing

The current platforms for genome editing encompass several classes of programmable nucleases, including meganucleases, zinc finger nucleases (ZFN), transcription activator-like effector nuclease (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 systems. These can be broadly organized into two classes based on their mode of DNA recognition — 1) meganucleases, ZFNs, and TALENs achieve DNA binding via protein-DNA interaction, while 2) Cas9 is guided via a short RNA molecule that base-pairs directly with the target DNA.

Meganucleases

Meganucleases are engineered versions of restriction enzymes that typically have extended DNA recognition sequences (12-40 nucleotides long), combined with a domain for nuclease activity (Exhibit 18).

Exhibit 18: **Meganuclease**



Source: Frontiers in Microbiology; 23 January 2017; Gustavo Romay, Claude Bragard; Antiviral Defenses in Plants through Genome Editing; https://www.frontiersin.org/articles/10.3389/fmicb.2017.00047/full

Although there are a wide range of meganucleases that naturally occur in nature, the ability to target with these enzymes remains restricted. Furthermore, the engineering of meganucleases has been challenging for most researchers because the DNA recognition and nuclease activity of these enzymes are interwoven in a single domain. Modification is therefore a highly complicated and expensive process that is not an attractive option on a larger scale.

In our opinion, meganucleases are largely impractical platform for gene editing beyond small-scale research purposes. Currently, private company Precision BioSciences is the sole company to exclusively employ a meganuclease-based genome editing platform. Nevertheless, this is a foundational technology that set the scope for the development of foundational platforms in genome editing.

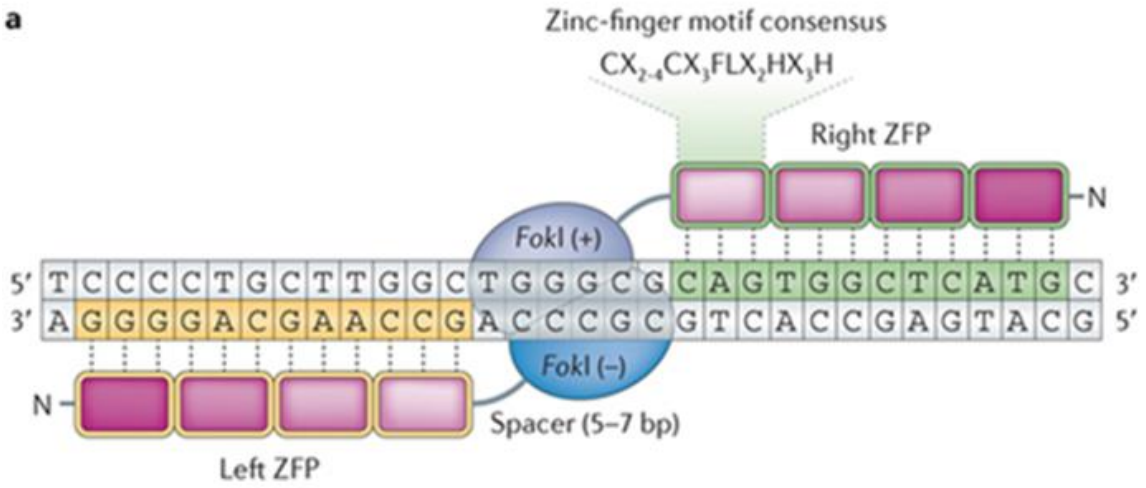
Zinc Finger Nucleases (ZFNs)

Zinc Finger Nucleases build on the concept of meganucleases, and are comprised of a DNA recognition domain (the zinc fingers), which is linked to a non-specific Flovobacterium okeanokoites nuclease—frequently referred to as *Fok1*. The DNA-binding domains of individual ZFNs typically contain three to six separate zinc finger repeats, each of which consists of 30 amino acids (stabilized by a zinc ion), which binds to a distinct DNA triplet. Importantly, the *Fok1* cleavage domain must form a dimer to cut DNA, which is achieved when two sets of fingers are directed to neighboring sequences, with each joined to a monomeric cleavage domain (Exhibit 19). Although more difficult to develop, the requirement for

dimerization presents a great advantage in terms of target specificity; the combined requirement for binding two proteins greatly enhances the specificity of this system, sufficient, in principle, to pick out a single target.

As reviewed above, the selectivity of ZFNs is determined by the zinc finger domains that have to be specifically designed for the genomic target of interest. Furthermore, since the position of the finger within the overall protein changes the binding affinity of the zinc fingers, the recognition domain has to be designed in context of the whole structure. As such, each minor change in the target sequence requires a complete redesign on the zinc finger structure. Together, the following presents a complex protein engineering framework for each target designed, an expensive and time-intensive process that relies largely on trial and error.

Exhibit 19: **Zinc Finger Nuclease**

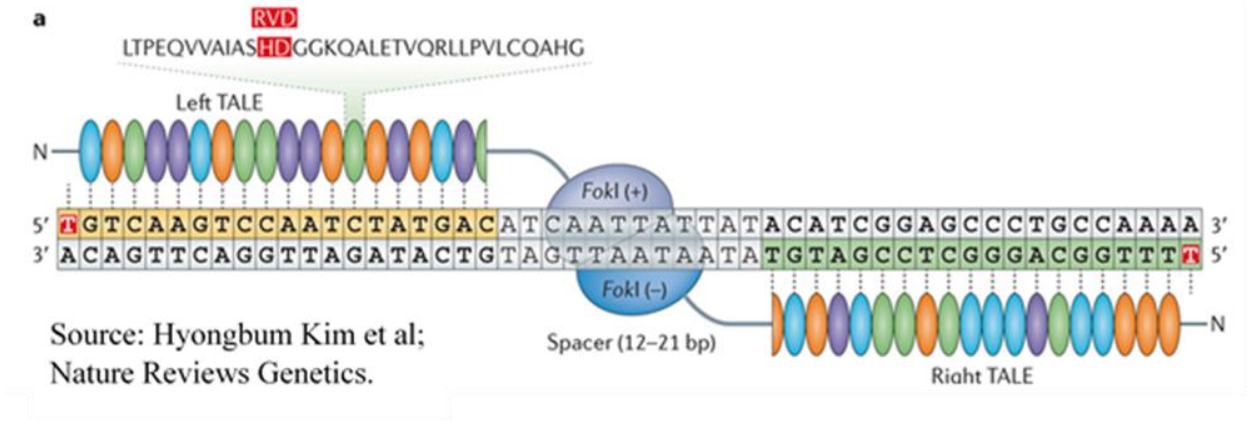


Source: Nature Reviews Genetics; 15, 321–334 (2014); Hyongbum Kim, Jin-Soo Kim; A guide to genome engineering with programmable nucleases; http://www.nature.com/nrg/journal/v15/n5/abs/nrg3686.html

Transcription Activator-Like Effector Nucleases (TALENs)

Transcription Activator-Like Effector Nucleases (TALENs) utilize the same cleavage principles as the ZFN system: they use *Fok1* as a cleavage domain, which is bound to a recognition site. Although the basic mechanism of action for ZFNs and TALENs may be the same, the DNA recognition domain is highly different. The fundamental blocks used to engineer the binding region of TALENs is a conserved repeat domain derived from naturally occurring TAL effectors encoded by phytopathogenic *Xanthoronas* bacteria. The DNA binding domain contains a repeated highly conserved 33–34 amino acid sequence with differing 12th and 13th amino acids, a segment referred to as Repeat Variable Di-residues (RDVs). Each repeat binds with a single DNA nucleotide (as opposed to a triplet in the ZFNs), with the RVD determining specific nucleotide recognition (Exhibit 20).

Exhibit 20: **Transcription Activator-Like Effector Nuclease**



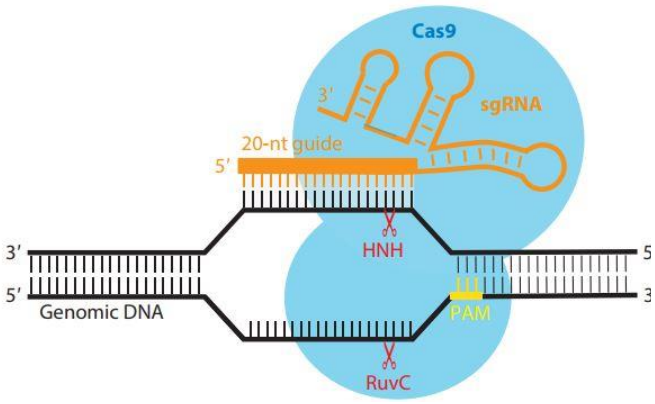
Source: Nature Reviews Genetics; 15, 321–334 (2014); Hyongbum Kim, Jin-Soo Kim; A guide to genome engineering with programmable nucleases; http://www.nature.com/nrg/journal/v15/n5/abs/nrg3686.html

In contrast with ZFNs, which have highly complex binding, the binding mechanism surrounding TALENs is relatively simple, with basic variations in the RVD necessary for determining the target sequence in TALENs. In addition, RVDs act independently on one another and TALENS can be considered as independently-acting subunits as opposed to a functional unit (as compared to ZFNs where changes in finger positioning vary binding affinity for the entire protein). Together, the TALEN system presents an effective tool for gene editing, which is faster to design and cheaper than its predecessors.

CRISPR-Cas9 System

The CRISPR-Cas9 technology originates from the type II CRISPR-Cas system, which is a naturally occurring defense mechanism that provides bacteria with a type of immunity to viruses. Similar to the zinc finger recognition domain and *Fok1* endonuclease of the ZFN system, CRISPR consists of two components: a guide RNA (DNA recognition) and a non-specific CRISPR-associated endonuclease (Cas9). The guide RNA, a short synthetic RNA, is comprised of a CRISPR RNA (crRNA), trans-acting crRNA (tracrRNA) duplex, which contains a sequence at the 5' side that determines the DNA target and an RNA structure at the 3' site that binds to Cas9. The endonuclease activity of Cas9 also requires a short sequence known as the protospacer-associated motif (PAM) (Exhibit 21).

Exhibit 21: **CRISPR-Cas9**



Source: Annual Review of Biophysics; 2017 May 22; 46505-529; Jiang F, Doudna JA; CRISPR-Cas9 Structures and Mechanisms; https://www.ncbi.nlm.nih.gov/pubmed/28375731

Arguably, the most important advantage of the CRISPR-Cas9 system over other genome editing technologies is its simplicity and efficiency. Indeed, the targeting domain can be completely changed by altering only the gRNA, a far simpler (basic molecular cloning as opposed to protein engineering), and more cost-effective system than other systems. Another significant advantage of the CRISPR/Cas system is that many sites can be concurrently targeted with a single enzyme and multiple guides, in contrast to needing to deliver a separate ZFNs or TALENs to each target (multiplexing). In short, the CRISPR-Cas9 system is a highly efficient and simple-to-use system.

Off-Target Effects

The specificity of genome editing tools is the main safety concern when evaluating such platforms for clinical application.

Accumulating lines of evidence point to undesirable side effects with genome editing platforms, including a variable level of off-target activity, or the introduction of cuts at sites other than the target DNA sequence. These off-target cuts are a significant cause for concern; since genetic modifications are permanent modifications to the genome, harmful off-target mutations can result in possible cellular toxicity or even tumorgenicity.

A recent study published in the Journal of Nature Methods has raised concerns that applying gene editing in humans may be premature, even with CRISPR-Cas9. The researchers sequenced an entire genome of CRISPR-edited mice to search for mutations, and found — in addition to the intended genetic edit — more than 100 deletions and insertions along with more than 1,500 single-nucleotide mutations. The phenomena of non-specific cleavage by nucleases is not unique to CRISPR Cas9 as it has been also reported for ZFNs and TALENs; therefore, many different avenues are currently being explored toward reducing the frequency of off-target effects and increasing the specificity of nucleases.

Delivery

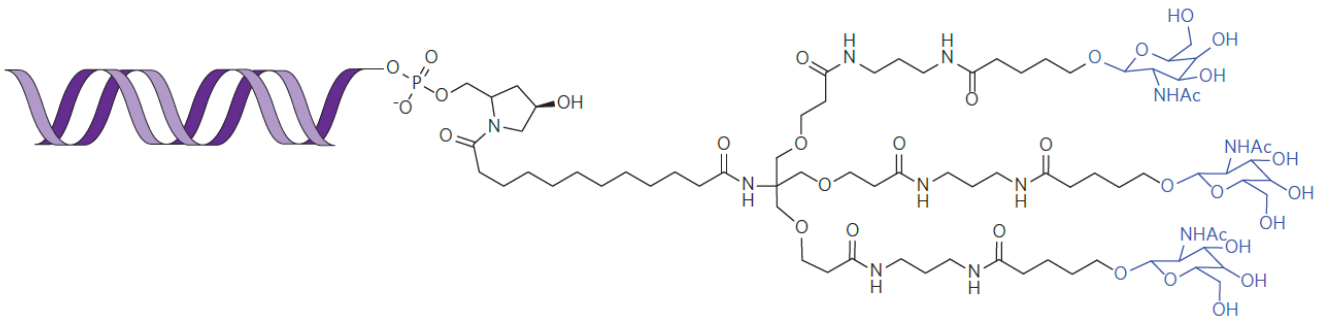
Key to the broad implementation of genome-editing technologies is the need for safe and effective delivery methods into target cells. A variety of different delivery methods have been used to introduce editing technologies to target cell types, both through an *ex vivo* treatment mode, or directly administered *in vivo*. Recently, viral vectors have emerged as the most promising delivery vehicles for genome editing nucleases. Several vectors present clinically relevant options, including adenovirus (AV), adeno-associated virus (AAV), and lentivirus. Moving forward, the clinical development of viral-vector delivery systems will include consideration of off-target genetic modifications, even in non-integrating AAV and Integrase-Deficient Lentiviral (IDLV) platforms. To overcome some challenges of delivery, nanoparticle and lipid based delivery systems are currently being developed and may provide attractive alternatives to viral vectors.

Non-Viral Vector

Despite the advancement of viral vector based gene delivery technology, several associated limitations, including immunogenicity, promiscuous tropism, limited DNA packaging capacity, and potential carcinogenesis due to genome integration, have propelled the development of synthetic non-viral gene therapy. Non-viral vectors have several inherent advantages that make them an attractive alternative for the delivery of therapeutic genetic materials to the site of action. For example, non-viral vectors are typically easier to manufacture and are able to deliver larger genetic payloads as compared to viral vectors. In addition, given that patients do not have pre-existing immunity against non-viral vectors as well as synthetic vectors tend to have low immunogenicity, non-viral vector based gene delivery is likely to be safer than viral vectors. That said, while helper proteins from viral vectors have evolved to increase the transduction efficiency for mammalian cells, synthetic vectors have a relatively low efficiency to bypass various cellular barriers and deliver genetic materials.

The rapid progress of material science, nanotechnology, and nucleic acid chemistry has distilled a host of synthetic vectors with an enhanced on-target delivery and transduction efficiency profile, including lipids, polymers (linear/branched, dendrimers, and polysaccharides), polymersomes, peptides, and inorganic nanoparticles. Of the leading non-viral delivery systems under clinical development is a siRNA-triantennary N-acetylgalactosamine (GalNAc) conjugate, known as patisiran (ALN-TTR02, Alnylam Pharmaceuticals), which recently reported positive Phase III study (APOLLO) results for the treatment of transthyretin (TTR)-mediated amyloidosis. Patisiran consists of a TTR targeting siRNA, which is covalently attached to three GalNAc molecules through a triantennary spacer molecule (Exhibit 22). The spacer length and ligand valency are optimized to allow the siRNA-GalNAc conjugate to bind to a receptor on the hepatocyte that results in a highly specific and efficient target delivery of the siRNA to the liver. In a completed Phase II study of Patisiran in patients with ATTR amyloidosis, patisiran demonstrated a well-tolerated safety profile with no observed drug-related serious adverse events (SAEs). On the efficacy side, 74% of patisiran treated patients (n=27) achieved a stable status or an improvement (a seven-point mean decrease in mNIS+7) in terms of neuropathy progression as measured by the modified neuropathy impairment score+7 (mNIS+7) during a two-year follow up period. Of note, the clinical outcome achieved by these patisiran treated patients compared favorably to an expected average of 26 – 30 point decrease in mNIS+7 among untreated patients with similar neuropathy impairment baseline from the separated historical data sets. Of note, multiple drug candidates in Alnylam's pipeline are powered by this si-RNA-GalNAc platform, which are being evaluated for different diseases in various clinical stages.

Exhibit 22: **siRNA–GalNAc Conjugates**



Source: Nature Materials; 2013 Nov;12(11):967-77; Kanasty R, Dorkin JR, Vegas A, Anderson D; Delivery materials for siRNA therapeutics; https://www.ncbi.nlm.nih.gov/pubmed/24150415

Acquisitions, Partnerships, IPOs, Secondary Public Offerings, and Performance of Select Gene Therapy Players

Acquisitions in the Gene Therapy Space

Based on our research, since 2012, there have been seven announced acquisitions, with four completed, two pending, and one terminated. Interestingly, Dimension was pursued by both Ultragenyx and REGENXBIO, with the former having won Dimension board of directors' hearts. We also note that the M&A activity in the gene therapy space, which started to pick up in 2016, remains low in terms of the number of deals as well as the transaction value. That said, we believe more deals could occur in the next several years given the clinical successes seen to date, as well as the significant market opportunity.

Exhibit 23: **Select Gene Therapy Acquisitions in the Past Five Years**

Target	Gene Therapy Strategy	Acquirer	Announcement Date	Transaction Status	Transaction Value ($,million)
Dimension Therapeutics	AAV	Ultragenyx Pharmaceutical	9/18/2017	Pending	151.00
Calimmune	Lentiviral, nonviral	CSL Behring	8/28/2017	Pending	416.00
Dimension Therapeutics	AAV	REGENXBIO	8/25/2017	Terminated	86.00
Bamboo Therapeutics	AAV	Pfizer	8/1/2016	Complete	645.00
Discovery Genomics	Transposon	Immusoft Corp.	3/8/2016	Complete	N/A
Precision Genome Engineering	Genome editing	bluebird bio	6/30/2014	Complete	156.01
DNAVEC Corp.	Lentiviral	I'rom Holdings Co.	10/25/2013	Complete	9.18

Source: FactSet, company reports, Raymond James research

Partnerships in the Gene Therapy Space

Exhibit 24: **Select Partnerships in the Gene Therapy Space**

Company	Target company	Deal terms	Indications	Date
Pfizer	Sangamo	$70 million upfront payment, up to $475 million milestone payments, double-digit royalties	SB-525 for hemophilia A	5/2017
Spark	Selecta	$15 million upfront payment in the context of cash and equity investment, another $15 million cash and equity investment within 12 months, up to $430 million milestone payments fpr each target, mid-single to low-teen digits royalties	Hemophilia A and up to four additional targets	12/2016
Regeneron	Intellia	$75 million upfront payment, $50 million equity investment, up to $40 million research payments, up to $320 million milestone payments, single to low teen digit royalties	CRISPR-Cas9 for up to 10 targets, including ATTR	4/2016
Fibrocell	Intrexon	$10 million technology access fee, up to $30 million and $22.5 million milestone payments, low double digits royalties	Chronic inflammatory and degenerative diseases of the joint, including arthritis and related conditions	1/2016
Vertex	CRISPR	$75 million upfront payment, $30 million equity investment, up to $420 million milestone payments for each program with a total of up to $2.6 billion milestone payments, single to low teen digit royalties	CRISPR-Cas9 for six targets, including beta-thalassemia and SCD	10/2015
BMS	uniQure	$100 million upfront payment in the context of cash and equity investment, up to $254 million milestone payments for S100A1 as well as up to $217 million milestone payments for each of the other targets, single to double digits royalties	S100A1 for congestive heart failure and other targets	10/2015
Biogen	AGTC	$124 million upfront payment in the context of cash and equity investment, up to >$1 billion milestone payments, mid-single to low-teen digit royalties	Rare eye diseases	6/2015
Sanofi Genzyme	Voyager	$100 million upfront payment in the context of cash and equity investment, up to $745 million milestone payments, tiered royalties	Parkinson's disease (VY-AADC01), Friedreich's ataxia (VY-FXN01), Huntington's disease, as well as other CNS disorders	2/2015
Chiesi	uniQure	~$40 million upfront payment in the context of cash and equity investment, 20 - 30% royalties	Hemophilia B	2/2015
Novartis	Intellia	$10 million upfront, up to $40 million research payments, up to $230.3 million milestone payments, mid-single digit royalties	CRISPR-Cas9 for CAR-T and HSC	1/2015
Adverum	REGENXBIO	$20 million milestone payments, low to high single digit royalties	ADVM-043 for A1AT deficiency	2015
Bayer	Dimension	$20 million upfront payment, up to $232 million milestone payments	DTX201 for Hemophilia A	6/2014
Bioverativ	Sangamo	$20 million upfront, up to $276 million milestone payments, double-digit royalties	ZFP gene editing for beta-thalassemia and SCD	1/2014
Pfizer	Spark	$20 million upfront, up to $260 million milestone payments, double-digit royalties	SPK-9001 for hemophilia	1/2014
AveXis	REGENXBIO	$2 million upfront, up to $12.25 million milestone payments, mid-single – low-teen digit royalties	AVXS-101 for SMA	2014
Audentes	REGENXBIO	>$1 million upfront, up to $25.3 million milestone payments, single - low teen digit royalties	XLMTM, Pompe disease and CN syndrome	2013 and 2014
Shire	Sangamo	$13 million upfront, unspecified milestone payments and royalties	ZFP gene editing for hemophilia A and B, Huntington's disease, as well as other indications	2/2012

Source: Company reports, Raymond James research

Exhibit 25: **IPOs in the Gene Therapy Space (Since 2015)**

Company	Ticker	Offer Date	Gross Proceeds ($, million)
Nightstar Therapeutics	NITE	9/27/2017	77
Krystal Biotech	KRYS	9/19/2017	40
CRISPR Therapeutics Ltd.	CRSP	10/18/2016	62
Audentes Therapeutics, Inc.	BOLD	7/19/2016	75
Selecta Biosciences, Inc.	SELB	6/21/2016	70
Intellia Therapeutics, Inc.	NTLA	5/5/2016	124
AveXis, Inc.	AVXS	2/10/2016	95
Editas Medicine, Inc.	EDIT	2/2/2016	109
Voyager Therapeutics, Inc.	VYGR	11/10/2015	81
Dimension Therapeutics, Inc.	DMTX	10/21/2015	72
REGENXBIO, Inc.	RGNX	9/16/2015	159
Spark Therapeutics, Inc.	ONCE	1/29/2015	185
Total			1,148

Note: some of the gross proceeds included over-allotments
Source: FactSet, Raymond James research

Exhibit 26: **Secondary Public Offerings in the Gene Therapy Space (Since 2012)**

Company	Ticker	Offer Date	Gross Proceeds ($, millions)
Spark Therapeutics, Inc.	ONCE	8/3/2017	403
bluebird bio, Inc.	BLUE	6/27/2017	400
Sangamo BioSciences, Inc.,	SGMO	6/21/2017	83
AveXis, Inc.	AVXS	6/20/2017	288
Audentes Therapeutics Inc.	BOLD	4/18/2017	86
REGENXBIO INC	RGNX	3/21/2017	87
Editas Medicine, Inc.	EDIT	3/16/2017	90
bluebird bio, Inc.	BLUE	12/6/2016	250
Abeona Therapeutics Inc	ABEO	10/27/2016	42
AveXis, Inc.	AVXS	9/8/2016	147
Spark Therapeutics, Inc.	ONCE	6/14/2016	181
Spark Therapeutics, Inc.	ONCE	12/15/2015	141
Fibrocell Science, Inc.	FCSC	7/22/2015	15
bluebird bio, Inc.	BLUE	6/23/2015	500
uniQure NV	QURE	4/9/2015	89
Avalanche Biotechnologies, Inc.	AAVL	1/7/2015	163
bluebird bio, Inc.	BLUE	12/15/2014	259
Applied Genetic Technologies Corp.	AGTC	7/24/2014	35
bluebird bio, Inc.	BLUE	7/8/2014	117
Sangamo BioSciences, Inc.	SGMO	3/20/2014	100
Fibrocell Science, Inc.	FCSC	9/26/2013	45
Sangamo BioSciences, Inc.,	SGMO	9/18/2013	74
Total			3,594

Note: Some of the gross proceeds included over-allotments
Source: FactSet, Raymond James research

Exhibit 27: **Performance of Raymond James Gene Therapy Index**

Company	Market Cap as of 1/1/2017 ($ million)	Market Cap as of 10/6/2017 ($ million)	Price as of 1/1/2017	Price as of 10/6/2017	YTD Return
bluebird bio	2,511	5,824	61.70	127.75	107%
AveXis, Inc.	1,322	3,311	47.73	103.71	117%
Spark Therapeutics	1,540	2,733	49.90	87.44	75%
Sangamo Therapeutics Inc	216	1,334	3.05	15.95	423%
Intellia Therapeutics	472	1,117	13.11	30.93	136%
Editas Medicine	581	1,053	16.23	25.01	54%
REGENXBIO	491	1,041	18.55	33.65	81%
CRISPR Therapeutics	805	783	20.26	19.30	-5%
Audentes Therapeutics, Inc.	397	721	18.27	26.01	42%
Abeona Therapeutics Inc.	195	713	4.85	17.70	265%
Voyager Therapeutics	326	556	12.74	20.71	63%
Nightstar Therapeutics	N/A	471	N/A	16.75	N/A
Selecta Biosciences Inc	316	436	17.15	19.75	15%
UniQure N.V.	141	274	5.60	10.70	91%
Adverum Biotechnologies	121	154	2.90	3.55	22%
Dimension Therapeutics, Inc.	109	151	4.35	6.00	38%
Krystal Biotech	N/A	96	N/A	9.94	N/A
Applied Genetic Technologies Corporation	169	72	9.35	4.00	-57%
Fibrocell Science Inc.	28	43	1.89	2.93	55%
Total	9,741	20,317			
Average	573	1,195			90%
NASDAQ / Biotechnology			2772.73	3562.45	28%
S&P 500			2238.83	2549.33	14%

Source: FactSet, Raymond James research

Adverum Biotechnologies, Inc. (ADVM-NASDAQ)

Biotechnology

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Breathing New Life Into Gene Therapy; Initiating With an Outperform Rating

Recommendation: We are initiating coverage of Adverum Biotechnologies with an **Outperform** rating and a price target of $6.00 (High Risk/Speculation suitability, given the stage of clinical development). Adverum is a recently reverse merged, early-stage gene therapy company with a diversified pipeline that could deliver surprisingly positive results in several orphan drug indications. With multiple product candidates slated to enter the clinic in the near future, a cash position of ~$186 million (pro forma), and a negative enterprise value, we recommend Adverum shares to risk-tolerant investors.

- **Repackaging established therapies – one-time treatments**. While the market is not currently ascribing any value to the company's pipeline, Adverum has the potential to move three product candidates into the clinic in the near future. We expect the company to start a Phase I/II study evaluating ADVM-043 for alpha-1 antitrypsin (A1AT) deficiency in 4Q17 with preliminary data anticipated in 2018. In addition, the company plans to file two INDs for ADVM-053 and ADVM-022 for hereditary angioedema (HAE) and wet age-related macular degeneration (AMD), respectively, in 2018.
- **Pipelines and IP sometimes get thrown out with the bath water.** Historically, some small-cap biotech companies that have been placed in the penalty box (usually due to a big clinical failure) and trade under or near cash levels are able to showcase a recovery, resulting in substantial appreciation of the stock price. A recent example includes the bidding war between REGENXBIO and Ultragenyx for the acquisition of Dimension Therapeutics (shares moved from $33 million in market cap to ~$150 million). With Adverum trading at an enterprise value of $(42) million, in our opinion, positive data from any of the company's programs could drive the shares significantly higher from the current levels.

Valuation: Using the sum-of-the-parts analysis, we derive a target price of $6.00. See page 62 for more detail.

GAAP EPS	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Full Year	Revenues (mil.)
2016A	(0.57)	(1.76)	(0.35)	(0.54)	$(3.14)	$1
2017E	(0.38)A	(0.27)A	(0.31)	(0.32)	(1.27)	1
2018E	(0.34)	(0.35)	(0.37)	(0.34)	(1.39)	0

Rows may not add due to rounding.

Rating
Outperform 2

Current and Target Price

Current Price (Oct-09-17)	$3.55
Target Price:	$6.00
52-Week Range	$4.22 - $2.40
Suitability	High Risk/Speculation

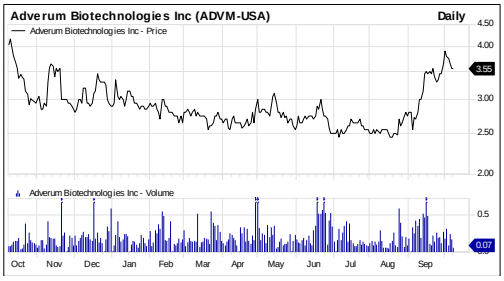
Market Data

Shares Out. (mil.)	43.3
Market Cap. (mil.)	$158
Avg. Daily Vol. (10 day)	190,387
Dividend/Yield	$0.00/0.0%
BVPS (Jun-17)	$4.45
LT Debt (mil.)/% Cap.	$0/0%

Earnings & Valuation Metrics

	2016A	2017E	2018E
P/E Ratios (GAAP)	NM	NM	NM

Adverum, headquartered in Menlo Park, California, is an early-stage gene therapy company which is the result of the merger of Avalanche and Annapurna Therapeutics in May 2016. Adverum has multiple product candidates in development, with all being at the preclinical/research stage. The most advanced products include: 1) ADVM-043, which utilizes a non-human primate (NHP) AAVrh10 vector to deliver the A1AT gene, is being developed for A1AT deficiency, with a Phase I/II study expected to start in 4Q17; 2) ADVM-053, which also uses the AAVrh10 vector to deliver the C1 esterase inhibitor (C1EI) gene, is being evaluated for HAE, with an IND filing expected in early 4Q17/1Q18; and 3) ADVM – 022, which consists of a proprietary AAV vector and a copy of the Eylea trangene, is being assessed for wet AMD, with an IND filing expected in 4Q17/1Q18.



Source: FactSet.

Company Description

Adverum, headquartered in Menlo Park, California, is an early-stage gene therapy company that is the result of the merger of Avalanche and Annapurna Therapeutics in May 2016. Adverum has multiple product candidates all currently at the preclinical/research stage of development. The most advanced products include: 1) ADVM-043, which utilizes a non-human primate (NHP) AAVrh10 vector to deliver the A1AT gene, for A1AT deficiency, with a Phase I/II study expected to start in 4Q17; 2) ADVM-053, which also uses the AAVrh10 vector to deliver the C1 esterase inhibitor (C1EI) gene, and is being evaluated for HAE, with an IND filing expected in 1Q18; and 3) ADVM-022, which consists of a proprietary AAV vector and a copy of the anti-VEGF gene, and is being assessed for wet AMD, with an IND filing expected in 1Q18. Taken together, we believe these three product candidates, if successful, could address a market opportunity of $30+ billion.

Newsworthy Catalysts

ADVM-043 for A1AT Deficiency

Potential to begin enrolling patients in a Phase I/II study (4Q17)

Results from the Phase I/II study (2018)

ADVM-053 for HAE

Potential to file an IND (2018)

ADVM-022 for Wet AMD

Potential to file an IND (2018)

Summary of Investment Risks

Clinical and Regulatory Risk

The clinical development of Adverum's products bears risk given that these products are not in the clinic yet. In addition, the failures of other companies' gene therapy products for wet AMD and A1AT deficiency could result in additional scrutiny, although Adverum's approaches are differentiated. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk

If approved, Adverum's products are likely to face competition from existing therapies. For example, in the wet AMD space, the approved anti-VEGF therapies (e.g., Regeneron's Eylea and Roche/Novartis' Lucentis) have demonstrated effectiveness, resulting in challenges that will need to be overcome, including the changing of physicians' prescribing habits. With respect to A1AT deficiency and HAE for which two other gene therapy products are being developed, respectively, a number of therapies currently exist and could also hamper marketing efforts.

Aside from competition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Adverum cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercial viable.

Financing Risk

Adverum currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Summary of Investment Highlights

ADVM-043 for A1AT Deficiency

Alpha-1 antitrypsin (A1AT) deficiency is a genetic disorder caused by mutations in the SERPINA1 gene, resulting in a low plasma level of the A1AT protein. Without sufficient functional A1AT, neutrophil elastase, an enzyme released from white blood cells to fight infection, can attack normal tissues, especially the lungs. Patients with A1AT deficiency usually develop lung diseases (e.g., emphysema or chronic obstructive pulmonary disease (COPD)) between ages 20 and 50, presenting early symptoms such as shortness of breath following mild activity, wheezing, weight loss, fatigue, and increased heartbeat upon standing. While there are approximately 100,000 people currently living with A1AT deficiency in the U.S., only about 10% are diagnosed as having the disease. Augmentation therapies (or enzyme replacement therapy, ERT) are capable of supplying the functional A1AT protein and potentially slowing down the progression of lung damage. Currently, there are four products available in the U.S. including Baxter's Aralast NP and Glassia, Grifols' Prolastin-C, and Behring's Zemaira. While these ERTs are efficacious, they are not convenient (weekly to monthly intravenous infusions) and are associated with the risk of viral contamination and allergic reactions. Therefore, in our opinion, a gene therapy as a one-time solution that can deliver stable, therapeutic levels of A1AT proteins could become an attractive therapeutic option.

Adverum's ADVM-043, which utilizes a non-human primate (NHP) AAVrh10 vector to deliver the A1ATgene intrapleurally (targeting the pleural mesothelium and the liver), is slated to enter a Phase I/II study for patients with A1AT deficiency in 4Q17. In preclinical studies, a single intravenous or intrapleural injection of ADVM-043 produced high levels of A1AT that were above the therapeutic threshold over the study period of 24 weeks. In addition, stable human A1AT mRNA expression was observed over the course of one year. In our opinion, the preclinical results support clinical testing of ADVM-043.

We have conducted an analysis of the space and recognize that at least one company has evaluated a gene therapy for A1AT deficiency and failed (see page 43 for more detail). That said, we remain cautiously optimistic about the clinical prospects and based on the preclinical results assume a probability of success of 20%, an outcome based annuity payment model with an annual payment of $130,000 in the U.S. and $104,000 in the EU, as well as a 40% peak market share. Taken together, we expect ADVM-043 to deliver peak sales of approximately $1 billion by 2029.

ADVM-053 for HAE

Hereditary angioedema (HAE), which currently affects approximately 6,500 to 8,000 patients in the U.S., is a genetic disorder caused by mutations in the C1 esterase inhibitor (C1EI) gene. The lack of functional C1EI results in leakage of intravascular fluid that manifests as an acute episode of edema, which can affect the GI tract, facial tissue, oropharynx, as well as the arms and legs. Current treatment options including C1EI enzyme replacement therapies aim to manage acute edema attacks and prophylactically prevent such events (see page 46 for more details). While these therapies are efficacious, they require frequent IV infusions (e.g., every three or four days for CINRYZE, Shire's C1EI product). According to a study published in 2012, the rate of angioedema attacks is inversely correlated with the intervals between C1EI protein infusions, with nearly zero attacks when the infusions are given daily (which is not practical). Therefore, much like A1AT deficiency, we believe a one-time solution to deliver stable, normal levels of C1EI proteins could be attractive.

Adverum's ADVM-053, which also utilizes the non-human primate AAVrh10 vector to deliver the C1EI gene intravenously, is being developed as a one-time prophylactic treatment for HAE. In preclinical studies, high C1EI protein levels above the therapeutic target were achieved in mice, which translated into functional improvements in vascular permeability (less leaky; see page 47 for more detail).

While multiple product candidates are being evaluated for HAE, ADVM-053 appears to be the only gene therapy product in development. If ADVM-053 can achieve stable, normal levels of C1EI proteins, we believe it would be able to compete effectively against the existing therapies and other pipeline products. Currently, the company is in the process of transferring the manufacturing process to a CMO to generate clinical materials for future trials. Once this is completed, the company plans to file an IND in 2018, with a Phase I study expected to start thereafter.

Given that ADVM-053 has not entered the clinic, we are not including this product in our model just yet and would rather view it as an upside to our valuation.

ADVM-022 for Wet AMD

Wet age-related macular degeneration (AMD), a disease that results in decline and eventual loss of central vision due to damage to the macula, is the leading cause of blindness in the elderly, and currently affects approximately 1,500,000 people in the U.S. While the anti-VEGF therapies (e.g., Eylea and Lucentis), the current standard of care for wet AMD, have proven to be effective in improving visual acuity in the majority of patients, they are associated with frequent intraocular injections (every one to two months for years). The repetitive injections in the eye often cause a great degree of inconvenience and discomfort, resulting in poor patient compliance, which eventually leads to vision loss in the long term. Given the good clinical outcomes and compliance issues associated with traditional anti-VEGF therapies as well as the progress being made in the gene therapy space, in our view, developing an anti-VEGF gene therapy product as a one-time solution is feasible and commercially viable.

Furthermore, we believe a VEGF gene therapy could compete effectively against these anti-VEGF monoclonal antibodies if it offers a similar efficacy and safety profile. Eylea and Lucentis, which are approved for wet AMD and other retinal disorders, generated U.S. sales of $3.3 billion and $1.4 billion, respectively, in 2016.

Adverum's ADVM-022, which uses a proprietary AAV vector to deliver the anti-VEGF gene (which encodes Eylea) intravitreally, is being developed as a one-time treatment for wet AMD. In a preclinical study using a laser-induced choroidal neovascularization model in NHPs, a single injection of ADVM-022 demonstrated similar efficacy as compared to Eylea in terms of the percentage of grade IV lesions in the treated eye at 28 days (1% for ADVM-022 vs. 0% for Eylea vs. 27% for a control) and beyond 20 weeks. Moving forward, the company plans to file an IND in 2018, with a Phase I study expected to start thereafter.

Can Gene Therapy Work in Wet AMD?

Two companies have previously developed an anti-VEGF gene therapy for wet AMD, including Avalanche (Annapurna reversed merged into Avalanche forming Adverum) and Genzyme (acquired by Sanofi) and REGENXBIO. Unfortunately, both Avalanche and Genzyme failed to demonstrate a statistically significant benefit (see pages 56-57 for more details).

Given these two failures, a critical question is whether Adverum's anti-VEGF gene therapy could succeed. As shown in Exhibit 12, Adverum's ADVM-022 differs from other anti-VEGF gene therapy products in terms of the vector, transgene, and route of administration, which we believe could result in a different clinical outcome.

Vector: Which Is Better?

ADVM-022 uses a different vector (a proprietary AAV vector) as compared to Avalanche's AVA-101 and Genzyme's GZ402663 (both used AAV2). Unfortunately, at this time, we have no clinical data and do not know the design of ADVM-022's vector, which makes it tough to determine if Adverum's choice is better than others.

Transgene

The transgene for ADVM-022 is an anti-VEGF antibody fragment vs. the native sFlt-1 for AVA-101 (used by Avalanche) and the chimeric sFlt-1 for GZ402663 (used by Genzyme). Flt-1 (fms-like tyrosine kinase -1) is a type of VEGF receptor, which binds VEGFs approximately 10 times stronger than another VEGF receptor, KDR. That said, the binding of Flt-1 to endogenous VEGFs does not significantly promote angiogenesis (formation of new blood vessels). We believe that an anti-VEGF transgene is a better choice than the Flt-1 gene given that anti-VEGF therapies have already been approved.

Route of Administration

ADVM-022 and GZ402663 are administered intravitreally, whereas others (RGX-314 and AVA-101) are injected subretinally. Both routes of administration have advantages and disadvantages. Pre-existing serum anti-vector neutralizing antibodies have a significant impact on the expression of transgenes delivered intravitreally but not to vectors injected subretinally. In addition, subretinal administration appears to be associated with greater transduction efficiency of the retinal pigment epithelium and photoreceptors. That said, subretinal administration has a higher risk for potential complications as well as a greater degree of variability of the procedure (e.g., intended volume is not injected), which may in turn affect the efficacy. In our opinion, the impact of these pre-neutralizing antibodies (prevalence rates ranging from 38% (AAV8) to 72% (AAV2)) and transduction efficiency are probably more profound than other factors, and therefore subretinal injection is likely to be a better choice if a wild type AAV vector is used. That said, Adverum appears to have developed a proprietary AAV vector that may overcome the challenges mentioned above and work well when injected intravitreally.

Given the prior failures in the wet AMD space and the fact that ADVM-022 has not entered the clinic, we are not including this product in our model just yet, and also view it as an upside.

Adverum's Portfolio

Product	Status	Market	Rights
ADVM-043	Preclinical	A1AT deficiency	Adverum
ADVM - 053	Preclinical	HAE	Adverum
ADVM - 022	Preclinical	Wet AMD	Adverum
Up to five undisclosed targets	Research	Inherited retinal disease	Adverum/ Editas Medicine
X-linked Retinoschisis and 3 undisclosed targets	Research	Ophthalmic disease	Adverum/ Regeneron Pharmaceuticals

Notes: A1AT -- Alpha-1 antitrypsin, HAE -- Hereditary angioedema, AMD -- age-related macular degeneration
Source: Adverum, Raymond James research

Summary of Investment Positives and Negatives

Positives	Negatives
A strong balance sheet	None of the product candidates have entered the clinic
Trading under cash	Failures of others' gene therapies would result in additional scrutiny of Adverum's product candidates for the same indications
A diversified pipeline	No clinical readouts in the near future
Product candidates target significant market opportunities	Small cap/low share volume

Source: Raymond James research

The A1AT Deficiency Franchise

A1AT Deficiency

Alpha-1 antitrypsin (A1AT) deficiency is an autosomal recessive disorder characterized by a low plasma level of the A1AT protein that is produced in the liver. A1AT belongs to a family of proteins called serine protease inhibitors (serpins), which play a role to modulate protease cascades in inflammatory and coagulation pathways. Importantly, A1AT is able to protect the body from its direct substrate neutrophil elastase, which, if not properly regulated, can attack normal tissues such as alveoli in the lung. Patients with A1AT deficiency usually develop lung diseases between ages 20 and 50, with early presentations such as shortness of breath followed by mild activity, wheezing, weight loss, fatigue, and increased heart rate upon standing. Over time, affected patients often develop emphysema (reduction of surface area in the lung), which leads to difficulty breathing and a barrel-shaped chest. In addition, approximately 10% of patients with A1AT deficiency develop liver diseases due to an accumulation of the mutant A1AT protein in the liver. In rare cases, people with the disease develop a skin condition called panniculitis, which is characterized by hardened skin with painful lumps or patches.

According to alpha-1 foundation, it is estimated that more than 100,000 individuals in the U.S. have A1AT deficiency, of which 10% are diagnosed with the disease. The current standard of care for A1AT deficiency is the management of A1AT deficiency associated emphysema, including inhaled bronchodilators, inhaled steroids, anticholinergics, oxygen therapy, and antibiotic treatment for respiratory infections. Additionally, augmentation therapies, such as enzyme replacement therapy (ERT), are capable of supplying the functional A1AT protein and potentially slowing the progression of lung damage and are often utilized for the treatment of individuals with established emphysema. Currently, four ERT products

are available in the U.S., including Aralast NP (Baxter), Prolastin-C (Grifols), Zemaira (SCL Behring), and Glassia (Baxter).

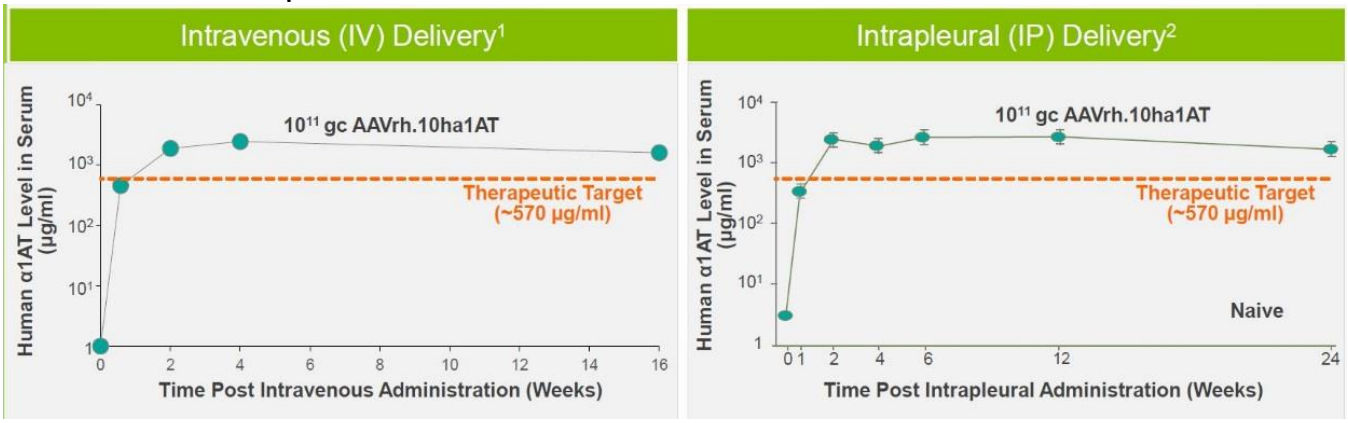
To date, A1AT deficiency has been viewed as an accessible target for gene therapy due to the fact that A1AT is a secreted serum protein whose level is easily measurable in the peripheral blood. In addition, the physiological level of A1AT has a range of between 11 – 25 µM, with a threshold level of 11 µM (about 570 µg/mL) which is necessary for the protection of lung damage in A1AT deficiency. Therefore, we believe such a wide range of A1AT in the circulating plasma should potentially allow for a relatively large margin of error for the gene therapy whose goal is achieving a therapeutic level of the A1AT protein in the serum for a long-lasting period. Importantly, the utilization of plasma or serum A1AT levels (above 11 µM) as the clinical endpoint for the development of A1AT deficiency therapy has been validated, as evidenced by the FDA approval of currently available augmentation therapeutic products. That being said, previous clinical studies of gene therapy targeting A1AT deficiency with an AAV2 or AAV1 vector carrying the wild-type M-A1AT gene that was delivered to muscle or liver was only able to achieve an inadequate transgene expression (3-5% of the therapeutic level).

ADVM-043

Adverum is developing a gene therapy candidate called ADVM-043 (or ANN-1001), which utilizes a non-human primate (NHP) AAVrh10 vector encoding the normal M-type A1AT to be delivered intrapleurally for the treatment of A1AT deficiency. Relative to the previously evaluated gene therapy candidates, the intrapleural delivery of ADVM-043 could potentially lead to expression of A1AT in the lung, which combined with the more efficient AAVrh10 vector in terms of transduction, could result in a high expression level of A1AT that is in the therapeutic range.

In the preclinical studies of ADVM-043, a single administration of the gene therapy candidate through either intravenous or intrapleural delivery demonstrated a sustained expression (24 weeks) of A1AT in mouse serum, which was above the therapeutic level (572 µg/mL) (Exhibit 1).

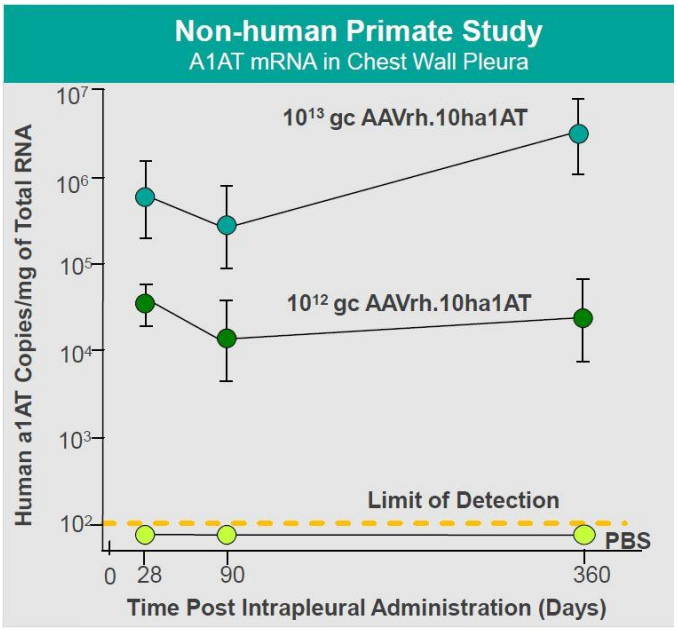
Exhibit 1: **Human A1AT Expression in Mice Serum After ADVM-043 Administration**



Source: Adverum Biotechnologies, Inc.

In addition, in a preclinical study where ADVM-043 was delivered intrapleurally in a NHP, a stable and sustained expression of A1AT mRNA was seen during a year follow-up period, which was also appeared to be dose-dependent (Exhibit 2).

Exhibit 2: **Human A1AT Expression in NHP Serum After ADVM-043 Administration**



Source: Adverum Biotechnologies, Inc.

On the safety front, ADVM-043 was well tolerated in treated mice and NHP. Dose-dependent levels of the anti-AAVrh10 neutralizing antibody were seen in the serum of all tested animals, which peaked at 28 days after vector administration and were maintained above the detection threshold during the whole study period (182 days in mice and 360 days in NHP). Taken together, given the proof-of-concept results demonstrated in preclinical studies seen to date, we believe ADVM-043 could potentially achieve a long-lasting and therapeutic expression level of A1AT in patients with A1AT deficiency in future clinical trials, although the level of the potential anti-vector neutralizing antibody needs to be closely monitored.

Clinical Development Plan for ADVM-043

With an open IND of ADVM-043 in the U.S. and the recent meeting with the FDA, the company plans to initiate a Phase I/II study in 4Q17 evaluating the safety and initial efficacy signal of ADVM-043 in patients with A1AT deficiency. Currently, the company is upgrading ADVM-043's manufacturing process to a commercial-grade baculovirus-based system, which is more scalable and should enable a seamless manufacturing process amenable to future clinical studies.

Can Gene Therapy Work for A1AT Deficiency?

Besides Adverum, Applied Genetic Technologies Corporation (AGTC) once evaluated a gene therapy product (rAAV1-CB-hAAT, or AGTC-0106), which utilized a recombinant AAV1 vector to deliver the human A1AT gene. AGTC conducted a Phase II study (NCT01054339) evaluating rAAV1-CB-hAAT in three dosing cohorts (6×10^{11}, 1.9×10^{12}, or 6×10^{12} vg /kg, n=3 for each). Of note, these patients received multiple intramuscular injections distributed across single or multiple muscle sites on a single occasion. Dose-dependent expression of serum A1AT was observed, with the highest dose cohort achieving a mean expression level of 0.572 µM on day 30, which then declined to 0.24 µM on day 90, with little change thereafter. None of these patients had serum A1AT levels of >1 µM over the course of study. Recall, the therapeutic threshold of serum A1AT levels is 11 µM. While no one developed antibodies against the A1AT proteins, all patients developed anti-AAV antibodies as well as interferon-γ enzyme-linked immunospot responses to the AAV peptides. On the safety front, AGTC-0106 appeared to be safe, with no serious adverse events reported.

While AGTC-0106 failed, Adverum's ADVM-043 could have a different fate given the differences in the vector and route of administration (Exhibit 3), which could lead to different clinical outcomes.

Exhibit 3: **ADVM-043 vs. AGTC-0106**

Product	Company	Transgene	Vector	Route of Administration
ADVM-043	Adverum	M-type A1AT	AAVrh10	Intrapleural (targeting pleural mesothelium and the liver)
AGTC-0106	Applied Genetic Technologies Corporation	M-type A1AT	AAV1	Intramuscular

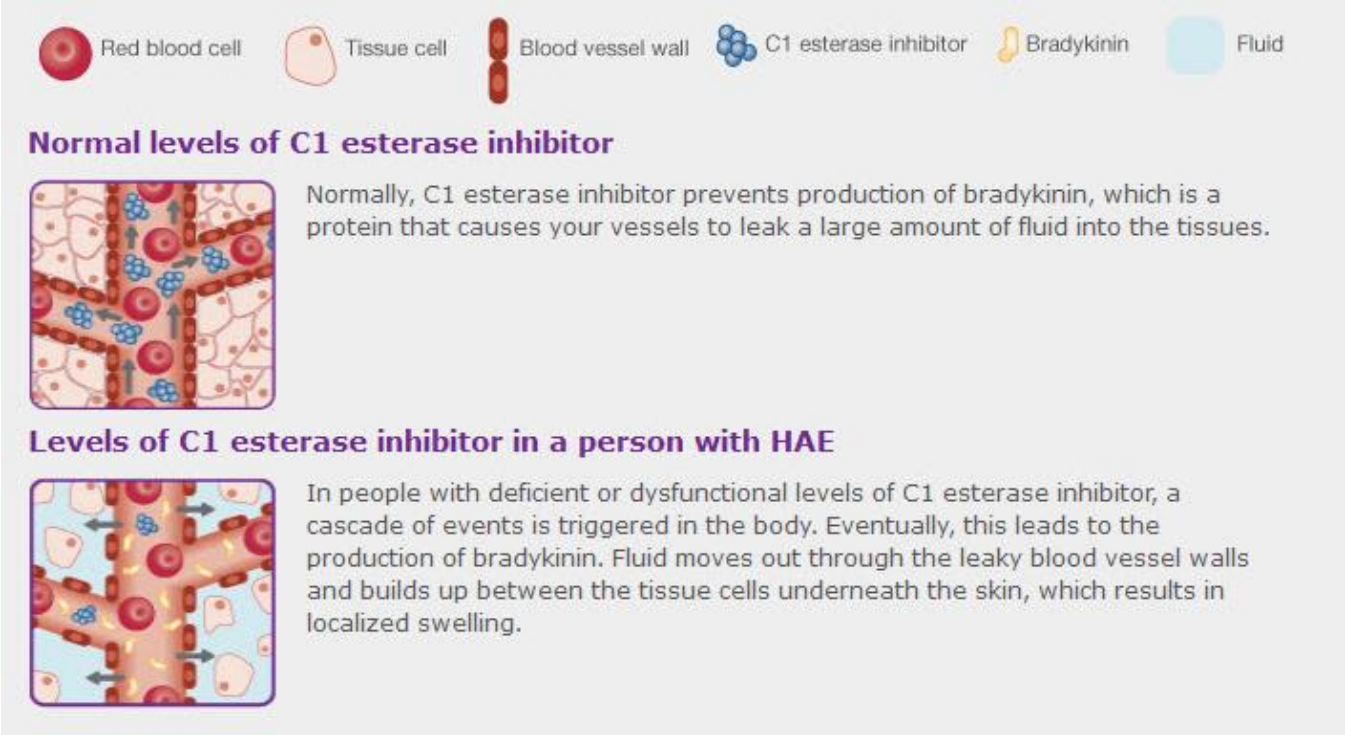
Source: Adverum; Human Gene Therapy, 2011; Raymond James research

The HAE Franchise

HAE

Hereditary angioedema (HAE) is an autosomal dominant genetic disorder characterized by mutations in the C1 esterase inhibitor (C1EI) gene that leads to a deficiency (Type I HAE) or non-functionality (Type II HAE) of the C1-INH protein, which is predominantly produced in the liver and whose function is to regulate proteases in the complement, fibrinolytic, and contact pathways. The lack of functional C1EI leads to an increased vascular permeability due to an uncontrolled release of bradykinin, resulting in a leak of intravascular fluid into the subcutaneous or submucosal space that manifests as an acute episode of edema (Exhibit 4). Therefore, patients with HAE suffer from unpredictable episodes of edema (usually resolves by itself within 24 to 48 hours), which can affect multiple anatomical locations, including the GI tract, facial tissue, oropharynx, as well as the arms and legs, with the obstruction in the airway being the most severe and life-threatening form due to a potential asphyxiation (lack of oxygen).

Exhibit 4: **What Is HAE?**



Source: http://howtogetridofhivesfast.com/hereditary-angioedema-cause-treatment

The incidence of HAE is between 1/10,000 and 1/50,000 in the U.S. and between 1/50,000 and 1/150,000 worldwide. Current treatment options for HAE include the management of acute edema attacks and prophylactic therapy. In regard to the management of acute attacks, strategies include increasing the plasma level of C1EI through ERT as well as inhibition of bradykinin 2 receptor (B2R) or kallikrein (which are mediators known to enhance vascular permeability). Approved drugs within the category of treatment for acute attacks include Berinert, Ruconest, kalbitor, and Firazyr, among which Firazyr appears to be the market leader, with $578.5 million generated in 2016 (Exhibit 5). With respect to prophylactic treatment, while long-term prophylaxis is recommended for patients who either experience more than 12 moderate-to-severe attacks per year or more than 24 days of symptoms per year despite on-demand treatment, short-term prophylaxis is suggested for patients undergoing surgical or other invasive, traumatic procedures, especially those who have a history of physical trauma associated edema. Available therapies for prophylaxis include Cinryze and the most recently approved Haegarda (June 2017), among which Cinryze generated $680 million in revenues in 2016.

Exhibit 5: **Approved Drugs for the Treatment of HAE**

Drug	Company	MOA	Indications/Usage	Year of FDA Approval
Cinryze	Shire	Plasma derived C1-INH protein	Prophylaxis	2008
Berinert	CSL Behring	Plasma derived C1-INH protein	Acute attacks	2009
Ruconest	Salix Pharma	recombinant C1-INH protein	Acute attacks	2014
Haegarda	CSL Behring	Plasma derived C1-INH protein	Prophylaxis	2017
Kalbitor	Shire	Kallikrein inhibitor	Acute attacks	2009
Firazyr	Shire	B2R inhibitor	Acute attacks	2011

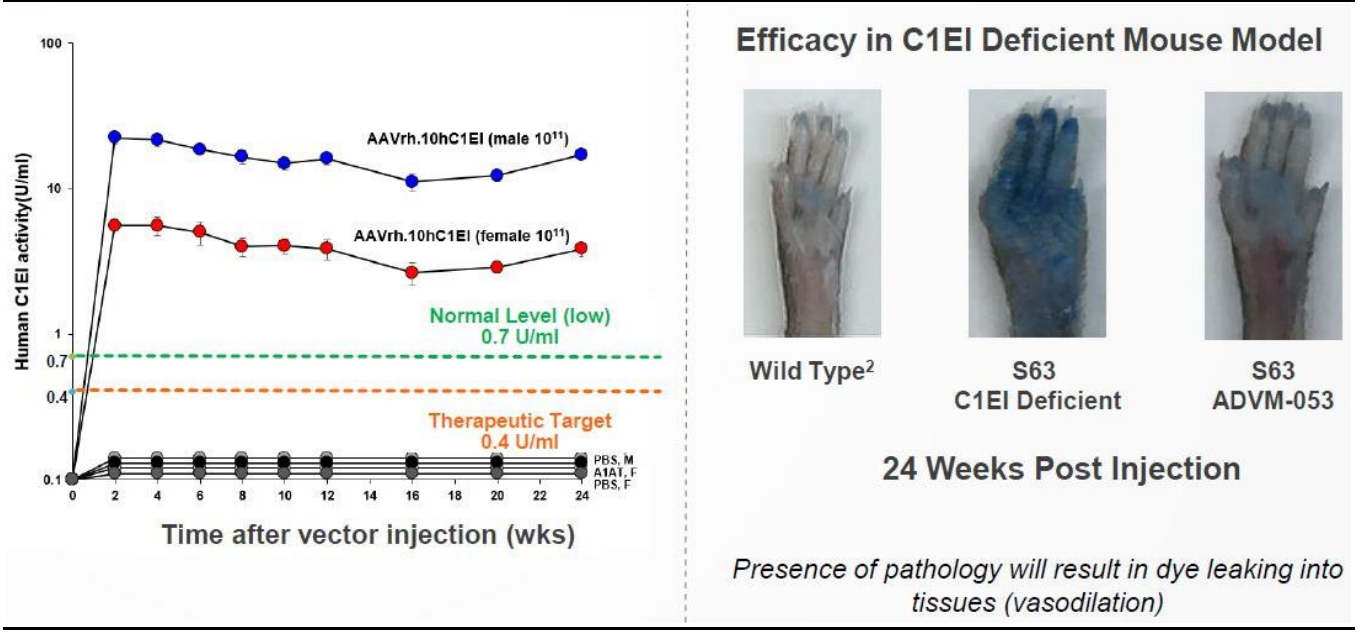
Source: Raymond James research

ADVM-053

Given that 1) the current prophylactic treatment options cannot completely eliminate the risk for acute attacks; and 2) they require bi-weekly IV infusion of the C1EI protein, which results in a significant burden to patients and caregivers, in our opinion, a gene therapy regimen that can provide a durable and adequate level of the functional C1EI protein could potentially achieve a better efficacy in terms of controlling acute attacks, meanwhile mitigating the burden on patients and caregivers.

Adverum is developing an AAVrh10 vector-based gene therapy candidate ADVM-053 with the goal to deliver a persistent level of the functional C1EI protein through a single intravenous injection, potentially serving as a prophylactic treatment option for patients with HAE. In a preclinical mouse model, a single intravenous injection of ADVM-053 demonstrated a durable expression level (six months) of the C1EI protein that is above the required therapeutic concentration (Exhibit 6). Interestingly, a difference in the expression level was seen between male and female mice. In addition, an increased level of the C1EI protein in ADVM-053 treated mice was able to translate into a functional improvement as evidenced by a decrease in vascular permeability to the level that appeared to be comparable to the wild type mice. While early, given the proof-of-principle efficacy of ADVM-053 in preclinical studies seen to date, we believe it could potentially generate meaningful results in future clinical studies.

Exhibit 6: **Preclinical Study Results of ADVM-053**



Source: Adverum Biotechnologies, Inc.

HAE Competitive Landscape

To our knowledge, ADVM-053 is the only gene therapy candidate currently being developed for HAE, although we noticed there are multiple drug candidates in different development stages targeting the same indication (Type I and Type II HAE) (Exhibit 7).

Exhibit 7: **HAE Pipeline**

Drug	Company	MOA	Stage
SHP643 (Lanadelumab)	Shire	kallikrein inhibitor	Phase III (completed)
BCX7353	BioCryst	kallikrein inhibitor	Phase II
IONIS-PKKRx	Ionis	Prekallikrein inhibitor	Phase I
KVD818	KalVista	kallikrein inhibitor	Phase I
SHP623	Shire	C1-INH protein	Phase I
ADVM-053	Adverum	Gene therapy	Preclinical
C1-INH	ProMetic Life Sciences	C1-INH protein	Preclinical
KVD900	KalVista	kallikrein inhibitor	Preclinical

Source: Raymond James research

The most advanced drug candidate in the pipeline for HAE is Lanadelumab, a fully humanized mAb against plasma kallikrein, which met the primary and all secondary endpoints in a randomized, double-blind, Phase III prevention study (HELP) in patients with HAE. During a 26-week treatment period in 125 patients who had 3.7 mean attacks per month at baseline, lanadelumab administered through subcutaneous injections every two or four weeks demonstrated a statistically significant reduction in the monthly attack rate as compared to those seen in the placebo group (-87% at 300 mg/every two weeks vs. -73% at 300 mg/every four weeks vs. -76% at 150 mg/every four weeks). On the safety front, the drug was well tolerated with no reported treatment related serious adverse events. The most commonly seen adverse event (AE) was mild to moderated injection site pain (43% in all lanadelumab arms vs. 29% in placebo).

Clinical Development Plan for ADVM-053

With a recent pre-IND meeting held with the FDA in 1Q17, the company is in the process of transferring the manufacturing process of ADVM-053 to a contract manufacturing organization to prepare for future clinical studies. According to the 2Q17 updates, the company expects to file an IND application in 1H18.

The Wet AMD Franchise

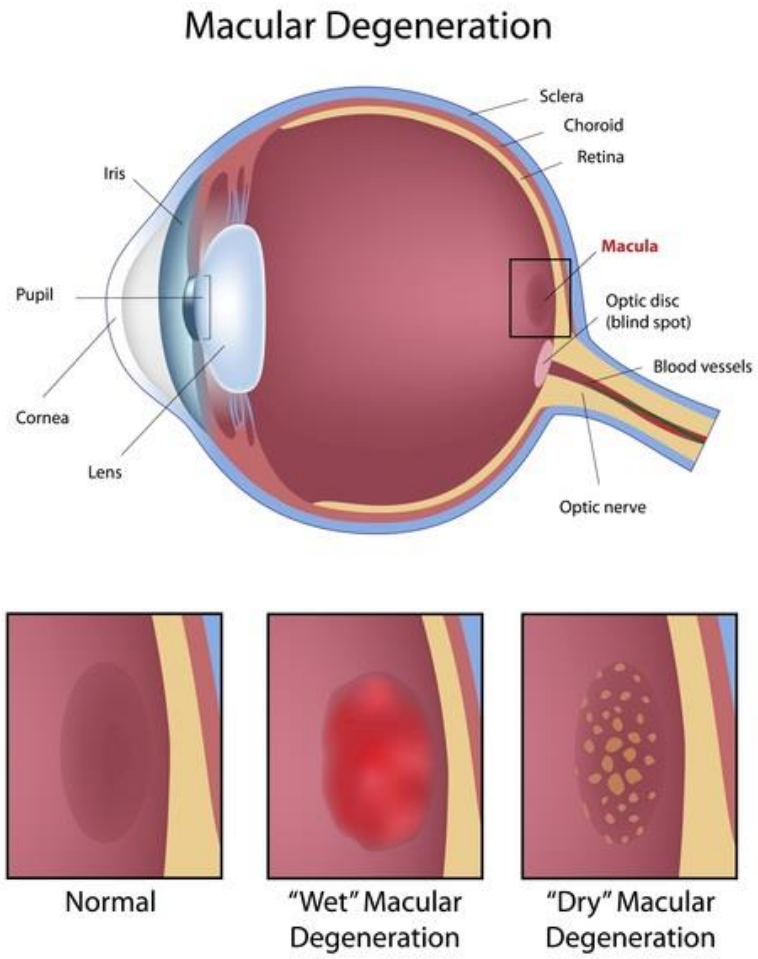
Biology of the Eye

If one pictures the human eye as a ball, the front part of that ball would contain the cornea and pupil, while the back part would contain the retina (approximately 0.5 mm thick) (Exhibit 8). In approximately the center position of the retina is the optic nerve, also known as the cranial nerve, which is made up of over a million nerve fibers and is used to transfer visual information from the eye to the brain. The optic nerve also houses the major blood vessels of the retina, which are responsible for supplying blood to the retina.

Approximately 4.5 mm to 5.0 mm from the optical nerve is a blood-free area known as the macula, the center of which is called the fovea. If one draws a 6 mm circle around the fovea, the encircling region is known as the central retina, while beyond this border the region is called the peripheral retina.

The structure of the eye is quite radical in design. Interestingly, the ganglion cells (the neurons of the retina) reside in the area of the retina closest to the front of the eye. Conversely, the photosensors (the rods and cones) lie in the outermost area of the retina against the RPE and choroid. When a visual stimulus enters the eye, the light must travel through the retina, activate the rods and cones, which subsequently secrete chemical messengers before returning back to an electrical message by the neurons found in the anterior of the retina. The visual image is then transmitted to the brain through the ganglion cells.

Exhibit 8: **The Structure of the Eye and Macular Degeneration**



Source: https://ghr.nlm.nih.gov/condition/age-related-macular-degeneration

Wet AMD

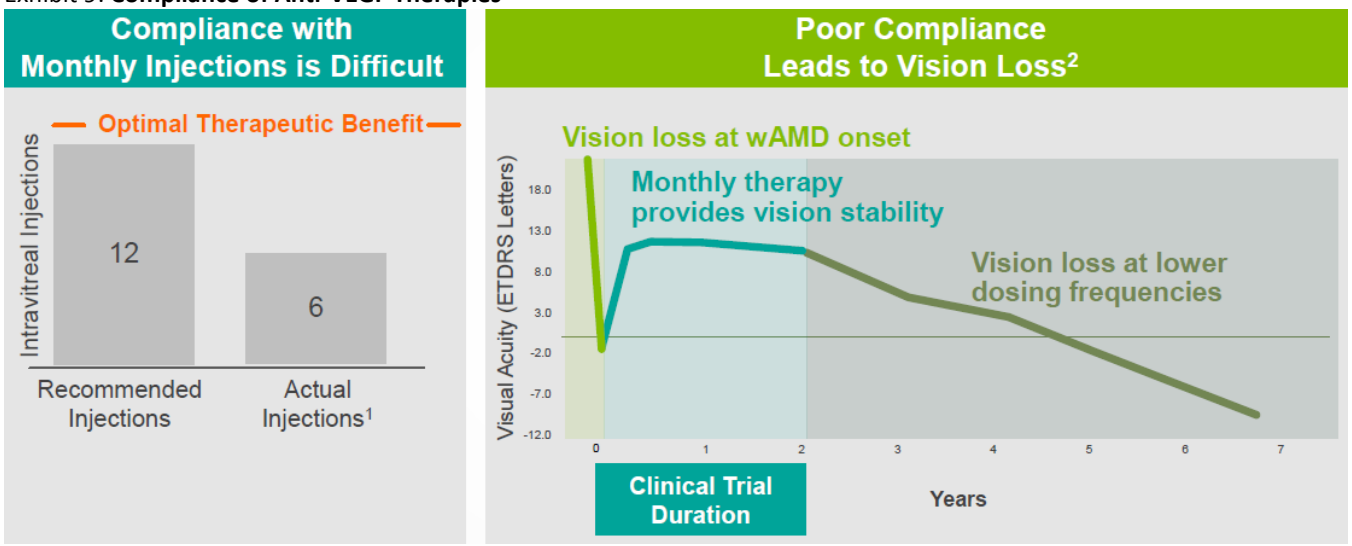
AMD is a disease that results in decline and eventual loss of central vision due to damage to the macula. A subset of AMD patients (10-15%) have wet AMD, which is caused by the growth of abnormal leaky blood vessels beneath the macula that eventually cause fluid leakage that results in physical changes in the structure of the retina and changes in vision. As the disease progresses, blindness can occur due to fibrous scarring of the retina. Wet AMD is the leading cause of blindness in the elderly; in the U.S., approximately 1,500,000 people suffer from wet AMD and about 200,000 new cases are diagnosed each year. Worldwide, approximately 500,000 new cases are diagnosed annually.

Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis (formation of new blood vessels), which is mediated primarily by the binding of VEGF to VEGF receptor (VEGFR), KDR. Flt-1 (fms-like tyrosine kinase -1), another VEGFR, binds VEGF approximately 10 times stronger than KDR, although the binding of Flt-1 to VEGF does not significantly promote angiogenesis. As VEGF can promote the growth of new blood vessels, anti-VEGF products have the potential to prevent the formation of abnormal leaky blood vessels seen in wet AMD patients.

The current standard of care for the treatment of wet AMD is anti-VEGF therapies, which have proven to be effective in improving visual acuity in the majority of patients. Currently, there are three anti-VEGF inhibitors that are most commonly used for the treatment of wet AMD: Regeneron's Eylea (aflibercept, approved in 2011), Roche/Novartis' Lucentis (ranibizumab, approved in 2006), and Roche's Avastin (bevacizumab, off-label use). Of note, Valeant's Macugen (pegaptanib) was the first approved anti-VEGF inhibitor (approved in 2004), although it does not appear to be a significant competitor to the aforementioned three anti-VEGF therapies.

While effective, these anti-VEGF therapies require frequent intraocular injections (every one to two months for years). Therefore, patients usually experience a great degree of inconvenience and discomfort associated with the repetitive injections in the eye, leading to poor patient compliance, which eventually results in vision loss in the long term (Exhibit 9). If VEGF gene therapies offer a similar efficacy and safety profile as compared to these anti-VEGF inhibitors, in our opinion, the former could potentially replace the latter in the marketplace given that they are positioned as a one-time treatment.

Exhibit 9: **Compliance of Anti-VEGF Therapies**

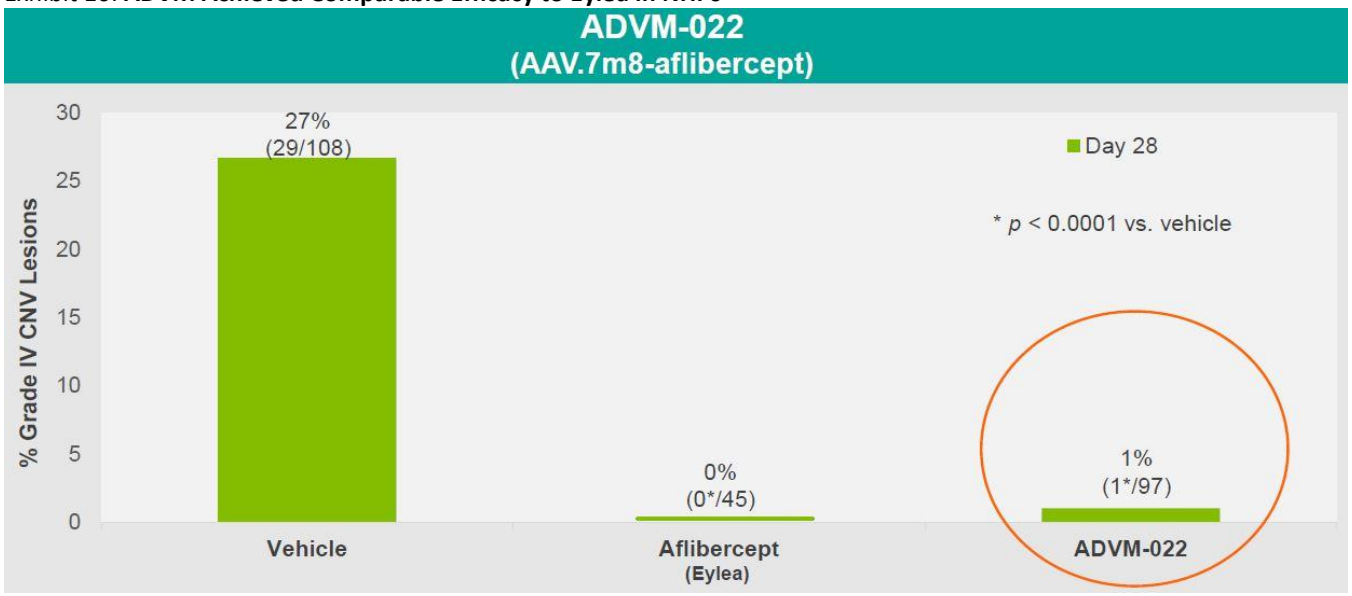


Source: Adverum Biotechnologies, Inc.

Adverum is developing an anti-VEGF gene therapy candidate called ADVM-022, which consists of an AAV.7m8 vector encapsulated anti-VEGFR antibody aflibercept (AAV.7m8-aflibercept). Compared to AVA-101, we believe ADVM-022 has a better design due to the following reasons: 1) Given the better transduction efficiency of the company's proprietary AAV.7m8 vector, ADVM-022 could potentially achieve a higher protein expression level compared to AAV2 based AVA-101; 2) given the demonstrated efficacy of aflibercept in patients with wet AMD, utilizing aflibercept as the transgene product could potentially achieve a better efficacy than the wild type Flt-1 protein; and 3) ADVM-022 is designed to be administered through a intravitreal injection, which is less invasive as compared to the subretinal procedure used for the delivery of AVA-101.

In a laser-induced choroidal neovascularization model in NHPs, which is the industry standard model for testing new wet AMD therapeutic candidates, ADVM-022 demonstrated a comparable efficacy to Eylea in terms of reducing the number of grade IV lesions in the eye at 28 days after the treatment (Exhibit 10). In addition, therapeutic protein levels were maintained at 20 weeks in targeted vitreous and retinal tissue. Given the proof-of-principle preclinical data seen to date, we believe ADVM-022 could potentially replace the current standard of care for patients with wet AMD if a comparable efficacy over the existing anti-VEGFR antibodies as well as the differentiated durability of efficacy can be validated in future clinical trials.

Exhibit 10: **ADVM Achieved Comparable Efficacy to Eylea in NHPs**



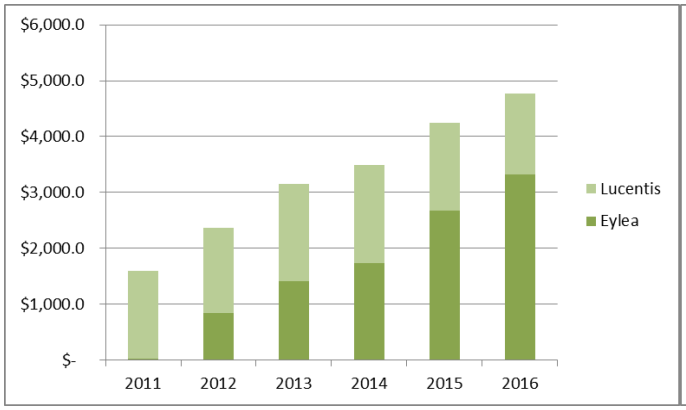
Source: Adverum Biotechnologies, Inc.

Wet AMD Competitive Landscape

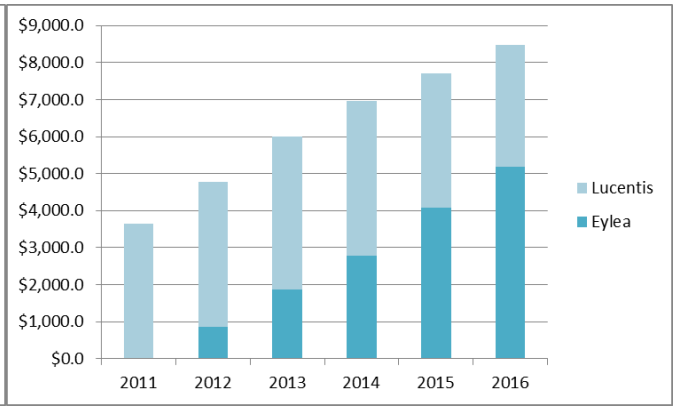
Three VEGF inhibitors have been approved for the treatment of wet AMD: Regeneron's Eylea (aflibercept), Roche's Lucentis, and Valeant's Macugen. Lucentis and Eylea generated worldwide revenues of $4.8, 6.0, 7.0, 7.7, and 8.5 billion in 2012-2016, respectively with Eylea currently taking the lead (Exhibit 11). In addition, Roche's Avastin has also been used off-label for the treatment wet AMD.

Exhibit 11: **Eylea and Lucentis Sales**

US Sales



Worldwide Sales



Source: Regeneron and Roche Company Reports, Raymond James research

Besides currently available anti-VEGF treatments, there are also other gene therapy products in development that could compete with ADVM-022 (Exhibit 12).

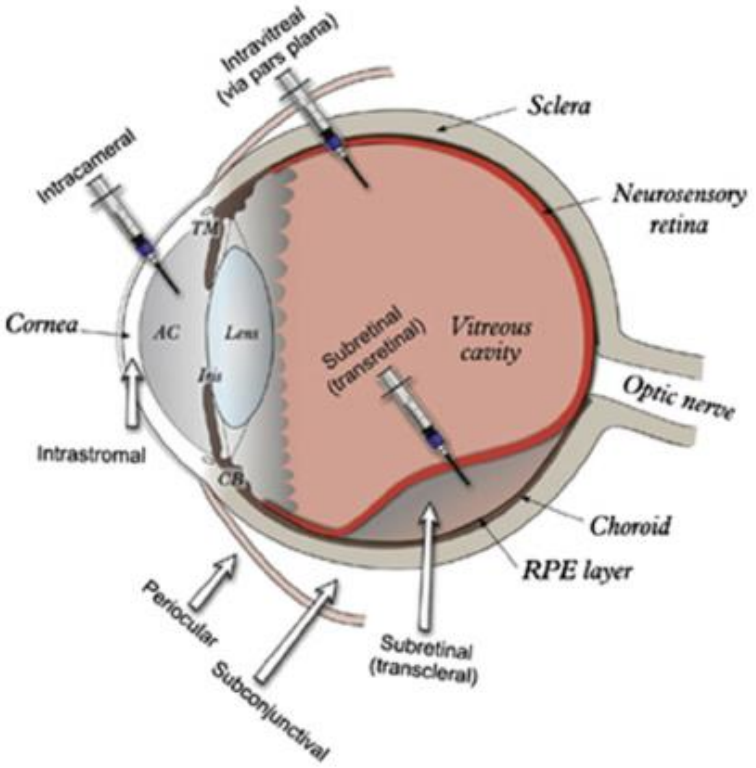
Exhibit 12: **VEGF Gene Therapies in Development**

Product	Company	Current Status	Vector	ROA	Transgene
RGX – 314	Adverum	Phase I	AAV8	Subretinal	anti-VEGF fab
AVA-101	Avalanche	Terminated	AAV2	Subretinal	Native sFlt-1
GZ402663	Sanofi (Genzyme)	Discontinued after Phase I	AAV2	Intravitreal	Chimeric sFlt-1
ADVM-022	Adverum	Preparing IND	Proprietary vector	Intravitreal	7m8-aflibercept)
ADVM-032	Adverum	Not selected for further development	Proprietary vector	Intravitreal	7m8-ranibizumab

Note: In May 2016, Avalanche Biotechnologies merged with Annapurna Therapeutics, with combined entity named Adverum Biotechnologies.
Source: Company reports, Raymond James research

Route of Administration: What Are the Differences Between Subretinal and Intravitreal Injections?

Exhibit 13: **Subretinal Injection vs. Intravitreal Injection**



Source: Dumitrescu, et al, Gene Therapy for Blinding Pediatric Eye Disorders, Advances in Pediatrics, 2015

Attributes	Subretinal injection	Intravitreal injection
Impact of pre-existing serum anti-vector neutralizing antibodies on transgene expression?	No (or at least not significant)	Yes
Transduction efficiency of the retinal pigment epithelium and photoreceptors	Higher	Lower
Invasiveness	More invasive	Less invasive
Current approach of delivering anti-VEGF proteins?	No	Yes
Risk for potential complications	Higher (a 1% risk of retinal detachment and a 60% risk of cataract progression could lead to a cataract surgery within a year)	Lower
Variability of the procedure	Higher (there might be some patients who do not get the intended injection volume)	Lower
Cost	More expensive	Less expensive

Source: Heier, et al, intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial, Lancet, 2017; Raymond James research

Transgene: Anti-VEGF Fab vs. Native sFlt-1 vs. Modified sFlt-1 vs. Anti-VEGF Antibodies

Avalanche's AVA-101 is designed to express native soluble Flt-1, which is a variant of the full length VEGFR-1 protein, whereas Sanofi's GZ402663 (AAV2-sFLT01) consists of a recombinant AAV2 vector that contains a gene expressing a soluble chimeric protein composed of domain 2 of the soluble human VEGF receptor 1 (Flt-1) and the Fc region of human immunoglobulin G (IgG) subclass 1. This AAV2-sFLT01 vector was generated through the HSV helper and HEK293 cell based manufacturing approach, with the purified vector containing ~60% genome containing full capsids. In contrast, both REGENXBIO and Adverum utilize a different transgene, which can produce an anti-VEGFR antibody (or an antibody fragment).

Development of AVA-101 Halted by Avalanche Biotechnologies Due to Lack of Efficacy

AVA-101, comprised of a wild type AAV2 vector that contained a gene expressing soluble Flt-1 (a naturally occurring anti-VEGF protein), was evaluated by Avalanche in a single-center (Australia), open-label Phase I/IIa study (NCT01494805). Of note, on May 12, 2016, Avalanche Biotechnologies merged with Annapurna Therapeutics, with the combined entity named Adverum Biotechnologies.

In June 2015, Avalanche announced top-line results from the Phase IIa portion of the study evaluating AVA-101 in patients with wet AMD aged 55 or older. This study randomized a total of 32 patients into an AVA-101 treatment group (n=21) or a control group (n=11), with 29 having a prior anti-VEGF therapy (a median of 10 injections). AVA-101 was administered to the patients in the treatment group on day seven. Lucentis was given to both groups at day 0 and week 4, and it was also allowed as a rescue therapy beginning at week 8. The primary endpoint was safety, and the secondary endpoints were mean BCVA change from baseline, the number of Lucentis rescue injections, and mean change in central retinal thickness from baseline as measured by SD-OCT.

On the safety front, no SAEs related to AVA-101 were reported, as all patients remained in the study throughout the 12-month period. Of note, all drug related AEs were mild or moderate and resolved over the course of 60 days. While one patient in the treatment group had a non-fatal myocardial infarction, this event was not deemed to be related the gene therapy. One patient in the control group experienced endophthalmitis.

While the safety endpoint was met, the efficacy outcomes were somewhat disappointing. Over the course of 52 weeks, the mean BCVA change from baseline for the treatment group was 2.2 letters vs. -9.3 letters for the control group. While the difference in the mean BCVA changes from the baseline between the two groups was statistically significant, the BCVA improvements achieved by AVA-101 appear to be relatively inferior to what have been reported for the monthly treatment of Lucentis in many other studies (12-month mean BCVA change: 2.2 letters vs. 6.3-11.0 letter). In addition, it did not appear that the gene therapy significantly reduced the number of Lucentis rescue injections, with the median number of rescue injections being 2 (range: 1-6) for the treatment group and 4 (range: 3-5) for the control group. In terms of the impact on central retinal thickness, the treatment group performed worse than the control group, as evidenced by an increase of 25 mm in retinal thickness from baseline in the treatment group vs. a reduction of 56 mm in the control group.

In the treatment group, 12 patients had neutralizing antibodies (nAb) to AAV2 before treatment, and three of the initial nine nAb-negative patients seroconverted after the gene therapy. That said, the principle investigators of this study do not think that these pre-existing nAbs to AAV2 necessarily decreased the clinical activity of the subretinally injected gene therapy.

Avalanche eventually concluded that there was no evidence of a complete and/or durable anti-VEGF response in the majority of patients treated with AVA-101 in the Phase IIa study, resulting in an ultimate decision not to initiate the planned Phase IIb trial to further evaluate this gene therapy for wet AMD.

Sanofi's AAV2-sFLT-01

GZ402663 (AAV2-sFLT-01), comprised an AAV-2 vector that expresses a modified soluble Flt1 receptor, originated from the collaboration established between Genzyme and Applied Genetic Technologies (AGTC) in December 2004. Following the acquisition of Genzyme, Sanofi took over the development of this gene therapy for wet AMD. Due to a lack of efficacy, in April 2015, Sanofi decided not to further develop GZ402663 for AMD.

GZ402663 was evaluated in an open-label, dose-escalating Phase I study (NCT01024998) at four outpatient retinal clinics in the U.S. The full results from this study were published in Lancet in May 2017. A total of 19 wet AMD patients were enrolled into five cohorts and received a single intravitreal injection of GZ402663 into one eye at different doses: cohort 1 - $2x10^8$ vg (n=3), cohort 2 - $2x10^9$ vg (n=3), cohort 3 - $6x10^9$ vg (n=3), cohort 4 - $2x10^{10}$ vg (n=3), and cohort 5 - $2x10^{10}$ vg (n=7). The median baseline BCVA of these cohorts ranged from 20/320 to 20/500. All of the 19 patients completed the 52-week core study, with 17 enrolled in a four-year extension study. Out of these 17 patients, three subsequently withdrew from the study, with two patients in each of the first three cohorts completed the four-year follow-up and one patient in cohort 4 and seven patients in cohort 5 about to complete the four-year follow-up.

With no MTD identified as there were no dose-limiting toxicities, $2x10^{10}$ vg was used in the expansion cohort 5, resulting in a total of 10 patients treated at the highest dose.

No AAV2-sFLT01 vector DNA sequences were found in the blood, nasopharynx, urine, or semen of any patients after the treatment with the gene therapy at any time throughout the study.

At baseline, there were detectable anti-AAV2 antibodies in 12 out of the 19 patients (63%), with 5/10 patients treated at the highest dose having no baseline anti-AAV2 antibodies. Although an increase in anti-AAV2 antibody titer was not observed among the patients in cohorts 1-2 after treatment, such an effect was seen in 62% of the 13 patients in cohorts 3-5. Specifically, three of the five patients in the last two cohorts who had no anti-AAV2 antibodies at baseline generated these antibodies after the gene therapy treatment.

In terms of efficacy, overall, the gene therapy event at the highest dose did not improve the BCVA score significantly, although improvements were seen in some patients during certain time periods (Exhibit 9). For example, the 10 patients in cohorts 4 and 5 achieved a slight improvement in the mean BCVA from baseline to week 8, which declined afterwards, resulting in an eventual reduction in the mean BCVA score at week 52 (Exhibit 14).

Exhibit 14: **BCVA Change for Patients in Cohorts 4 and 5**

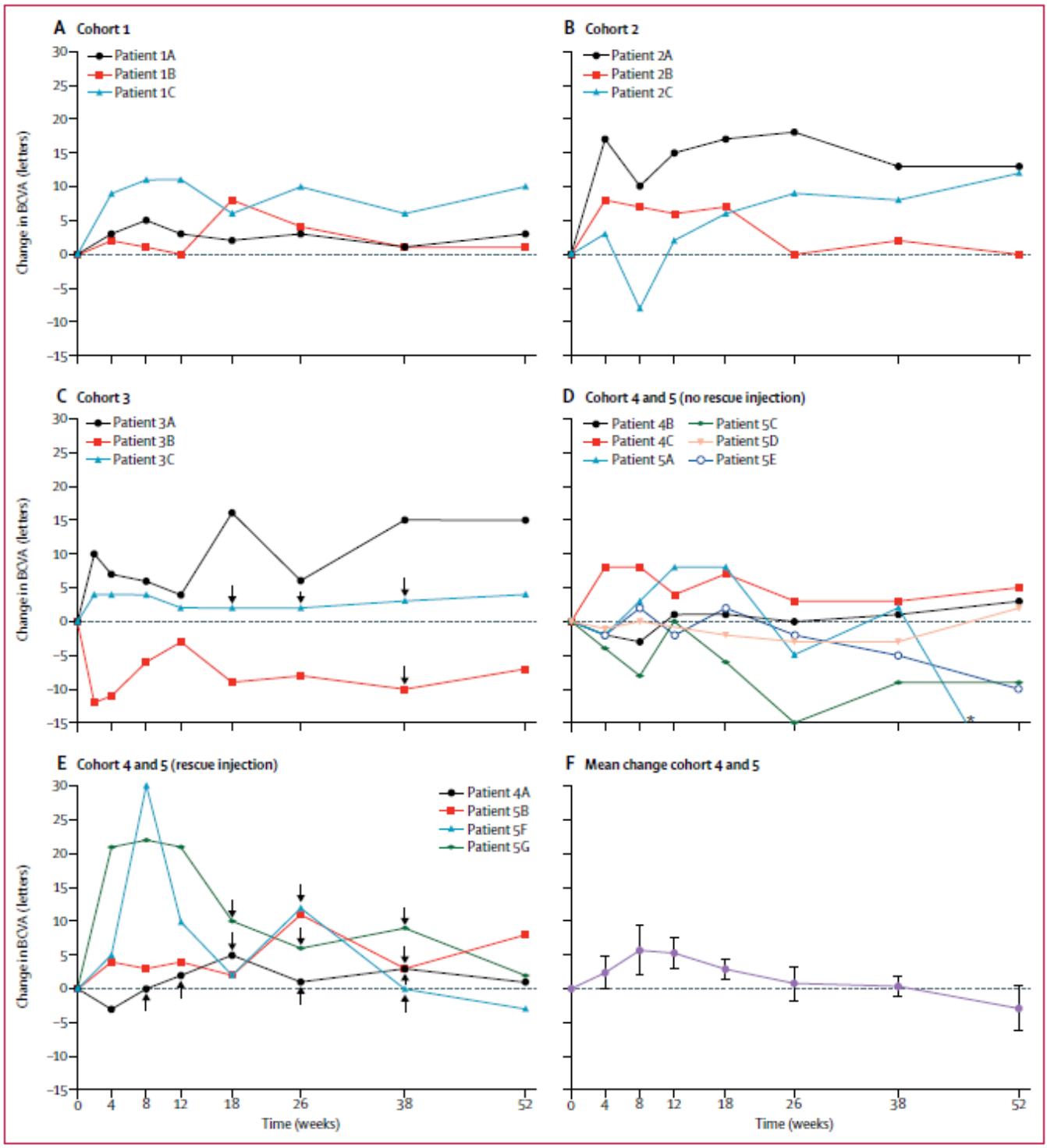


***Figure 5*: Change from baseline best corrected visual acuity after intravitreous injection of AAV2-sFLT01**
Patients had measurement of BCVA at baseline and each study visit after injection of 2×10^{9} vg (A, cohort 1), 2×10^{9} vg (B, cohort 2), 6×10^{9} vg (C, cohort 3), or 2×10^{10} vg (D–F, cohorts 4 and 5). Patients in cohorts 4 and 5 who did not receive any anti-VEGF rescue injections are shown in (D) and those that received rescue injections are shown in (E). The mean change from baseline BCVA for all ten patients in cohorts 4 and 5 who received 2×10^{10} vg is shown in (F). Arrows indicate an anti-VEGF injection was given at that timepoint. *BCVA was reduced from baseline by 28 letters by week 52. BCVA=best corrected visual acuity.

Source: Heier, et al, intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial, Lancet, 2017

On the safety front, GZ402663 appeared to be safe and well tolerated, with no systemic adverse events associated with the injection of the gene therapy, although two patients in cohort 4 experienced possibly drug related adverse events. In addition, one case of intraocular inflammation was observed in the 10 patients treated at the highest dose, although this event was resolved following the use of topical steroids.

Why Did GZ402663 Fail?

A Suboptimal Dose Led to Reduction in sFLT-01 Expression Over Time?

Based on the available data from four patients who were treated at the highest dose, the detectable amounts of sFLT-01 peaked at 12-26 weeks and then decreased between 26 and 52 weeks. According to the investigators, this could have been caused by the dose of $2x10^{10}$ vg, which was not the MTD and could be suboptimal based on the findings from non-human primate studies.

The Impact of Serum Anti-AAV2 Antibodies on Transgene Expression?

The clinical data generated in this study appeared to suggest that the pre-existing serum anti-AAV2 antibodies had a negative impact on transgene expression when the gene therapy was administered intravitreally. Among the five out of 10 patients treated at the highest dose who did not have any detectable anti-AAV2 serum antibodies at baseline, four had detectable expression of sFLT-01 in aqueous humour (the fluid that fills the space between the lens and the cornea) after treatment. In contrast, the four patients who were treated at the same dose with baseline anti-AAV2 titers of 1:400, 1:400, 1:3200, and 1:3200 did not show any detectable expression of sFLT-01 in aqueous humour. These findings were also supported by multiple non-human primate studies. It appears that the impact of pre-existing neutralizing antibodies on transgene expression is more profound when a gene therapy is delivered via an intravitreal injection than a subretinal approach. Therefore, for a study that utilizes the intravitreal route of administration, in our opinion, it is prudent to stratify patients based on the level of their anti-vector neutralizing antibodies.

Financial and Market Analysis

Revenues

Exhibit 15: **Market Model for A1AT Deficiency**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
# of patients with A1AT deficiency	108,541	109,301	110,066	110,837	111,613	112,394	113,181	113,952	114,729	115,511	116,299	117,092	117,890	118,694	119,503
# of patients diagnosed	10,854	10,930	11,007	11,084	11,161	11,239	11,318	11,395	11,473	11,551	11,630	11,709	11,789	11,869	11,950
# of patients without or with mild AAVrh10 neutralizing antibody	8,575	8,635	8,695	8,756	8,817	8,879	8,941	9,002	9,064	9,125	9,188	9,250	9,313	9,377	9,441
# of patients for ADVM-043 at peak	3,430	3,454	3,478	3,502	3,527	3,552	3,577	3,601	3,625	3,650	3,675	3,700	3,725	3,751	3,776
Total addressable market opportunity ('000)	$ 1,114,721	$ 1,122,524	$ 1,130,382	$ 1,138,295	$ 1,146,263	$ 1,154,286	$ 1,162,366	$ 1,170,291	$ 1,178,269	$ 1,186,302	$ 1,194,389	$ 1,202,532	$ 1,210,730	$ 1,218,984	$ 1,227,294
Peak market opportunity ('000)	$ 445,888	$ 449,010	$ 452,153	$ 455,318	$ 458,505	$ 461,715	$ 464,947	$ 468,116	$ 471,308	$ 474,521	$ 477,756	$ 481,013	$ 484,292	$ 487,594	$ 490,918
# of accumulated patients treated								720	1,360	1,916	2,756	3,700	3,725	3,751	3,776
sales of ADVM-043 ('000)								$ 93,623	$ 176,740	$ 249,123	$ 358,317	$ 481,013	$ 484,292	$ 487,594	$ 490,918
Market penetration								8%	15%	21%	30%	40%	40%	40%	40%
Risk un-adjusted revenues after royalty payment								$ 87,070	$ 164,369	$ 231,685	$ 333,235	$ 447,342	$ 450,391	$ 453,462	$ 456,553

EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
# of patients with A1AT deficiency	170,667	171,179	171,692	172,207	172,724	173,242	173,762	174,249	174,737	175,227	175,718	176,211	176,705	177,200	177,697
# of patients diagnosed	17,067	17,118	17,169	17,221	17,272	17,324	17,376	17,425	17,474	17,523	17,572	17,621	17,670	17,720	17,770
# of patients without or with mild AAVrh10 neutralizing antibody	13,483	13,523	13,564	13,604	13,645	13,686	13,727	13,766	13,804	13,843	13,882	13,921	13,960	13,999	14,038
# of patients for ADVM-043 at peak	5,393	5,409	5,425	5,442	5,458	5,474	5,491	5,506	5,522	5,537	5,553	5,568	5,584	5,600	5,615
Total addressable market opportunity ('000)	$ 1,402,199	$ 1,406,405	$ 1,410,624	$ 1,414,856	$ 1,419,101	$ 1,423,358	$ 1,427,628	$ 1,431,630	$ 1,435,643	$ 1,439,667	$ 1,443,702	$ 1,447,749	$ 1,451,807	$ 1,455,876	$ 1,459,957
Peak market opportunity ('000)	$ 560,879	$ 562,562	$ 564,250	$ 565,943	$ 567,640	$ 569,343	$ 571,051	$ 572,652	$ 574,257	$ 575,867	$ 577,481	$ 579,099	$ 580,723	$ 582,350	$ 583,983
# of accumulated patients treated									1,104	2,076	2,915	4,176	5,584	5,600	5,615
sales of ADVM-043 ('000)									$ 114,851	$ 215,950	$ 303,177	$ 434,325	$ 580,723	$ 582,350	$ 583,983
Market penetration									8%	15%	21%	30%	40%	40%	40%
Risk un-adjusted revenues after royalty payment									$ 106,812	$ 200,834	$ 281,955	$ 403,922	$ 540,072	$ 541,586	$ 543,104

A1AT Deficiency	Key assumptions	Rationale
A1AT deficiency prevalence	0.03%	Literature review
A1AT deficiency diagnostic rate	10%	Literature review
% of patients without or with mild AAVrh10 neutralizing antibody	79%	Literature review
Total number of addressable patients for ADVM-043 in 2017 (US and EU)	25,641	Calculated based on aforementioned assumptions
Pricing of ADVM-043	$130,000 (US), $104,000 (EU)	Annuity payment model as long as the gene therapy is effective; The current annual cost for maintenance augment therapies is around $100,000
Market share at peak	40%	To our knowledge, ADVM-043 is currently the only gene therapy candidate in the clinical pipeline.
Drug Risk	20%	Still in early stage (poised to enter a Phase I/II study by YE17) without any clinical data seen to date
Commercialization time	1Q24 (US), 1Q25 (EU)	Company guidance and our estimate
Commercial rights	worldwide	We assume Adverum will be in charge of a worldwide commercialization of ADVM-043 given the orphan status of the disease

Source: Raymond James research

Operating Expenses

Building off of the R&D expense reported for 2Q17, we are projecting R&D of $36 million for 2017E, increasing to $195 million for 2021E. The R&D assumptions from 2017 to 2021 take into account continued expenditure for the clinical trials associated with the company's A1AT deficiency program, as well as other early stage programs.

Based on the SG&A expense reported for 2Q17, we are projecting SG&A of $21 million for 2017E, increasing to $27 million in 2021E. These estimates reflect a ramp in the growth associated with the assumption of hiring a 50-person sales force starting in 2023 ahead of a potential U.S. commercial launch of ADVM-043 in 2024.

The COGS for ADVM-043 is expected to be 5% of the revenues.

Net Income and EPS

The net income for 2Q17 was $(11.4) million, or $(0.27) per share. We are projecting net income of $(54.6) million or $(1.27) per diluted share in 2017E, decreasing to $(222.3) million or $(2.73) per diluted share for in 2021E.

Cash

Based on our estimates, we expect a cash burn rate of approximately $11 million per quarter for the full year 2017, and we believe the current cash position is sufficient to fund operations into 2019. However, we have modeled three capital raises into our estimates. We expect the company to raise approximately $100 million in 4Q18, $200 million in 2019, and $200 million in 2020. We have included these raises in our model as a necessity for the company to sustain operations until it can potentially reach profitability.

Valuation and Price Target Analysis

Valuation

We value Adverum using the sum of the parts analysis of the company's A1AT deficiency program as well as its current cash levels. To derive a value for the A1AT program, we conduct a risk-adjusted net present value (rNPV) analysis, which utilizes the net income as a proxy of the free cash flow (FCF). The revenues for ADVM-043 are derived from our market model (Exhibit 17), whereas the R&D and SGA expenses are estimated largely based on the number of patients on clinical trials and the size of a sales force, respectively. To calculate the NPV, the approximate FCF based on the net income for any given year is discounted at a rate of 15% back to the present time. To account for the clinical/regulatory risk, the NPV is further multiplied by a probability of success assigned to the lead program. At this point, we consider the other, earlier-stage programs as upside to our valuation. Using this methodology, we derive a risk-adjusted per share NPV of $2.34 for ADVM-043. Combining with the cash value of $3.48 per share, we derive a price target of $5.82, which we round to $6.00.

Exhibit 16: **Valuation Analysis**

Product	POS	Per share value	Weighting
ADVM-043 for A1AT deficiency	20%	$2.34	40%
Cash	N/A	$3.48	60%
Total		$5.82	

Key assumptions	
Discount rate	15%
Fully diluted shares outstanding ('000)	53,602

Source: Raymond James research

Exhibit 17: **rNPV of ADVM-043**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031
Revenues (risk-unadjusted, '000)								$ 87,070	$ 271,180	$ 432,518	$ 615,190	$ 851,264	$ 990,464	$ 995,048	$ 999,657
COGS								4,353	13,559	21,626	30,759	42,563	49,523	49,752	49,983
R&D	6,693	14,941	21,688	31,773	33,361	6,672	6,739	6,806	6,874	6,943	7,013	7,083	7,154	7,225	7,297
SGA	2,916	7,280	7,644	8,026	8,428	8,849	15,292	25,056	26,309	27,625	29,006	30,456	20,304	16,243	12,995
Income before tax	(9,609)	(22,221)	(29,333)	(39,799)	(41,789)	(15,521)	(22,031)	50,854	224,438	376,325	548,412	771,162	913,483	921,827	929,382
Tax	-	-	-	-	-	-	-	-	44,888	75,265	109,682	154,232	182,697	184,365	185,876
Tax rate	0%	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%
Net income	(9,609)	(22,221)	(29,333)	(39,799)	(41,789)	(15,521)	(22,031)	50,854	179,550	301,060	438,729	616,929	730,786	737,462	743,506
Present time	10/6/2017														
Discount period	0.24	1.24	2.24	3.24	4.24	5.24	6.24	7.24	8.24	9.24	10.24	11.24	12.24	13.24	14.24
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(9,297)	(18,696)	(21,460)	(25,319)	(23,117)	(7,466)	(9,215)	18,497	56,790	82,802	104,927	128,300	132,155	115,967	101,668
Total NPV ('000)	626,536														
Fully diluted shares outstanding ('000)	53,602														
Per share value	11.69														
Probability of success	20%														
Risk-adjusted per share value	**2.34**														

Source: Raymond James research

Bull/Bear Analysis

In our bull case, we assume higher (50% vs. 20%) probability of success for the company's A1AT deficiency program, which results in a value of about $9.00 per share, indicating a 163% return from the current level. In our bear case, we assume a zero chance of success for the A1AT deficiency program and derive a value of about $3.00, which reflects the current cash levels of the company, suggesting 2% loss from the current level.

Exhibit 18: **Bull/Bear Analysis**

Probability of success	Bull	Base	Bear
ADVM-043 for A1AT deficiency	50%	20%	0%
Valuation	$9.32	$5.82	$3.48
Return	163%	64%	-2%

Note: Closing price of 10/9/17 was used to calculate the potential returns.

Source: Raymond James research

Management

Amber Salzman, Ph.D., President and Chief Executive Officer

Dr. Amber Salzman was appointed president and chief executive officer of Adverum in October 2016 after joining the company earlier in the year as president and chief operating officer after the merger of Annapurna Therapeutics with Avalanche Biotechnologies. Dr. Salzman was the president and chief executive officer of Annapurna Therapeutics between 2012 and 2016. She has served in leadership roles at large pharmaceutical companies, small pharmaceutical companies, and in the rare disease community, including her role as chief executive officer of Cardiokine Inc. prior to its acquisition by Cornerstone Therapeutics, Inc. in 2011. Dr. Salzman had a 25-year career at GlaxoSmtihKline plc, where she served as a member of the R&D executive team, leading drug development projects and clinical trials in more than 30,000 patients worldwide. Since 2001, Dr. Salzman has served as president of the Stop ALD Foundation, a patient-advocacy group seeking improvements in treatments for patients with adrenoleukodystrophy (ALD), and played a key role in developing a lentiviral gene therapy treatment for this disease. Dr. Salzman received a B.A. in computer science from Temple University and a Ph.D. in mathematics from Bryn Mawr College.

Leone Patterson, Chief Financial Officer

Leone Patterson joined Adverum as chief financial officer in 2016 and leads the finance, investor relations, human resources, and information technology functions. Prior to joining Adverum, she served as chief financial officer at Diadexus, Inc. Previously, Ms. Patterson served as vice president and chief financial officer at Transcept Pharmaceuticals Inc. until it was acquired in a reverse merger with Paratek Pharmaceuticals, Inc. in 2014. From 2010 to 2013, Ms. Patterson was vice president and global corporate controller of NetApp, Inc., a data management and storage company. Previously, she was vice president of finance at Exelixis, Inc. Ms. Patterson previously served as vice president of global business planning and analysis of the vaccines and diagnostics division of Novartis AG and was vice president and corporate controller at Chiron. Ms. Patterson began her career in the audit practice of accounting firm KPMG, where she held various positions including senior manager. Ms. Patterson earned a B.S. in business administration and accounting from Chapman University. She earned an Executive M.B.A. and graduated with honors from St. Mary's College.

Athena Countouriotis, M.D., Senior Vice President, Chief Medical Officer

Dr. Athena Countouriotis has significant experience leading clinical development teams and programs, from preclinical through clinical stages of development and approval. Over the course of her career, she has been involved in multiple clinical programs, with a focus on orphan oncology indications, which have supported regulatory approvals in the United States and Europe. Before joining Adverum, Dr. Countouriotis served as senior vice president and chief medical officer at Halozyme Therapeutics. Previously, she was chief medical officer at Ambit Biosciences through the company's initial public offering and acquisition by Daiichi Sankyo. Dr. Countouriotis also worked within Pfizer and Bristol-Myers Squibb in various leading clinical development roles for Sutent®, Mylotarg®, Bosulif®, and Sprycel®. She holds an M.D. from Tufts University School of Medicine, completed her pediatric residency at the University of California, Los Angeles, and did additional training at the Fred Hutchinson Cancer Research Center in the pediatric hematology/oncology program.

Mehdi Gasmi, Ph.D., Chief Science and Technology Officer

Dr. Mehdi Gasmi joined the company in 2013 and leads process development, manufacturing, and quality control functions for Adverum's gene therapy product candidates. He is also responsible for the development of Adverum's novel vector technology platform. A gene therapy veteran, Dr. Gasmi has worked in the field since 1996 at various academic institutions, including City of Hope and the University of California, San Diego, and at gene therapy companies including Chiron, Cell Genesys, and Ceregene. Dr. Gasmi has extensive experience in the design, development, and manufacturing of lentiviral and recombinant AAV vectors for clinical applications. Prior to Adverum, Dr. Gasmi was vice president of biomanufacturing at Généthon. He received an M.S. and Ph.D. in biochemistry from the Claude Bernard University in Lyon, France.

Adverum Income Statement

All figures in thousands ($), except per share data

	FY16A	1Q17A	2Q17A	3Q17E	4Q17E	FY17E	1Q18E	2Q18E	3Q18E	4Q18E	FY18E
Revenues											
ADVM-022 for wet AMD											
ADVM-043 for wet A1AT deficiency											
ADVM-053 for wet HAE											
Collaboration revenue	1,455	462	463			925					-
Total revenues	1,455	462	463	-	-	925	-	-	-	-	-
Operating expenses:											
Cost of sales						-					-
Research and development	31,670	9,061	8,492	8,917	9,362	35,832	9,831	10,322	10,838	12,633	43,624
General and administrative	24,355	7,989	4,064	4,267	4,481	20,801	4,705	4,940	5,187	7,010	21,841
Goodwill impairment charge	60,714	-	-								
Total operating expenses	116,739	17,050	12,556	13,184	13,843	56,633	14,535	15,262	16,025	19,642	65,464
Operating income	**(115,284)**	**(16,588)**	**(12,093)**	**(13,184)**	**(13,843)**	**(55,708)**	**(14,535)**	**(15,262)**	**(16,025)**	**(19,642)**	**(65,464)**
Other income (expense):											
Other income (expense), net	762	489	663			1,152					-
Total other income (expense)	762	489	663	-	-	1,152	-	-	-	-	-
Income (loss) before taxes	**(114,522)**	**(16,099)**	**(11,430)**	**(13,184)**	**(13,843)**	**(54,556)**	**(14,535)**	**(15,262)**	**(16,025)**	**(19,642)**	**(65,464)**
Income tax expense (benefit)	(775)	-	-	-	-	-	-	-	-	-	-
Income tax rate (%)			0%	0%	0%	0%	0%	0%	0%	0%	0%
Net income (loss)	**(113,747)**	**(16,099)**	**(11,430)**	**(13,184)**	**(13,843)**	**(54,556)**	**(14,535)**	**(15,262)**	**(16,025)**	**(19,642)**	**(65,464)**
Net unrealized (loss) gain on marketable securities	**6**	**(88)**	**(49)**								
Foreign currency translation adjustment	**(2)**	**(118)**	**(141)**								
Comprehensive (loss) income	**(113,743)**	**(16,305)**	**(11,620)**	**(13,184)**	**(13,843)**	**(54,952)**	**(14,535)**	**(15,262)**	**(16,025)**	**(19,642)**	**(65,464)**
Net (loss) per share, basic	**(3.14)**	**(0.38)**	**(0.27)**	**(0.31)**	**(0.32)**	**(1.27)**	**(0.34)**	**(0.35)**	**(0.37)**	**(0.34)**	**(1.39)**
Net (loss) per share, diluted	**(3.14)**	**(0.38)**	**(0.27)**	**(0.31)**	**(0.32)**	**(1.27)**	**(0.34)**	**(0.35)**	**(0.37)**	**(0.34)**	**(1.39)**
Weighted average shares outstanding, basic	36,246	42,144	43,009	43,109	43,209	42,868	43,309	43,409	43,509	57,895	47,030
Weighted average shares outstanding, diluted	36,246	42,144	43,009	43,109	43,209	42,868	43,309	43,409	43,509	57,895	47,030

Adverum Income Statement

All figures in thousands ($), except per share data

	FY16A	FY17E	FY18E	FY19E	FY20E	FY21E
Revenues						
ADVM-022 for wet AMD				-	-	-
ADVM-043 for wet A1AT deficiency						
ADVM-053 for wet HAE						
Collaboration revenue	1,455	925	-			
Total revenues	1,455	925	-	-	-	-
Operating expenses:						
Cost of sales		-	-	-	-	-
Research and development	31,670	35,832	43,624	53,455	121,378	194,946
General and administrative	24,355	20,801	21,841	22,933	24,079	27,383
Goodwill impairment charge	60,714					
Total operating expenses	116,739	56,633	65,464	76,388	145,457	222,330
Operating income	**(115,284)**	**(55,708)**	**(65,464)**	**(76,388)**	**(145,457)**	**(222,330)**
Other income (expense):						
Other income (expense), net	762	1,152	-			
Total other income (expense)	762	1,152	-			
Income (loss) before taxes	**(114,522)**	**(54,556)**	**(65,464)**	**(76,388)**	**(145,457)**	**(222,330)**
Income tax expense (benefit)	(775)	-	-	-	-	-
Income tax rate (%)		0%	0%	0%	0%	0%
Net income (loss)	**(113,747)**	**(54,556)**	**(65,464)**	**(76,388)**	**(145,457)**	**(222,330)**
Net unrealized (loss) gain on marketable securities	**6**					
Foreign currency translation adjustment	**(2)**					
Comprehensive (loss) income	**(113,743)**	**(54,952)**	**(65,464)**	**(76,388)**	**(145,457)**	**(222,330)**
Net (loss) per share, basic	**(3.14)**	**(1.27)**	**(1.39)**	**(1.13)**	**(1.79)**	**(2.73)**
Net (loss) per share, diluted	**(3.14)**	**(1.27)**	**(1.39)**	**(1.13)**	**(1.79)**	**(2.73)**
Weighted average shares outstanding, basic	36,246	42,868	47,030	67,430	81,164	81,564
Weighted average shares outstanding, diluted	36,246	42,868	47,030	67,430	81,164	81,564

Adverum Balance Sheet

Figures in $ thousands except per share data

ASSETS	3Q16	4Q16	1Q17	2Q17
Current Assets:				
Cash and Cash Equivalents	231,271	222,170	71,569	39,523
Short-term investments	-	-	137,934	157,895
Receivable from collaborative partner	1,785	886	-	-
Prepaid expenses and other current assets	2,840	2,218	3,137	2,223
Total Current Assets	235,896	225,274	212,640	199,641
Property and equipment, net	4,335	4,169	4,149	3,798
Deposit and other long-term assets	140	140	140	140
Intangible assets	16,200	5,000	5,000	5,000
TOTAL ASSETS	256,571	234,583	221,929	208,579
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current Liabilities:				
Accounts payable	3,067	1,474	3,383	1,125
Restructuring liabilities	25	25	-	-
Accrued expenses and other current liabilities	5,777	6,451	6,630	5,226
Deferred rent, current portion	89	96	103	112
Deferred revenue, current portion	1,691	1,850	1,850	1,850
Total Current Liabilities	10,649	9,896	11,966	8,313
Deferred rent, net of current portion	378	352	325	293
Deferred revenue, net of current portion	6,834	7,099	6,637	6,174
Deferred tax liability	2,025	1,250	1,250	1,250
Other noncurrent liabilities	455	386	370	369
TOTAL LIABILITIES	20,341	18,983	20,548	16,399
STOCKHOLDERS' EQUITY				
Common stock	4	4	4	5
Additional paid-in capital	411,766	413,518	415,603	418,022
Accumulated other comprehensive loss	(19)	(7)	(212)	(403)
Accumulated deficit	(175,521)	(197,915)	(214,014)	(225,444)
TOTAL STOCKHOLDERS' EQUITY	236,230	215,600	201,381	192,180
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	256,571	234,583	221,929	208,579

Adverum Statement of Cash Flows

Figures in thousands ($) except per share data

	3Q16	4Q16	1Q17	2Q17
Operating Activities:				
Net loss	(14,301)	(22,394)	(16,099)	(11,430)
Adjustments to Reconcile Net Loss to Net Cash Used:				
Depreciation and amortization	453	487	516	540
Stock-based compensation expense	2,949	1,564	1,896	2,243
Goodwill impairment charge	394	11,200	-	-
Amortization of premium and accrued interest on marketable securities	-	-	87	116
Non-cash research and development expense	24	(16)	2	22
Changes in Operating Assets and Liabilities:				
Receivable from collaborative partner	48	95	886	-
Prepaid expenses and other current assets	(2,386)	1,388	(437)	1,013
Accounts payable	171	(928)	1,610	(1,944)
Accrued expenses and other current liabilities	1,660	(144)	229	(1,495)
Restructuring liabilities	-	-	(25)	-
Deferred revenue	1,361	424	(462)	(463)
Deferred rent	(20)	(18)	(20)	(23)
Net Cash Provided (Used) in Operating Activities	(9,647)	(8,342)	(11,817)	(11,421)
Investing Activities:				
Purchases of investments	-	-	(138,591)	(34,197)
Maturities of investments	-	-	-	14,000
Purchases of property and equipment	(362)	(924)	(263)	(469)
Net Cash Provided (Used) in Investing Activities	(362)	(924)	(138,854)	(20,666)
Financing Activities:				
Proceeds from issuance of common stock pursuant to option exercises	284	130	187	155
Taxes paid related to net share settlement of restricted stock units	(493)	-	-	-
Proceeds from employee stock purchase plan	113	73	-	-
Proceeds from a financing arrangement	100	-	-	-
Net Cash Provided (Used) in Financing Activities	4	203	187	155
Effect of foreign currency exchange rate on cash and cash equivalents	(26)	(38)	(117)	(114)
Net Decrease in Cash and Cash Equivalents	(10,031)	(9,101)	(150,601)	(32,046)
Cash and Cash Equivalents at Beginning of Period	241,302	231,271	222,170	71,569
Cash and Cash Equivalents at End of Period	231,271	222,170	71,569	39,523

Audentes Therapeutics, Inc. (BOLD-NASDAQ)

Biotechnology

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Rating
Market Perform 3

Current and Target Price

Current Price (Oct-09-17)	$26.15
Target Price:	NM
52-Week Range	$33.43 - $13.13
Suitability	High Risk/Speculation

Market Data

Shares Out. (mil.)	27.8
Market Cap. (mil.)	$727
Avg. Daily Vol. (10 day)	252,813
Dividend/Yield	$0.00/0.0%
BVPS (Jun-17)	$5.83
LT Debt (mil.)/% Cap.	$0/0%

Earnings & Valuation Metrics

	2016A	2017E	2018E
P/E Ratios (GAAP)	NM	NM	NM

To BOLDly Tackle Ultra Orphan Diseases That No One Else Will; Initiating at Market Perform

Recommendation: We are initiating coverage of Audentes Therapeutics with a **Market Perform** rating and High Risk/Speculation suitability given the stage of clinical development. Audentes is developing state of the art gene therapy constructs that can meaningfully alter the course of several ultra-orphan diseases. Two product candidates (AT132 and AT342) are currently in Phase I/II studies based off of compelling, long-lasting efficacy data in pre-clinical animal models. Additionally, we expect two corporate-sponsored trials evaluating two additional products (AT982 and AT307) to start in 2018 in indications which have little in the way of competition. While we like the company's business model of focusing on rare diseases, in our opinion, the company's current market capitalization adequately reflects the solid preclinical results seen to date, the potential for promising clinical data expected within the next 12 months, and a cash position of ~$123.5 million (pro forma). Therefore, we believe it is prudent for investors to stay on the sidelines and reassess once clinical results are reported.

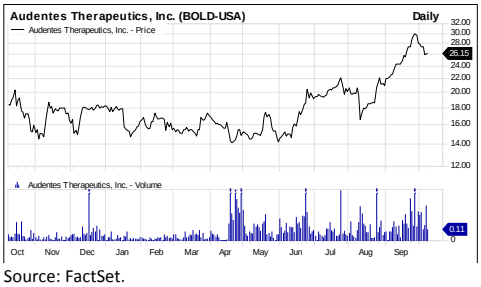
- **X-Linked Myotubular Myopathy (XLMTM) – Long name, but small numbers.** AT132 is currently in a Phase I/II study targeting patients with XLMTM, an ultra-orphan indication that affects approximately 40 newborn boys in the U.S. every year. Animal models demonstrate that one administration of AT132, an AAV8vector designed to target muscle and deliver a fully-functional MTM1 gene, was able to restore some muscle function, but more importantly, improve overall survival in 100% of the animals tested. The company plans to complete three studies, all of which are designed to provide an idea of the natural history of the disease (INCEPTUS and RENCUS) as well as the safety and efficacy of AT132 in patients (ASPIRO). Results the ASPIRO study are expected over the next six months and could provide the basis for a pivotal trial addressing a combined U.S./EU market opportunity of ~$680 million (includes the incidence and prevalence).
- **Pompe disease drives the majority of the value**. AT982, which also utilizes the same AAV8 vector but delivers a copy of the alpha-glucosidase (GAA) gene, is currently being evaluated in an investigator-sponsored study for Pompe disease, with preliminary data expected in 2018. The company plans to file an investigational new drug (IND) application for a corporate-sponsored clinical trial evaluating this gene therapy in 1H18. In our opinion, the clinical evaluation of AT982 is warranted given the promising preclinical results, which showcased AT982's superiority over the existing enzyme replacement therapy. Assuming a potential U.S. approval in 2023 and EU approval in 2024, we expect AT982 could generate accumulated sales of $4.1 billion (risk-unadjusted) from 2023 to 2027.

Valuation: Using the sum of the parts analysis of the company clinical assets, we derive a fair value of $27. See page 88 for more detail.

GAAP EPS	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Full Year	Revenues (mil.)
2016A	NA	NA	(0.94)	(0.91)	$(5.59)	$0
2017E	(0.83)A	(0.87)A	(0.91)	(0.95)	(3.58)	0
2018E	(0.83)	(0.86)	(0.90)	(0.93)	(3.51)	0

Rows may not add due to rounding.

Audentes Therapeutics, headquartered in San Francisco, California, is a clinical-stage gene therapy company focusing on ultra-orphan indications. The company currently has about 117 employees, with the working force roughly equally split across the manufacturing, research, and development functions. Audentes has four product candidates in development: 1) AT132, which utilizes an AAV8 vector licensed from REGENXBIO to deliver a functional copy of the MTM1 gene intravenously, is being evaluated in a Phase I/II study for XLMTM, with preliminary data expected in 4Q17/1Q18; 2) AT342, which also uses the AAV8 vector but delivers a different transgene (UGT1A1), is being assessed in a Phase I/II trial for Crigler-Najjar Syndrome, with preliminary data also expected in 1Q18; 3) AT982, which consists of an AAV9 vector (also licensed from REGENXBIO) and a copy of the GAA gene, is being evaluated in an investigator-sponsor trial for Pompe disease, with a corporate IND filing expected in 1H18; and 4) AT307, which utilizes the same AAV9 vector to deliver a copy of the CASQ2 gene into the heart, is slated to enter the clinic for catecholaminergic polymorphic ventricular tachycardia (CPVT).



Source: FactSet.

Company Description

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Newsworthy Catalysts

Product	Timing	Description
AT132 for XLMTM	4Q17 / 1Q18	Preliminary data from the Phase I/II ASPIRO study
	2H18	Potential to initiate a discussion with the regulatory agency
AT342 for CN	4Q17	Results from the Phase I/II LUSTRO lead-in study
	4Q17 / 1Q18	Preliminary data from the Phase I/II VALENS study
	2H18	Potential to initiate a discussion with the regulatory agency
AT982 for Pompe disease	1H18	IND filing
AT307 for CPVT	YE17	IND filing

Source: Audentes Therapeutics, Raymond James research

Summary of Investment Risks

Clinical and Regulatory Risk

The clinical development of Audentes' products bears risk given that no clinical data has been reported for these products. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk

In general, the commercial success of a gene therapy is dependent on pricing/reimbursement. If Audentes cannot secure a reasonable price to compensate for the ultra-rare nature of most of the diseases being evaluated, the company's products may not be commercially viable.

In addition, Audentes' products could face competition from existing therapies. For example, in the Pompe disease space, the approved enzyme replacement therapy (Sanofi's Lumizyme) has demonstrated effectiveness, which could result in pressure on the adoption of Audentes' gene therapy if/when it is commercialized.

Financing Risk

Audentes currently has no product revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Summary of Investment Highlights

Three Critical Readouts Expected in the Next 12 Months for XLMTM

AT132, the company's flagship candidate, targeting the delivery of the MTM1 gene via an AAV8 vector to skeletal muscle to address patients with XLMTM, has received orphan drug designations from both the FDA and EMA. Preclinical results in mouse and canine models demonstrated long lasting results (some dogs have been followed out for five years) in terms of survival, muscle strength, and respiratory function after a single administration of the gene therapy. Importantly, the treatment appears to not have any significant treatment related events to date. The company's current clinical strategy for AT132 consists of three studies:

- **ASPIRO**: A multicenter, open-label, dose-escalating study evaluating AT132 in a total of 12 patients. With the first patient dosed in September 2017, preliminary results from this study (likely from three patients) are expected in 1Q18 (likely at the J.P. Morgan Healthcare Conference).

- **INCEPTUS**: A prospective natural history run-in study enrolled 18 patients who will both serve as a control and a baseline for the ASPIRO study. Importantly, this study serves as a feeder into the ASPIRO study.

- **RECENSUS**: A retrospective chart review of 120 XLMTM patients, which serves as a historical control for the ASPIRO study, has demonstrated that 64% of patients died below the age of 18 months.

Based on our discussions with management, we believe the company will obtain the data from all three studies, in particular, six months of duration data from ASPIRO, before talking to the regulators. Given

the ultra-orphan nature of the disease, we believe it may be possible for the company to obtain a break-through designation and file for accelerated approval in 2019.

Same Game Plan, Different Indication: Targeting CN

CN patients have high levels of bilirubin in the blood, which can subsequently lead to kernicterus, or severe brain and nerve damage. While phototherapy is the standard of care, it becomes less and less effective over time. AT342 is the company's second most advanced program also utilizing an AAV8 vector but containing the functional version of the UGT1A1 gene which is missing (or ineffective) in many patients diagnosed with CN. Copying the same play book as XLMTM, the company is running a Phase I/II run-in study, which will subsequently feed eligible patients into the safety and efficacy portion of the study.

- LUSTRO: The Phase I/II study evaluating 16-18 patients with severe CN in an effort to ascertain the disease course, natural history, bilirubin variability, and phototherapy use. While not completely enrolled, patients have been followed for an average of 8-12 weeks. Results from this lead-in study are expected in 4Q17.

- VALENS: A parallel Phase I/II study evaluating three doses of AT342 in 12 patients is underway, with the primary endpoint being changes in serum bilirubin and hours on phototherapy within 12 weeks of starting therapy at 18 weeks (after a tapering of phototherapy has been initiated). Results from this study (one to three patients) are expected in 4Q17/1Q18.

Based on our subsequent conversations with management, we expect the company to initiate discussions with both the U.S. and European regulators in 2018 with the potential for initiating pivotal studies that very same year.

2018 Clinical Studies to Tackle Pompe and CPVT

Although early, we expect at least two INDs to be filed in YE17, including one targeting Pompe Disease and another focused on catacholaminergic polymorphic ventricular tachycardia (CPVT). Both indications have marketed products used for treatment, but for compliance, cost, or efficacy/safety reasons, new methods to treat these patients are being developed. In the case of Pompe, we acknowledge that Sanofi's Lumizyme has generated over $800 million in worldwide sales, even in the face of side effects including hypersensitivity reactions and anaphylaxis. A competitive analysis of the landscape demonstrates several companies developing similar enzyme replacements, with Audentes being the only gene therapy company focused on a long-term solution. Preclinical results appear promising in both programs, which, in our opinion, support clinical evaluation.

Audentes' Portfolio

Product	Status	Market	Rights
AT132	Phase I/II	XLMTM	Audentes
AT342	Phase I/II	Crigler-Najjar Syndrome	Audentes
AT982	Preclinical	Pompe disease	Audentes
AT307	Preclinical	CPVT	Audentes

Source: Audentes, Raymond James research

The XLMTM Franchise

Background of X-Linked Myotubular Myopathy (XLMTM)

X-Linked Myotubular Myopathy (XLMTM) belongs to a group of disorders called centronuclear myopathies, in which the nucleus is located at the center of the rod-shaped muscles cells (instead of at either end) due to mutations in genes such as MTM1, DNM2, RYR1, and TTN. In regards to XLMTM, it is a rare disease caused by mutations in the MTM1 gene that affects the production of myotubularin, whose function is to regulate nuclear localization and cell signaling, all of which are required for the normal development and function of skeletal muscle.

The incidence of XLMTM is estimated to be one in 50,000 male births. Based on our estimates, there are approximately 150 and 240 young boys living with this disease in the U.S. and EU, respectively.

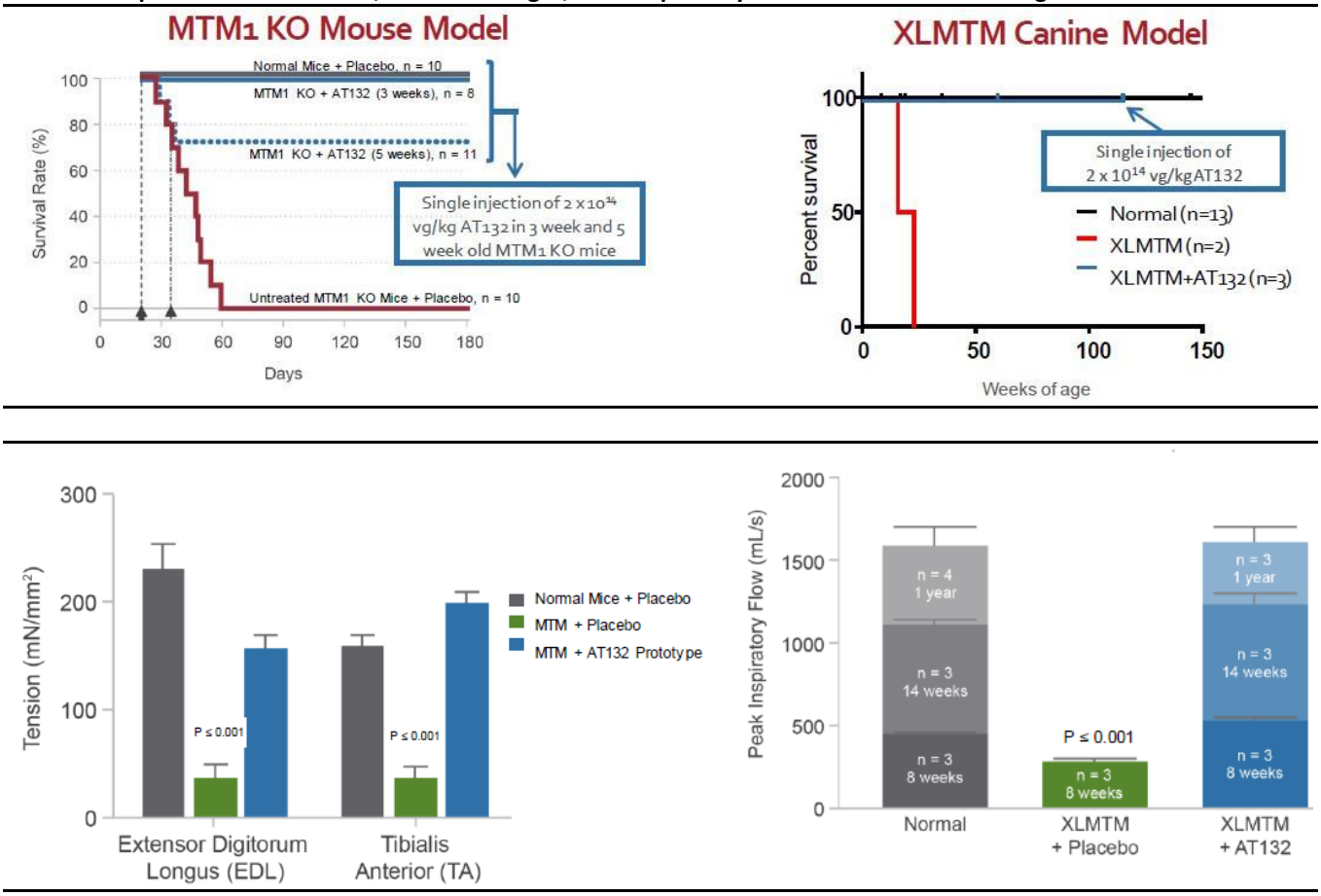
Most males with XLMTM present at birth with severe hypotonia (low muscle tone), extreme muscle weakness and wasting, feeding challenges, as well as severe respiratory insufficiency or failure, which lead to an estimated 50% mortality rate at 18 months.

Given that there is no approved therapy for the treatment of XLMTM, management of patients is based on supportive care, which is conducted by a panel of specialists including a pulmonologist, neurologist, physical therapist and/or rehabilitation medicine specialist, and clinical geneticist.

Preclinical Study Results of AT132

Audentes is developing AT132, an AAV8 vector targeting skeletal muscle/liver and delivering a functional copy of the MTM1 gene, with the goal to correct the disease phenotype following a single intravenous administration. Notably, AT132 received orphan designation from both the FDA and EMA. To date, a preclinical study of a single administration of AT132 at 2x10^14 vg/kg dose level in both canine and murine models of the disease demonstrated dramatic improvements in all outcomes, including histology, muscle strength, respiratory function, and survival (Exhibit 1).

Exhibit 1: **Improvement in Survival, Muscle Strength, and Respiratory Function in Mouse and Dog XLMTM Models**



Source: Audentes Therapeutics

Additionally, in a non-human primate (NHP) study, an intravenous administration of AT132 achieved robust MTM1 protein expression between 8x to 20x of endogenous levels in target skeletal muscle. On the safety front, AT132 appeared to be safe and well tolerated, with no significant treatment related adverse events seen to date.

Clinical Program for AT132

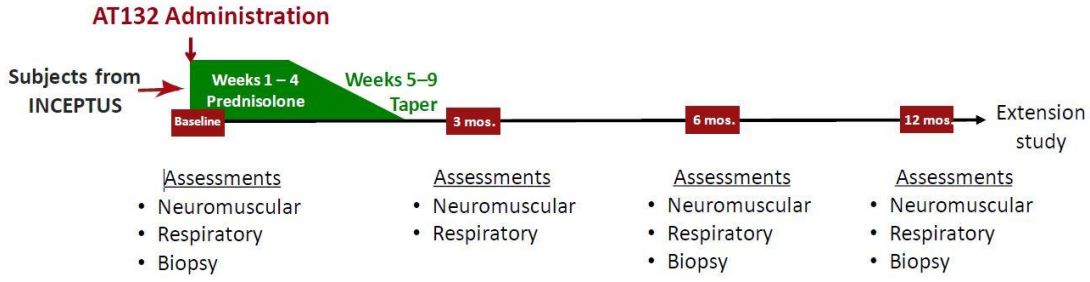
The company's clinical program for AT132 consists of three studies with the goal to evaluate the efficacy and safety of AT132 in children with XLMTM as well as to study the natural history of the disease. These studies include:

- **INCEPTUS:** The INCEPTUS study is a Phase I/II run-in study, which enrolled 18 XLMTM patients who are less than four years old to characterize the disease (respiratory and neuromuscular signatures) and evaluate the disease burden on patients and caregivers. In addition, the INCEPTUS study is expected to identify patients who are eligible to participate in the ASPRIRO study as well as serve as a patient control.

- **ASPIRO:** The ASPIRO study is a multicenter, multinational, open-label, dose-escalating, delayed treatment concurrent control Phase I/II study evaluating the safety and preliminary efficacy of AT132 administered intravenously in approximately 12 XLMTM patients who are less than five years of age.

  The study is expected to enroll nine subjects to be assigned to three ascending dose (1.0, 3.0, and 5.0 x 10^14 vg/kg) cohorts, as well as one delayed-treatment concurrent control subject for each cohort (three subjects in total). Primary endpoints of the study include safety (adverse events and certain laboratory measures, immunological parameters) and assessments of neuromuscular and respiratory function. Secondary endpoints include the burden of disease, health related quality-of life (QOL), and muscle tissue histology and biomarkers. The primary efficacy analysis is expected to be conducted at 12 months after the treatment, with interim evaluations anticipated at earlier time points (Exhibit 2). In addition, after the primary 12-month assessment, subjects are expected to be followed for another four years to assess the long-term safety, durability of effect, and developmental progression.

Exhibit 2: **ASPIRO Phase I/II Clinical Study Design**



Source: Audentes Therapeutics

- **RECENSUS:** With the goal to further characterize the clinical manifestations and natural history of XLMTM, the company is conducting the RECENSUS study to review the medical chart of approximately 120 living and deceased XLMTM patients retrospectively. Data from an initial analysis of 112 male patients in the study reported in March 2017 showed that XLMTM is a life-threatening disease with a neonatal manifestation, which is consistent with previously published results. Key findings revealed in the analysis include: 1) The overall mortality was 44%, with a higher mortality associated with patients who were below 18 months of age (64% vs. 32% with those >18 months old); 2) infants with XLMTM spent 35% of their time in the hospital and had an average of 3.7 surgeries in their first year of life; 3) 95% of XLMTM infants were hypotonic at birth, among which 90% required respiratory support; 4) 60% of patients had a tracheostomy, 48% of patients required 24-hour ventilation, while others spent an average of 8.5 hours per day on a ventilator; 5) among evaluated patients, the majority received the most invasive forms of ventilation; and 6) the mean time required for a confirmed diagnosis upon disease manifestation was significantly shortened from 35.1 months (1996 – 2000) to 4.4 months (2011 – 2014), which is likely due to an increasing physician's awareness as well as improved diagnostic techniques.

The Crigler-Najjar Syndrome Franchise

Background of Crigler-Najjar Syndrome

Crigler-Najjar syndrome (CN) is an ultra-rare, congenital autosomal recessive monogenic disease caused by mutations in the gene encoding the UGT1A1 (uridine-diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1) enzyme whose function is to convert unconjugated bilirubin to a water-soluble form (conjugated, nontoxic) that can be excreted from the body. Due to the loss of or reduced function of UGT1A1, CNS patients have an extremely high level of unconjugated bilirubin in their blood (hyperbilirubinemia) that results in a yellow colored skin and whitening of the eyes (jaundice). In addition, accumulation of unconjugated bilirubin in the brain and nerve tissues (kernicterus) can lead to irreversible brain and neurological damage, including increased muscle tone (hypertonia), arching of their backs, hearing problems, and intellectual disability. Based on the severity of the disease, CN can be divided into two types: Type I CN (no UGT1A1 function) is the very severe form with a high mortality due to kernicterus (a very severe type of brain damage); Type II CN (<20% of normal UGT1A1 function) are less likely to develop kernicterus and are more likely to survive into adulthood.

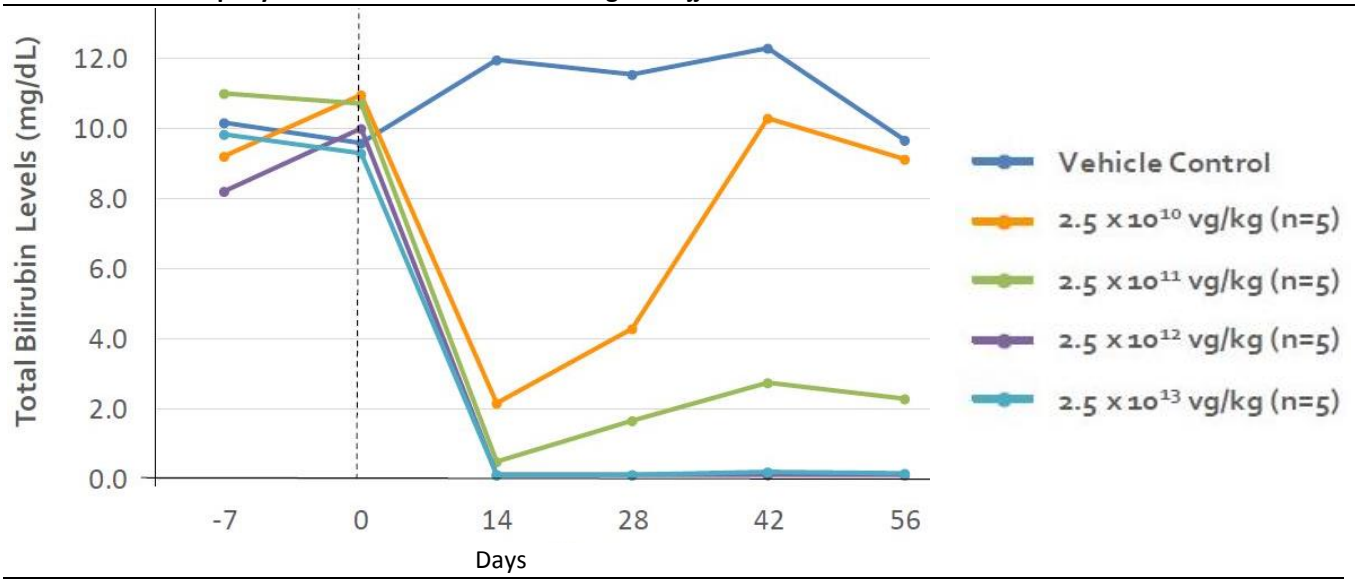
The incidence of CN is estimated to be one in 1,000,000 newborns, translating into about four new patients every year in the U.S. The current standard of care for type I CN is a daily (10-12 hours) phototherapy, which utilizes a fluorescent (blue) light focused on the bare skin to accelerate the bilirubin decomposition and excretion, therefore decreasing serum bilirubin levels.

However, phototherapy begins to lose efficacy starting around age four due to thickening of the skin and a reduction in surface area to body mass ratio, therefore, leaving liver transplantation the only effective treatment option at this point. In addition, while ineffective for Type I CN, three weeks of phenobarbital induction therapy is effective for the treatment of Type II CN, which is able to lower bilirubinemia by 60-70%.

Preclinical Results AT342

With the goal to achieve a meaningful and durable reduction in serum bilirubin level, the company is developing a gene therapy candidate AT342 to serve as a better treatment option relative to the daily phototherapy as well as to potentially eliminate the need for liver transplantation. AT342 is built on an AAV8 vector consisting of a functional version of the UGT1A1 gene. In a dose-ranging preclinical study of AT342 in a CN mouse model, a single tail vein injection of a AT342 at dose levels of 2.5x10^12 vg/kg or 2.5x10^13 vg/kg achieved a rapid reduction and normalization in bilirubin levels, which was maintained up to 56 days (Exhibit 3). In addition, previously published results demonstrated that administration of AAV8-UGT1A1 in newborn CN mice was able to significantly and durably (up to 17 months) reduce the bilirubin level, even at a 5-8% of the normal UGT1A1 level expressed in the liver.

Exhibit 3: **AT342 Rapidly Reduces Bilirubin Levels in Crigler-Najjar Mouse Model**



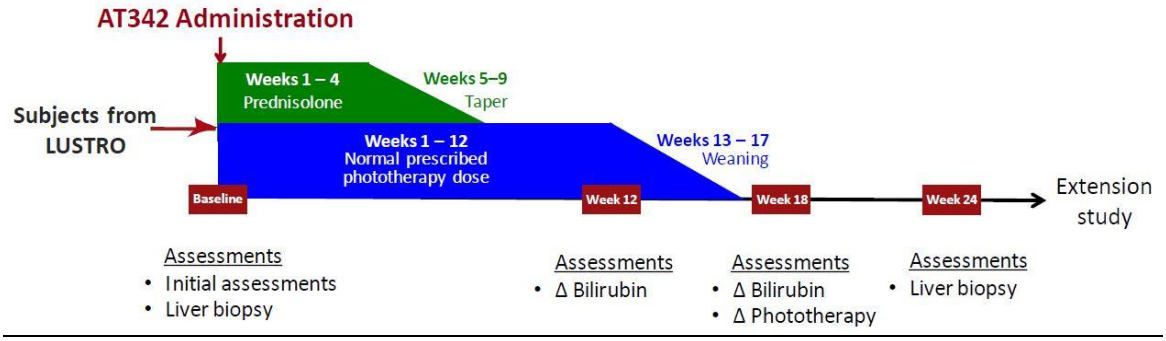
Source: Audentes Therapeutics

Clinical Program for AT132

According to the 2Q17 conference call, the company is initiating an open-label, dose-ascending, delayed treatment concurrent control study (VALENS) evaluating the safety and preliminary efficacy of AT342 in approximately 12 CN patients who are greater than or equal to one year of age, with preliminary data anticipated in 4Q17/1Q18. The VALENS study is expected to enroll nine patients with three of each to be assigned at dose levels of 2.5x10^12, 1.0x10^13, and 2.5x10^13vg/kg, respectively, as well as another three patients who will receive a delayed treatment at each dose level and serve as the concurrent control.

Primary endpoints of the study include safety and changes in serum bilirubin and number of hours on phototherapy. Secondary endpoints include the percentage of patients who no longer need phototherapy, UGT protein expression, as well as DNA and RNA levels from liver biopsy at 24 weeks. In regard to the treatment regimen, enrolled patients are expected to remain on prescribed phototherapy for 12 weeks following administration of AT342. If a meaningful decrease in bilirubin at 12 weeks is seen, patients will be tapered down and weaned off of phototherapy over a five-week period (from week 13 to week 17). The primary efficacy analyses are expected to be conducted at the 12- and 18-week time points, with an additional minimum of five years follow-up anticipated to assess the long-term safety and durability of effect (Exhibit 4). In parallel, the company is conducting a Phase I/II run-in study (LUSTRO), which is designed to characterize the disease, natural history, bilirubin variability, and phototherapy time in patients with CN, with preliminary data expected in 4Q17. Additionally, the study is expected to identify patients eligible for enrollment in the VALENS study and to serve as a within-patient control.

Exhibit 4: **VALENS Phase I/II Clinical Study Design**



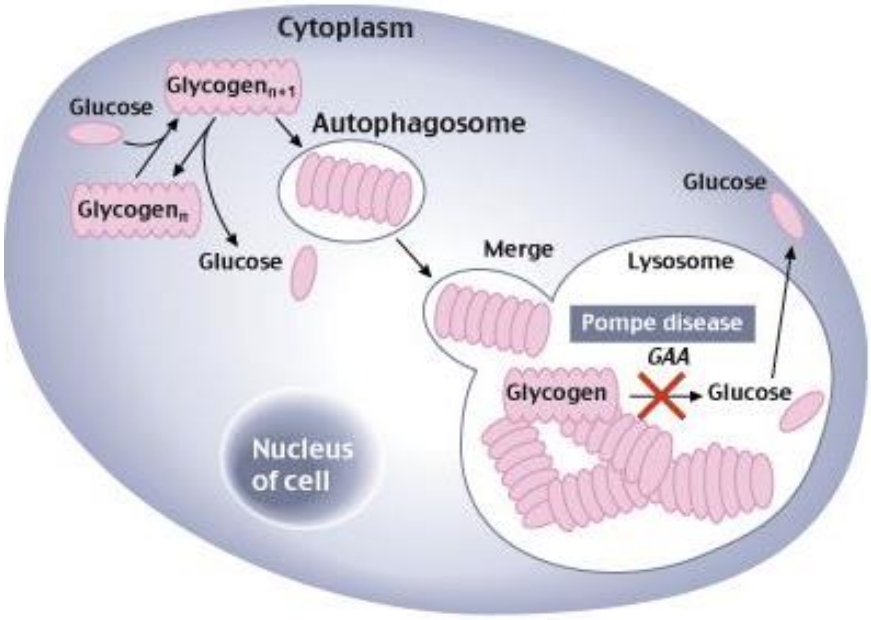
Source: Audentes Therapeutics

The Pompe Disease Franchise

Background of Pompe Disease

Pompe disease, or glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by mutations in the gene encoding the lysosomal enzyme alpha-glucosidase (GAA), which results in a deficiency of GAA protein and an accumulation of glycogen in multiple tissues including cardiac, skeletal, and smooth muscle (Exhibit 5). Patients with Pompe disease are generally divided into two subtypes in which infantile patients (25%) with early disease onset are often characterized by cardiomegaly (thickening of the heart muscle), muscle weakness, hypotonia, respiratory distress, and death due to cardiorespiratory failure in the first year, and patients with late onset disease (childhood or juvenile) who typically have 1-40% of normal enzyme levels and usually have no cardiomyopathy, but often experience progressively difficult walking and a decline in respiratory function. The incidence of Pompe disease is approximately one in 40,000 newborns, with the rate of progression being highly variable and correlated with the age of symptom onset and the degree of enzyme deficiency.

Exhibit 5: **The Mechanism of Pompe Disease**



Source: http://www.socialstyrelsen.se/rarediseases/pompedisease

Currently, the only effective therapy for Pompe disease is Lumizyme/Myozyme (Alglucosidase alfa), which is an enzyme replacement therapy (ERT) approved for the treatment of the infantile form in 2006, the late onset form (>8 year old) in 2010, and eventually all-age patients in 2014. According to Sanofi-Genzyme, Lumizyme achieved worldwide annual sales of about $848 million including $383 million in the EU and $281 million in the U.S. in 2016.

The approval of Lumizyme for infantile Pompe disease was based on three clinical studies where Lumizyme demonstrated a significant survival benefit as well as multiple other clinical metrics including improvements in the Alberta Infant Motor Scale (AIMS) and the left ventricular mass index (LVMI). In a multicenter, open-label study where 18 infants who were seven months old or younger were enrolled and dosed intravenously with Lumizyme at either 20 mg/kg or 40 mg/kg every two weeks, Lumizyme treated patients achieved a 100% survival at 18 months, with 83% of them being alive without an invasive ventilator support, which compared favorably with an only 2% survival rate seen in historical controls (61 patients born between 1982 and 2002 and diagnosed by six-months old). In another multicenter, open-label study where 21 patients who aged between 3.0 months and 3.5 years were enrolled and dosed with 20 mg/kg of Lumizyme every other week, a 75% and 80% survival rate was seen in patients who were free of invasive ventilator support at the time of receiving the first treatment and who were on the invasive ventilator support at baseline, respectively, which led to a combined survival rate of 76.2% (16/21) at week 52. Lastly, in a single center, open-label study there where 18 infants who were below six month olds, 16 patients (89%) survived to 18 months without an invasive ventilator support.

In regards to the late-onset Pompe disease, the approval of Lumizyme was based on positive results from a 2:1 randomized, double-blinded, placebo controlled study in 90 patients who were between 10 and 70 years old and were treatment naïve to ERT. In this study, Lumizyme administered intravenously every other week for 18 months demonstrated a statistically significant improvement (P=0.004) in the mean forced vital capacity at 78 weeks (56.2%, n=60), which is a measure of respiratory function, as compared to that seen at baseline (55%) and in the control group (52.8%, n=30). In addition, while Lumizyme treated patients achieved an increase of the mean six-minute walk test (6MWT) by 25 meters (330 meters at baseline), a three-meters decrease of the mean 6MWT was seen in the control group, resulting in a delta of 28 meters (p=0.06).

On the safety front, while the most common adverse events (AEs) were hypersensitivity reactions for both the infantile (51%) and late onset diseases, serious adverse reactions such as anaphylaxis were seen in the late onset form, with one patient who had a history of Wolff Parkinson-White syndrome experiencing a supraventricular tachycardia. In addition, immunogenicity associated with the injected enzyme was seen, as evidenced by the presence of antibodies developed against the protein in 89% and 100% of patients enrolled in studies for the early and late onset disease, respectively. Of note, some patients in the clinical studies and in the post-marketing setting developed IgE antibodies against Lumizyme, who appeared to have a higher risk for the development of hypersensitivity reactions and anaphylaxis.

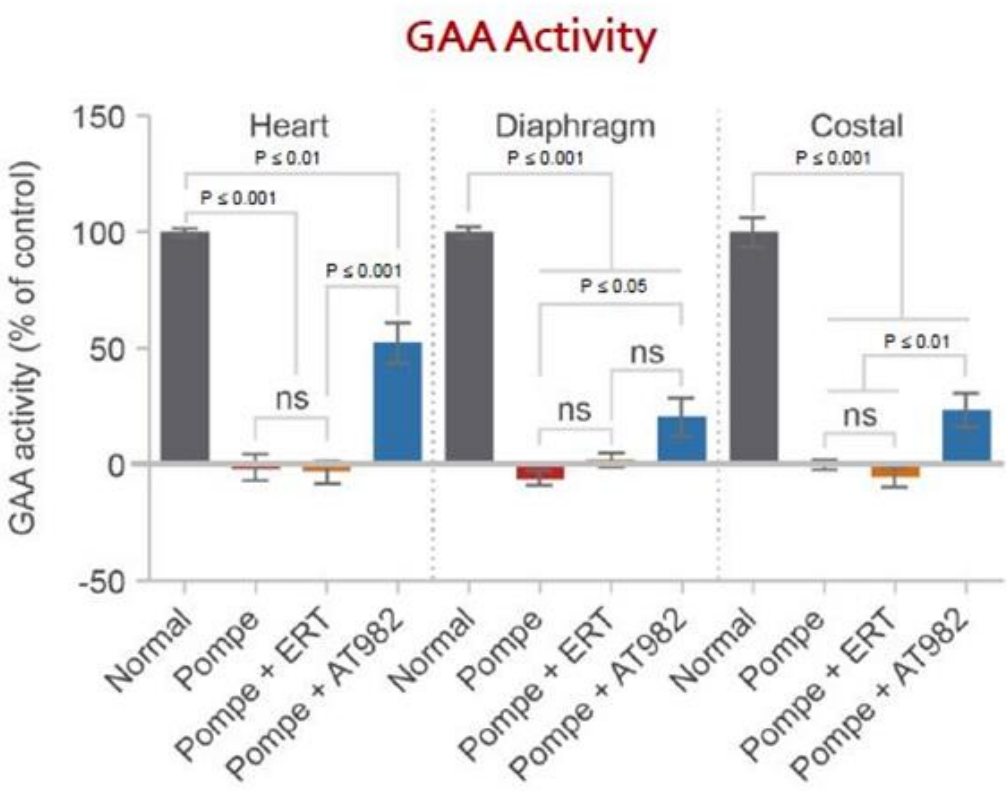
Despite the demonstrated efficacy of Lumizyme for the treatment of Pompe disease, the ERT is associated with several limitations, including: 1) a frequent administration (bi-weekly); 2) a majority of patients (93%) develop antibodies against the protein which comprises the efficacy while causing immunogenicity-associated side effects; 3) a black box warning related to the risk of life-threatening anaphylaxis and other severe allergic and immune mediated reactions; 4) long-term follow-up study suggested a decrease in respiratory and motor function as well as a disease progression despite the treatment, which is likely due to the inability of the injected enzyme to cross the blood brain barrier, which leads to glycogen accumulation in the nervous system; and 5) a hefty lifetime cost with the treatment, which is estimated to be in excess of $7 million for patients with infantile onset disease.

Preclinical Results of AT982

AT982 consists of an AAV9 vector that delivers a GAA gene expression cassette containing a desmin promoter capable of increasing GAA activity in targeted tissues. Of note, while AAV9 has a tropism for the heart, muscle, and motor neurons, the desmin promoter appears to be capable of increasing gene expression in muscle as well as in motor neurons.

In a recent preclinical study evaluating the efficacy of a systemic administration of AT982 in six mice dosed at approximately 5 x 10^12 vg/kg, AT982 significantly increased GAA activity in the heart, diaphragm, and costal muscle compared to that seen in both untreated mice and mice treated with ERT during a three-month time window (Exhibit 6).

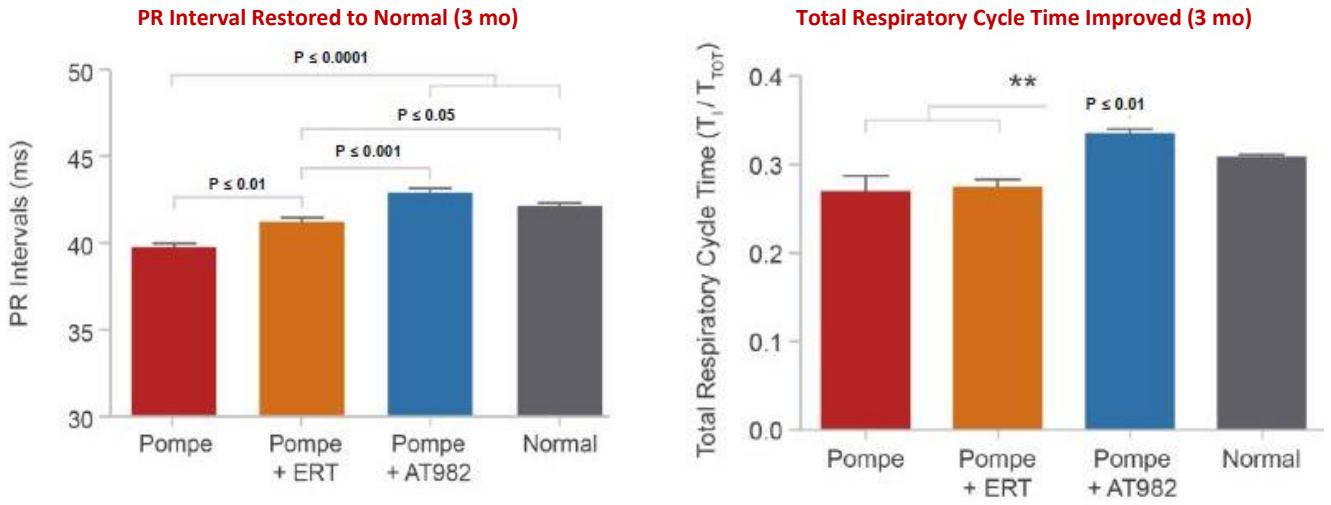
Exhibit 6: **AT982 Significantly Increases GAA Activity Compared to ERT in Multiple Muscle Tissues**



Source: Audentes Therapeutics

In addition, AT982 demonstrated a statistically significant increase in breathing frequency, a decrease in expiratory time, and an increase in the timing of the total respiratory cycle as compared with both ERT treated and non-treated mice, which resulted in outcomes comparable to those in normal mice (Exhibit 7).

Exhibit 7: **AT982 Restores Several Respiratory Parameters**



Source: Audentes Therapeutics

Clinical Programs for AT982

Currently the company is conducting additional IND-enabling preclinical studies of AT982 delivered through a systemic approach or intrathecal approach, with a goal to file an IND in 1H18. In parallel, the company is collaborating with University of Florida, who has submitted an investigator sponsored IND for a Phase I/II proof-of-concept study of AT982 in adults with Pompe disease. This study plans to evaluate the safety and GAA protein expression level in six to eight patients who are currently on ERT, after an injection of AT982 into the tibialis anterior (TA) muscle of the leg as well as a re-administration of AT982 into the TA muscle of the contralateral leg.

Competitive Landscape for Pompe Disease

To date, therapeutic candidates currently under development for Pompe disease are mostly ERTs, with Sanofi-Genzyme's GZ402666 being in the most advanced stage for treatment naïve patients with late-onset disease. GZ402666 is a second-generation GAA ERT that has a greater affinity for M6P receptors expressed on muscle cells and therefore could potentially enhance the enzyme uptake, resulting in an improved clinical efficacy of GAA with a lower dose.

Exhibit 8: **Pipeline for Pompe Disease**

Product	Company	MOA	Phase	Trial ID
GZ402666 (neoGAA)	Sanofi-Genzyme	ERT	III	NCT02782741
ATB200/AT2221	Amicus	ERT	I/II	NCT02675465
VAL-1221	Valerion	ERT	I/II	NCT02898753
JR-162	JCR Pharmaceuticals	ERT	Outside US	NA
AT982	Audentes/Regenxbio	Gene therapy	Preclinical	NA
CX717	RespireRx Pharmaceuticals	Small molecule (Glutamatergic AMPA receptor agonist)	Preclinical	NA
OXY2810	Oxyrane	ERT	Preclinical	NA

Source: Raymond James research

The CPVT Franchise

Background of the CASQ2 Subtype of Catecholaminergic Polymorphic Ventricular Tachycardia (CASQ2-CPVT)

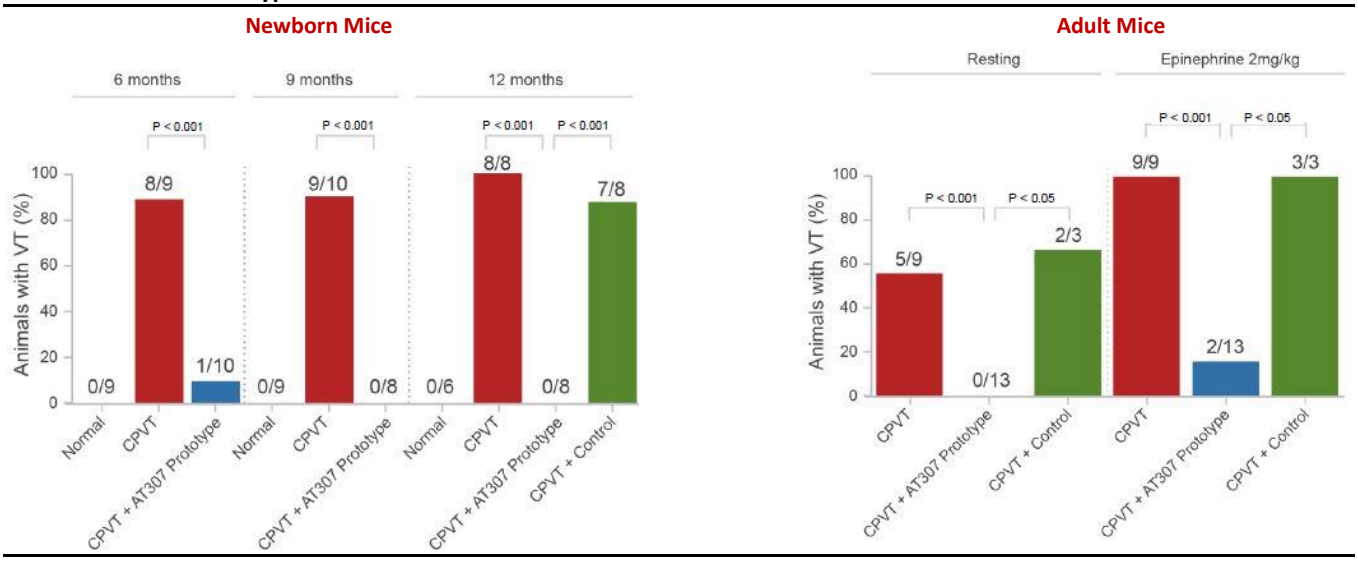
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare monogenic disease that is characterized by an abnormal heart rhythm in response to physical activity or emotional stress. Patients with CPVT can have episodes of lightheadedness, dizziness, fainting, and cardiac arrest that can lead to sudden death. While the prevalence of CPVT is one in 10,000 people worldwide, mutations in the calsequestrin 2 (CASQ2) gene, which has a function to regulate the calcium storage in cardiomyocytes, accounts for 1-2% of all CPVT cases. Currently, only limited treatment options for CPVT are available, including beta-blockers, a sodium channel blocker (flecainide), as well as anti-arrhythmia therapies such as sympathectomy and implantation of cardiac defibrillators. That said, a significant portion (30-40%) of the patients with CPVT remain symptomatic despite being put on the current available therapies.

Preclinical Results of AT307

Audentes' gene therapy candidate AT307 consists of an AAV9 vector that is designed to deliver the CASQ2 gene in the heart. Currently, the company is evaluating a number of different promoters and other vector structural elements to optimize the expression level of AT307, with the goal to achieve a sustainable and clinically meaningful expression of the functional calsequestrin 2 protein through a single administration of AT307, therefore potentially resulting in a reduction of the life-threatening arrhythmic events.

In a proof-of-concept preclinical study of a prototype product candidate of AT307 in a murine model of CASQ2-CPVT where stress-induced arrhythmias and cellular changes can be triggered upon epinephrine administration, a single administration of the AT307 prototype in nine mice resulted in a significant increase in the CASQ2 protein expression, which is comparable to the level seen in normal animals. In addition, cardiomyocytes isolated from the affected mice treated with the AT307 prototype had a comparable electrophysiology relative to that seen in normal mice. Lastly, a significant reduction in ventricular tachycardia (VT) was seen in the prototype treated newborn and adult mice, with the effect maintained for up to a year.

Exhibit 9: **AT307 Prototype Prevents VT in Newborn Mice and Reverses VT in Adult Mice**



Source: Audentes Therapeutics

Financial and Market Analysis

Exhibit 10: **Market Model for XLMTM**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with XLMTM	150	151	152	153	154	155	156	157	159	160	161	162	163	164	165	166	167	169
# of new patients with XLMTM	40	41	41	41	42	42	42	42	43	43	43	44	44	44	44	45	45	45
# of XLMTMpatients without or with mild AAV8 neutralizing antibody	150	151	152	153	154	155	156	157	159	160	161	162	163	164	165	166	167	169
# of new XLMTM patients without or with mild AAV8 neutralizing antibody	40	41	41	41	42	42	42	42	43	43	43	44	44	44	44	45	45	45
# of patients for AT132 at peak	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152
Total addressable market opportunity ('000)	$ 300,000	$ 302,100	$ 304,215	$ 306,344	$ 308,489	$ 310,648	$ 312,823	$ 314,955	$ 317,102	$ 319,264	$ 321,441	$ 323,632	$ 325,838	$ 328,060	$ 330,296	$ 332,548	$ 334,815	$ 337,098
Peak market opportunity ('000)	$ 270,000	$ 271,890	$ 273,793	$ 275,710	$ 277,640	$ 279,583	$ 281,540	$ 283,460	$ 285,392	$ 287,338	$ 289,297	$ 291,269	$ 293,255	$ 295,254	$ 297,267	$ 299,293	$ 301,334	$ 303,388
# of patients treated				3	35	47	55	38	38	39	39	39	39	40	40	40	41	41
# of accumulated patients treated				3	39	85	141	179	217	256	295	334	374	413	453	494	534	575
sales of AT132 ('000)				$ 6,127	$ 70,995	$ 93,734	$ 110,684	$ 76,302	$ 76,823	$ 77,346	$ 77,874	$ 78,405	$ 78,939	$ 79,477	$ 80,019	$ 80,565	$ 81,114	$ 81,667
Market penetration				2%	25%	55%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%

EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with SMA	236	237	237	238	239	239	240	241	241	242	243	244	244	245	246	246	247	248
# of new patients with XLMTM	51	51	52	52	52	52	52	52	52	53	53	53	53	53	53	53	54	54
# of XLMTMpatients without or with mild AAV8 neutralizing antibody	236	237	237	238	239	239	240	241	241	242	243	244	244	245	246	246	247	248
# of new XLMTM patients without or with mild AAV8 neutralizing antibody	51	51	52	52	52	52	52	52	52	53	53	53	53	53	53	53	54	54
# of patients for AT132 at peak	212	213	214	214	215	215	216	217	217	218	219	219	220	220	221	222	222	223
Total addressable market opportunity ('000)	$ 377,368	$ 378,500	$ 379,635	$ 380,774	$ 381,916	$ 383,062	$ 384,211	$ 385,288	$ 386,368	$ 387,451	$ 388,537	$ 389,626	$ 390,718	$ 391,813	$ 392,912	$ 394,013	$ 395,117	$ 396,225
Peak market opportunity ('000)	$ 339,631	$ 340,650	$ 341,672	$ 342,697	$ 343,725	$ 344,756	$ 345,790	$ 346,759	$ 347,731	$ 348,706	$ 349,683	$ 350,664	$ 351,646	$ 352,632	$ 353,621	$ 354,612	$ 355,606	$ 356,602
# of patients treated					5	55	72	85	47	47	47	48	48	48	48	48	48	48
# of accumulated patients treated					5	60	132	217	264	311	359	406	454	502	550	598	646	695
sales of AT132 ('000)					$ 7,638	$ 88,127	$ 115,551	$ 135,443	$ 75,487	$ 75,698	$ 75,910	$ 76,123	$ 76,336	$ 76,550	$ 76,765	$ 76,980	$ 77,196	$ 77,412
Market penetration					2%	25%	55%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Total US and EU risk-unadjusted revenues of AT132 ('000)				$ 5,698	$ 73,129	$ 169,131	$ 210,398	$ 196,923	$ 141,648	$ 142,331	$ 143,019	$ 143,711	$ 144,406	$ 145,106	$ 145,809	$ 146,517	$ 147,228	$ 147,944

XLMTM	Key Assumptions	Rationale
XLMTM prevalence	0.000046%	Literature review
XLMTM incidence in newborns	0.001%	Literature review
US/EU birth rate	1.24%/1%	Literature review
# of patients with XLMTM	~150	Calculated based on previously mentioned assumptions
# of new patients with XLMTM per year	~40	Calculated based on previously mentioned assumptions
Pricing of AT132	$2 million (US), $1.6 million (EU)	One-time payment; Spinraza, the only approved drug for SMA, has a first year cost of $750,000 and an annual cost of $375,000 (maintenance price)
Market share at peak	90%	The only gene therapy candidate in the pipeline which could potentially modify the disease
Drug Risk	50%	Given the similar MOA of the disease compared to SMA, which was partially validated by AveXis's clinical studies
Commercialization time	2020 (US), 2021 (EU)	Company guidance
Commercial rights	worldwide now	We assume Audentes will be in charge of a worldwide commercialization of AT132 given the ultra orphan status of the disease.

Source: Raymond James research

Pompe Disease

Exhibit 11: **Market Model for Pompe Disease**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
# of patients with pompe disease	3,256	3,279	3,302	3,325	3,348	3,372	3,395	3,419	3,442	3,465	3,489	3,513	3,537	3,561	3,585	3,610
# of new patients with Pompe disease each year	101	102	102	103	104	105	105	106	107	107	108	109	110	110	111	112
# of patients without or with mild AAV9 neutralizing antibody	2,768	2,787	2,807	2,826	2,846	2,866	2,886	2,906	2,926	2,946	2,966	2,986	3,006	3,027	3,047	3,068
# of new patients without or with mild AAV9 neutralizing antibody	86	86	87	88	88	89	89	90	91	91	92	93	93	94	94	95
# of patients for AT-982 at peak	1,661	1,672	1,684	1,696	1,708	1,720	1,732	1,743	1,755	1,767	1,779	1,792	1,804	1,816	1,828	1,841
Total addressable market opportunity ('000)	$2,767,808	$2,787,183	$2,806,693	$ 2,826,340	$ 2,846,124	$2,866,047	$ 2,886,109	$2,905,785	$ 2,925,595	$2,945,540	$ 2,965,621	$2,985,838	$3,006,194	$3,026,688	$3,047,322	$3,068,097
Peak market opportunity ('000)	$1,660,685	$1,672,310	$1,684,016	$ 1,695,804	$ 1,707,675	$1,719,628	$ 1,731,666	$1,743,471	$ 1,755,357	$1,767,324	$ 1,779,372	$1,791,503	$1,803,716	$1,816,013	$1,828,393	$1,840,858
# of patients treated							58	291	585	1,031	55	56	56	56	57	57
# of accumulated patients treated							58	348	933	1,964	2,020	2,075	2,131	2,187	2,244	2,301
sales of AT-982 ('000)							$ 57,722	$ 290,579	$ 585,119	$1,030,939	$ 55,160.54	$ 55,537	$ 55,915	$ 56,296	$ 56,680	$ 57,067
Market penetration							2%	10%	20%	35%	60%	60%	60%	60%	60%	60%

EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
# of patients with pompe disease	5,120	5,135	5,151	5,166	5,182	5,197	5,213	5,227	5,242	5,257	5,272	5,286	5,301	5,316	5,331	5,346
# of new patients with Pompe disease each year	128	128	129	129	130	130	130	131	131	131	132	132	133	133	133	134
# of patients without or with mild AAV9 neutralizing antibody	4,352	4,365	4,378	4,391	4,404	4,418	4,431	4,443	4,456	4,468	4,481	4,493	4,506	4,519	4,531	4,544
# of new patients without or with mild AAV9 neutralizing antibody	109	109	109	110	110	110	111	111	111	112	112	112	113	113	113	114
# of patients for AT-982 at peak	2,611	2,619	2,627	2,635	2,643	2,651	2,659	2,666	2,673	2,681	2,688	2,696	2,704	2,711	2,719	2,726
Total addressable market opportunity ('000)	$3,481,603	$3,492,048	$3,502,524	$ 3,513,032	$ 3,523,571	$3,534,142	$ 3,544,744	$3,554,680	$ 3,564,643	$3,574,635	$ 3,584,654	$3,594,702	$3,604,778	$3,614,882	$3,625,014	$3,635,175
Peak market opportunity ('000)	$2,088,962	$2,095,229	$2,101,515	$ 2,107,819	$ 2,114,143	$2,120,485	$ 2,126,846	$2,132,808	$ 2,138,786	$2,144,781	$ 2,150,793	$2,156,821	$2,162,867	$2,168,929	$2,175,008	$2,181,105
# of patients treated								89	446	894	1,568	67	68	68	68	68
# of accumulated patients treated								89	534	1,428	2,996	3,064	3,131	3,199	3,267	3,335
sales of AT-982 ('000)								$ 71,094	$ 356,464	$ 714,927	$1,254,629	$ 53,921	$ 54,072	$ 54,223	$ 54,375	$ 54,528
Market penetration								2%	10%	20%	35%	60%	60%	60%	60%	60%
Total US and EU risk-unadjusted revenues of AT-982 ('000)							$ 53,682	$ 336,355	$ 875,672	$1,623,655	$1,218,104	$ 101,795	$ 102,288	$ 102,783	$ 103,282	$ 103,783

Pompe Disease	Key Assumptions	Rationale
Prevalence	0.001%	Literature review
Incidence in newborns	0.0025%	Literature review
US/EU birth rate	1.24%/1%	Literature review
% of patients without or with mild AAV9 neutralizing antibody	85%	Literature review
Number of patients with Pompe disease who are eligible for AT982	~3,000 (U.S.), ~4,500 (EU)	Calculated based on previously mentioned assumptions
Number of new patients annually with Pompe disease who are eligible for AT982	~90 (U.S.), ~100 (EU)	Calculated based on previously mentioned assumptions
Pricing of AT982	$1 million (US), $0.8 million (EU)	One time upfront payment; Lumizyme's average annual cost is $298,000
Market share at peak	60%	AT982 is currently the only gene therapy candidate in the pipeline, could compete effectively with Lumizyme
Drug Risk	35%	In the early clinical trial stage with no clinical data reported to date.
Commercialization time	1H23 (US), 1H24 (EU)	Company guidance and our estimate
Commercial rights	worldwide	We assume Audentes will be in charge of a worldwide commercialization of AT982 given the ultra orphan status of the disease.

Source: Raymond James research

CASQ2-CPVT

Exhibit 12**: Market Model for CASQ2-CPVT**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
# of patients with CPVT	32,562	32,790	33,020	33,251	33,484	33,718	33,954	34,186	34,419	34,653	34,890	35,128	35,367	35,608	35,851	36,095
# of patients with CASQ2-CPVT	1,302	1,312	1,321	1,330	1,339	1,349	1,358	1,367	1,377	1,386	1,396	1,405	1,415	1,424	1,434	1,444
# of patients for AT307 at peak	912	918	925	931	938	944	951	957	964	970	977	984	990	997	1,004	1,011
Total addressable market opportunity ('000)	$1,302,498	$1,311,615	$1,320,797	$ 1,330,042	$ 1,339,353	$1,348,728	$ 1,358,169	$1,367,428	$ 1,376,751	$1,386,136	$ 1,395,586	$1,405,100	$1,414,679	$1,424,324	$1,434,034	$1,443,810
Peak market opportunity ('000)	$ 911,749	$1,836,262	$1,849,115	$ 1,862,059	$ 1,875,094	$1,888,219	$ 1,901,437	$1,914,400	$ 1,927,451	$1,940,591	$ 1,953,821	$1,967,141	$1,980,551	$1,994,053	$2,007,648	$2,021,334
# of patients treated							48	144	289	485	12	7	7	7	7	7
Accumulated # of patients treated							48	191	480	965	977	984	990	997	1,004	1,011
sales of AT307 ('000)							$ 47,536	$ 143,580	$ 289,118	$ 485,148	$ 11,529	$ 6,660	$ 6,705	$ 6,751	$ 6,797	$ 6,843
Market penetration							5%	15%	30%	50%	65%	70%	70%	70%	70%	70%

EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
# of patients with CPVT	51,200	51,354	51,508	51,662	51,817	51,973	52,129	52,275	52,421	52,568	52,716	52,863	53,011	53,160	53,309	53,458
# of patients with CASQ2-CPVT	2,048	2,054	2,060	2,066	2,073	2,079	2,085	2,091	2,097	2,103	2,109	2,115	2,120	2,126	2,132	2,138
# of patients for AT132 at peak	1,434	1,438	1,442	1,447	1,451	1,455	1,460	1,464	1,468	1,472	1,476	1,480	1,484	1,488	1,493	1,497
Total addressable market opportunity ('000)	$1,638,402	$1,643,317	$1,648,247	$ 1,653,191	$ 1,658,151	$1,663,126	$ 1,668,115	$1,672,791	$ 1,677,479	$1,682,181	$ 1,686,896	$1,691,624	$1,696,366	$1,701,121	$1,705,889	$1,710,670
Peak market opportunity ('000)	$1,146,881	$1,150,322	$1,153,773	$ 1,157,234	$ 1,160,706	$1,164,188	$ 1,167,680	$1,170,953	$ 1,174,235	$1,177,527	$ 1,180,827	$1,184,137	$1,187,456	$1,190,785	$1,194,122	$1,197,469
# of patients treated								73	220	442	738	7	4	4	4	4
# of accumulated patients treated								73	293	735	1,473	1,480	1,484	1,488	1,493	1,497
sales of AT307 ('000)								$ 58,548	$ 176,135	$ 353,258	$ 590,414	$ 5,782	$ 3,319	$ 3,328	$ 3,338	$ 3,347
Market penetration								5%	15%	30%	50%	65%	70%	70%	70%	70%
Total US and EU risk-unadjusted revenues of AT307 ('000)	$ -	$ -	$ -	$ -	$ -	$ -	$ 44,208	$ 187,979	$ 432,685	$ 779,717	$ 559,807	$ 11,571	$ 9,323	$ 9,374	$ 9,425	$ 9,477

CASQ2-CPVT	Key Assumptions	Rationale
CPVT prevalence	0.01%	Literature review
% of CPVT patients with CASQ2 mutations	4%	Literature review
% of Type II SMA	51%	Literature review
# of patients with CASQ2-CPVT who are eligible for AT307	~1,400 in U.S., ~2,000 in EU	Calculated based on previous assumptions
Pricing of AT307	$1 million (U.S.) $0.8 million (EU)	One time upfront payment; Initial implantable cardioverter-defibrillators (ICD) implantation costs (2006 U.S. number) from $28,500 to $55,200, with an annual follow-up cost ranging from $4,800 to $17,000. Therefore, NPV of the cost of ICD should be above $1 million (similar to Luxturna's (Spark) cost calculation)
Market share at peak	70%	AT307 is currently the only gene therapy candidate in the pipeline which could potentially modify the disease
Drug Risk	35%	In the early clinical trial stage with no clinical data reported to date.
Commercialization time	1H23 (US), 1H24 (EU);	Based on company guidance and our estimate
Commercial rights	worldwide	We assume Audentes will be in charge of a worldwide commercialization of AT307 given the ultra orphan status of the disease.

Source: Raymond James research

Crigler-Najjar Syndrome

Exhibit 13: **Market Model for Crigler-Najjar Syndrome**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
# of patients with CNS	326	328	330	333	335	337	340	342	344	347	349	351	354	356	359	361	363	366	368	371
# of new patients with CNS each year	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5
# of patients for AT342 at peak	293	295	297	299	301	303	306	308	310	312	314	316	318	320	323	325	327	329	332	334
Total addressable market opportunity ('000)	$ 651,249	$ 655,808	$ 660,398	$ 665,021	$ 669,676	$ 674,364	$ 679,085	$ 683,714	$ 688,375	$ 693,068	$ 697,793	$ 702,550	$ 707,340	$ 712,162	$ 717,017	$ 721,905	$ 726,827	$ 731,782	$ 736,770	$ 741,793
Peak market opportunity ('000)	$ 586,124	$ 590,227	$ 594,359	$ 598,519	$ 602,709	$ 606,928	$ 611,176	$ 615,343	$ 619,538	$ 623,761	$ 628,014	$ 632,295	$ 636,606	$ 640,946	$ 645,315	$ 649,715	$ 654,144	$ 658,603	$ 663,093	$ 667,614
# of patients treated						7	34	85	172	14	4	4	4	4	4	4	5	5	5	5
Accumulated # of patients treated						7	41	126	298	312	316	321	325	329	334	338	343	347	352	356
sales of AT342 ('000)						$ 13,487	$ 67,908	$ 170,929	$ 344,188	$ 27,249	$ 8,653	$ 8,712	$ 8,771	$ 8,831	$ 8,891	$ 8,952	$ 9,013	$ 9,074	$ 9,136	$ 9,198
Market penetration						2%	10%	25%	50%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%

EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
# of patients with CNS	512	514	515	517	518	520	521	523	524	526	527	529	530	532	533	535	536	538	539	541
# of new patients with CNS each year	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
# of patients for AT342 at peak	461	462	464	465	466	468	469	470	472	473	474	476	477	478	480	481	482	484	485	487
Total addressable market opportunity ('000)	$ 819,201	$ 821,658	$ 824,123	$ 826,596	$ 829,076	$ 831,563	$ 834,057	$ 836,395	$ 838,740	$ 841,091	$ 843,448	$ 845,812	$ 848,183	$ 850,560	$ 852,944	$ 855,335	$ 857,733	$ 860,137	$ 862,548	$ 864,965
Peak market opportunity ('000)	$ 737,281	$ 739,493	$ 741,711	$ 743,936	$ 746,168	$ 748,406	$ 750,652	$ 752,756	$ 754,866	$ 756,982	$ 759,103	$ 761,231	$ 763,365	$ 765,504	$ 767,650	$ 769,802	$ 771,959	$ 774,123	$ 776,293	$ 778,469
# of patients treated							10	52	131	263	18	5	5	5	5	5	5	5	5	5
# of accumulated patients treated							10	63	194	457	474	480	485	490	496	501	506	512	517	523
sales of AT342 ('000)							$ 16,681	$ 83,640	$ 209,685	$ 420,545	$ 28,552	$ 8,458	$ 8,482	$ 8,506	$ 8,529	$ 8,553	$ 8,577	$ 8,601	$ 8,625	$ 8,650
Market penetration							2%	10%	25%	50%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Total US and EU risk-unadjusted revenues of AT342 ('000)						$ 12,543	$ 78,668	$ 236,748	$ 515,101	$ 416,449	$ 34,601	$ 15,968	$ 16,045	$ 16,123	$ 16,201	$ 16,280	$ 16,359	$ 16,438	$ 16,518	$ 16,599

Crigler-Najjar Syndrome (CNS)	Key Assumptions	Rationale
Prevalence	0.0001%	Literature review
CNS incidence in newborns	0.0001%	Literature review
US/EU birth rate	1.24%/1%	Literature review
# of patients with CNS who are eligible for AT342	~300 in U.S., ~500 in EU	Calculated based on previous assumptions
Number of new patients annually with CNS who are eligible for AT342	4 in U.S., 5 in EU	Calculated based on previous assumptions
Pricing of AT342	$2 million (U.S.) $1.6 million (EU)	Similar to XLMTM, ultra orphan disease, with no disease modifying treatment
Market share at peak	90%	AT342 is currently the only gene therapy candidate in the pipeline which could potentially modify the disease; ultra orphan disease.
Drug Risk	35%	In the early clinical trial stage with no clinical data reported to date.
Commercialization time	4Q22 (US), 4Q23 (EU);	Based on company guidance and our estimate
Commercial rights	worldwide	We assume Audentes will be in charge of a worldwide commercialization of AT342 given the ultra orphan status of the disease.

Source: Raymond James research

Operating Expenses

Building off of the R&D expense reported for 2Q17, we are projecting R&D of $74 million for 2017E, changing to $85 million for 2022E. The R&D assumptions from 2017 to 2022 take into account continued expenditure for the clinical trials associated with the company's four clinical programs.

Based on the SG&A expense reported for 2Q17, we are projecting SG&A of $16 million for 2017E, increasing to $41 million in 2022E. These estimates reflect changes in the sales force ahead of potential commercial launches of four product candidates starting from 2020.

The COGS for these gene therapies are expected to be 1% of the revenues.

Net Income and EPS

The net income for 2Q17 was $(22.7) million, or $(0.87) per share. We are projecting net income of $(90.0) million or $(3.58) per diluted share in 2017E, changing to $54.3 million or $1.18 per diluted share for in 2022E.

Cash

Based on our estimates, we expect a cash burn rate of approximately $44 million for 2H17, and we believe the current cash position is sufficient to fund operations into 4Q18. We have modeled three capital raises -- approximately $150 million in 1Q18, $200 million in 2019, and $100 million in 2020. We have included these raises into our model as a necessity for the company to sustain operations until it can potentially reach profitability.

Valuation and Price Target Analysis

Valuation

We value Audentes using the sum of the parts analysis of the company's four programs: 1) AT132 for XLMTM; 2) AT982 for Pompe disease; 3) AT342 for CN; and 4) AT307 for CPVT. To derive a value for each of these programs, we conduct a risk-adjusted net present value (rNPV) analysis, which utilizes the net income as a proxy of the free cash flow (FCF). The revenues for each product are derived from our market models (see pages 85-87 for more detail), whereas the R&D and SG&A expenses are estimated largely based on the number of patients on clinical trials and the size of a sales force, respectively. To calculate the NPV, the approximate FCF based on the net income for any given year is discounted at a rate of 15% back to the present time. To account for the clinical/ regulatory risk, the NPV is further multiplied by a probability of success (POS) assigned to each program. Using this methodology, we derive a risk-adjusted per share NPV of $7.28, $9.95, $2.53, and $3.41 for AT132, AT982, AT342, and AT307, respectively. Combining with the cash value of $3.93 per share, we derive a fair value of $27.09, which we round to $27.

Exhibit 14: **Valuation Analysis**

Product	POS	Per share value	Weighting
AT132 for XLMTM	50%	7.28	27%
AT982 for Pompe disease	35%	9.95	37%
AT342 for CN	35%	2.53	9%
AT307 for CPVT	35%	3.41	13%
Cash	N/A	3.93	14%
Total		27.09	

Source: Raymond James research

Exhibit 15: **rNPV of AT132**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ 5,698	$ 73,129	$ 169,131	$ 210,398	$ 196,923	$ 141,648	$ 142,331
COGS				57	731	1,691	2,104	1,969	1,416	1,423
R&D	10,554	22,967	24,115.15	9,187	4,593	1,148	1,160	1,171	1,183	1,195
SGA	2,187	4,706	6,441	6,763	7,101	7,456	7,829	8,221	1,644	1,726
Income before tax	(12,741)	(27,673)	(30,556)	(10,309)	60,703	158,835	199,305	185,562	137,404	137,987
Tax	-	-	-	-	-	-	-	37,112	27,481	27,597
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*20%*	*20%*	*20%*
Net income	(12,741)	(27,673)	(30,556)	(10,309)	60,703	158,835	199,305	148,450	109,923	110,389
Present time	10/9/2017									
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(12,342)	(23,309)	(22,381)	(6,566)	33,620	76,495	83,465	54,059	34,808	30,396
NPV of net income (2017-2025)	217,849									
Terminal value at 2025	757,351									
NPV of terminal value	239,822									
Total NPV ('000)	457,671									
Fully diluted shares outstanding ('000)	31,454									
Per share value	14.55									
Probability of success	50%									
Risk-adjusted per share value	**7.28**									

Source: Raymond James research

Exhibit 16: **rNPV of AT982**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ -	$ 53,682	$ 336,355	$ 875,672	$ 1,623,655	$ 1,218,104	$ 101,795	$ 102,288	$ 102,783
COGS						-	537	3,364	8,757	16,237	12,181	1,018	1,023	1,028
R&D	10,104	20,567	23,395	27,565	33,443	35,115	17,558	3,512	3,547	3,582	3,618	3,654	3,691	3,728
SGA	2,187	4,706	4,941	5,188	5,447	11,720	16,806	17,646	18,528	19,455	20,428	10,214	1,021	1,032
Income before tax	(12,291)	(25,273)	(28,336)	(32,753)	(38,891)	(46,835)	18,781	311,834	844,841	1,584,382	1,181,878	86,909	96,553	96,996
Tax	-	-	-	-	-	-	-	62,367	168,968	316,876	236,376	17,382	19,311	19,399
Tax rate	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%
Net income	(12,291)	(25,273)	(28,336)	(32,753)	(38,891)	(46,835)	18,781	249,467	675,873	1,267,505	945,502	69,527	77,242	77,597
% YoY increase								1228.27%	170.93%	87.54%	-25.40%	-92.65%	11.10%	0.46%
Present time	10/9/2017													
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(11,906)	(21,288)	(20,755)	(20,861)	(21,539)	(22,556)	7,865	90,845	214,021	349,015	226,391	14,476	13,985	12,217

NPV of net income (2017-2029)	797,694
Terminal value at 2029	533,651
NPV of terminal value	96,618
Total NPV ('000)	894,311
Fully diluted shares outstanding ('000)	31,454
Per share value	28.43
Probability of success	35%
Risk-adjusted per share value	**9.95**

Source: Raymond James research

Exhibit 17: **rNPV of AT342**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ 12,543	$ 78,668	$ 236,748	$ 515,101	$ 416,449	$ 34,601	$ 15,968	$ 16,045	$ 16,123	$ 16,201
COGS						125	787	2,367	5,151	4,164	346	160	160	161	162
R&D	10,554	21,167	24,025	25,226	26,488	13,244	2,649	1,324	1,338	1,351	1,365	1,378	1,392	1,406	1,420
SGA	2,187	4,706	4,941	5,188	8,447	10,070	10,573	11,102	11,657	12,240	12,852	6,426	643	649	656
Income before tax	(12,741)	(25,873)	(28,966)	(30,414)	(34,935)	(10,896)	64,660	221,954	496,956	398,694	20,038	8,004	13,850	13,907	13,964
Tax	-	-	-	-	-	-	-	44,391	99,391	79,739	4,008	1,601	2,770	2,781	2,793
Tax rate	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%
Net income	(12,741)	(25,873)	(28,966)	(30,414)	(34,935)	(10,896)	64,660	177,564	397,565	318,955	16,031	6,403	11,080	11,125	11,171
% YoY increase													73.04%	0.41%	0.41%
Present time	10/9/2017														
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(12,342)	(21,793)	(21,216)	(19,371)	(19,348)	(5,247)	27,078	64,661	125,892	87,826	3,838	1,333	2,006	1,752	1,529

NPV of net income (2017-2029)	213,317
Terminal value at 2029	76,246
NPV of terminal value	13,804
Total NPV ('000)	227,121
Fully diluted shares outstanding ('000)	31,454
Per share value	7.22
Probability of success	35%
Risk-adjusted per share value	**2.53**

Source: Raymond James research

Exhibit 18: **rNPV of AT307**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ -	$ 44,208	$ 187,979	$ 432,685	$ 779,717	$ 559,807	$ 11,571	$ 9,323	$ 9,374	$ 9,425
COGS						-	442	1,880	4,327	7,797	5,598	116	93	94	94
R&D	10,104	20,867	23,410	27,581	33,460	35,133	17,566	3,513	3,548	3,584	3,620	3,656	3,692	3,729	3,767
SGA	2,187	4,706	4,941	5,188	5,447	11,720	16,806	17,646	18,528	19,455	20,428	10,214	1,021	1,032	1,042
Income before tax	(12,291)	(25,573)	(28,351)	(32,769)	(38,907)	(46,853)	9,394	164,940	406,282	748,881	530,161	(2,414)	4,516	4,519	4,522
Tax	-	-	-	-	-	-	-	32,988	81,256	149,776	106,032	-	903	904	904
Tax rate	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%
Net income	(12,291)	(25,573)	(28,351)	(32,769)	(38,907)	(46,853)	9,394	131,952	325,025	599,105	424,129	(2,414)	3,612	3,615	3,618
														0.08%	0.07%
Present time	10/9/2017														
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(11,906)	(21,540)	(20,766)	(20,871)	(21,548)	(22,564)	3,934	48,051	102,922	164,967	101,553	(503)	654	569	495

NPV of net income (2017-2029)	302,383
Terminal value at 2029	24,190
NPV of terminal value	4,380
Total NPV ('000)	306,763
Fully diluted shares outstanding ('000)	31,454
Per share value	9.75
Probability of success	35%
Risk-adjusted per share value	**3.41**

Source: Raymond James research

Bull/Bear Analysis

In our bull case, we assume higher probability of success for the company's four programs, which results in a value of about $37 per share, indicating a 41% return from the current level. In our bear case, we decrease the probability of success and derive a value of about $13, suggesting downside risk of 50%.

Exhibit 19: **Bull/Bear Analysis**

Probability of success of each program	Bull	Base	Bear
AT132 for XLMTM	70%	50%	30%
AT982 for Pompe disease	50%	35%	10%
AT342 for CN	50%	35%	10%
AT307 for CPVT	50%	35%	10%
Valuation	$37	$27	$13
Return	41%	-4%	-50%

Note: The closing price of 10/9/17 was used to calculate the potential returns
Source: Raymond James research

Management

Matthew R. Patterson, President and Chief Executive Officer

Mr. Patterson is the co-founder of Audentes Therapeutics and has served as president and CEO since the company's inception in November 2012. He has more than 20 years of experience in the research, development, and commercialization of innovative treatments for rare diseases and has held positions of senior management in both private and public biotechnology companies. Previously, Mr. Patterson worked for Genzyme Corporation, BioMarin Pharmaceutical, and Amicus Therapeutics. Prior to Audentes, he was an entrepreneur-in-residence with OrbiMed, the world's largest health-care dedicated investment firm. Mr. Patterson is a member of the board of directors of Gilda's Club of New York City, which provides social and emotional support for people living with cancer. He also currently serves as vice chairman of the Alliance for Regenerative Medicine (ARM). Mr. Patterson received his B.A. in biochemistry from Bowdoin College.

Natalie Holles, Senior Vice President, Chief Operating Officer

Ms. Holles has served as senior vice president and chief operating officer since August 2015. Most recently, Ms. Holles served as senior vice president of corporate development at Hyperion Therapeutics, Inc. from 2013 through its acquisition by Horizon Pharma, plc in May 2015. From 2010 to 2013, Ms. Holles provided executive-level strategy and business development advisory services to a number of privately-held biopharmaceutical companies, most recently acting as executive vice president of corporate development at Immune Design, Inc. Earlier in her career, Ms. Holles served as vice president of business development at KAI Pharmaceuticals, Inc. (acquired by Amgen in 2012) and previously held corporate development and commercial roles at InterMune, Inc. (acquired by Roche in 2014) and Genentech, Inc. Ms. Holles holds an M.A. in molecular, cellular and developmental biology from the University of Colorado, Boulder, where she was a Howard Hughes Medical Institute pre-doctoral fellow, and an A.B. in human biology from Stanford University.

Tom Soloway, Senior Vice President, Chief Financial Officer

Mr. Soloway has served as senior vice president and chief financial officer since October 2015. Prior to joining Audentes, Mr. Soloway served as the senior vice president and chief financial officer of Ascendis Pharma A/S, a Danish biopharmaceutical company, where he helped lead a successful initial public offering on NASDAQ. Prior to Ascendis, Mr. Soloway co-founded Transcept Pharmaceuticals, Inc. At Transcept, he held positions of increasing responsibility, serving initially as senior vice president of operations and chief financial officer and over time as executive vice president and chief operating officer. In this role, he oversaw project planning, manufacturing, pharmaceutical sciences, legal, human resources, regulatory, and corporate communications. Prior to joining Transcept, Mr. Soloway financed and advised early stage healthcare and life sciences companies as a principal at Montreux Equity Partners, a venture capital firm. Mr. Soloway earned a B.S. in entrepreneurial studies from the University of Southern California and an M.B.A. from Georgetown University.

Suyash Prasad, M.D., Senior Vice President, Chief Medical Officer

Dr. Prasad has served as senior vice president and chief medical officer since February 2014. He has a wide range of experience and achievement in international drug development across Phase I to IV, with a specific focus in the clinical development of therapies to treat rare pediatric disorders. Dr. Prasad has worked in drug development for the past 14 years in positions of increasing responsibility at BioMarin Pharmaceutical, Inc., Genzyme Corporation, and Eli Lilly and Company. Dr. Prasad has significant experience with the development and commercialization of enzyme replacement therapies to treat lysosomal storage disorders, including Cerezyme®, Aldurazyme®, Fabrazyme®, and Myozyme®. For Pompe Disease, he led the global medical planning activities for Lumizyme® for the treatment of adult Pompe Disease and for Myozyme® to treat infantile Pompe. Most recently, he was responsible for the clinical development of novel treatments for phenylketonuria (PKU) and achondroplasia. Dr. Prasad graduated in medicine at the University of Newcastle-upon-Tyne, UK, where he received commendations for pediatrics, obstetrics and gynecology, and medical ethics. He is a United Kingdom board certified physician with a sub-specialty interest in pediatric critical care, and is a member of the Royal College of Physicians (MRCP) and the Royal College of Pediatrics and Child Health (MRCPCH). He received his diploma in pharmaceutical medicine from the Royal College of Physicians of the United Kingdom, and has recently become an elected fellow to the Faculty of Pharmaceutical Medicine (FFPM) and is a past recipient of the Outstanding Contribution Award from the Faculty of Pharmaceutical Medicine of the UK Royal College of Physicians. Dr. Prasad also currently sits on the board of the National PKU Association.

John Gray, Senior Vice President, Chief Scientific Officer

John Gray has served as senior vice president and chief scientific officer since May 2017 and prior to that was senior vice president of research and development. Dr. Gray has over 20 years of experience designing genetic therapies and vaccines, and developing manufacturing processes for those products. For 11 years prior to joining Audentes, Dr. Gray was the director of Vector Production and Development at St. Jude Children's Research Hospital, where he led a team devoted to advancing the gene therapy vector science. In the area of lentiviral vector production, his team derived the GPRG stable cell line, the first such line to be used to successfully produce an HIV-based vector tested in a human clinical trial (for treatment of X-linked Severe Combined Immunodeficiency). He also contributed significantly to the Hemophilia B gene therapy project, for which he designed the self-complementary AAV Factor IX vector expression cassette and developed the production process used to manufacture the first two batches of clinical vector. During his tenure at St. Jude, Dr. Gray also worked on Chimeric Antigen Receptor modified cell therapy, lysosomal storage disorder gene therapy, and multiple hematopoietic stem/progenitor cell gene therapy projects. Prior to joining St. Jude Children's Research Hospital in 2003, Dr. Gray was a researcher in the laboratory of Dr. Richard Mulligan, where for five years he served as the assistant director of the Harvard Gene Therapy Initiative. Prior to this, he worked for five years at Pfizer Animal Health designing bacterial and viral vectors for vaccine applications. Dr. Gray has a B.A. degree in biochemistry from the University of California, Berkeley, and a Ph.D. degree in biochemistry from the University of Colorado, Boulder.

Audentes Statement

All figures in thousands ($), except per share data

	FY16A	1Q17A	2Q17A	3Q17E	4Q17E	FY17E	1Q18E	2Q18E	3Q18E	4Q18E	FY18E
Revenues											
AT132 for XLMTM											-
AT982 for Pompe disease											-
AT342 for Crigler-Najjar Syndrome											-
AT307 for CASQ2-CPVT											-
Total revenues		-	-	-	-	-	-	-	-	-	-
Operating expenses:											
Cost of sales						-					-
Research and development	48,770	14,587	18,776	19,715	20,701	73,778	21,736	22,822	23,963	25,162	93,683
General and administrative	11,276	3,658	4,065	4,268	4,482	16,473	4,571	4,663	4,756	4,833	18,823
Total operating expenses	60,046	18,245	22,841	23,983	25,182	90,251	26,307	27,485	28,719	29,994	112,506
Operating income	**(60,046)**	**(18,245)**	**(22,841)**	**(23,983)**	**(25,182)**	**(90,251)**	**(26,307)**	**(27,485)**	**(28,719)**	**(29,994)**	**(112,506)**
Other income (expense)											
Interest income, net	472	147	115			262					
Other expense, net	(94)	(17)	(13)			(30)					-
Total other income (expense)	378	130	102	-	-	232	-	-	-	-	-
Income (loss) before taxes	**(59,668)**	**(18,115)**	**(22,739)**	**(23,983)**	**(25,182)**	**(90,019)**	**(26,307)**	**(27,485)**	**(28,719)**	**(29,994)**	**(112,506)**
Income tax expense (benefit)	-	-	-	-	-	-					-
Net income (loss)	**(59,668)**	**(18,115)**	**(22,739)**	**(23,983)**	**(25,182)**	**(90,019)**	**(26,307)**	**(27,485)**	**(28,719)**	**(29,994)**	**(112,506)**
Net (loss) per share, basic	**(5.59)**	**(0.83)**	**(0.87)**	**(0.91)**	**(0.95)**	**(3.58)**	**(0.83)**	**(0.86)**	**(0.90)**	**(0.93)**	**(3.51)**
Net (loss) per share, diluted	**(5.59)**	**(0.83)**	**(0.87)**	**(0.91)**	**(0.95)**	**(3.58)**	**(0.83)**	**(0.86)**	**(0.90)**	**(0.93)**	**(3.51)**
Weighted average shares outstanding, basic	10,674	21,755	26,213	26,313	26,413	25,173	31,870	31,970	32,070	32,170	32,020
Weighted average shares outstanding, diluted	10,674	21,755	26,213	26,313	26,413	25,173	31,870	31,970	32,070	32,170	32,020

Audentes Statement

All figures in thousands ($), except per share data

	FY16A	FY17E	FY18E	FY19E	FY20E	FY21E	FY22E
Revenues							
AT132 for XLMTM			-	-	5,698	73,129	169,131
AT982 for Pompe disease			-	-	-	-	-
AT342 for Crigler-Najjar Syndrome			-	-	-	-	12,543
AT307 for CASQ2-CPVT			-	-	-	-	-
Total revenues		-	-	-	5,698	73,129	181,674
Operating expenses:							
Cost of sales		-	-	-	57	731	1,817
Research and development	48,770	73,778	93,683	94,946	89,559	97,984	84,640
General and administrative	11,276	16,473	18,823	21,264	22,327	26,444	40,966
Total operating expenses	60,046	90,251	112,506	116,210	111,943	125,159	127,423
Operating income	**(60,046)**	**(90,251)**	**(112,506)**	**(116,210)**	**(106,245)**	**(52,030)**	**54,252**
Other income (expense)							
Interest income, net	472	262					
Other expense, net	(94)	(30)	-				
Total other income (expense)	378	232	-				
Income (loss) before taxes	**(59,668)**	**(90,019)**	**(112,506)**	**(116,210)**	**(106,245)**	**(52,030)**	**54,252**
Income tax expense (benefit)	-	-	-				
Net income (loss)	**(59,668)**	**(90,019)**	**(112,506)**	**(116,210)**	**(106,245)**	**(52,030)**	**54,252**
Net (loss) per share, basic	**(5.59)**	**(3.58)**	**(3.51)**	**(3.11)**	**(2.65)**	**(1.29)**	**1.33**
Net (loss) per share, diluted	**(5.59)**	**(3.58)**	**(3.51)**	**(3.11)**	**(2.65)**	**(1.29)**	**1.18**
Weighted average shares outstanding, basic	10,674	25,173	32,020	37,420	40,042	40,442	40,842
Weighted average shares outstanding, diluted	10,674	25,173	32,020	37,420	40,042	40,442	45,984

Audentes Balance Sheet

Figures in $ thousands except per share data

ASSETS	3Q16	4Q16	1Q17	2Q17
Current Assets:				
Cash and cash equivalents	87,067	36,359	18,764	54,574
Short-term investments	32,113	68,524	62,964	90,434
Restricted cash	1,242	730	820	820
Prepaid expenses and other current assets	4,846	2,824	3,358	3,563
Total Current Assets	125,268	108,437	85,906	149,391
Restricted cash - long-term	2,930	3,020	3,280	3,280
Property and equipment, net	18,885	18,936	19,489	22,245
Goodwill	3,631	3,631	3,631	3,631
Intangible assets	8,000	8,000	8,000	8,000
Other assets	36	33	1,433	2,045
TOTAL ASSETS	158,750	142,057	121,739	188,592
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current Liabilities:				
Accounts payable	2,725	2,424	1,506	4,009
Accrued liabilities	7,112	9,871	7,063	10,709
Deferred rent	307	265	134	137
Total Current Liabilities	10,144	12,560	8,703	14,855
Deferred rent and asset retirement obligation - long-term	2,411	2,486	2,778	3,879
Contingent acquisition consideration payable	4,574	4,380	4,470	4,544
Deferred tax liability, net	3,260	3,260	3,260	3,260
TOTAL LIABILITIES	20,389	22,686	19,211	26,538
STOCKHOLDERS' EQUITY				
Common Stock	-	-	-	-
Additional paid-in-capital	219,098	219,811	221,083	303,356
Accumulated deficit	(80,735)	(100,411)	(118,526)	(141,265)
Accumulated other comprehensive loss	(2)	(29)	(29)	(37)
TOTAL STOCKHOLDERS' EQUITY	138,361	119,371	102,528	162,054
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	158,750	142,057	121,739	188,592

Audentes Statement of Cash Flows

Figures in thousands ($) except per share data

	3Q16	4Q16	1Q17	2Q17
Operating Activities:				
Net loss	(15,369)	(19,676)	(18,115)	(22,739)
Adjustments to reconcile net loss to net cash used:				
Amortization of discount on investments	37	(151)	-	-
Depreciation and amortization	643	698	732	769
Stock-based compensation	599	698	1,055	1,468
(Accretion of discount) amortization of premium on investments		-	(25)	(37)
Accretion of asset retirement obligation	11	5	8	10
Change in fair value of contingent acquisition consideration payable	114	(194)	90	74
Loss on disposal of property and equipment	66	(66)	-	-
Other	(66)	71	45	100
Changes in Operating Assets and Liabilities:				
Additions to restricted cash	4,196	422	(350)	-
Prepaid expenses and other current assets	3,707	2,176	(491)	(292)
Other assets	-	(41)	(1,400)	(620)
Accounts payable	142	400	(1,230)	1,870
Accrued liabilities	207	3,597	(3,029)	2,219
Facility lease obligations	(94)	(1,494)	-	-
Deferred rent	-	1,522	153	1,094
Net Cash Provided (Used) in Operating Activities	(10,003)	(12,545)	(22,557)	(16,084)
Investing Activities:				
Purchases of property and equipment	(5,512)	(2,294)	(752)	(1,465)
Proceeds from sales of property and equipment	-	1	-	-
Proceeds from sales and maturities of marketable securities	21,454	14,827	32,010	17,000
Purchases of marketable securities	(10,781)	(51,224)	(26,430)	(44,446)
Net Cash Provided (Used) in Investing Activities	9,357	(38,178)	4,828	(28,911)
Financing Activities:				
Proceeds from exercise of stock options	49	15	134	227
Proceeds from issuance of common stock, net of offering costs	-	-	-	80,578
Proceeds from issuance of common stock from initial public offering, net of offering costs	75,208	-	-	-
Net Cash Provided (Used) in Financing Activities	75,257	15	134	80,805
Net Decrease in Cash and Cash Equivalents	74,611	(50,708)	(17,595)	35,810
Cash and Cash Equivalents at Beginning of Period	12,456	87,067	36,359	18,764
Cash and Cash Equivalents at End of Period	87,067	36,359	18,764	54,574

REGENXBIO Inc. (RGNX-NASDAQ)

Biotechnology

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Rating
Outperform 2

An Enviable Platform With Partners and Potential; Initiating at Outperform

Recommendation: We are initiating coverage of REGENXBIO Inc. with an **Outperform** rating and a target price of $39 (High Risk/Speculation suitability, given the stage of clinical development). In our opinion, REGENXBIO is a major player in the gene therapy space with a powerful AAV technology platform that has generated 10 partnerships with leading biotech/gene therapy companies (e.g., Biogen, Shire, and AveXis), resulting in over 25 partnered and unpartnered assets. With a platform that could continue to attract partners or even an acquirer, a wholly owned pipeline of four products addressing large areas of unmet need, multiple clinical milestones expected within 12 months, and a cash position of ~$190 million (pro forma), we recommend REGENXBIO shares to risk-tolerant investors.

- **A platform validated by multiple partnerships**. In our opinion, the established partnerships and the genesis of 25+ product candidates to date are a strong validation of the company's NAV platform (next generation AAV vectors). Currently, the company has 100+ patents and patent applications worldwide covering the NAV vectors, including AAV7, AAV8, AAV9, and AAVrh10. Importantly, as compared to some earlier generation AAV vectors, REGENXBIO's NAV vectors appear to offer several advantages such as higher rates of transfection/longer gene expression, lower rates of immune response, and improved manufacturing. Given the broad intellectual property (IP) portfolio as well as the attractive attributes, in our opinion, the NAV platform could continue to drive shareholder value by generating both wholly owned product candidates and those that can drive additional partnerships.
- **Partnered programs could be a significant revenue source**. For the 20+ partnered programs, REGENXBIO is eligible to receive single to low teen digit royalties on the net sales, in addition to upfront and milestone payments. Eight of these programs are already in the clinic, including AveXis' AVXS-101, which has demonstrated promising clinical results in patients with spinal muscular atrophy (SMA) Type 1. Based on our estimates, these clinical-stage assets have the potential to generate combined peak sales of $10+ billion, 5-13% of which would be allocated to REGENXBIO, representing a probability adjusted net present value (NPV) of $15/share.
- **Multiple wholly owned assets, multiple ways to win.** Currently, the company has a total of four wholly owned product candidates, all of which utilize the NAV platform. Towards the end of the year, we expect the company to provide the first results from two clinical studies evaluating two different NAV AAV8 based gene therapies (RGX-314 and RGX-501) for wet age-related macular degeneration (AMD) and homozygous familial hypercholesterolemia (HoFH), respectively. In addition, a Phase I study evaluating RGX-111 in Mucopolysaccharidosis type I (MPS I) is expected to start in 1H18. If any one of these studies produces positive results, we believe the shares could trade significantly higher from current levels.

Valuation: Using a sum-of-the-parts analysis, we derive a target price of $39. See page 126 for more detail.

GAAP EPS	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Full Year	Revenues (mil.)
2016A	(0.41)	(0.55)	(0.69)	(0.74)	$(2.38)	$5
2017E	(0.82)A	(0.69)A	(0.68)	(0.71)	(2.89)	1
2018E	(0.73)	(0.67)	(0.69)	(0.65)	(2.73)	0

Rows may not add due to rounding.

Current and Target Price

Current Price (Oct-09-17)	$32.30
Target Price:	$39.00
52-Week Range	$33.95 - $15.25
Suitability	High Risk/Speculation

Market Data

Shares Out. (mil.)	30.9
Market Cap. (mil.)	$998
Avg. Daily Vol. (10 day)	477,980
Dividend/Yield	$0.00/0.0%
BVPS (Jun-17)	$6.86
ROE %	-36%
LT Debt (mil.)/% Cap.	$0/0%

Earnings & Valuation Metrics

	2016A	2017E	2018E
P/E Ratios (GAAP)	NM	NM	NM

REGENXBIO Inc., headquartered in Rockville, Maryland, is a clinical-stage gene therapy company with a unique AAV technology platform (the NAV platform) and a broad wholly owned pipeline. The NAV platform, built on the next generation AAV vectors, has attracted 10 partners (including Biogen, Shire, and AveXis, to name a few) and produced over 20 partnered products. In addition, the NAV platform has generated four wholly owned product candidates targeting a variety of indications (e.g., AMD and CNS diseases). Two of these products are already in the clinic: 1) RGX-314, which utilizes the NAV AAV8 vector to express anti-VEGF monoclonal antibody fragments, is being evaluated in a dose-escalation Phase I study for wet AMD, with an interim update expected by the end of 2017; and 2) RGX-501, which also uses the NAV AAV8 vector to deliver the LDLR (low-density lipoprotein receptor) gene, is being investigated in a dose-escalation study for HoFH, with an interim update also expected by YE17.

Source: FactSet.

Company Description

REGENXBIO, headquartered in Rockville, Maryland, is a clinical-stage gene therapy company with a unique AAV technology platform (the NAV platform) and a broad wholly owned pipeline. The NAV platform, built on the next generation AAV vectors, has attracted 10 partners (including Biogen, Shire, and AveXis, to name a few) and produced over 20 partnered products. In addition, the NAV platform has generated four wholly owned product candidates targeting a variety of indications (e.g., AMD and CNS diseases). Two of these products are already in the clinic: 1) RGX-314, which utilizes the NAV AAV8 vector to express anti-VEGF monoclonal antibody fragments, is being evaluated in a dose-escalation Phase I study for wet AMD, with an interim update expected by the end of 2017; and 2) RGX-501, which also uses the NAV AAV8 vector to deliver the LDLR (low-density lipoprotein receptor) gene, is being investigated in a dose-escalation study for HoFH, with an interim update also expected by YE17. Taken together, we believe the first two clinically advanced indications could address a combined U.S./EU market opportunity of $30+ billion.

Newsworthy Catalysts

RGX-314 for wet AMD

- Potential to provide an interim update (YE17)

RGX-501 for HoFH

- Potential to provide an interim update (YE17)

RGX-111 for MPS I

- Potential to dose the first patient in a Phase I study (1H18)

RGX-121 for MPS II

- Potential to submit an IND (4Q17)

AveXis' AVXS-101 for SMA

- Potential for AveXis to initiate a pivotal study of AVXS-101 for SMA Type 1 in the U.S. (4Q17)
- Potential for AveXis to initiate a Phase I/IIa study of AVXS-101 for SMA Type 2 in the U.S. (4Q17/2018)
- Potential for AveXis to initiate a pivotal study of AVXS-101 for SMA Type 1 in the EU (4Q17)
- Potential for AveXis to provide an update on the outcomes of the end-of-Phase I meeting with the FDA (4Q17)

Summary of Investment Risks

Clinical and Regulatory Risk

The clinical development of REGENXBIO's wholly owned products bears risk given that we have not seen any clinical data to date. In addition, the failures of other companies' gene therapy products for wet AMD would result in additional scrutiny of REGENXBIO's product candidate for the same indication although REGENXBIO's approach is differentiated. While a broad pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk

If approved, REGENXBIO's products are likely to face competition from existing therapies. For example, in the wet AMD space, the approved anti-VEGF therapies (e.g., Regeneron's Eylea and Roche/Novartis' Lucentis) have demonstrated effectiveness (although there are some compliance issues), resulting in challenges associated with changing physicians' prescribing behaviors. With respect to HoFH, for which another gene therapy product (RGX-501) is being evaluated, a number of existing interventions could also pose competition. That said, RGX-501 has the potential to be used in conjunction with some of these therapies.

Aside from competition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If REGENXBIO cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercially viable.

Financing Risk

REGENXBIO currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Summary of Investment Highlights

A Powerful Gene Therapy Platform, with a Lot of Admirers

In our opinion, the company's NAV platform is composed of next generation AAV vectors licensed from U Penn and produced using a proprietary technology. The company currently has a broad and deep IP portfolio consisting of 100+ patents and patent applications worldwide covering the NAV vectors, including AAV7, AAV8, AAV9, and AAVrh10. According to the company, the NAV technology platform offers several potential benefits:

Higher Gene Expression

In animal studies, REGENXBIO's NAV vectors have demonstrated greater levels of gene expression than earlier generation AAV vectors. For example, the expression of the reporter gene LacZ delivered by the AAV8 vector was 10- to 100-fold higher than that achieved by an early generation AAV2 vector.

Longer Gene Expression

Some NAV vectors have demonstrated stable gene expression for over eight years in animals and over four years in humans (e.g., AAV8 in hemophilia B patients was evaluated in an investigator sponsored trial, the results of which were published in the New England Journal of Medicine [link]).

Broad and Novel Tissue Selectivity

The NAV platform has generated AAV9 for gene delivery into the central nervous system (CNS) and AAV8 for the eye and other tissues.

Lower Immune Response

The prevalence of pre-existing neutralizing antibodies for AAV8 is much lower than that for AAV2. In addition, a clinical study indicated that AAV8 as compared to AAV2 caused less of an immune response from T cells.

Improved Manufacturing

As the NAV vectors are secreted by AAV producer cells, there is no need for lysing the cells. Cell lysis can affect purification and yield.

Because of the broad and deep IP portfolio as well as the aforementioned attractive attributes, the NAV platform has resulted in ten licensees and 20+ partnered programs (Exhibit 1) as well as four wholly owned internal products.

Exhibit 1: **Programs Partnered With REGENXBIO**

	Research		Preclinical		Clinical	
Target	Indication	Licensee	Indication	Licensee	Indication	Licensee
Hematologic / liver	*Citrullinemia Type I*	Dimension Therapeutics	*Hemophilia A*	Dimension Therapeutics / Bayer	*Hemophilia A*	Shire
	PKU	Dimension Therapeutics	*GSDIa*	Dimension Therapeutics	*OTC Deficiency*	Dimension Therapeutics
	Wilson Disease	Dimension Therapeutics			*Crigler-Najjar*	Audentes
					A1AT Deficiency	Adverum
Retina	*Achromatopsia*	Biogen				
	Choroideremia	Biogen				
CNS	*Parkinson's with GBA*	Prevail Therapeutics	*ALS SOD1*	avexis	*SMA*	avexis
	Undisclosed	Voyager / genzyme	*Rett Syndrome*	avexis	*MPS IIIA*	LysoGene
			Undisclosed	Voyager		
			MPS IIIA	Esteve		
Cardiac / skeletal muscle	*Friedreich's Ataxia*	Voyager / genzyme	*CPVT*	Audentes	*XLMTM*	Audentes
	Friedreich's Ataxia	Adverum			*Pompe Disease*	Audentes

Source: REGENXBIO.

Wholly Owned Programs Create Multiple Shots on Goal

RGX-314 for Wet AMD

The unmet need. Wet age-related macular degeneration (AMD), a disease that results in decline and eventual loss of central vision due to damage to the macula, is the leading cause of blindness in the elderly, currently affecting approximately 1,500,000 people in the U.S. While the anti-VEGF therapies (e.g., Eylea and Lucentis), the current standard of care for wet AMD, have proven to be effective in improving visual acuity in the majority of patients, they are associated with frequent intraocular injections (every 1-2 months for years). The repetitive injections in the eye often cause a great degree of inconvenience and discomfort, resulting in poor patient compliance, which eventually leads to vision loss in the long term. Given the good clinical outcomes and compliance issues associated with traditional anti-VEGF therapies as well as the progress being made in the gene therapy space, in our view, developing an anti-VEGF gene therapy product as a one-time solution is reasonable. Furthermore, we believe a VEGF gene therapy could compete effectively against these anti-VEGF monoclonal antibodies if it offers a similar efficacy and safety profile. Eylea and Lucentis, which are approved for wet AMD and other retinal disorders, generated U.S. sales of $3.3 billion and $1.4 billion in 2016, respectively.

REGENXBIO's solution in the making. REGENXBIO's RGX-314, which utilizes the NAV AAV8 vector to express anti-VEGF monoclonal antibody fragments, is being developed as a one-time subretinal treatment for wet AMD. Currently, a multi-center, multi-cohort, open-label, dose-escalation Phase I study (NCT03066258) evaluating RGX-314 in previously treated wet AMD patients is ongoing. Besides evaluating safety, the study will also assess the efficacy of the gene therapy by measuring the best corrected visual acuity (BCVA) and central retinal thickness (CRT). A total of 18 patients are expected to be enrolled into three dosing cohorts (3×10^9, 1×10^{10}, and 6×10^{10} genome copies/eye, n=6 for each), with every one of them required to have a documented response to an anti-VEGF therapy at trial entry. Of note, for each patient, only one eye is treated with the gene therapy, whereas the other eye is managed with standard of care (anti-VEGF antibodies). The dosing of the first cohort of six patients was completed in September 2017 (first patient dosed in May 2017), with an interim update expected by the end of 2017. While no clinical data has been reported to date, in our opinion, the clinical evaluation of RGX-314 is supported by the preclinical studies in which high-level expression of anti-VEGF proteins in animals were achieved and largely maintained over the course of 120 days.

Can gene therapy work in wet AMD? Besides REGENXBIO, three other companies were/are involved in the development of an anti-VEGF gene therapy for wet AMD, including Avalanche (which merged with Annapurna Therapeutics, with the combined entity becoming Adverum), Genzyme (acquired by Sanofi), and Adverum (which is developing different gene therapies as compared to Avalanche). Unfortunately, both Avalanche and Genzyme failed to demonstrate a statistically significant benefit (see pages 111-112 for more details).

Given these two failures, a critical question is: would REGENXBIO's anti-VEGF gene therapy have a similar fate? As shown in Exhibit 7 on page 109, REGENXBIO's RGX-314 differs from other anti-VEGF gene therapy products in terms of the vector, transgene, and route of administration, which may result in different clinical outcomes.

- **Vector – AAV8 appears to be better.** RGX-314 has a different vector (AAV8) as compared to Avalanche's AVA-101 and Genzyme's GZ402663 (both used AAV2). If a gene therapy is delivered intravitreally, in our opinion, AAV8 is a better choice than AAV2 given the impact of pre-existing neutralizing antibodies on the expression of transgenes injected via this route of administration and the fact that such neutralizing antibodies against AVV8 are significantly less prevalent than those against AAV2 (prevalence: 38% vs. 72%). In addition, preclinical studies using non-human primates demonstrated that AAV8 was more efficient than AAV2 at the same dose in terms of transducing photoreceptor cells and that the expression of a reporter gene was 10- to100-fold greater.

- **Transgene**. The transgene for RGX-314 contains an anti-VEGF antibody fragment vs. the native sFlt-1 for AVA-101 and the chimeric sFlt-1 for GZ402663. Of note, the approved anti-VEGF therapy Lucentis is an anti-VEGF antibody fragment, whereas Eylea is a fusion protein consisting of human VEGF receptor extracellular domains and the Fc portion of a human IgG1. Flt-1 (fms-like tyrosine kinase-1) is a type of VEGF receptor, which binds VEGFs approximately 10 times stronger than another VEGF receptor, KDR, although the binding of Flt-1 to endogenous VEGFs does not significantly promote angiogenesis (formation of new blood vessels). We believe that an anti-VEGF transgene is a better choice than the Flt-1 gene given that anti-VEGF therapies have already been approved.

- **Route of administration**. RGX-314 and AVA-101 are injected subretinally, whereas other products (GZ402663, ADVM-022, and ADVM-032) were administered intravitreally. Both routes of administration have advantages and disadvantages. Pre-existing serum anti-vector neutralizing antibodies have a significant impact on the expression of transgenes delivered intravitreally but not those injected subretinally. In addition, subretinal administration appears to be associated with greater transduction efficiency of the retinal pigment epithelium and photoreceptors. That said, subretinal administration is more invasive and has a higher risk for potential complications as well as a greater degree of variability of the procedure (e.g., intended volume is not injected), which may in turn affect the efficacy. In our opinion, the impact of these pre-neutralizing antibodies (prevalence rates ranging from 38% [AAV8] to 72% [AAV2]) and transduction efficiency are probably more profound than other factors, and therefore subretinal injection is likely to be a better choice. Of note, Spark Therapeutics uses a recombinant AAV2 vector for its RPE65 gene therapy product, which is administered through an injection into the subretinal space.

RGX-501 for HoFH

HoFH, a monogenic disease, is caused by a defect in the LDLR (low-density lipoprotein receptor) gene, which plays an essential role in facilitating uptake and degradation of LDL in the liver. The worldwide HoFH prevalence is estimated to be about 1 in 200,000, with approximately 2,000 patients currently being affected by this disease in the U.S.

REGENXBIO's RGX-501, a gene therapy product utilizing the AAV8 vector to deliver the human LDLR gene to liver cells, is currently being evaluated in a dose-escalation Phase I/II study (NCT02651675) for patients with HoFH. In this study, a single dose of RGX-501 is administered intravenously. The primary endpoint is safety, and the secondary endpoints include the percent change in LDL-C (low-density lipoprotein cholesterol) levels and other lipids at 12 weeks and beyond. Of note, concurrent lipid lowering medications including statins, ezetimibe, bile acid sequestrants, and PCSK9 inhibitors are allowed. The study is expected to enroll a total of 12 patients into three dose cohorts, with the first patient already dosed in March 2017 and an interim update expected by the end of 2017. While no clinical data has been reported to date, in our opinion, the clinical evaluation of RGX-501 is supported by preclinical findings of significant reductions in plasma cholesterol levels as well as in atherosclerosis (obstruction of blood flow caused by a buildup of cholesterol plaque or other substances in the walls of arteries) seen in mice.

There are a number of interventions available for lowering LDL-C, with several approved by the FDA for the management of HoFH, including lipoprotein apheresis, statins, mipomersen, lomitapide, and two PCSK9 inhibitors (Amgen's Repatha and Sanofi/Regeneron's Praluent). That said, in our opinion, these therapies are not direct competitors of RGX-501. Instead, we believe RGX-501 could be synergistic with these therapies given that they have different mechanisms of action (MOAs) in terms of lowering LDL-C levels. For example, the newly approved PCSK9 inhibitors can bind to PCSK9 and prevent circulating PCSK9 from binding to LDLRs, resulting in an increased number of LDLRs available to clear LDL-C. Therefore, in theory, PCSK9 inhibitors should be more effective when patients have more functional LDLRs, which could be achieved by RGX-501. According to the company, a clinical trial evaluating a PCSK9 inhibitor demonstrated that its effectiveness relies on patients having functional LDLR.

In the gene therapy arena, to the best of our knowledge, RGX-501 is the only product currently in the clinic, although there are other LDLR gene therapy product candidates in preclinical testing.

The MPS Programs

Mucopolysaccharidosis (MPS) is a group of rare genetic diseases, each of which is caused by deficiency in one of 10 specific enzymes within lysosomes (membrane enclosed organelles responsible for disposing of wastes inside cells). Mucopolysaccharidosis type I (MPS I) is a non-sex linked disorder caused by deficiency of alpha-iduronidase (IDUA), an enzyme which is essential for the breakdown of polysaccharides heparan sulfate and dermatan sulfate in lysosomes. Of note, MPS I is extremely rare, with global annual new cases of approximately 500-1,000. Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a rare, sex linked disorder resulting from a deficiency in IDS (lysosomal enzyme iduronate-2-sulfatase), another enzyme that is essential for the degradation of polysaccharides heparan sulfate and dermatan sulfate in the lysosomes. Similarly, the global annual incidence of MPS II is approximately 500 to 1,000.

REGENXBIO is developing RGX-111 for MPS I and RGX-121 for MPS II. RGX-111, which utilizes the NAV AAV9 vector to deliver the human IDUA gene to the CNS through an intracisternal administration, has an active IND for a Phase I study, with the first patient expected to be dosed in 1H18. Similarly, RGX-121 also uses the NAV AAV9 vector but delivers a different transgene (IDS) to the CNS via intracisternal administration. The company plans to submit an IND for RGX-121 for MPS II in 4Q17.

REGENXBIO's Wholly Owned Portfolio

Product	Status	Market	Rights
RGX-314	Phase I	Wet AMD	REGENXBIO
RGX-501	Phase I/II	HoFH	REGENXBIO
RGX-111	IND active	MPS I	REGENXBIO
RGX-121	Preclinical	MPS II	REGENXBIO

AMD -- age-related macular degeneration, HoFH -- Homozygous familial hypercholesterolemia, and MPS – Mucopolysaccharidosis
Source: REGENXBIO, Raymond James research.

Summary of Investment Positives and Negatives

Positives	Negatives
A powerful AVV vector platform	No clinical data from the company's wholly owned programs
Multiple partnerships with leading biotech/gene therapy companies	The failures of others' gene therapies for wet AMD cast doubt into REGENXBIO's product
A broad wholly owned pipeline that creates multiple shots on goal	A setback in any of these programs could negatively impact shares
An attractive acquisition target	Small cap/low share volume

Source: Raymond James research.

The Wet AMD Franchise

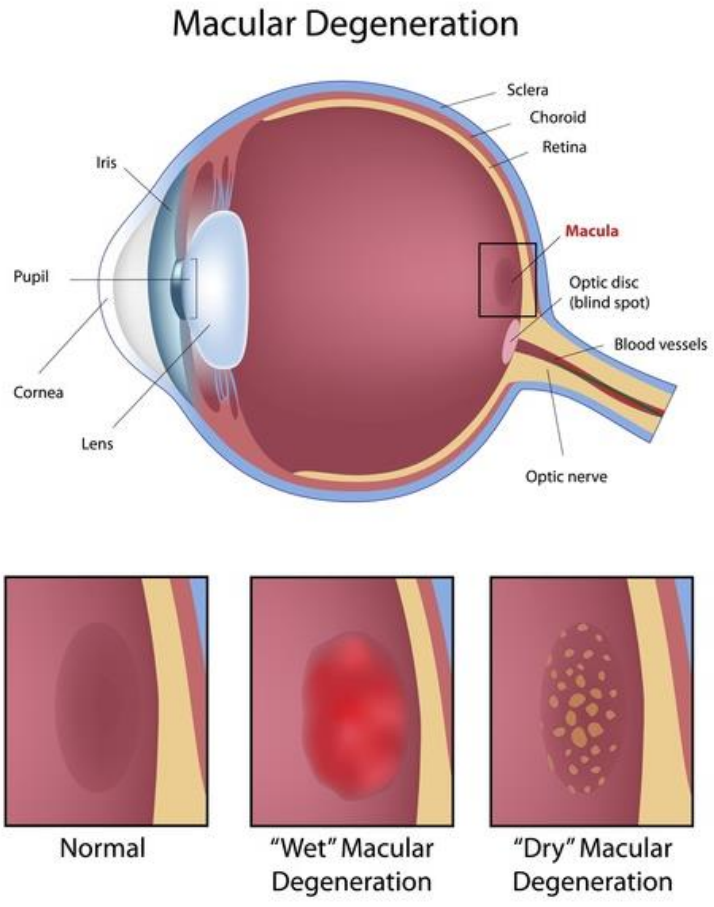
Biology of the Eye

If one pictures the human eye as a ball, the front part of that ball would contain the cornea and pupil, while the back part would contain the retina (approximately 0.5 mm thick) (Exhibit 2). In approximately the center position of the retina is the optic nerve, also known as the cranial nerve, which is made up of over a million nerve fibers and is used to transfer visual information from the eye to the brain. The optic nerve also houses the major blood vessels of the retina, which are responsible for supplying blood to the retina.

Approximately 4.5 mm to 5 mm from the optical nerve is a blood free area known as the macula, the center of which is called the fovea. If one draws a 6 mm circle around the fovea, the encircling region is known as the central retina, while beyond this border, the region is called the peripheral retina.

The structure of the eye is quite radical in design. Interestingly, the ganglion cells (the neurons of the retina) reside in the area of the retina closest to the front of the eye. Conversely, the photosensors (the rods and cones) lie in the outermost area of the retina against the retinal pigment epithelium (RPE) and choroid. When a visual stimulus enters the eye, the light must travel through the retina and activate the rods and cones, which subsequently secrete chemical messengers, before returning back to an electrical message by the neurons found in the anterior of the retina. The visual image is then transmitted to the brain through the ganglion cells.

Exhibit 2: **The Structure of the Eye and Macular Degeneration**



Source: https://ghr.nlm.nih.gov/condition/age-related-macular-degeneration.

Wet AMD

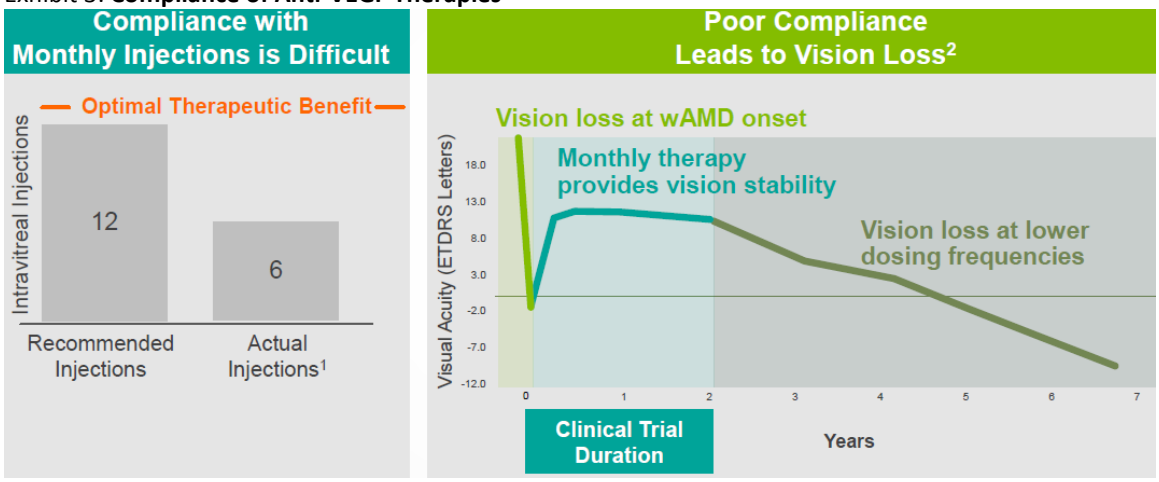
AMD is a disease that results in decline and eventual loss of central vision due to damage to the macula. A subset of AMD patients (10-15%) have wet AMD, which is caused by the growth of abnormal leaky blood vessels beneath the macula that eventually cause fluid leakage that results in physical changes in the structure of the retina and changes in vision. As the disease progresses, blindness can occur due to fibrous scarring of the retina. Wet AMD is the leading cause of blindness in the elderly – in the U.S., approximately 1,500,000 people suffer from wet AMD and about 200,000 new cases are diagnosed each year. Worldwide, approximately 500,000 new cases are diagnosed annually.

Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis (formation of new blood vessels), which is mediated primarily by the binding of VEGF to VEGF receptor (VEGFR), KDR. Flt-1 (fms-like tyrosine kinase-1), another VEGFR, binds VEGF approximately 10 times stronger than KDR, although the binding of Flt-1 to VEGF does not significantly promote angiogenesis. As VEGF can promote the growth of new blood vessels, anti-VEGF products have the potential to prevent the formation of abnormal leaky blood vessels seen in wet AMD patients.

The current standard of care for the treatment of wet AMD is anti-VEGF therapies, which have proven to be effective in improving visual acuity in the majority of patients. Currently, there are three anti-VEGF inhibitors that are most commonly used for the treatment of wet AMD: Regeneron's Eylea (aflibercept, approved in 2011), Roche/Novartis' Lucentis (ranibizumab, approved in 2006), and Roche's Avastin (bevacizumab, off-label use). Of note, Valeant's Macugen (pegaptanib) was the first approved anti-VEGF inhibitor (approved in 2004), although it does not appear to be a significant competitor to the aforementioned three anti-VEGF therapies.

While effective, these anti-VEGF therapies require frequent intraocular injections (every 1-2 months for years). Therefore, patients usually experience a great degree of inconvenience and discomfort associated with the repetitive injections in the eye, leading to poor patient compliance, which eventually results in vision loss in the long term (Exhibit 3). If VEGF gene therapies offer a similar efficacy and safety profile as compared to these anti-VEGF inhibitors, in our opinion, the former could potentially replace the latter in the marketplace given that they are positioned as a one-time treatment.

Exhibit 3: **Compliance of Anti-VEGF Therapies**



[1] Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration, Am J Ophthalmol. 2014; 157(4):825-833, Holekamp NM, et al.

[2] Multiple studies (MARINA/ANCHOR & HORIZON/SEVEN-UP, SECURE, CATT) indicate that vision benefits are lost at less than recommended dosing frequencies.

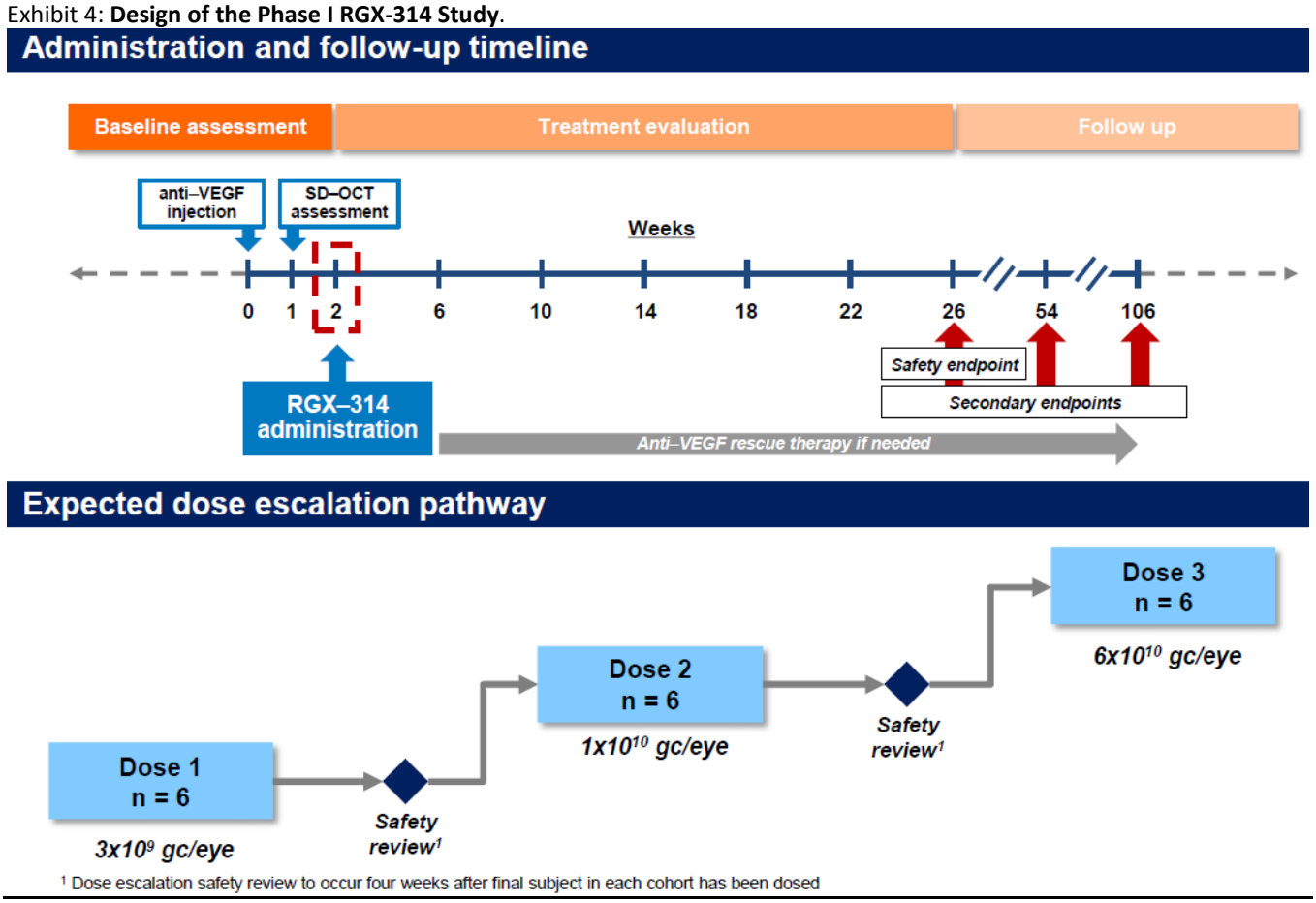
Source: Adverum.

RGX-314 for Wet AMD

RGX-314, which utilizes the NAV AAV8 vector to express anti-VEGF monoclonal antibody fragments, is being developed as a one-time subretinal treatment for wet AMD. In May, 2017, the first patient was dosed in a multi-center, multi-cohort, open-label, dose-escalation Phase I study evaluating RGX-314 in patients with previously treated wet AMD, with an interim update expected by the end of 2017. With the primary endpoint being safety, the secondary endpoints include the effect of RGX-314 on best corrected visual acuity (BCVA) and central retinal thickness (CRT) as measured by Spectral Domain Optical Coherence Tomography (SD-OCT), as well as the expression levels of anti-VEGF fragments in the eye. Eligible patients must be those who require frequent anti-VEGF therapy, with a documented response (assessed by SD-OCT) to an anti-VEGF treatment at week 1 of the study. As illustrated in Exhibit 4, two weeks before the administration of RGX-314, patients are given an anti-VEGF injection (the company steers physicians to use Lucentis), followed by a SD-OCT assessment for response one week later.

A total of 18 patients are expected to be enrolled into three dosing cohorts (3 x 10^9, 1 x 10^{10}, and 6 x 10^{10} gc/eye), with a safety review anticipated to occur four weeks after the dosing of the final subject in each cohort (Exhibit 4). For each cohort, the baseline vision is required to be 20/100 to 20/400 for the initial patient and 20/63 to 20/400 for the remaining patients. For each patient, only one eye is treated with the gene therapy, whereas the other eye is treated with standard of care.

Exhibit 4: **Design of the Phase I RGX-314 Study**.

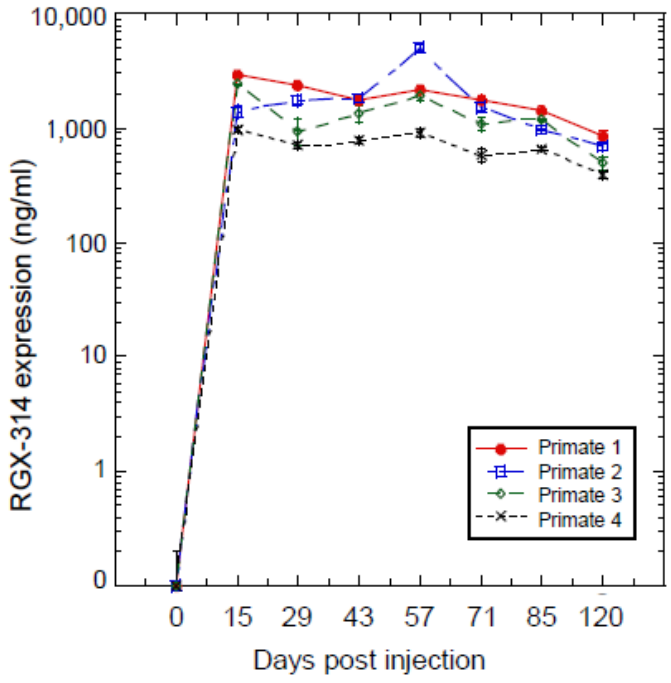


Source: REGENXBIO.

Preclinical Activity of RGX-314

In non-human primate (NHP) models, a one-time subretinal injection of RGX-314 generated a rapid, high-level expression of anti-VEGF proteins (~15 days post-injection) in all animals and doses tested. The high level expression was seen over the course of 120 days (Exhibit 5), although there appeared to be a downward trend.

Exhibit 5: **Expression of RGX-314 in Non-Human Primates**

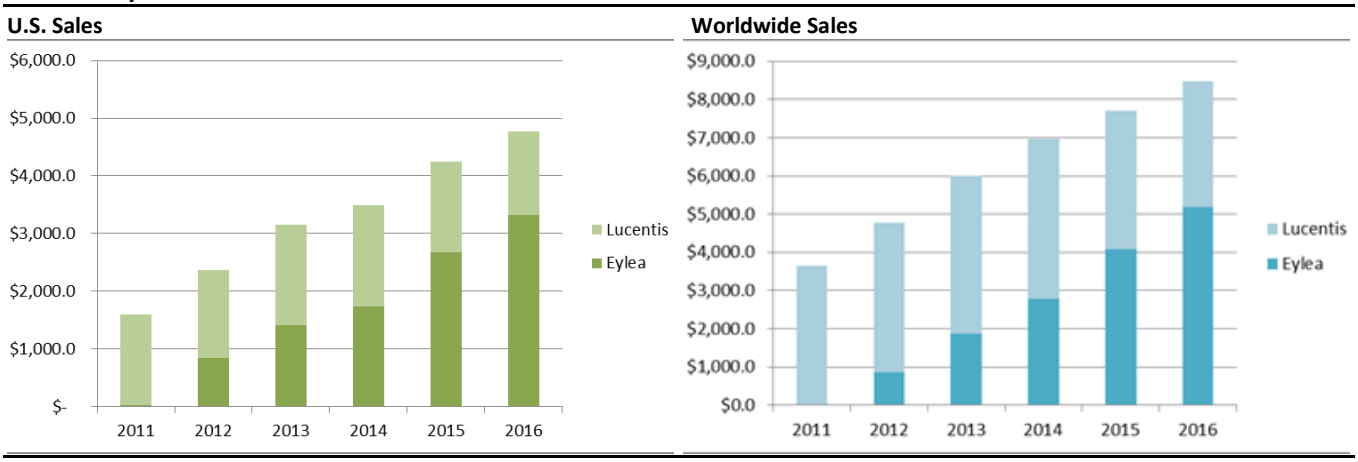


Source: REGENXBIO.

Wet AMD Competitive Landscape

Three VEGF inhibitors have been approved for the treatment of wet AMD: Regeneron's Eylea (aflibercept), Roche's Lucentis, and Valeant's Macugen. Lucentis and Eylea combined generated worldwide revenues of $4.8 billion, $6.0 billion, $7.0 billion, $7.7 billion, and $8.5 billion in 2012-2016, respectively, with Eylea currently taking the lead (Exhibit 6). In addition, Roche's Avastin has also been used off-label for the treatment wet AMD.

Exhibit 6: **Eylea and Lucentis Sales**



Source: Regeneron and Roche company reports, Raymond James research.

Besides currently available anti-VEGF treatments, there are also other gene therapy products in development that could compete with RGX-314 (Exhibit 7).

Exhibit 7: **VEGF Gene Therapies in Development**

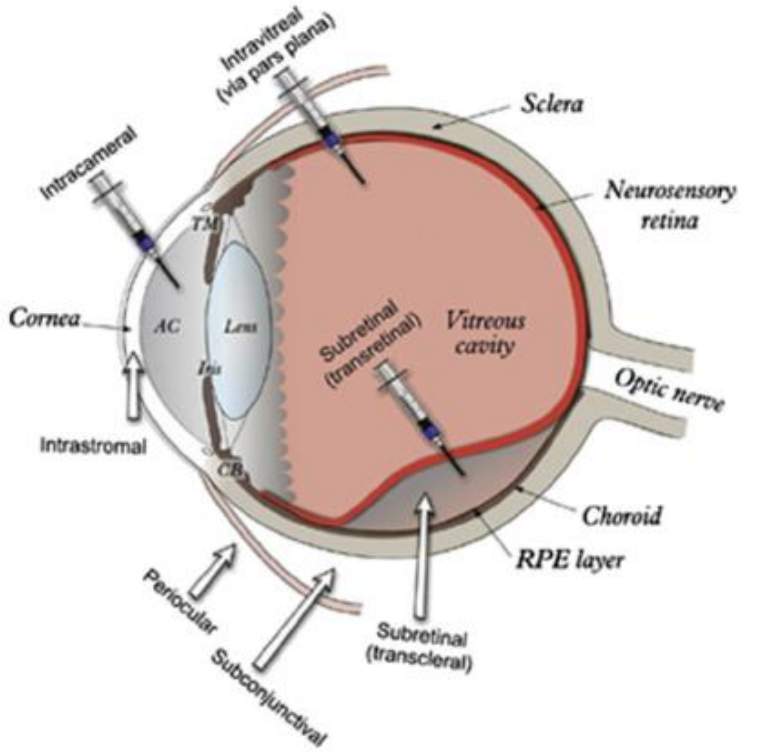
Product	Company	Current Status	Vector	ROA	Transgene
RGX-314	REGENXBIO	Phase I	AAV8	Subretinal	anti-VEGF fab
AVA-101	Avalanche	Terminated	AAV2	Subretinal	Native sFlt-1
GZ402663	Sanofi (Genzyme)	Discontinued after Phase I	AAV2	Intravitreal	Chimeric sFlt-1
ADVM-022	Adverum	Preparing IND	Proprietary vector	Intravitreal	7m8-aflibercept)
ADVM-032	Adverum	Not selected for further development	Proprietary vector	Intravitreal	7m8-ranibizumab

Note: In May 2016, Avalanche Biotechnologies merged with Annapurna Therapeutics, with the combined entity named Adverum Biotechnologies.

Source: Company reports, Raymond James research.

Route of Administration: What Are the Differences Between Subretinal and Intravitreal Injections?

Exhibit 8: **Subretinal Injection vs. Intravitreal Injection**



Source: Dumitrescu, et al, Gene Therapy for Blinding Pediatric Eye Disorders, Advances in Pediatrics, 2015.

Attributes	Subretinal injection	Intravitreal injection
Impact of pre-existing serum anti-vector neutralizing antibodies on transgene expression?	No (or at least not significant)	Yes
Transduction efficiency of the retinal pigment epithelium and photoreceptors	Higher	Lower
Invasiveness	More invasive	Less invasive
Current approach of delivering anti-VEGF proteins?	No	Yes
Risk for potential complications	Higher (a 1% risk of retinal detachment and a 60% risk of cataract progression could lead to a cataract surgery within a year)	Lower
Variability of the procedure	Higher (there might be some patients who do not get the intended injection volume)	Lower
Cost	More expensive	Less expensive

Source: Heier, et al, intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial, Lancet, 2017. Raymond James research.

Transgene: Anti-VEGF Fab vs. Native sFlt-1 vs. Modified sFlt-1 vs. Anti-VEGF Antibodies

Avalanche's AVA-101 is designed to express native soluble Flt-1, which is a variant of the full length VEGFR-1 protein, whereas Sanofi's GZ402663 (AAV2-sFLT01) consists of a recombinant AAV2 vector that contains a gene expressing a soluble chimeric protein composed of domain 2 of the soluble human VEGF receptor 1 (Flt-1) and the Fc region of human immunoglobulin G (IgG) subclass 1. This AAV2-sFLT01 vector was generated through the HSV helper and HEK293 cell based manufacturing approach, with the purified vector containing ~60% genome containing full capsids. In contrast, both REGENXBIO and Adverum utilize a different transgene that can produce an anti-VEGFR antibody (or an antibody fragment).

The Development of AVA-101 Was Halted by Avalanche Biotechnologies Due to a Lack of Efficacy

AVA-101, comprised of a wild type AAV2 vector that contained a gene expressing soluble Flt-1 (a naturally occurring anti-VEGF protein), was evaluated by Avalanche in a single-center (Australia), open-label Phase I/IIa study (NCT01494805). Of note, on May 12, 2016, Avalanche Biotechnologies merged with Annapurna Therapeutics, with the combined entity named Adverum Biotechnologies.

In June 2015, Avalanche announced top-line results from the Phase IIa portion of the study evaluating AVA-101 in patients with wet AMD aged 55 or older. This study randomized a total of 32 patients into an AVA-101 treatment group (n=21) or a control group (n=11), with 29 having a prior anti-VEGF therapy (a median of 10 injections). AVA-101 was administered to the patients in the treatment group on day seven. Lucentis was given to both groups at day 0 and week 4, and it was also allowed as a rescue therapy beginning at week 8. The primary endpoint was safety, and the secondary endpoints were mean BCVA change from baseline, the number of Lucentis rescue injections, and mean change in central retinal thickness from baseline as measured by SD-OCT.

On the safety front, no serious adverse events (SAEs) related to AVA-101 were reported as all patients remained in the study throughout the 12-month period. Of note, all drug related AEs were mild or moderate and resolved over the course of 60 days. While one patient in the treatment group had a non-fatal myocardial infarction, this event was not deemed to be related to the gene therapy. One patient in the control group experienced endophthalmitis.

While the safety endpoint was met, the efficacy outcomes were somewhat disappointing. Over the course of 52 weeks, the mean BCVA change from baseline for the treatment group was 2.2 letters vs. -9.3 letters for the control group. While the difference in the mean BCVA changes from the baseline between the two groups was statistically significant, the BCVA improvements achieved by AVA-101 appear to be relatively inferior to what have been reported for the monthly treatment of Lucentis in many other studies (12-month mean BCVA change: 2.2 letters vs. 6.3-11.0 letters). In addition, it did not appear that the gene therapy significantly reduced the number of Lucentis rescue injections, with the median number of rescue injections being two (range: 1-6) for the treatment group and four (range: 3-5) for the control group. In terms of the impact on central retinal thickness, the treatment group performed worse than the control group, as evidenced by an increase of 25 mm in retinal thickness from baseline in the treatment group vs. a reduction of 56 mm in the control group.

In the treatment group, 12 patients had neutralizing antibodies (nAb) to AAV2 before treatment, and three of the initial nine nAb-negative patients seroconverted after the gene therapy. That said, the principle investigators of this study do not think that these pre-existing nAbs to AAV2 necessarily decreased the clinical activity of the subretinally injected gene therapy.

Avalanche eventually concluded that there was no evidence of a complete and/or durable anti-VEGF response in the majority of patients treated with AVA-101 in the Phase IIa study, resulting in an ultimate decision not to initiate the planned Phase IIb trial to further evaluate this gene therapy for wet AMD.

Sanofi's AAV2-sFLT01

GZ402663 (AAV2-sFLT-01), comprised of an AAV-2 vector that expresses a modified soluble Flt1 receptor, originated from the collaboration established between Genzyme and Applied Genetic Technologies (AGTC) in December 2004. Following the acquisition of Genzyme, Sanofi took over the development of this gene therapy for wet AMD. Due to a lack of efficacy, in April 2015, Sanofi decided not to further develop GZ402663 for AMD.

GZ402663 was evaluated in an open-label, dose-escalating Phase I study (NCT01024998) at four outpatient retinal clinics in the U.S. The full results from this study were published in Lancet in May, 2017. A total of 19 wet AMD patients were enrolled into five cohorts and received a single intravitreal injection of GZ402663 into one eye at different doses: cohort 1 - $2x10^8$ vg (n=3), cohort 2 - $2x10^9$ vg (n=3), cohort 3 - $6x10^9$ vg (n=3), cohort 4 - $2x10^{10}$ vg (n=3), and cohort 5 - $2x10^{10}$ vg (n=7). The median baseline BCVA of these cohorts ranged from 20/320 to 20/500. All of the 19 patients completed the 52-week core study, with 17 enrolled in a 4-year extension study. Out of these 17 patients, three subsequently withdrew from the study, with two patients in each of the first three cohorts completing the four-year follow-up and one patient in cohort 4 and seven patients in cohort 5 about to complete the four-year follow-up.

With no maximum tolerated dose (MTD) identified as there were no dose-limiting toxicities, $2x10^{10}$ vg was used in the expansion cohort 5, resulting in a total of 10 patients treated at the highest dose.

No AAV2-sFLT01 vector DNA sequences were found in the blood, nasopharynx, urine, or semen of any patients after the treatment with the gene therapy at any time throughout the study.

At baseline, there were detectable anti-AAV2 antibodies in 12 out of the 19 patients (63%), with five out of the 10 patients treated at the highest dose having no baseline anti-AAV2 antibodies. Although an increase in anti-AAV2 antibody titer was not observed among the patients in cohorts 1-2 after treatment, such an effect was seen in 62% of the 13 patients in cohorts 3-5. Specifically, three of the five patients in the last two cohorts who had no anti-AAV2 antibodies at baseline generated these antibodies after the gene therapy treatment.

In terms of efficacy, overall, the gene therapy event at the highest dose did not improve the BCVA score significantly, although improvements were seen in some patients during certain time periods (Exhibit 9). For example, the 10 patients in cohorts 4 and 5 achieved a slight improvement in the mean BCVA from baseline to week 8, which declined afterwards, resulting in an eventual reduction in the mean BCVA score at week 52 (Exhibit 9).

Exhibit 9: **BCVA Change for Patients in Cohorts 4 and 5**

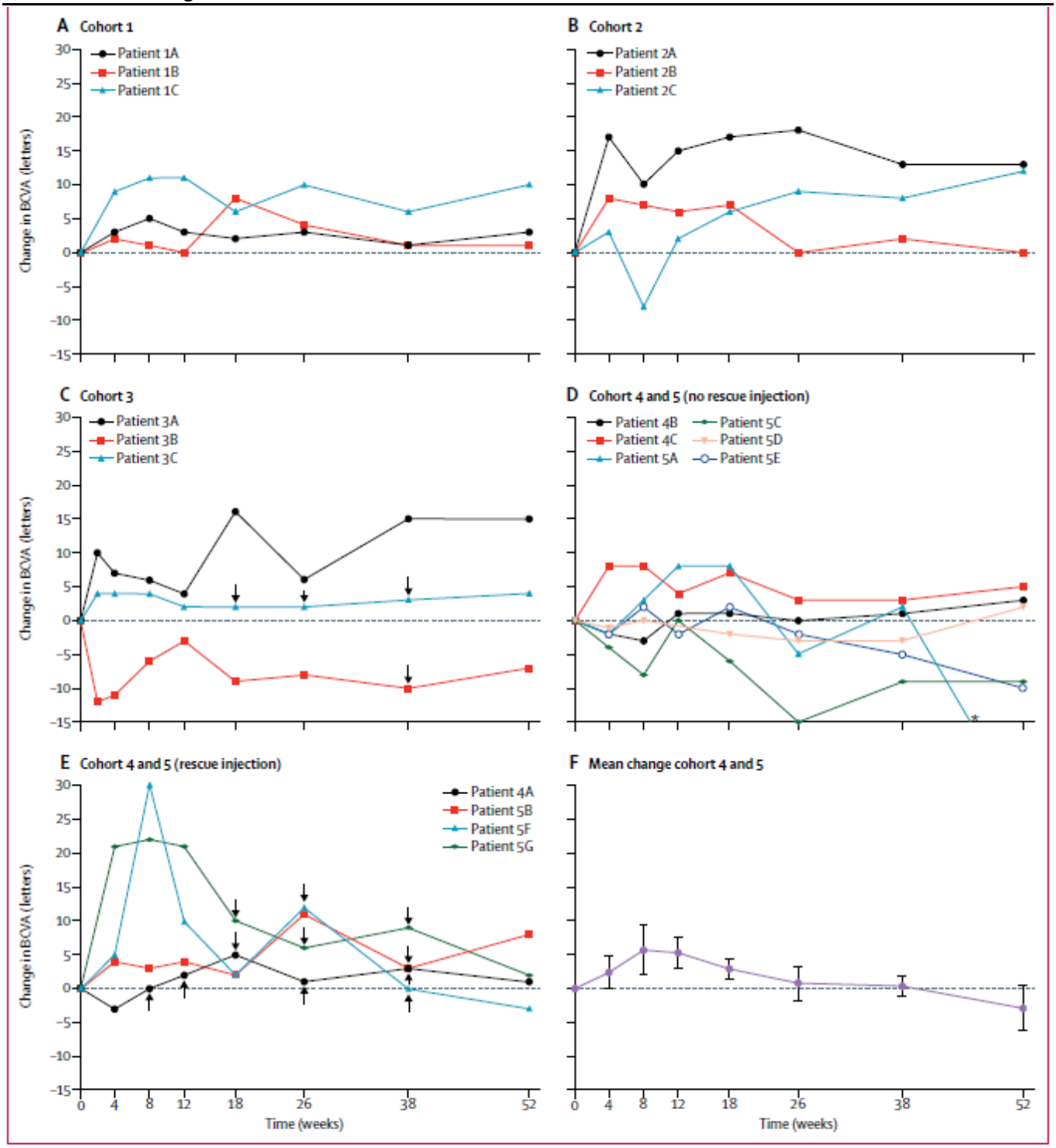


***Figure 5*: Change from baseline best corrected visual acuity after intravitreous injection of AAV2-sFLT01**
Patients had measurement of BCVA at baseline and each study visit after injection of 2×10^{4} vg (A, cohort 1), 2×10^{9} vg (B, cohort 2), 6×10^{9} vg (C, cohort 3), or 2×10^{10} vg (D–F, cohorts 4 and 5). Patients in cohorts 4 and 5 who did not receive any anti-VEGF rescue injections are shown in (D) and those that received rescue injections are shown in (E). The mean change from baseline BCVA for all ten patients in cohorts 4 and 5 who received 2×10^{10} vg is shown in (F). Arrows indicate an anti-VEGF injection was given at that timepoint. *BCVA was reduced from baseline by 28 letters by week 52. BCVA=best corrected visual acuity.

Source: Heier, et al, intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial, Lancet, 2017.

On the safety front, GZ402663 appeared to be safe and well tolerated, with no systemic adverse events associated with the injection of the gene therapy, although two patients in cohort 4 experienced possibly drug related adverse events. In addition, one case of intraocular inflammation was observed in the 10 patients treated at the highest dose, although this event was resolved following the use of topical steroids.

Why Did GZ402663 Fail?

A Suboptimal Dose Led to Reduction in sFLT-01 Expression Over Time?

Based on the available data from four patients who were treated at the highest dose, the detectable amounts of sFLT01 peaked at 12-26 weeks and then decreased between 26 and 52 weeks. According to the investigators, this could have been caused by the dose of $2x10^{10}$ vg, which was not the MTD and could be suboptimal based on the findings from non-human primate studies.

The Impact of Serum Anti-AAV2 Antibodies on Transgene Expression?

The clinical data generated in this study appeared to suggest that the pre-existing serum anti-AAV2 antibodies had a negative impact on transgene expression when the gene therapy was administered intravitreally. Among the five out of ten patients treated at the highest dose who did not have any detectable anti-AAV2 serum antibodies at baseline, four had detectable expression of sFLT01 in aqueous humour (the fluid that fills the space between the lens and the cornea) after treatment. In contrast, the four patients who were treated at the same dose with baseline anti-AAV2 titers of 1:400, 1:400, 1:3200, and 1:3200 did not show any detectable expression of sFLT01 in aqueous humour. These findings were also supported by multiple non-human primate studies. It appears that the impact of pre-existing neutralizing antibodies on transgene expression is more profound when a gene therapy is delivered via an intravitreal injection than a subretinal approach. Therefore, for a study that utilizes the intravitreal route of administration, in our opinion, it is prudent to stratify patients based on the level of their anti-vector neutralizing antibodies.

The HoFH Franchise

HoFH Background

Homozygous familial hypercholesterolemia (HoFH), a monogenic disease, is caused by a defect in the LDLR (low-density lipoprotein receptor) gene, which plays an essential role in facilitating uptake and degradation of LDL in the liver. LDL, the primary carrier of cholesterol in the blood, can cause the plaque buildup in the arteries. Since HoFH patients have a defective LDLR gene (low expression or completely defective), they have very high levels of cholesterol in the blood (usually >500 mg/dL), which can result in aggressive plaque buildup, life threatening coronary artery disease (CAD), and aortic valve disease. As HoFH patients experience atherosclerosis (a cardiovascular disease) or blockage of the arteries over time, they face a high risk of heart attacks, which can occur among children and teenagers. The worldwide HoFH prevalence is estimated to be about 1 in 200,000, with approximately 11,000 patients globally being the primary candidates for a gene therapy, according to REGENXBIO.

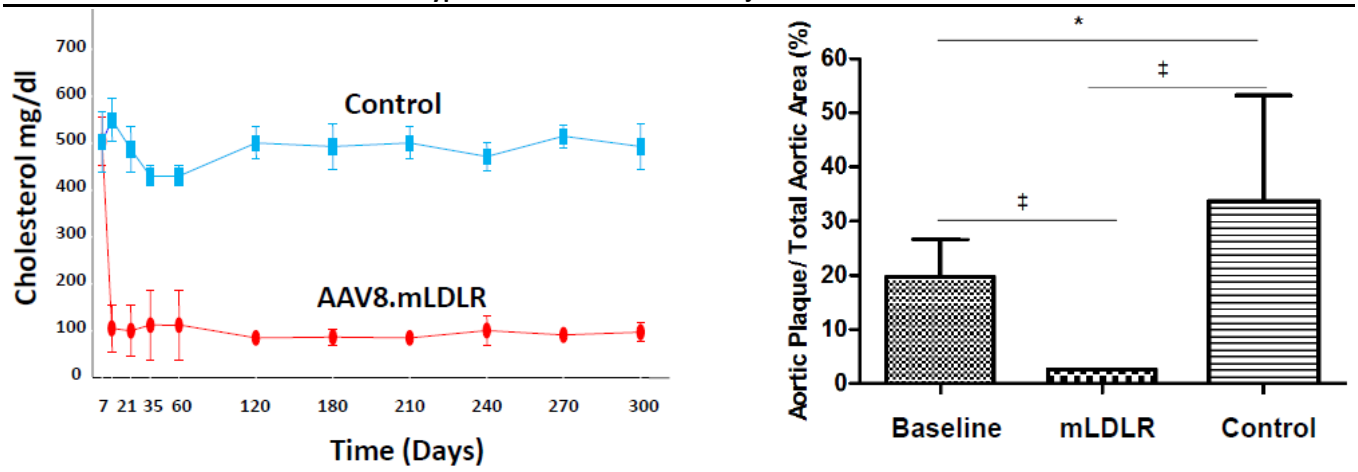
RGX-501 for HoFH

RGX-501 is a gene therapy product utilizing the AAV8 vector to deliver the human LDLR gene to liver cells, with a goal of producing functional and sufficient LDLRs and subsequently reducing high levels of cholesterol in the blood. According to REGENXBIO, there are three reasons why the liver is chosen as the target organ: 1) approximately 75% of the body's LDLRs are generated in the liver and are responsible for >90% of the degradation of LDL; 2) the liver is the only organ that can excrete cholesterol; and 3) as shown by some studies, liver transplantation in HoFH patients appears to fix the disease, which suggests restoring LDLR's function in the liver can correct HoFH.

Preclinical Testing

In a preclinical study, a single intravenous injection of AAV8.mLDLR (AAV8 vectors loaded with mouse LDLR gene) was administered to mice with germ line interruptions in the Ldlr and Apobec1 genes (Ldlr $^{-/-}$Apobec $^{-/-}$). Of note, Ldlr $^{-/-}$Apobec $^{-/-}$ mice can closely mimic the metabolic and clinical aspects of HoFH, including hypercholesterolemia (high cholesterol) with a lipoprotein profile comparable to that of HoFH patients. As compared to a control vector (AAV8.null), AAV8.mLDLR significantly reduced plasma cholesterol and non-HDL cholesterol levels in these mice, resulting in a near complete normalization of hypercholesterolemia that lasted for almost a year (Exhibit 10). In addition, mice treated with the gene therapy achieved an 87% regression in atherosclerosis (obstruction of blood flow caused by a buildup of cholesterol plaque or other substances in the walls of arteries) after three months of treatment, whereas the mice treated with the control vector experienced a 65% progression in atherosclerosis over two months (Exhibit 10).

Exhibit 10: **The Outcomes of Familial Hypercholesterolemia Mice Injected With AAV8.mLDLR**



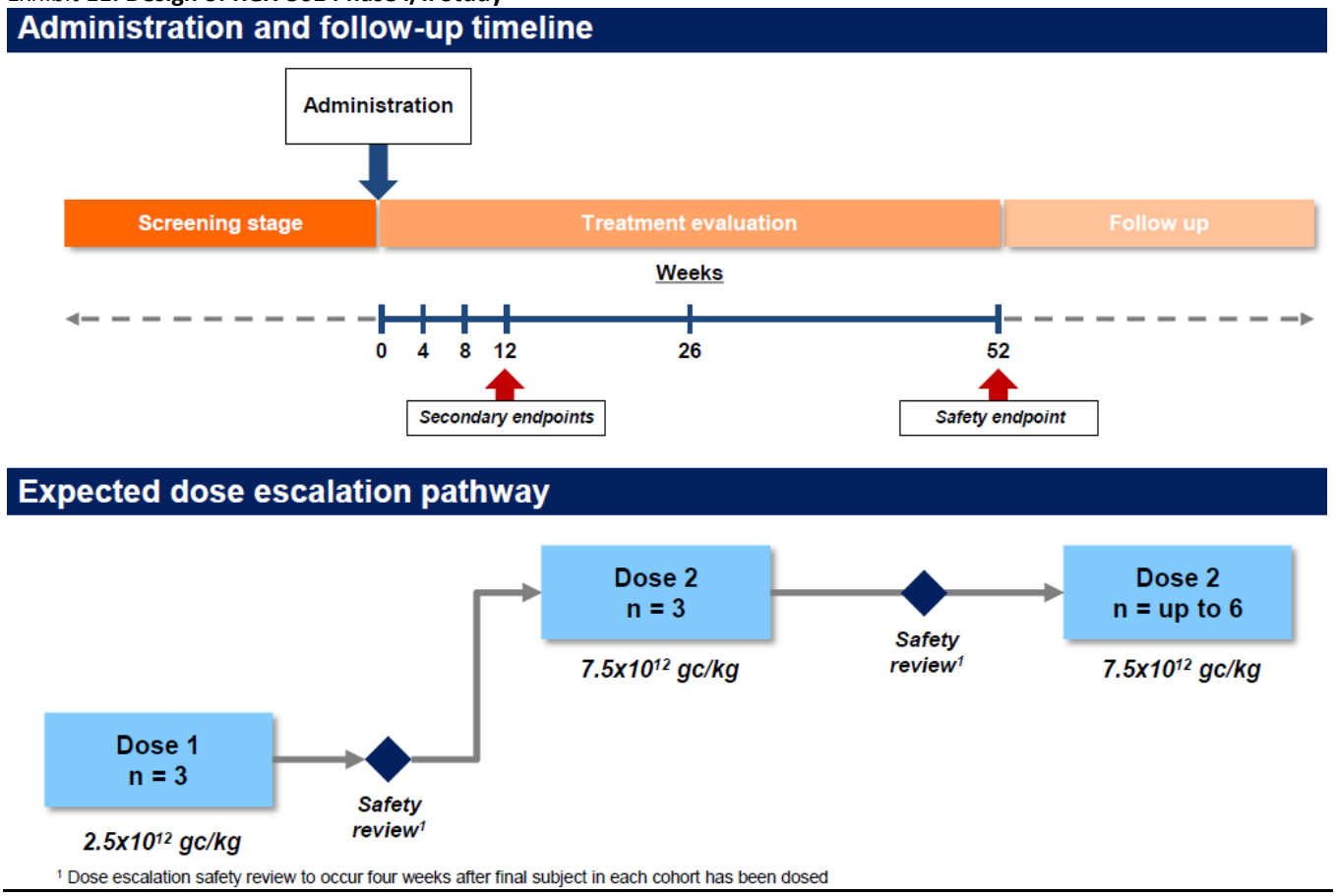
Source: Gene therapy in a humanized mouse model of familial hypercholesterolemia leads to marked regression of atherosclerosis, PLoS One, 2010; REGENXBIO.

Clinical Development

RGX-501, granted an orphan drug designation, is currently being evaluated in an investigator sponsored, dose-escalation, Phase I/II study (NCT02651675) for patients with HoFH (Exhibit 11). Of note, a single dose of RGX-501 is administered intravenously. The primary endpoint is safety, and the secondary endpoints include percent change in LDL-C (low-density lipoprotein cholesterol) levels and other lipids at 12 weeks and beyond. The study is expected to enroll a total of 12 patients into three dose cohorts, with the first

patient dosed in March 2017 and an interim update expected by the end of 2017. The University of Pennsylvania is the site for all RGX-501 administration, whereas other sites could be used for treatment evaluation and follow-up. Eligible patients must have molecularly defined LDLR mutations at both LDLR alleles, with a baseline AAV8 neutralizing antibody titer ≤ 1:10. Concurrent lipid lowering medications include statins, ezetimibe, bile acid sequestrants, and PCSK9 inhibitors are allowed and must be stable for ≥4 weeks before the baseline visit and remain stable until 12 weeks after vector administration.

Exhibit 11**: Design of RGX-501 Phase I/II Study**



Source: REGENXBIO.

HoFH Competitive Landscape

There are a number of interventions available for lowering LDL-C, with several specifically approved by the FDA for the management of HoFH, including lipoprotein apheresis, statins, mipomersen, lomitapide, and two PCSK9 inhibitors (Repatha and Praluent) (Exhibit 12). While several different kinds of therapies exist for HoFH, in our opinion, they are not direct competitors of RGX-501. Instead, we believe RGX-501 could be synergistic with these therapies given that they have different mechanisms of actions (MOAs) in terms of lowering LDL-C levels. For example, the newly approved PCSK9 inhibitors (Amgen's Repatha and Sanofi/Regeneron's Praluent) can bind to PCSK9 and prevent circulating PCSK9 from binding to LDLRs, resulting in an increased number of LDLRs available to clear LDL-C. Therefore, in theory, PCSK9 inhibitors should be more effective when patients have more functional LDLRs, which could be achieved by RGX-501. According to the company, a clinical trial evaluating a PCSK9 inhibitor demonstrated that its effectiveness relies on patients having functional LDLR.

Exhibit 12: **Existing Therapies for HoFH**

Interventions/ Approved drugs	MOAs	Mean % LDL-C reduction
Lipoprotein apheresis	A physical approach of removing LDL-C that is done weekly or biweekly	50–60%
Statins (e.g. Lipitor)	Statins can block cholesterol synthesis by inhibiting HMG-CoA reductase	18% among 29 patients treated by Lipitor in a registrational trial
Ezetimibe	Ezetimibe can reduce cholesterol absorption in small intestine by inhibiting Niemann-Pick C1 like protein	18% as a monotherapy; 25% when combined with statin
Mipomersen (Kynamro)	An antisense oligonucleotide targets human mRNA for apo B-100 (the principal apolipoprotein of LDL and its metabolic precursor, VLDL), resulting in inhibition of apo B 100 translation	25% as an add-on therapy to maximally tolerated lipid-lowering medications
Lomitapide	Lomitapide prevents the production of lipoproteins	40% when added to baseline lipid lowering medications
PCSK9 inhibitors/ Repatha (evolocumab) and Praluent (alirocumab)	Anti-PCSK9 monoclonal antibodies can bind to PCSK9 and therefore prevent circulating PCSK9 from binding to the LDLRs, resulting in an increased number of LDLRs available to clear LDL	An additional 45% and 58% reduction for alirocumab 75 mg and 150 SQ every 2 weeks, respectively, when added to maximally tolerated statin therapy; An additional 64% and 58% reduction for evolocumab 140 mg every 2 weeks and 420 mg SQ every 4 weeks, respectively, when added to maximally tolerated statin therapy

Source: Prescribing information of these drugs; the Journal of the American College of Cardiology, 2016; Raymond James research.

In terms of gene therapies in development for HoFH, to the best of our knowledge, RGX-501 is the only product currently in the clinic.

The MPS programs

Mucopolysaccharidosis (MPS) is a group of rare genetic diseases, with each caused by deficiency one of 10 specific enzymes within lysosomes (membrane enclosed organelles responsible for disposing of wastes inside cells). As a result, MPS patients have difficulties in metabolizing complex carbohydrates, resulting in accumulation of these large molecules in the cells of the body, which eventually leads to many different physical symptoms and abnormalities.

MPS I

Mucopolysaccharidosis type I (MPS I) is a non-sex linked disorder caused by deficiency of alpha-iduronidase (IDUA), an enzyme that is essential for the breakdown of polysaccharides heparan sulfate and dermatan sulfate in lysosomes. Of note, MPS I is extremely rare, with global annual new cases of approximately 500-1,000.

Because of IDUA deficiency, these polysaccharides (or glycosaminoglycans [GAGs]) accumulate in the body of MPS I patients over time, resulting in a variety of physical and clinical symptoms, including short stature, coarse facial features, clouding of the cornea, enlarged liver and spleen, a large tongue, skeletal abnormalities, joint stiffness, and a prominent forehead. In addition, MPS I patients may also experience some CNS symptoms, including cognitive impairment, spinal cord compression, and excessive accumulation of fluid in the brain.

The current standard of care for attenuated MPS I such as Hurler and Hurler-Scheie is an enzyme replacement treatment, Aldurazyme, which is a recombinant form of human IDUA currently being marketed by Genzyme and BioMarin Pharmaceutical. While Aldurazyme can improve MPS I patients' growth, mobility, and respiratory function, the enzyme replacement therapy does not help with the CNS symptoms because the enzyme cannot cross the blood-brain barrier. Bone marrow transplant (BMT) is sometimes used for severe MPS I patients. While BMT is effective with demonstrated improvements in survival, growth, and other symptoms, its use is often limited to patients aged less than two as the risk-benefit ratio is more favorable among younger patients due to the relatively high mortality rate (15-25%). Clearly, there is a significant unmet need requiring more effective therapies for MPS I patients.

REGENXBIO's RGX-111, granted an orphan drug designation and a rare pediatric disease designation, utilizes the AAV9 vector to deliver the human IDUA gene to the CNS through intracisternal administration. In preclinical studies, delivery of IDUA via the AAV9 vector into MPS I cats achieved IDUA expression to levels equivalent to or greater than non-disease animals. In addition, storage correction was seen throughout the CNS (e.g., cerebrum, perivascular, and meninges).

MPS II

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a rare, sex linked disorder resulting from a deficiency in the IDS (lysosomal enzyme iduronate-2-sulfatase), another enzyme that is essential for the degradation of polysaccharides heparan sulfate and dermatan sulfate in the lysosomes. Patients with MPS II also develop diverse physical/clinical symptoms as well as CNS problems. Similarly, the global annual incidence of MPS II is approximately 500 to 1,000. The current standard of care for MPS II is a recombinant IDS, Elaprase, which was approved in 2006 by the FDA and is being marketed by Shire. Again, as an enzyme replacement therapy, Elaprase does not treat CNS manifestations as it cannot cross the blood-brain barrier.

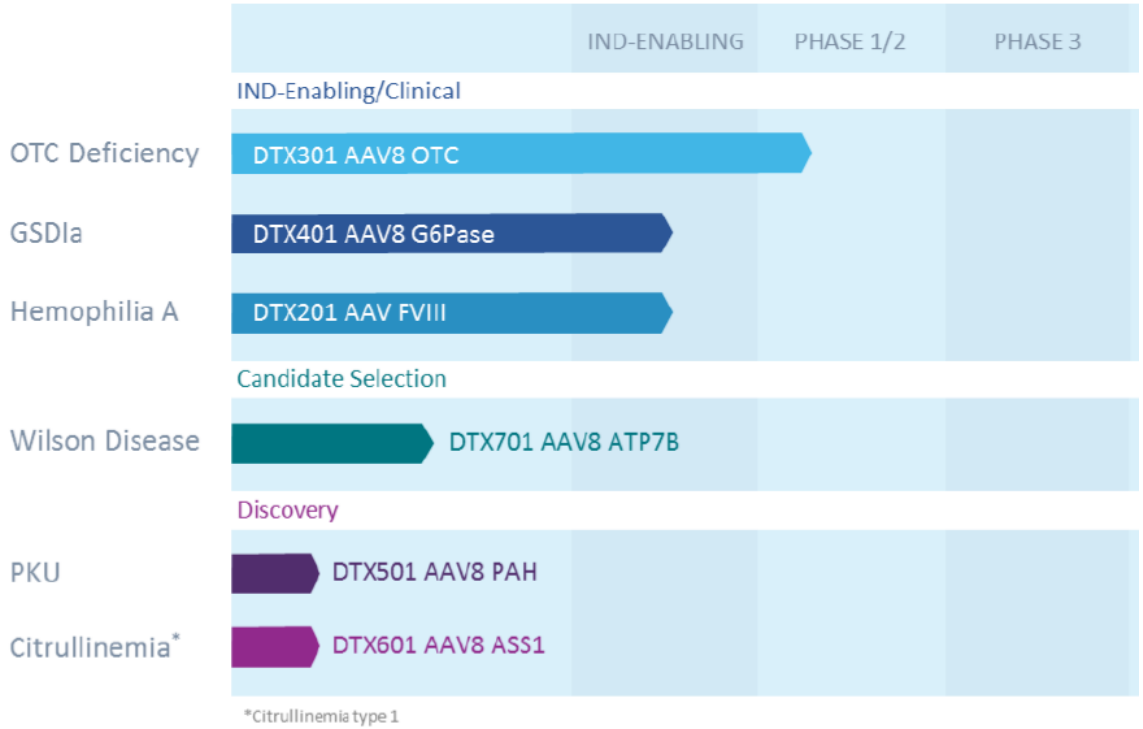
Similar to RGX-111, RGX-121 also uses the AAV9 vector but delivers a different transgene (IDS) to the CNS via intracisternal administration. The company has also received an orphan product designation and a rare pediatric disease designation for RGX-121.

The Proposed Dimension Acquisition Was Outbid

The Dimension Acquisition

In August 2017, REGENXBIO announced its intent to acquire Dimension in an all-stock transaction, which, if closed, would bring in multiple product candidates (Exhibit 13): 1) DTX301, which utilizes the NAV AAV8 vector to deliver the OTC gene to liver cells, is being evaluated in a Phase I/II study for OTC deficiency; 2) DTX401, comprised of the NAV AAV8 vector that delivers the glucose-6-phosphatase (G6Pase) gene to liver cells, is being developed for glycogen storage disease type Ia (GSDIa), with an IND expected to be filed in early 2018; 3) DTX201, based on the NAV technology to deliver the Factor VIII gene to liver cells, is being developed for hemophilia A, with an IND also expected to be filed in early 2018; and 4) additional preclinical product candidates (all of which utilize the NAV vector technology) for phenylketonuria (PKU), Wilson disease, and citrullinemia type I. Besides obtaining these product candidates, REGENXBIO could also obtain manufacturing technology and intellectual property developed by Dimension. In exchange, Dimension shareholders will receive 0.1573 shares of REGENXBIO for each share of Dimension and obtain a collective ownership of approximately 10.9% of the combined entity.

Exhibit 13: **Dimension's Pipeline** (As of September 2017)



Source: REGENXBIO.

While REGENXBIO's proposed acquisition of Dimension was originally expected to close by the end of 2017, Ultragenyx announced a better offer to acquire Dimension for $5.50 per share in cash. Recently, Dimension determined that Ultragenyx's proposal was a superior offer, and REGENXBIO decided not to increase its bid, resulting in the termination of the original merger agreement signed between REGENXBIO and Dimension.

Partnerships

Exhibit 14: **Deal Terms of Licensed Programs Currently in or Approaching Clinical Studies**

Deal partner	Indication	Phase	Deal time	Upfront payment	Milestone payment	Annual maintenance fee	Royalty
AveXis	SMA	Phase III to start (type I) Phase I/IIa to start (type 2)	2014	$2 million	$12.25 million	$50,000	mid-single to low-teen digits
Adverum	A1AT deficiency	Phase I	2015	NA	$20 million	Not disclosed	mid-high single digit
Audentes	XLMTM/Pompe	Phase I/II	July 2013	$0.3 million + 50,228 shares	$17.7 million	Not disclosed	mid-high single digit
	CN syndrome	Phase I/II	November 2014	$0.6 million	$7.6 million	Not disclosed	mid-single to low-teen digits
Dimension	OTC deficiency	Phase I/II		NA	NA	NA	mid-high single digit
Shire	Hemophilia A	IND filed		NA	NA	NA	mid-high single digit

Source: Company reports, Raymond James research.

Financial and Market Analysis

Revenues

Exhibit 15: **Market Model for Wet AMD**

wet AMD																															
US	1Q17	2Q17	3Q17	4Q17	2017	1Q18	2Q18	3Q18	4Q18	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
# of patients with wet AMD ('000)	1,492	1,495	1,497	1,500	1,500	1,503	1,505	1,508	1,511	1,511	1,521	1,532	1,542	1,553	1,564	1,575	1,586	1,596	1,607	1,618	1,629	1,640	1,651	1,663	1,674	1,685	1,697	1,709	1,720
Implied # of patients wet AMD (treated by anti-VEGF) ('000)	496	497	498	499	499	499	500	501	502	502	506	509	513	516	520	523	527	531	534	538	542	545	549	553	556	560	564	568	572
# of patients with wet AMD who respond to anti-VEGF therapies ('000)	397	397	398	399	399	400	400	401	402	402	404	407	410	413	416	419	422	424	427	430	433	436	439	442	445	448	451	454	457
# of patients for RGX-314 at peak ('000)	40	40	40	40	40	40	40	40	40	40	40	41	41	41	42	42	42	42	43	43	43	44	44	44	45	45	45	45	46
Total addressable market opportunity ('000)	$ 2,976,000	$ 2,981,199	$ 2,986,398	$ 2,991,597	$11,966,387	$ 2,996,832	$ 3,002,067	$ 3,007,303	$ 3,012,538	$12,050,152	$12,134,503	$12,219,444	$12,304,980	$12,391,115	$12,477,853	$12,562,919	$12,648,565	$12,734,795	$12,821,612	$12,909,022	$12,997,027	$13,085,633	$13,174,842	$13,264,660	$13,355,090	$13,446,136	$13,537,803	$13,630,095	$13,723,017
Peak market opportunity ('000)	$ 1,190,400	$ 1,192,480	$ 1,194,559	$ 1,196,639	$ 1,196,639	$ 1,198,733	$ 1,200,827	$ 1,202,921	$ 1,205,015	$ 1,205,015	$ 1,213,450	$ 1,221,944	$ 1,230,498	$ 1,239,112	$ 1,247,785	$ 1,256,292	$ 1,264,856	$ 1,273,479	$ 1,282,161	$ 1,290,902	$ 1,299,703	$ 1,308,563	$ 1,317,484	$ 1,326,466	$ 1,335,509	$ 1,344,614	$ 1,353,780	$ 1,363,010	$ 1,372,302
sales of RGX-314 ('000)														$ 61,956	$ 374,336	$ 628,146	$ 885,400	$ 1,146,132	$ 1,282,161	$ 1,290,902	$ 1,299,703	$ 1,308,563	$ 1,317,484	$ 1,326,466	$ 1,335,509	$ 1,344,614	$ 1,353,780	$ 1,363,010	$ 1,372,302
Market penetration														1%	3%	5%	7%	9%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%

EU	1Q17	2Q17	3Q17	4Q17	2017	1Q18	2Q18	3Q18	4Q18	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
wet AMD incidence	2,353	2,355	2,357	2,359	2,359	2,360	2,362	2,364	2,366	2,366	2,373	2,380	2,387	2,394	2,401	2,408	2,415	2,422	2,428	2,435	2,442	2,449	2,456	2,463	2,469	2,476	2,483	2,490	2,497
Implied # of patients wet AMD (treated by anti-VEGF) ('000)	782	783	783	784	784	785	785	786	786	786	789	791	793	796	798	800	803	805	807	809	812	814	816	819	821	823	825	828	830
# of patients with wet AMD who respond to anti-VEGF therapies ('000)	626	626	627	627	627	628	628	629	629	629	631	633	635	637	639	640	642	644	646	648	649	651	653	655	657	659	660	662	664
# of patients for RGX-314 at peak ('000)	63	63	63	63	63	63	63	63	63	63	63	63	63	64	64	64	64	64	65	65	65	65	65	65	66	66	66	66	66
Total addressable market opportunity ('000)	$15,018,654	$15,029,910	$15,041,165	$15,052,421	$15,052,421	$15,063,710	$15,074,999	$15,086,289	$15,097,578	$15,097,578	$15,142,871	$15,188,299	$15,233,864	$15,279,566	$15,325,405	$15,368,361	$15,411,437	$15,454,635	$15,497,953	$15,541,393	$15,584,955	$15,628,638	$15,672,445	$15,716,373	$15,760,426	$15,804,601	$15,848,900	$15,893,324	$15,937,872
Peak market opportunity ('000)	$ 1,501,865	$ 1,502,991	$ 1,504,117	$ 1,505,242	$ 1,505,242	$ 1,506,371	$ 1,507,500	$ 1,508,629	$ 1,509,758	$ 1,509,758	$ 1,514,287	$ 1,518,830	$ 1,523,386	$ 1,527,957	$ 1,532,540	$ 1,536,836	$ 1,541,144	$ 1,545,463	$ 1,549,795	$ 1,554,139	$ 1,558,495	$ 1,562,864	$ 1,567,244	$ 1,571,637	$ 1,576,043	$ 1,580,460	$ 1,584,890	$ 1,589,332	$ 1,593,787
sales of RGX-314 ('000)															$ 76,627	$ 461,051	$ 770,572	$ 1,081,824	$ 1,394,816	$ 1,554,139	$ 1,558,495	$ 1,562,864	$ 1,567,244	$ 1,571,637	$ 1,576,043	$ 1,580,460	$ 1,584,890	$ 1,589,332	$ 1,593,787
Market penetration															0.5%	3.0%	5.0%	7.0%	9.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%

wet AMD	Key assumptions	Rationale
wet AMD prevalence	0.461%	Literature review
% of patients treated by anti-VEGF therapy	33%	Our estimate is based on an implied number of eyes treated by anti -VEGF therapy (Lucentis, Eylea and Avastin); Although some patients could receive treatment for two eyes, we assume all patients received treatment for one eye.
% of anti-VEGF responders	80%	Literature review
Number of wet AMD patients who respond to anti-VEGF therapies	Approximately 400,000 in U.S. 627,000 in EU	Calculated based on previously mentioned assumptions
Pricing of RGX-314	$30,000 (US), $24,000 (EU)	Annuity payment; The annual cost for Eylea and Lucentis is estimated to be $15,000 and $25,000, respectively.
Market share at peak	10%	Crowded market with three approved anti-VEGF products. More than 10 product candidates in the pipeline
EU royalty %	20%	We assume REGENXBIO will seek a partnership to commercialize RGX-314 in EU.
Drug Risk	30%	Phase I trial just initiated with no data reported.
Commercialization time	3Q22 (US), 3Q23 (EU)	Company guidance and our estimate
Commercial rights	worldwide now	We assume REGENXBIO will eventually seek a partnership to commercialize RGX-314 in EU.

Source: Raymond James research.

Exhibit 16: **Market Model for HoFH**

HoFH

US	1Q17	2Q17	3Q17	4Q17	2017	1Q18	2Q18	3Q18	4Q18	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
# of patients with HoFH	1,990	1,993	1,997	2,000	2,000	2,004	2,007	2,011	2,014	2,014	2,028	2,042	2,057	2,071	2,085	2,100	2,114	2,128	2,143	2,158	2,172	2,187	2,202	2,217	2,232	2,247	2,263	2,278
# of HoFH patients without or with mild AAV8 neutralizing antibody	1,393	1,395	1,398	1,400	1,400	1,402	1,405	1,407	1,410	1,410	1,420	1,430	1,440	1,450	1,460	1,470	1,480	1,490	1,500	1,510	1,521	1,531	1,541	1,552	1,562	1,573	1,584	1,595
# of patients for RGX-501 at peak	836	837	839	840	840	841	843	844	846	846	852	858	864	870	876	882	888	894	900	906	912	919	925	931	937	944	950	957
Total addressable market opportunity ('000)	$ 348,175	$ 348,784	$ 349,392	$ 350,000	$ 1,400,000	$ 350,612	$ 351,225	$ 351,838	$ 352,450	$ 1,409,800	$ 1,419,669	$ 1,429,606	$ 1,439,614	$ 1,449,691	$ 1,459,839	$ 1,469,791	$ 1,479,811	$ 1,489,899	$ 1,500,057	$ 1,510,283	$ 1,520,579	$ 1,530,945	$ 1,541,382	$ 1,551,891	$ 1,562,470	$ 1,573,122	$ 1,583,847	$ 1,594,645
Peak market opportunity ('000)	$ 208,905	$ 209,270	$ 209,635	$ 210,000	$ 840,000	$ 210,368	$ 210,735	$ 211,103	$ 211,470	$ 845,880	$ 851,801	$ 857,764	$ 863,768	$ 869,814	$ 875,903	$ 881,875	$ 887,887	$ 893,940	$ 900,034	$ 906,170	$ 912,347	$ 918,567	$ 924,829	$ 931,134	$ 937,482	$ 943,873	$ 950,308	$ 956,787
# of accumulated patients treated														14	73	176	370	596	900	906	912	919	925	931	937	944	950	957
sales ofRGX-501 ('000)														$ 14,497	$ 58,495	$ 103,383	$ 193,578	$ 226,007	$ 304,074	$ 6,136	$ 6,178	$ 6,220	$ 6,262	$ 6,305	$ 6,348	$ 6,391	$ 6,435	$ 6,479
Market penetration														1%	5%	12%	25%	40%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%

EU	1Q17	2Q17	3Q17	4Q17	2017	1Q18	2Q18	3Q18	4Q18	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036
# of patients with HoFH	3,138	3,140	3,142	3,145	3,145	3,147	3,149	3,152	3,154	3,154	3,164	3,173	3,183	3,192	3,202	3,211	3,220	3,229	3,238	3,247	3,256	3,265	3,274	3,283	3,293	3,302	3,311	3,320
# of HoFH patients without or with mild AAV8 neutralizing antibody	2,196	2,198	2,200	2,201	2,201	2,203	2,205	2,206	2,208	2,208	2,215	2,221	2,228	2,235	2,241	2,248	2,254	2,260	2,266	2,273	2,279	2,286	2,292	2,298	2,305	2,311	2,318	2,324
# of patients for RGX-501 at peak	1,318	1,319	1,320	1,321	1,321	1,322	1,323	1,324	1,325	1,325	1,329	1,333	1,337	1,341	1,345	1,349	1,352	1,356	1,360	1,364	1,368	1,371	1,375	1,379	1,383	1,387	1,391	1,395
Total addressable market opportunity ('000)	$ 439,275	$ 439,604	$ 439,933	$ 440,262	$ 1,761,049	$ 440,592	$ 440,923	$ 441,253	$ 441,583	$ 1,766,332	$ 1,771,631	$ 1,776,946	$ 1,782,276	$ 1,787,623	$ 1,792,986	$ 1,798,012	$ 1,803,052	$ 1,808,105	$ 1,813,173	$ 1,818,256	$ 1,823,352	$ 1,828,463	$ 1,833,588	$ 1,838,727	$ 1,843,881	$ 1,849,049	$ 1,854,232	$ 1,859,430
Peak market opportunity ('000)	$ 263,565	$ 263,762	$ 263,960	$ 264,157	$ 1,056,629	$ 264,355	$ 264,554	$ 264,752	$ 264,950	$ 1,059,799	$ 1,062,978	$ 1,066,167	$ 1,069,366	$ 1,072,574	$ 1,075,792	$ 1,078,807	$ 1,081,831	$ 1,084,863	$ 1,087,904	$ 1,090,953	$ 1,094,011	$ 1,097,078	$ 1,100,153	$ 1,103,236	$ 1,106,329	$ 1,109,430	$ 1,112,539	$ 1,115,658
# of accumulated patients treated															13	67	162	339	544	818	821	823	825	827	830	832	834	837
sales of RGX-501 ('000)															$ 10,758	$ 43,182	$ 75,879	$ 141,396	$ 163,946	$ 219,410	$ 1,835	$ 1,840	$ 1,845	$ 1,850	$ 1,855	$ 1,861	$ 1,866	$ 1,871
Market penetration															1%	5%	12%	25%	40%	60%	60%	60%	60%	60%	60%	60%	60%	60%

HoFH	Key assumptions	Rationale
HoFH prevalence	0.0006%	Literature review
% of patients without or with mild AAV8 neutralizing antibody	70%	Literature review
Number of HoFH patients eligible for RGX-501	~1,500 (U.S.), ~2,200 (EU)	Calculated based on previously mentioned assumptions
Pricing of RGX-501	$1 million (US), $0.8 million (EU)	Based on our literature review, the annual cost of a weekly or bi-weekly LDL apheresis treatment is about $165,000 or $230,000 in the US, which does not include other concurrent cost.
Market share at peak	60%	It appears that currently RGX-501 is the only gene therapy candidate in the pipeline.
Drug Risk	30%	In the early clinical trial stage with no clinical data reported to date.
Commercialization time	2Q22 (US), 2Q23 (EU)	Company guidance and our estimate
Commercial rights	worldwide	We assume REGENXBIO will be in charge of a worldwide commercialization of RGX-501 given the ultra orphan status of the disease.

Source: Raymond James research.

Exhibit 17: **Market Model for SMA Type 1**

AveXis SMA Type I													
US	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**
# of patients with SMA	9,000	9,063	9,126	9,190	9,255	9,319	9,385	9,449	9,513	9,578	9,643	9,709	9,775
# of patients with SMA Type I	1,260	1,269	1,278	1,287	1,296	1,305	1,314	1,323	1,332	1,341	1,350	1,359	1,369
# of new patients with SMA Type I	242	244	246	247	249	251	253	254	256	258	260	261	263
# of SMA type I patients without or with mild AAV9 neutralizing antibody	1,260	1,269	1,278	1,287	1,296	1,305	1,314	1,323	1,332	1,341	1,350	1,359	1,369
# of new SMA type I patients without or with mild AAV9 neutralizing antibody	242	244	246	247	249	251	253	254	256	258	260	261	263
# of patients for AVXS-101 at peak	882	888	894	901	907	913	920	926	932	939	945	951	958
Total addressable market opportunity ('000)	$1,260,000	$1,268,820	$1,277,702	$ 1,286,646	$ 1,295,652	$ 1,304,722	$ 1,313,855	$ 1,322,812	$ 1,331,830	$ 1,340,909	$ 1,350,051	$ 1,359,255	$ 1,368,521
Peak market opportunity ('000)	$ 882,000	$ 888,174	$ 894,391	$ 900,652	$ 906,957	$ 913,305	$ 919,698	$ 925,968	$ 932,281	$ 938,637	$ 945,036	$ 951,478	$ 957,965
# of patients treated				26	130	391	657	178	179	180	182	183	184
# of accumulated patients treated				26	155	547	1,204	1,382	1,561	1,741	1,923	2,106	2,290
sales of AVXS-101 ('000)				$ 25,733	$ 129,565	$ 391,417	$ 656,927	$ 178,039	$ 179,253	$ 180,475	$ 181,705	$ 182,944	$ 184,191
Market penetration				2%	10%	30%	50%	70%	70%	70%	70%	70%	70%
EU	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**
# of patients with SMA	14,151	14,194	14,236	14,279	14,322	14,365	14,408	14,448	14,489	14,529	14,570	14,611	14,652
# of patients with SMA Type I	1,981	1,987	1,993	1,999	2,005	2,011	2,017	2,023	2,028	2,034	2,040	2,046	2,051
# of new patients with SMA Type I	307	308	309	310	311	312	313	314	315	315	316	317	318
# of SMA type I patients without or with mild AAV9 neutralizing antibody	1,981	1,987	1,993	1,999	2,005	2,011	2,017	2,023	2,028	2,034	2,040	2,046	2,051
# of new SMA type I patients without or with mild AAV9 neutralizing antibody	307	308	309	310	311	312	313	314	315	315	316	317	318
# of patients for AVXS-101 at peak	1,387	1,391	1,395	1,399	1,404	1,408	1,412	1,416	1,420	1,424	1,428	1,432	1,436
Total addressable market opportunity ('000)	$1,584,944	$1,589,699	$1,594,468	$ 1,599,251	$ 1,604,049	$ 1,608,861	$ 1,613,688	$ 1,618,211	$ 1,622,746	$ 1,627,295	$ 1,631,856	$ 1,636,430	$ 1,641,017
Peak market opportunity ('000)	$1,109,461	$1,112,789	$1,116,127	$ 1,119,476	$ 1,122,834	$ 1,126,203	$ 1,129,581	$ 1,132,747	$ 1,135,922	$ 1,139,106	$ 1,142,299	$ 1,145,501	$ 1,148,712
# of patients treated					40	201	605	1,011	220	221	221	222	223
# of accumulated patients treated					40	241	846	1,858	2,078	2,299	2,520	2,742	2,965
sales of AVXS-101 ('000)					$ 32,081	$ 160,886	$ 484,106	$ 809,105	$ 176,135	$ 176,629	$ 177,124	$ 177,621	$ 178,118
Market penetration					2%	10%	30%	50%	70%	70%	70%	70%	70%

Source: Raymond James research.

Exhibit 18: **Market Model for SMA Type 2**

AveXis SMA Type II														
US	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**
# of patients with SMA	9,000	9,063	9,126	9,190	9,255	9,319	9,385	9,449	9,513	9,578	9,643	9,709	9,775
# of patients with SMA Type II	4,590	4,622	4,654	4,687	4,720	4,753	4,786	4,819	4,852	4,885	4,918	4,952	4,985
# of new patients with SMA Type II	109	110	111	111	112	113	114	114	115	116	117	118	118
# of SMA type II patients without or with mild AAV9 neutralizing antibody	4,590	4,622	4,654	4,687	4,720	4,753	4,786	4,819	4,852	4,885	4,918	4,952	4,985
# of new SMA type II patients without or with mild AAV9 neutralizing antibody	109	110	111	111	112	113	114	114	115	116	117	118	118
# of patients for AVXS-101 at peak	3,213	3,235	3,258	3,281	3,304	3,327	3,350	3,373	3,396	3,419	3,443	3,466	3,490
Total addressable market opportunity ('000)	$4,590,000	$4,622,130	$4,654,485	$ 4,687,066	$ 4,719,876	$ 4,752,915	$ 4,786,185	$ 4,818,814	$ 4,851,666	$ 4,884,742	$ 4,918,043	$ 4,951,571	$ 4,985,327
Peak market opportunity ('000)	$3,213,000	$3,235,491	$3,258,139	$ 3,280,946	$ 3,303,913	$ 3,327,040	$ 3,350,330	$ 3,373,170	$ 3,396,166	$ 3,419,319	$ 3,442,630	$ 3,466,099	$ 3,489,729
# of patients treated						95	479	1,446	2,426	81	82	82	83
# of accumulated patients treated						95	574	2,019	4,445	4,526	4,608	4,690	4,773
sales of AVXS-101 ('000)						$ 95,058	$ 478,619	$ 1,445,644	$ 2,425,833	$ 81,214	$ 81,767	$ 82,325	$ 82,886
Market penetration						2%	10%	30%	50%	70%	70%	70%	70%
EU	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**
# of patients with SMA	14,151	14,194	14,236	14,279	14,322	14,365	14,408	14,448	14,489	14,529	14,570	14,611	14,652
# of patients with SMA Type II	7,217	7,239	7,261	7,282	7,304	7,326	7,348	7,369	7,389	7,410	7,431	7,452	7,472
# of new patients with SMA Type II	138	139	139	139	140	140	141	141	142	142	142	143	143
# of SMA type II patients without or with mild AAV9 neutralizing antibody	7,217	7,239	7,261	7,282	7,304	7,326	7,348	7,369	7,389	7,410	7,431	7,452	7,472
# of new SMA type II patients without or with mild AAV9 neutralizing antibody	138	139	139	139	140	140	141	141	142	142	142	143	143
# of patients for AVXS-101 at peak	5,052	5,067	5,082	5,098	5,113	5,128	5,144	5,158	5,173	5,187	5,202	5,216	5,231
Total addressable market opportunity ('000)	$5,773,724	$5,791,045	$5,808,418	$ 5,825,843	$ 5,843,321	$ 5,860,851	$ 5,878,433	$ 5,894,910	$ 5,911,433	$ 5,928,003	$ 5,944,619	$ 5,961,281	$ 5,977,990
Peak market opportunity ('000)	$4,041,607	$4,053,731	$4,065,893	$ 4,078,090	$ 4,090,325	$ 4,102,596	$ 4,114,903	$ 4,126,437	$ 4,138,003	$ 4,149,602	$ 4,161,233	$ 4,172,897	$ 4,184,593
# of patients treated							147	737	2,217	3,705	100	100	100
# of accumulated patients treated							147	884	3,101	6,806	6,905	7,005	7,105
sales of AVXS-101 ('000)							$ 117,569	$ 589,491	$ 1,773,430	$ 2,964,001	$ 79,706	$ 79,929	$ 80,153
Market penetration							2%	10%	30%	50%	70%	70%	70%

SMA	Key assumptions	Rationale
SMA prevalence	0.0028%	Literature review
% of Type I SMA	14%	Literature review
% of Type II SMA	51%	Literature review
SMA incidence rate (at birth)	0.01%	Literature review, one in 10,000 newborns annually
% of Type I SMA in newborns with SMA	60%	Literature review
% of Type II SMA in newborns with SMA	27%	Literature review
Number of SMA type I patients eligible for AVXS-101	~1,300 in U.S., ~2,000 in EU	Calculated based on previous assumptions
Number of SMA type II patients eligible for AVXS-101	~4,800 in U.S., ~7,400 in EU	Calculated based on previous assumptions
Number of annually new SMA type I patients eligible for AVXS-101	~250 in U.S., ~300 in EU	Calculated based on previous assumptions
Number of annually new SMA type II patients eligible for AVXS-101	~100 in U.S., ~140 in EU	Calculated based on previous assumptions
Pricing of AVXS-101	$1 million (U.S.) $0.8 million (EU)	Annuity payment; Spinraza, the only approved drug for SMA, costs $125,000 per injection, with a first year cost of $750,000 and an annual maintenance cost of $375,000
Market share at peak	70%	Given the better safety and efficacy profile of AVXS-101 as compared to that seen in clinical studies of Spinraza
Drug Risk	60%	We assume a blended 60% probability of success of AVXS-101 for type I (70%) and type II (50%) SMA
Commericalization time	Type I: 4Q20 (US), 4Q21 (EU); Type II: 4Q22 (US), 4Q23 (EU)	Based on company guidance and our estimate
Commerical rights	worldwide	Given the orphan status of SMA

Source: Raymond James research.

Operating Expenses

Building off of the R&D expense reported for 2Q17, we are projecting R&D expenses of $60 million for 2017, increasing to $199 million for 2020. The R&D assumptions from 2017 to 2020 take into account continued expenditure for the clinical trials associated with the company's wet AMD, HoFH, as well as other franchises.

Based on the SG&A expense reported for 2Q17, we are projecting SG&A expenses of $26 million for 2017, increasing to $30 million for 2020.

The COGS for RGX-314 and RGX-501 are expected to be 5% of the revenues from the corresponding product.

Net Income and EPS

The net income for 2Q17 was $(21.0) million, or $(0.69) per share. We are projecting net income of $(85.8) million or $(2.89) per diluted share in 2017, decreasing to $(226.6) million or $(5.40) per diluted share in 2020.

Cash

Based on our estimates, we expect a cash burn rate of approximately $21 million per quarter for the full year 2017, and we believe the current cash position is sufficient to fund operations into 3Q19. However, we have modeled three capital raises into our estimates. We expect the company to raise approximately $150 million in 2Q18, $150 million in 2Q19, and $150 million in 2Q20. We have included these raises into our model as a necessity for the company to sustain operations until it can potentially reach profitability in 2023.

Valuation and Price Target Analysis

Valuation

We value REGENXBIO using a sum-of-the-parts analysis of two internal programs: 1) RGX-314 for wet AMD; and 2) RGX-501 for HoFH, as well as potential royalty streams generated from licensing programs (in clinical or approaching clinical phases) that are in collaborations with other companies, including 1) SMA Type 1 and 2 from AveXis; 2) XLMTM and Pompe disease from Audentes; 3) A1AT deficiency from Adverum; 4) OTC deficiency from Dimension (which is expected to be acquired by Ultragenyx); and 5) hemophilia A from Shire. To derive a value for each of these programs, we conduct a risk-adjusted net present value (rNPV) analysis, which utilizes the net income as a proxy of the free cash flow (FCF). The revenues for each product are derived from our market models (see pages 121-124 for more detail), whereas the R&D and SG&A expenses are estimated largely based on the number of patients on clinical trials and the size of a sales force, respectively. To calculate the NPV, the approximate FCF based on the net income for any given year is discounted at a rate of 15% back to the present time. To account for the clinical/regulatory risk, the NPV is further multiplied by a probability of success assigned to each program. Using this methodology, we derive a risk-adjusted per share NPV of $18.11, $1.00, $10.01, and $5.13 for RGX-314, RGX-501, AVXS-101, and other partnered clinical assets, respectively. Combining these values with the cash value of $5.16 per share, we derive a price target of $39.41, which we round to $39.

Exhibit 19: **Valuation Analysis**

Product	POS	Per share value	Weighting
RGX-314 for wet AMD	30%	18.11	46%
RGX-501 for HoFH	30%	1.00	3%
Royalties from AveXis	60%	10.01	25%
Royalties from others	25-50%	5.13	13%
Cash as of 3Q17 (pro forma)	N/A	5.16	13%
Total		39.41	

Key assumptions:

Discount rate	15%
Fully diluted shares outstanding (‘000)	36,795

Source: Raymond James research.

Exhibit 20: **rNPV of RGX-314**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034	12/31/2035	12/31/2036	12/31/2037
Revenues (risk-unadjusted, '000)						$ 61,956	$ 389,661	$ 720,356	$ 1,039,514	$ 1,362,496	$ 1,561,124	$ 1,601,730	$ 1,611,402	$ 1,621,136	$ 1,630,933	$ 1,640,793	$1,650,717	$1,660,706	$1,670,758	$1,680,876	$1,691,059
COGS (including royalties to be paid)						3,098	19,483	36,018	51,976	68,125	78,056	80,087	80,570	81,057	81,547	82,040	82,536	83,035	83,538	84,044	84,553
R&D	16,778	32,658	86,791	158,631	79,315	15,863	16,656	17,489	18,364	19,282	20,246	21,258	22,321	23,437	24,609	25,839	27,131	28,488	29,912	31,408	32,978
SGA	6,451	13,586	14,265	14,979	24,728	36,464	38,287	40,202	42,212	44,322	46,538	48,865	32,577	34,206	35,916	37,712	39,597	41,577	43,656	45,839	48,131
Income before tax	(23,229)	(46,245)	(101,057)	(173,610)	(104,043)	6,531	315,235	626,648	926,963	1,230,768	1,416,284	1,451,520	1,475,934	1,482,437	1,488,862	1,495,203	1,501,453	1,507,605	1,513,652	1,519,586	1,525,397
Tax	-	-	-	-	-	-	-	125,330	185,393	246,154	283,257	290,304	295,187	296,487	297,772	299,041	300,291	301,521	302,730	303,917	305,079
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Net income	(23,229)	(46,245)	(101,057)	(173,610)	(104,043)	6,531	315,235	501,318	741,570	984,614	1,133,027	1,161,216	1,180,747	1,185,949	1,191,089	1,196,162	1,201,162	1,206,084	1,210,922	1,215,668	1,220,318
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23	18.23	19.23	20.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(22,501)	(38,953)	(74,019)	(110,574)	(57,623)	3,145	132,014	182,559	234,825	271,119	271,292	241,775	213,775	186,710	163,061	142,396	124,340	108,565	94,783	82,743	72,225
Total NPV ('000)	2,221,656																				
Fully diluted shares outstanding ('000)	36,795																				
Per share value	60.38																				
Probability of success	30%																				
Risk-adjusted per share value	**18.11**																				

Source: Raymond James research.

Exhibit 21: **rNPV of RGX-501**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034	12/31/2035	12/31/2036
Revenues (risk-unadjusted, '000)						$ 14,497	$ 69,253	$ 146,565	$ 269,457	$ 367,403	$ 468,020	$ 225,546	$ 8,012	$ 8,060	$ 8,107	$ 8,155	$ 8,203	$ 8,252	$ 8,301	$ 8,350
COGS						725	3,463	7,328	13,473	18,370	23,401	11,277	401	403	405	408	410	413	415	417
R&D	15,428	32,658	36,541	40,618	42,649	2,132	2,154	2,175	2,197	2,219	2,241	2,264	2,286	2,309	2,332	2,356	2,379	2,403	2,427	2,451
SGA	6,451	13,586	14,265	14,979	17,828	20,819	21,860	22,953	24,101	25,306	26,571	27,899	1,395	1,409	1,423	1,437	1,452	1,466	1,481	1,496
Income before tax	(21,879)	(46,245)	(50,807)	(55,597)	(60,477)	(9,179)	41,777	114,109	229,687	321,508	415,807	184,106	3,931	3,939	3,947	3,955	3,962	3,970	3,978	3,985
Tax	-	-	-	-	-	-	-	22,822	45,937	64,302	83,161	36,821	786	788	789	791	792	794	796	797
Tax rate	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Net income	(21,879)	(46,245)	(50,807)	(55,597)	(60,477)	(9,179)	41,777	91,287	183,749	257,207	332,645	147,285	3,144	3,151	3,157	3,164	3,170	3,176	3,182	3,188
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23	18.23	19.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(21,193)	(38,953)	(37,214)	(35,411)	(33,494)	(4,421)	17,495	33,243	58,186	70,823	79,649	30,666	569	496	432	377	328	286	249	217
Total NPV ('000)	122,331																			
Fully diluted shares outstanding ('000)	36,795																			
Per share value	3.32																			
Probability of success	30%																			
Risk-adjusted per share value	**1.00**																			

Source: Raymond James research.

Exhibit 22: **rNPV of AVXS-101**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029
Royalties from SMA type I and II (AveXis) ('000)				2,573	302,228	455,465	340,232	52,030	52,282	52,535	52,789	52,973	53,157
Present time	10/9/2017												
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	-	-	-	1,639	167,385	219,351	142,483	18,947	16,556	14,466	12,640	11,029	9,624
Total NPV ('000)	614,120												
Fully diluted shares outstanding ('000)	36,795												
Per share value	16.69												
Probability of success	60%												
Risk-adjusted per share value	**10.01**												

Source: Raymond James research.

Bull/Bear Analysis

In our bull case, we assume higher probability of success for the company's four programs, which results in a value of about $56 per share, indicating a 73% return from the current level. In our bear case, we decrease the probability of success and derive a value of about $12, suggesting downside risk of 63%.

Exhibit 23: **Bull/Bear Analysis**

POS	Bull	Base	Bear
RGX-314 for wet AMD	50%	30%	0%
RGX-501 for HoFH	50%	30%	0%
Royalties from AveXis	80%	60%	40%
Royalties from others	25-50%	25-50%	0%
Valuation	$56	$39	$12
Return	73%	21%	-63%

Note: The closing price of 10/9/17 was used to calculate the potential returns
Source: Raymond James research.

Management

Ken Mills, President and Chief Executive Officer

Ken Mills is the founding president and chief executive officer of REGENXBIO. Prior to REGENXBIO, Mr. Mills was the chief financial officer and vice president of business development at Meso Scale Diagnostics, a privately held life sciences company. There, he served as a member of the founding management team, and worked to establish the company's operations and ongoing business strategy. In this position, Mr. Mills supervised all company activities, including direct management of corporate and business development, strategic planning, finance, and accounting activities. Prior to Meso Scale Diagnostics, he was director of business development for IGEN International, a medical diagnostics company. Mr. Mills received an S.B. in chemistry from the Massachusetts Institute of Technology.

Olivier Danos, Ph.D., Chief Scientific Officer

Dr. Olivier Danos is the chief scientific officer for REGENXBIO. Prior to joining REGENXBIO, Dr. Danos was senior vice president of cell and gene therapy at Biogen Inc. At Biogen, Dr. Danos led company efforts dedicated to identifying and developing new technologies for gene transfer and genome engineering. Dr. Danos also co-founded and is an executive member of the board of directors of Lysogene, a NAV Technology licensee focused on the development of gene therapy product candidates for the treatment of Mucopolysaccharidosis Type IIIA. Prior to Biogen, Dr. Danos served as senior vice president of molecular medicine, synthetic biology and gene regulation at Kadmon Pharmaceuticals. Earlier in his career, Dr. Danos was director of the Gene Therapy Consortium of the University College of London, scientific director at Genethon, and senior director of research at Somatix Therapy Corporation. Dr. Danos has directed research focused on gene therapy at the Necker - Enfants Malades Hospital in Paris, the French National Centre for Scientific Research, and the Pasteur Institute in Paris.

Stephen Yoo, M.D., Chief Medical Officer

Dr. Stephen Yoo is chief medical officer at REGENXBIO. Prior to joining REGENXBIO, Dr. Yoo was medical science director of clinical development at AstraZeneca and group director of clinical development at MedImmune, AstraZeneca's global biologics research and development arm. In these roles, he led the late-phase clinical project teams while providing strategic and operational leadership to physicians and scientists. In previous roles at MedImmune, he provided strategic clinical leadership for early phase programs. Earlier in his career, Dr. Yoo served as associate director of clinical development at Abbott Laboratories. Dr. Yoo holds an M.D. from the University of California, Los Angeles School of Medicine and a B.A. in molecular and cell biology from the University of California, Berkeley.

Vit Vasista, Chief Financial Officer

Vit Vasista is the chief financial officer at REGENXBIO. Prior to joining REGENXBIO, Mr. Vasista served as principal at PRTM Management Consultants, where he developed operational strategies for both private and public organizations, including the development of market entry strategies, innovative business models, and operational improvements. Earlier in his career, Mr. Vasista served as director of business development at Meso Scale Diagnostics, a privately held life sciences company. Mr. Vasista received an MBA from the Wharton School at the University of Pennsylvania, an M.S. in mechanical engineering from Stanford University, and an S.B. in mechanical engineering from the Massachusetts Institute of Technology.

Faraz Ali, Chief Business Officer

Faraz Ali is chief business officer at REGENXBIO. Prior to joining REGENXBIO, Mr. Ali was vice president and head of global commercial development and external affairs at bluebird bio, where he led all commercial planning efforts, provided significant early input into bluebird bio’s portfolio strategy, and provided critical cross-functional leadership during the company’s initial growth phase by establishing new functions, processes, and external relationships. Prior to bluebird bio, he held roles of increasing global commercial responsibility at Genzyme Corporation, including head of U.S. marketing and strategic planning for the rare disease business unit. Earlier in his career, Mr. Ali served in leadership roles at GE Healthcare. Mr. Ali holds an MBA with distinction from Harvard Business School and a B.S. in electrical engineering from Stanford University.

	FY16A	1Q17A	2Q17A	3Q17E	4Q17E	FY17E	1Q18E	2Q18E	3Q18E	4Q18E	FY18E
Revenues											
RGX-314 for wet AMD											
RGX-501 for HoFH											
Royalties from AveXis (SMA type I and II)											
Royalties from Audentes (XLMTM)											
Royalties from Audentes (Pompe)											
Royalties from Adverum (A1AT deficiency)											
Royalties from Dimension (OTC deficiency)											
Royalties from Shire (Hemophilia A)											
License revenue	4,303	455				455					-
Reagent sales	213	-	-			-					-
Grant revenue	73	-	7			7					-
Total revenues	4,589	455	7	-	-	462	-	-	-	-	-
Operating expenses:											
Cost of sales	959	91	1,317	-	-	1,408					-
Research and development	45,482	16,619	13,917	14,613	15,343	60,492	15,957	16,596	17,259	15,505	65,317
General and administrative	23,590	6,622	6,355	6,419	6,483	25,878	6,548	6,613	6,679	7,332	27,172
Other operating expenses (income)	(102)	45	29								
Total operating expenses	69,929	23,377	21,618	21,031	21,826	87,779	22,505	23,209	23,939	22,837	92,489
Operating income	**(65,340)**	**(22,922)**	**(21,611)**	**(21,031)**	**(21,826)**	**(87,317)**	**(22,505)**	**(23,209)**	**(23,939)**	**(22,837)**	**(92,489)**
Other income (expense):											
Investment income	1,938	929	583			1,512					-
Total other income (expense)	1,938	929	583	-	-	1,512	-	-	-	-	-
Income (loss) before taxes	**(63,402)**	**(21,993)**	**(21,028)**	**(21,031)**	**(21,826)**	**(85,805)**	**(22,505)**	**(23,209)**	**(23,939)**	**(22,837)**	**(92,489)**
Income tax expense (benefit)	(435)	-	-	-	-	-					-
Net income (loss)	**(62,967)**	**(21,993)**	**(21,028)**	**(21,031)**	**(21,826)**	**(85,805)**	**(22,505)**	**(23,209)**	**(23,939)**	**(22,837)**	**(92,489)**
Other comprehensive income	**686**	**(539)**	**(74)**								
Comprehensive loss	**(62,281)**	**(22,532)**	**(21,102)**								
Net loss attributable to common stockholders	**(62,967)**	**(21,993)**	**(21,028)**								
Net (loss) per share, basic	**(2.38)**	**(0.82)**	**(0.69)**	**(0.68)**	**(0.71)**	**(2.89)**	**(0.73)**	**(0.67)**	**(0.69)**	**(0.65)**	**(2.73)**
Net (loss) per share, diluted	**(2.38)**	**(0.82)**	**(0.69)**	**(0.68)**	**(0.71)**	**(2.89)**	**(0.73)**	**(0.67)**	**(0.69)**	**(0.65)**	**(2.73)**
Weighted average shares outstanding, basic	26,409	26,673	30,662	30,762	30,862	29,740	30,962	34,812	34,912	35,012	33,925
Weighted average shares outstanding, diluted	26,409	26,673	30,662	30,762	30,862	29,740	30,962	34,812	34,912	35,012	33,925

Regenxbio Income Statement

All figures in thousands ($), except per share data

	FY16A	FY17E	FY18E	FY19E	FY20E
Revenues					
RGX-314 for wet AMD				-	-
RGX-501 for HoFH					
Royalties from AveXis (SMA type I and II)					2,573
Royalties from Audentes (XLMTM)					429
Royalties from Audentes (Pompe)					
Royalties from Adverum (A1AT deficiency)					
Royalties from Dimension (OTC deficiency)					
Royalties from Shire (Hemophilia A)					
License revenue	4,303	455	-	-	-
Reagent sales	213	-	-	-	-
Grant revenue	73	7	-	-	-
Total revenues	4,589	462	-	-	3,002
Operating expenses:					
Cost of sales	959	1,408	-	-	-
Research and development	45,482	60,492	65,317	123,333	199,249
General and administrative	23,590	25,878	27,172	28,531	29,957
Other operating expenses (income)	(102)				
Total operating expenses	69,929	87,779	92,489	151,864	229,207
Operating income	**(65,340)**	**(87,317)**	**(92,489)**	**(151,864)**	**(226,205)**
Other income (expense):					
Investment income	1,938	1,512	-	-	-
Total other income (expense)	1,938	1,512	-	-	-
Income (loss) before taxes	**(63,402)**	**(85,805)**	**(92,489)**	**(151,864)**	**(226,205)**
Income tax expense (benefit)	(435)	-	-	-	-
Net income (loss)	**(62,967)**	**(85,805)**	**(92,489)**	**(151,864)**	**(226,205)**
Other comprehensive income	**686**				
Comprehensive loss	**(62,281)**				
Net loss attributable to common stockholders	**(62,967)**				
Net (loss) per share, basic	**(2.38)**	**(2.89)**	**(2.73)**	**(4.02)**	**(5.39)**
Net (loss) per share, diluted	**(2.38)**	**(2.89)**	**(2.73)**	**(4.02)**	**(5.39)**
Weighted average shares outstanding, basic	26,409	29,740	33,925	37,762	41,995
Weighted average shares outstanding, diluted	26,409	29,740	33,925	37,762	41,995

REGENXBIO Inc Balance Sheet

Figures in $ thousands except per share data

ASSETS	3Q16	4Q16	1Q17	2Q17
Current Assets:				
Cash and Cash Equivalents	28,108	24,840	82,045	57,649
Marketable Securities	63,662	64,714	63,764	104,434
Accounts Receivable	679	1,032	228	50
Prepaid Expenses	2,171	1,775	1,843	2,432
Other Current Assets	2,000	1,010	922	1,252
Total Current Assets	96,620	93,371	148,802	165,817
Marketable Securities	93,087	69,412	63,742	46,417
Property and Equipment, net	5,804	9,324	11,061	11,524
Restricted Cash	225	225	225	225
Other Assets	239	400	297	393
TOTAL ASSETS	195,975	172,732	224,127	224,376
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current Liabilities:				
Accounts Payable	5,376	1,543	4,129	3,948
Accured Expenses and Other Current Liabilities	9,006	8,126	5,829	7,514
Total Current Liabilities	14,382	9,669	9,958	11,462
Deferred Rent, Net of Current Portion	1,367	1,326	1,271	1,217
TOTAL LIABILITIES	15,749	10,995	11,229	12,679
STOCKHOLDERS' EQUITY				
Common Stock	3	3	3	3
Additional Paid-in-Capital	274,349	276,354	350,047	363,393
Accumulated Other Comprehensive Loss	853	(33)	(572)	(646)
Accumulated Deficit	(94,979)	(114,587)	(136,580)	(151,053)
TOTAL STOCKHOLDERS' EQUITY	180,226	161,737	212,898	211,697
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	195,975	172,732	224,127	224,376

REGENXBIO Inc Statement of Cash Flows

Figures in thousands ($) except per share data

	3Q16	4Q16	1Q17	2Q17
Operating Activities:				
Net loss	(18,154)	(19,608)	(21,993)	(14,473)
Adjustments to reconcile net loss to net cash used:				-
Stock-based compensation expense	1,829	2,000	2,591	2,483
Net amortization of premiums and accretion of discounts on marketable debt securities	515	502	469	476
Depreciation and amortization	160	280	554	703
Realized gains on sales of marketable securities	(20)	20	(480)	-
Unrealized foreign currency transaction gains	(2)	2	-	-
Other non-cash adjustments	-	(399)	41	(1)
Changes in Operating Assets and Liabilities:				-
Accounts receivable	106	(386)	803	179
Prepaid expenses	(691)	396	(68)	(589)
Other current assets	(563)	990	88	(330)
Other assets	27	(68)	10	(96)
Accounts payable	2,665	(3,409)	2,468	255
Accrued expenses and other current liabilities	1,609	(718)	(1,920)	1,889
Advance payments	-	-	-	-
Deferred rent	701	(25)	(44)	(45)
Net Cash Provided (Used) in Operating Activities	(11,818)	(20,423)	(17,481)	(9,549)
Investing Activities:				0
Purchases of marketable securities	(1)	(12,810)	(5,188)	(41,405)
Maturities of marketable securities	12,000	34,455	10,500	17,510
Sales of marketable securities	23	-	780	-
Purchases of property and equipment	(2,223)	(4,435)	(2,929)	(1,680)
Net Cash Provided (Used) in Investing Activities	9,799	17,210	3,163	(25,575)
Financing Activities:				
Proceeds from exercise of stock options	44	5	161	168
Proceeds from issuance of common stock under employee stock purchase plan	-	-	147	-
Proceeds from public offering of common stock, net of underwriting discounts and commissions	-	-	71,299	10,695
Issuance costs for public offering of common stock	-	-	(84)	(135)
Issuance costs for potential public offering of common stock	-	(60)	-	-
Net Cash Provided (Used) in Financing Activities	44	(55)	71,523	10,728
Net Decrease in Cash and Cash Equivalents	(1,975)	(3,268)	57,205	(24,396)
Cash and Cash Equivalents at Beginning of Period	30,083	28,108	24,840	82,045
Cash and Cash Equivalents at End of Period	28,108	24,840	82,045	57,649

Spark Therapeutics, Inc. (ONCE-NASDAQ)

Biotechnology

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The Gene Therapy Revolution Starts With a Spark; Initiating Coverage at Outperform

Recommendation: We are initiating coverage of Spark Therapeutics with an **Outperform** rating and a target price of $96 (High Risk/Speculation suitability given the stage of clinical development). In our opinion, Spark is a premier gene therapy company, with an ophthalmology franchise poised to bring the first gene therapy to the U.S. market within the next few months, in addition to a platform tackling the multi-billion dollar market of hemophilia. With an approval expected in the near future, encouraging clinical data seen with the hemophilia A program, a marquee partner (Pfizer) driving development in hemophilia B, a platform technology to address large areas of unmet need, and a cash position of ~$571 million (pro forma), we recommend Spark shares to risk-tolerant investors.

- **Keeping an eye on the prize – the first U.S. gene therapy is on the horizon.** The company's most advanced gene therapy product, LUXTURNA, has demonstrated compelling results among 41 patients with RPE65-mediated inherited retinal diseases (IRDs) including a successful registration-directed pivotal trial. While there is an advisory committee meeting scheduled on October 12, 2017, we expect LUXTURNA to be approved on or before the PDUFA date of January 12, 2018, in the U.S., followed by a potential EU approval in 3Q18. Although there may be challenges in the commercial setting (e.g., patient identification, logistics of training physicians, and potential payor pushback), we believe LUXTURNA could eventually be adopted among the majority of addressable patients, generating accumulated U.S. and EU sales of ~$2.4 billion (risk-unadjusted) from 2018 to 2022.
- **One-time treatment to stem the bleeding.** Based on our analysis, the company's hemophilia A (HA) product, SPK-8011, has generated promising preliminary data, achieving clinically meaningful factor VIII activity levels of 11% and 14% in two patients treated at the lowest dose. Importantly, when the dose was doubled, the factor VIII activity levels appeared to increase proportionally. Based on our analysis, we believe SPK-8011 has the potential to become a best-in-class gene therapy for moderate to severe HA, with a potentially better safety profile and less interpatient variability as compared to competitors in development. That said, even if SPK-8011 is not a differentiated product per se, in our opinion, the HA market is large enough to accommodate multiple gene therapies. Assuming an outcome-based annuity payment model and a 25% market share for the addressable patient population, we expect SPK-8011 to generate peak sales of $1.9 billion (risk-unadjusted) by 2027, which we believe could last for eight years.
- **An attractive takeout candidate**. Given the significant progress made in the space, we believe gene therapy is one of the next-wave therapeutics, which is likely to continue to draw attention from big pharma/large biotech companies. As a leading gene therapy player with multiple late-stage product candidates, we believe Spark represents an attractive acquisition target.

Valuation: Using a sum-of-the-parts analysis of the company's clinical assets, we derive a target price of $96. See page 172 for more detail.

GAAP EPS	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Full Year	Revenues (mil.)
2016A	(0.95)	(1.04)	(1.07)	(1.28)	$(4.29)	$20
2017E	(1.70)A	(2.40)A	(1.68)	(1.78)	(7.51)	3
2018E	(1.88)	(1.30)	(1.08)	(0.44)	(4.68)	115

Rows may not add due to rounding.

Rating
Outperform 2

Current and Target Price

Current Price (Oct-09-17)	$85.67
Target Price:	$96.00
52-Week Range	$91.00 - $35.07
Suitability	High Risk/Speculation

Market Data

Shares Out. (mil.)	36.5
Market Cap. (mil.)	$3,127
Avg. Daily Vol. (10 day)	413,096
Dividend/Yield	$0.00/0.0%
Book Value (Jun-17)	$10.60
LT Debt (mil.)/% Cap.	$1/0%

Earnings & Valuation Metrics

	2016A	2017E	2018E
P/E Ratios (GAAP)	NM	NM	NM

Spark Therapeutics, Inc., headquartered in Philadelphia, Pennsylvania, is a leading gene therapy company currently focusing on three areas: inherited retinal diseases (IRDs), liver-mediated diseases, and neurodegenerative diseases. The IRD franchise consists of the following product candidates: 1) LUXTURNA, 2) SPK-7001, and 3) two additional preclinical assets. With respect to the liver franchise, there are two clinical programs (and one undisclosed preclinical asset): 1) SPK-8011 and 2) SPK-9001. Finally, in regard to the central nervous system (CNS) franchise, the company has a preclinical program each for neuronal ceroid lipofuscinosis type 2 (CLN2) disease and Huntington's disease.

Source: FactSet.

Company Description

Spark Therapeutics, headquartered in Philadelphia, Pennsylvania, is a leading gene therapy company currently focusing on three areas: IRDs, liver-mediated diseases, and neurodegenerative diseases. The IRD franchise consists of the following product candidates: 1) LUXTURNA, which utilizes a recombinant AAV2 vector to deliver a functional RPE65 gene, has been evaluated in a successful Phase III study for RPE65-mediated IRDs, with a PDUFA date of January 12, 2018; 2) SPK-7001, which consists of the same vector used for LUXTURNA and a copy of the Choroideremia (CHM) gene, is being evaluated in a Phase I/II study for patients with CHM; and 3) two additional preclinical assets. With respect to the liver franchise, there are two clinical programs (and one undisclosed preclinical asset): 1) SPK-8011, which consists of a novel AAV vector (Spark200) and a human factor VIII gene, is being evaluated in a Phase I/II study for hemophilia A, with promising data; and 2) SPK-9001, which also uses a novel AAV vector (Spark100) to deliver the factor IX gene, is in Phase I/II testing for hemophilia B. Of note, SPK-9001 has been licensed to Pfizer. Finally, in regard to the central nervous system (CNS) franchise, the company has a preclinical program each for neuronal ceroid lipofuscinosis type 2 (CLN2) disease and Huntington's disease.

Newsworthy Catalysts

Product	Timing	Description
LUXTURNA for RPE65 Mediated IRDs		
	October 12, 2017	Advisory committee meeting on LUXTURNA's BLA
	January 12, 2018	PDUFA date
	2Q18	Treatment of a first patient by LUXTURNA in the U.S.
	3Q18	EMA's decision on approval
SPK-7001 for Choroideremia		
	As early as mid-2018	Two-year analysis of the first 10 patients
	2H18	Preliminary data from the five additional patients
SPK-8011 for Hemophilia A		
	November, 2017	Enrollment update on the Phase I/II study
	December, 2017	An update on the Phase I/II study at ASH
SPK-9001 for Hemophilia B		
	December, 2017	An update on the Phase I/II study at ASH

Source: Spark Therapeutics, Raymond James research.

Summary of Investment Risks

Clinical and Regulatory Risk

While we believe LUXTURNA is likely to be approved given the clinical data seen to date, there are uncertainties (e.g., the advisory committee's view on the novel primary endpoint and manufacturing) that could derail the current regulatory path.

Except for LUXTURNA, other clinical/preclinical product candidates may not deliver clinically meaningful results in the ongoing/future studies.

Commercial Risk

The commercial rollout of LUXTURNA could face challenges in identifying patients and obtaining insurance coverage. With respect to SPK-8011, there are multiple gene therapy products in development for hemophilia A, resulting in potentially fierce competition if all products exhibit comparable efficacy and safety profiles.

In general, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Spark cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercially viable.

Financing Risk

Spark currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Summary of Investment Highlights

LUXTURNA for RPE65-Mediated IRDs

RPE65-mediated inherited retinal diseases (IRDs) are rare genetic disorders caused by mutations in the RPE65 gene, which encodes an enzyme essential for the production of a molecule called chromophore. Loss of chromophore production together with progressive photoreceptor degeneration causes severe and progressive loss of vision. RPE65-mediated IRDs are extremely rare, currently affecting a total of approximately 4,700 people in the U.S. and the European markets combined. Currently, there are no approved pharmacological therapies for this disease.

A Successful Phase III Can Support Approval

Spark's LUXTURNA (voretigene neparvovec), which utilizes a recombinant AAV2 vector to deliver a functional RPE65 gene, has been evaluated in three clinical trials for RPE65-mediated IRDs, with all demonstrating compelling results. In our opinion, LUXTURNA is likely to be approved for the following reasons:

A Novel But Approvable Endpoint

To best evaluate the therapeutic benefits of LUXTURNA, the company developed the multi-luminance mobility test (MLMT) with input from the FDA. The MLMT is based on a maze test that evaluates an individual's ability to navigate under different light conditions, ranging from one lux (equivalent to a moonless summer night or indoor nightlight) to 400 lux (equivalent to an office setting).

Given the FDA's involvement in the development of the MLMT as well as the validation of this test among 26 normal-sighted people and 28 visually impaired patients, in our opinion, the MLMT score is an approvable endpoint, although it will be one of the topics discussed during the upcoming advisory committee meeting (October 12, 2017).

The Pivotal Study Met the Primary Endpoint

Notably, the registration-directed, controlled Phase III study met the primary endpoint among the intent to treat (ITT) population, a statistically significant improvement in the MLMT score seen in the treatment group as compared to the control group (p = 0.001). Excluding two patients who never received the gene therapy, the treated patients (n=20) achieved an average improvement of 1.9 lux levels, significantly greater than the 0.2 lux levels seen in the control patients (n=9) at year one. Importantly, 19 of these 20 patients responded to the treatment, with 13 being able to pass the MLMT at one lux level (the most difficult visual setting) at year one, which was not observed in any of the control patients at year one (see page 148 for more details).

The treatment effects appear to be long-lasting. The improvements (measured by both the MLMT and FST scores) achieved among the 19 patients in the initial treatment arm of the Phase III study were maintained at year two, with no sign of deterioration so far. In addition, the eight patients treated in a Phase I study largely maintained treatment effects over the course of four years.

On the safety front, LUXTURNA did not cause serious adverse events (SAEs) or deleterious immune responses in the Phase III study, with the most common adverse events seen in the treated eyes caused by the surgical procedure.

Regulatory Status

The company has completed the rolling submission of a BLA for LUXTURNA for patients with vision loss as a result of a biallelic RPE65 mutation-mediated IRD. The BLA was accepted by the FDA in July 2017, with an advisory committee meeting scheduled on October 12, 2017, and a PDUFA date of January 12, 2018. In addition, a marketing authorization application (MAA) seeking for a similar label, which was submitted to the European Medicines Agency (EMA) in July 2017, has been validated, with a potential approval expected in 3Q18. According to the company, both the BLA and MAA packages included data from the three clinical studies that collectively treated 41 patients with the gene therapy. As discussed before, we believe the completed clinical studies can support the potential U.S. and EU approvals.

The Briefing Documents Suggest That a Positive AdCom Outcome Is Likely

According to the briefing documents published yesterday (link), the upcoming advisory committee (AdCom) meeting slated to discuss Spark's BLA for LUXTURNA on Thursday, October 12, is expected to discuss three main topics: 1) whether a two-light level improvement in the MLMT score is clinically

meaningful; 2) the appropriate patient population for LUXTURNA; and 3) the potential benefits and risks of re-dosing. Based on our analysis of the clinical data seen to date, we continue to believe that the MLMT score is an approvable endpoint and that a two-light level improvement is clinically meaningful, a view that is likely to be adopted by the majority (if not all) of the committee members. Furthermore, in our opinion, the discussion of defining a patient population that can benefit most from LUXTURNA should not affect the approvability of this gene therapy. That said, the market opportunity could be impacted depending on the broadness of the drug label. Finally, we believe the FDA wants to evaluate the possibility of repeat administration primarily due to the fact that the long-term durability of treatment effects remains unclear at this point. From a safety perspective, the subretinal injection in conjunction with the use of prednisone either did not elicit immune responses (T cell responses or the formation of anti-AAV or RPE-65 antibodies) or such responses were not significant among all the patients treated in the three clinical trials. Therefore, in our opinion, the risk of significant immune responses induced by re-dosing is low, although re-dosing has not been evaluated in the clinic. If repeat administration is not recommended (which we view as a likely outcome), in our opinion, LUXTURNA is still likely to be approved given the clinical benefits associated with this gene therapy. Taken together, we expect a favorable recommendation from the AdCom committee and an ultimate approval.

The Competitive Landscape of RPE65-Mediated IRD

Currently, there are no approved pharmacological therapies for the treatment of RPE65 mutated IRDs. In terms of the pipeline products for this disease, besides Spark's LUXTURNA, MeiraGTx's OPTIRPE65 is the only other gene therapy drug candidate that we are aware of. OPTIRPE65, which consists of an optimized AAV2/5 vector loaded with an optimized hRPE65 promoter and a codon-optimized hRPE65 gene, is currently being evaluated in a dose escalation Phase I/II study for patients with Leber Congenital Amaurosis (LCA) caused by RPE65 mutations. Although no clinical data has been reported, preclinical studies of OPTIRPE65 demonstrated that the AAV2/5 powered vector achieved an at least 300-fold increase in RPE65 expression in a mouse model as compared to AAV2 vector. The OPTIRPE65 study (NCT02781480), which started in April 2016, completed dosing of the second cohort (a total of three dose cohorts) in February 2017. According to ClinicalTrials.gov, the final data collection of this study is expected in October 2018. If MeiraGTx plans to initiate a pivotal study afterwards, a potential approval may not occur until 2024 (In Spark's case, it took approximately 5.5 years from Phase III start to a potential approval). Given the stage of development, in our opinion, OPTIRPE65 is not likely to be a threat to LUXTURNA in the next several years, by which the majority of target patients may have already been treated with LUXTURNA.

The Market Opportunity for LUXTURNA

Currently, Spark has the global rights to LUXTURNA and plans to commercialize it globally by itself, with an initial focus on the U.S. and European markets. Assuming a one-time payment model with a per-patient price tag of $1,000,000 in the U.S. and $800,000 in the EU, we expect LUXTURNA to deliver peak sales of $811 million by 2021, with accumulated sales of $2.4 billion from 2018 to 2022. After 2022, we expect the sales to decline dramatically as only new patients would be treated by then.

Given the ultra-rare nature of the RPE65 IRDs, the company plans to start with a small but targeted field team to introduce the product to centers of excellence (COEs), which are specialized in treating such diseases. The company has fully mobilized the field team (the majority are medical science liaisons (MSLs) and diagnostic specialists) and identified 5-8 COEs (would be 8-10 at launch) for the commercial launch of LUXTURNA upon its approval. After approval, the company will need to settle on the price, obtain payor coverage, and train physicians, which means no patients are likely to be treated until 2Q18.

The prelaunch will focus on five primary areas including patient identification, stakeholder education, developing a high-quality delivery and distribution model, ensuring market access, and building a patient-centric organization. In our opinion, the company's sales/marketing strategy is reasonable. That said, the commercial rollout of LUXTURNA could encounter some headwinds given that RPE65 IRDs are under-diagnosed and could require significant physician training.

SPK-8011 for Hemophilia A

Hemophilia A (HA), a rare genetic bleeding disorder caused by a deficiency in the clotting factor VIII, currently affects approximately 20,000 and 40,960 people in the U.S. and EU, respectively. The plasma levels of factor VIII range from 50-150% for healthy people, 6-49% for patients with mild hemophilia A, 1-5% for those with a moderate disease, and <1% for those with a severe disease. It appears there is no consensus surrounding a target factor VIII activity level among physicians.

SPK-8011 Has Demonstrated Encouraging Clinical Data

Spark's SPK-8011, which consists of a novel AAV vector and a codon-optimized human factor VIII gene, is being evaluated as a potential one-time therapy in a Phase I/II dose-escalation study (NCT03003533) for hemophilia A patients with factor VIII activity levels of ≤ 2%. For safety reasons, there is a wait time required between patients and between doses in this study. Of note, patients with detectable antibodies against the AAV-Spark200 capsid are excluded. According to the company, approximately 60% of HA patients do not have pre-existing neutralizing antibodies against the vector used in Spark's hemophilia trials, with another ~11% having lower titers of such antibodies that can be managed to allow for the SPK-8011 treatment.

In early August, 2017, the company provided the first results from this trial. As of the August 1, 2017, data cutoff, three patients had received a single injection of the gene therapy, with the first two treated at an initial dose level of 5×10^{11} vg/kg and the third at a second dose level of 1×10^{12} vg/kg. Notably, the first two patients had been followed for 23 and 12 weeks, with both achieving stable factor VIII activity of 11% and 14% of the normal levels (both appeared to have plateaued), respectively. While the third patient had not been followed long enough, management indicated that this patient's factor activity level was tracking proportionally higher but had plateaued. Specifically, the factor activity for the third patient at the early stage was slightly higher than 2x of that seen for the first two patients at the same time period. Therefore, we believe the third patient could eventually achieve stable factor VIII activity of approximately 22-30%. According to a natural history study, when the factor VIII activity level is ≥ 12%, the number of annual joint bleeds is nearly zero. Despite a small number of patients, in our opinion, SPK-8011 has demonstrated quite encouraging proof-of-concept data, which could be even more compelling at higher doses. Spark management does not think the severity of a patient's disease (e.g., moderate vs. severe) has any impact on the treatment outcomes of SPK-8011. On the safety front, the gene therapy appeared to be well tolerated, with no SAEs reported to date. Specifically, there were no factor VIII inhibitors, thrombotic events, immune response, spontaneous bleeds, or elevations in liver enzymes. Of note, none of these three patients had required use of corticosteroids.

Based on our conversation with management, a second patient was treated with the second dose recently, although no data has been disclosed. Another update on this study is expected at the 2017 American Society of Hematology (ASH) conference, which is expected to include data from 5-8 patients depending on the number of patients evaluated at the second dose as well as whether a higher dose would be tested before ASH.

SPK-8011 Regulatory Timeline

Spark started its Phase I/II study in December 2016. According to ClinicalTrials.gov, a total of 30 patients are expected to be enrolled, with an estimated primary completion date of August 2019. Given the current enrollment pace as well as the design, we expect Spark's Phase I/II to complete enrollment of 7-10 patients at a target dose in 2H18 and one-year follow-up for all patients in 2H19. Since the company plans to change the manufacturing process, a bridging study of 4-5 patients is needed after the completion of the current Phase I/II study, although these patients may not need to be followed for one year. Therefore, we expect Spark to initiate a Phase III study for SPK-8011 in 1Q20, followed by potential enrollment completion in 4Q20, a BLA filing in 1Q22, a U.S. approval in 1Q23, and an EU approval in 1Q24. According to Spark, a Phase III hemophilia study is expected to enroll 50-150 patients, with the enrollment target for an HA trial reaching the high end of the range. Similarly, BioMarin guided that its HA Phase III study would enroll fewer than 100 patients with one year of follow-up.

Can SPK-8011 Be Best-in-Class?

Currently, there are five companies developing gene therapies for HA, with BioMarin taking the lead in the race.

Gene Therapy Candidates for Hemophilia A

Company	Product	Vector	Transgene	Clinical Status
BioMarin	BMN-270	AAV5	BDD-FVIII-SQ	Phase III (to start in 4Q17)
Spark	SPK-8011	AAVSpark200	Codon optimized BDD-FVIII	Phase I/II
Sangamo/Pfizer	SB-525	AAV2/6	FVIII	Phase I/II
Shire	SHP654	AAV8	BDD-FVIII	Preclinical
Dimension/Bayer	DTX201	AAVrh10	BDD-FVIII	Preclinical

Source: Company data, Raymond James research.

Given the data seen to date with Spark's SPK-8011 and BioMarin's BMN-270 (see the following table), in our opinion, it is premature to make a conclusion on whether the former has a much better product profile than the latter. That said, SPK-8011 has the potential to deliver a differentiated profile on multiple fronts: 1) less interpatient variability on the FVIII activity levels achieved; 2) a better safety profile with fewer liver toxicities; and 3) a lower therapeutic dose that could lead to lower COGS.

According to Spark, the key factors that contribute to the consistent results (little interpatient variability) seen so far in its hemophilia trials include: 1) sensitive immuno-monitoring assays that can evaluate if a patient has pre-existing neutralizing antibodies; 2) a consistent manufacturing process with 10+ years of experience (lot-to-lot variability can lead to inconsistent results from one patient to another); and 3) the use of mammalian cell line versus other cell lines used by others.

Comparison Between SPK-8011 and BMN-270

Product	SPK-8011		BMN-270	
Dose (vg/kg)	5×10^{11}	1×10^{12}	4×10^{13}	6×10^{13}
# of patients	2	2	6	7
Patient baseline FVIII activity levels	≤ 2%		< 1%	< 1%
Follow-up (weeks)	23, 12	N/A	20	52
Mean FVIII activity levels (range)	12.5% (11%-14%)	Expected to be around 25%	31% (7%-45%)	104% (20%-218%)
Median FVIII activity levels	N/A	N/A	34%	89%
Average annualized bleeding rate after gene therapy	N/A (no spontaneous bleeds so far)	N/A	1 (0-2.3)	0.5 (0-1.1)
Average annualized FVIII infusions after gene therapy	N/A	N/A	4.8 (0, 11.6)	8.5 (0-20.8)
Safety	No SAEs so far: no inhibitors to FVIII, thrombotic events, immune response, or elevations in liver enzymes; no use of corticosteroids so far		One related SAE which was resolved after intervention, 73% ALT elevations (all grade 1), 47% AST elevations	
% of HA patients without pre-existing NAbs	60% (~11% have low titers)		~90%	
Regulatory plan	Will pick a dose and then move into a pivotal study		Two separate Phase III studies will be initiated to evaluate each of the two doses	

Notes: ALT – Alanine transaminase; AST – Aspartate aminotransferase. In BMN-270's study, it appears the FVIII activity levels among patients treated at the dose of 4×10^{13} vg/kg continued to increase over time, with the mean value increasing from 5% (n=6) at four weeks to 31% (n=6) at 20 weeks and to 51% (n=3) at 32 weeks.

Source: Spark Therapeutics, BioMarin Pharmaceutical, Raymond James research.

Market Opportunity for SPK-8011

Spark also has the global rights to SPK-8011. Assuming an outcome based annuity payment model with an annual payment of $400,000 in the U.S. and $320,000 in the EU as well as a 25% peak market share given the potential competition, we expect SPK-8011 to deliver peak sales of $1.9 billion by 2027, which we expect to last for eight years

SPK-7001 for Choroideremia

Choroideremia (CHM) is also a genetic eye disorder caused by mutations in the CHM gene. With no approved therapies, CHM is currently affecting approximately 11,000 males in the U.S. and the European markets combined.

Spark's SPK-7001, which consists of the same vector (AAV2) used for LUXTURNA and a copy of the CHM gene, is being evaluated in a Phase I/II study for patients with CHM. Initially, this study enrolled 10 patients with late-stage disease. According to an interim analysis of the data cut as of March 29, 2017, SPK-7001 was well tolerated among these 10 patients, without product-related SAEs, although there was one procedure-related SAE. One the efficacy front, the results were disappointing. As of March 29, 2017, five, four, and one patients had one year, 18 months, and two years of follow-up, respectively. Results on at least one endpoint (e.g., visual acuity and light sensitivity) favoring the treated eye over the control eye

were seen in only four of the 10 patients, and they were not even statistically significant. Spark concluded that there were no consistent and conclusive differences between the treated and control eyes based on the interim efficacy data. According to Spark, the lack of efficacy at the interim analysis could be attributed to the duration of follow-up (the target follow-up is two years) as well as the later stage of the disease. Therefore, the company plans to continue to follow these 10 patients, with the two-year analysis expected in March/April 2018. In addition, the company will enroll an additional five patients at an earlier stage of the disease. All of these five patients were expected to be enrolled by the end of 3Q17, with preliminary results expected in 2H18 and two-year data anticipated in 2H19. Therefore, the company is not likely to start a pivotal study until late 2019. Assuming a three-year Phase III study that starts in 4Q19, we expect the company to submit a BLA in 4Q22, followed by a potential U.S. approval in 4Q23 and a potential EU approval in 4Q24.

Given the data seen to date as well as the stage of development, we are cautiously optimistic about the clinical prospects of SPK-7001. Assuming a 25% probability of success and a one-time payment model with a per-patient price tag of $1,000,000 in the U.S. and $800,000 in the EU, we expect SPK-7001 to deliver peak sales of $1.1 billion by 2027, with accumulated sales of $3.3 billion from 2023 to 2028. After 2028, we expect the sales to decline dramatically as only new patients would be treated by then.

Spark's Portfolio

Product	Status	Market	Rights
Inherited retinal diseases (IRDs)			
LUXTURNA	FDA/EMA review	RPE65 mediated IRDs	Spark
SPK-7001	Phase I/II	Choroideremia	Spark
LHON	Preclinical	LHON	Spark
Undisclosed	Preclinical	Undisclosed	Spark
Liver-mediated diseases			
SPK-8011	Phase I/II	Hemophilia A	Spark
SPK-9001	Phase I/II	Hemophilia B	Pfizer (royalties to spark)
Undisclosed	Preclinical	Undisclosed	Spark
Neurodegenerative diseases			
CLN2 disease	Preclinical	CLN2 disease	Spark
Huntington's disease	Preclinical	Huntington's disease	Spark

Notes: LHON – Leber hereditary optic neuropathy, CLN2 – neuronal ceroid lipofuscinosis type 2
Source: Spark Therapeutics, Raymond James research.

The Retinal Franchise

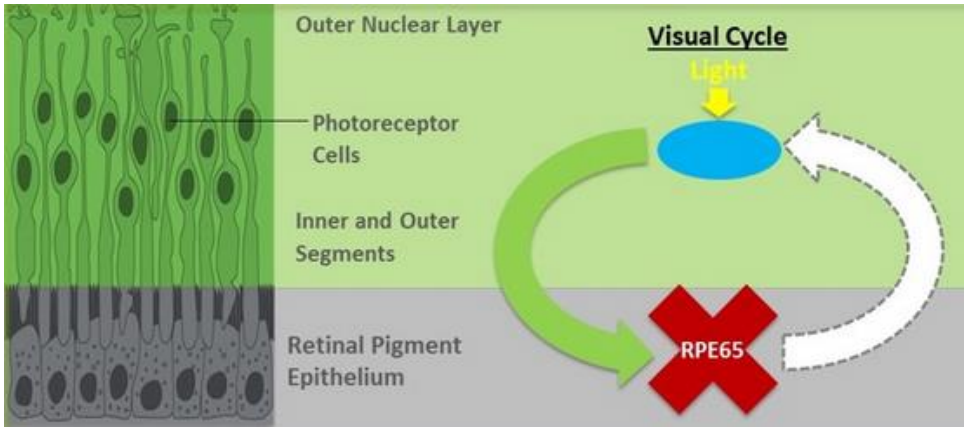
The company's most advanced investigational product candidate for the retinal franchise is LUXTURNA (voretigene neparvovec), which is being developed to treat an inherited retinal disease (IRD) caused by biallelic mutations in the RPE65 gene.

LUXTURNA for RPE65-Mediated IRDs

Background of RPE65-Mediated IRD

RPE65-mediated IRD is a rare autosomal recessive retinal degenerative disease that causes blindness. RPE65 is highly expressed in the retinal pigment epithelium, where it encodes enzymes essential for the production of a molecule called chromophore, which forms the visual pigment found in rod and cone photoreceptors in the retina. Loss of chromophore production together with progressive photoreceptor degeneration causes severe and progressive loss of vision (Exhibit 1).

Exhibit 1: **The Role of RPE65**



Source: Spark Therapeutics.

Historically, RPE65-mediated IRDs have been clinically diagnosed as Leber congenital amaurosis (LCA), early-onset severe retinal dystrophy, or early-onset retinitis pigmentosa. Recently, however, the diagnosis of IRDs has begun to shift from clinical classification to diagnosis based on the underlying genetic components of the disease. Currently, there are no approved therapeutics for the treatment of RPE65-mediated IRD.

Endpoints for Measuring Functional Vision

Since no therapies have been approved for RPE65-mediated IRD, there are no clinical endpoints that have been utilized to evaluate an investigational drug candidate for this disease in a successful registrational study. While there are multiple traditional vision endpoints including visual fields (peripheral vision) and visual acuity (central vision), these measures may not accurately capture a patient's ability to perform daily activities in the real world setting. With the input from the FDA, the company developed a novel test, the multi-luminance mobility test (MLMT), which is designed to best assess the therapeutic benefits of the company's gene therapy product, LUXTURNA.

The Multi-Luminance Mobility Test

The MLMT is based on a maze system with a grid of arrows to guide participants to move around obstacles before reaching a door at the end of the maze (Exhibit 2). Given that patients with the RPE65 mutation have trouble seeing in dim light, they were asked to pass the maze at different light levels within a certain time frame in the Phase III study of LUXTURNA. In respect to the light condition used in the MLMT test, the brightness of light was determined by seven lux levels:

1) 1 lux: approximately equivalent to a moonless summer night or indoor nightlight;

2) 4 lux: approximately equivalent to an outdoor parking lot at night or Christmas tree lights;

3) 10 lux: approximately equivalent to an hour following sunset in a city setting or a bus stop at night;

4) 50 lux: approximately equivalent to an outdoor train station at night or the inside of a stairwell;

5) 125 lux: approximately equivalent to half-an-hour before sunrise or the interior of a shopping mall or train or bus at night;

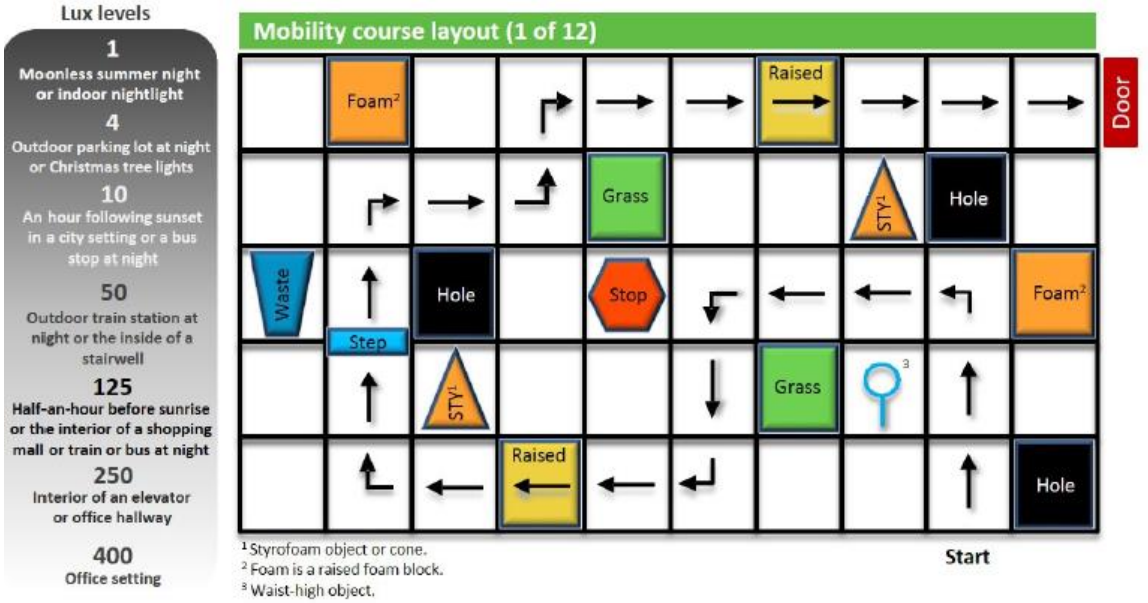
6) 250 lux: approximately equivalent to the interior of an elevator or office hallway; and

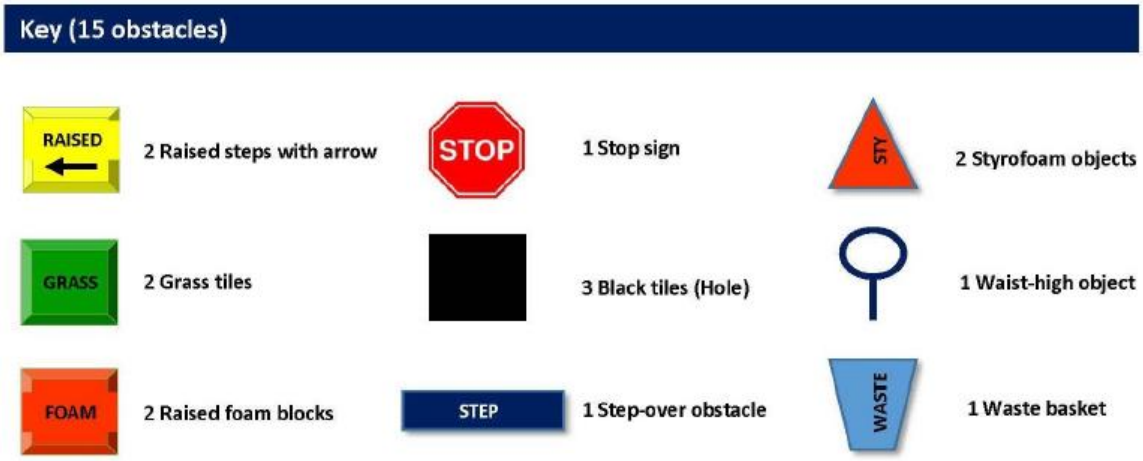
7) 400 lux: approximately equivalent to an office setting.

Each run for the MLMT was videotaped and graded on a pass or fail basis. Specifically, a grade of "fail" was given to an attempt if the participant (1) was reguided, stepped off the course, skipped tiles, or collided with obstacles on four or more occasions in total or (2) took longer than three minutes to complete the course. The lowest light levels under which a patient can pass the maze before (baseline) and after the gene therapy were recorded by two independent viewers and an adjudicator in case the two initial grades did not agree.

Of note, the MLMT has demonstrated a high reproducibility, given that an approximately 97.5% agreement was reached for grading of the same video based on a sample of more than 2,500 videos. Given a person's mobility is determined by his/her visual acuity, visual field, light perception, and contrast sensitivity, in our opinion, the MLMT is likely to be a better metric to evaluate a person's functional vision, capturing a true visual improvement when evaluating active agents.

Exhibit 2: **The MLMT Test**





Correlation of Light Level and MLMT Lux Score

Light Level	MLMT Lux Score
1 lux	6
4 lux	5
10 lux	4
50 lux	3
125 lux	2
250 lux	1
400 lux	0

Source: Spark Therapeutics.

Validation of MLMT

In order to test the reliability of MLMT especially the impact of the performance of this test on a patient's functional vision, the company conducted a non-Investigational New Drug study (MLMTVS) with 26 normal-sighted individuals and 28 visually impaired patients (they had some form of an IRD). During a one-year period with no intervening medical treatment for enrolled participants, while all normal-sighted individuals showed no change in the MLMT score (were able to complete the MLMT at the lowest lux level at both time points), all visually impaired subjects had no visual improvement, with five of them showing a decline in MLMT score. In addition, results suggested that the difficulty of 12 different courses in the MLMT were comparable based on the demonstrated performance seen from both normal-sighted and visually impaired subjects.

Full-Field Light Sensitivity Threshold

The full-field light sensitivity threshold (FST) is another test that measures the luminance threshold (light sensitivity) as determined by the function of rod photoreceptors using full-field stimuli. A button box is used by the participant to indicate whether or not the brief, full-field stimulus can be perceived. Therefore, the participant's visual function can be evaluated through assessing the dimmest flash of light that can be perceived by the participant.

Clinical Development of LUXTURNA

LUXTURNA, which has orphan drug designations in the U.S. and EU as well as a breakthrough therapy designation in the U.S., has been evaluated in three clinical trials, showcasing compelling results.

The same surgeon at the Children's Hospital of Philadelphia (CHOP) treated all patients enrolled in the two Phase I clinical trials, whereas five surgeons at CHOP or the University of Iowa performed the procedure for all patients evaluated in the Phase III trial.

Phase I 101 Trial

The first clinical study of LUXTURNA was initiated in October 2007, with a primary goal to assess safety and tolerability and a secondary objective to evaluate both objective and subjective measures of efficacy and the relevance of these measurements as a clinical endpoint. 12 patients with RPE65-mediated IRD enrolled and received a single dose of LUXTURNA in one eye. LUXTURNA was investigated at three doses: 1.5×10^{10} (n=3), 4.8×10^{10} (n=6), or 1.5×10^{11} (n=3) vector genomes. On the safety front, the gene therapy was well tolerated, with no related serious adverse events.

Phase I 102 Trial

In November 2010, the company initiated a second clinical study, the 102 trial, to evaluate the safety and efficacy of LUXTURNA in the untreated eyes of the 11 eligible patients from the aforementioned 101 study. Of note, one patient with glaucoma from the 101 study was deemed ineligible for the second study. A single dose of LUXTURNA at 1.5×10^{11} vector genomes, the highest dose evaluated in the first study, was administered into the previously untreated eye of each of the 11 patients.

Eight out of the 11 patients achieved a vision improvement of at least one light level, with five improved to the minimum light level, the same level at which all subjects with normal vision were evaluated in the previously discussed MLMT validation study. As compared to the baseline, these eight patients achieved durable improvement in MLMT scores over the course of four years. In addition, the mean FST (full-field light sensitivity threshold), which measures the light sensitivity of the entire visual field of an eye, increased at year 1, and also appears to be largely durable throughout the four years of follow-up. Of note, all these eight patients who responded well to the gene therapy also met the inclusion criteria of the Phase III pivotal study (see discussions below).

In terms of safety, one subject experienced an SAE due to the treatment given for a rare complication resulting from the vitrectomy procedure prior to the administration of LUXTURNA. Therefore, the SAE was not deemed to be related to the gene therapy or the subretinal injection procedure.

Phase III Pivotal Study

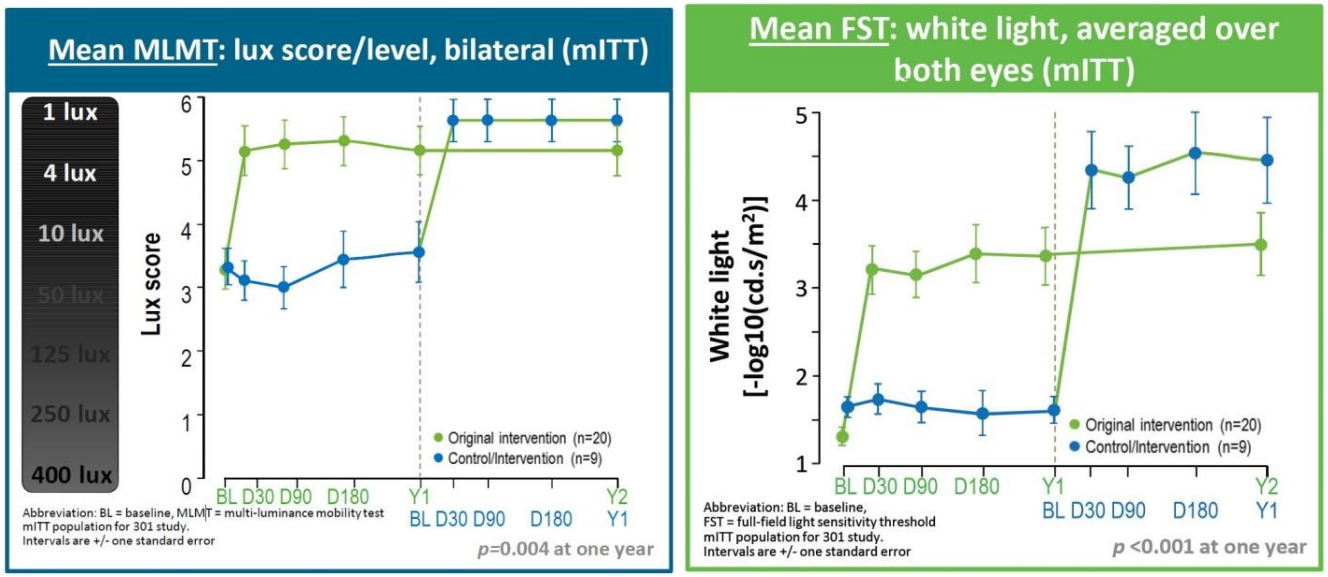
Given the encouraging results seen in the two Phase I studies, the company initiated a pivotal Phase III trial evaluating LUXTURNA in patients with confirmed RPE65-mediated IRD in October 2012. The primary endpoint was the change of the MLMT score at multiple time points from baseline over one year under different light conditions ranging from one lux to 400 lux. The secondary endpoints include FST, MLMT changed score for the assigned first injected eye only, and visual acuity, which are slated to be evaluated statistically in the order of hierarchy. These endpoints are evaluated at baseline and 30/90/180 days and one year after treatment.

A total of 31 patients with an average age of 14.6 years (range: 4-44) enrolled at either CHOP or the University of Iowa were randomized at a 2:1 ratio into either the treatment (n=21) or control (n=10) group, with the two arms balanced for age and the baseline lux level. For patients in the treatment group, both eyes were injected with a single dose of 1.5×10^{11} vector genomes of LUXTURNA, with one surgery for one eye and both eyes treated within a period of 6 to 18 days. With respect to the patients in the control arm, they did not receive a sham injection (as there were pediatric patients) and were allowed to cross over to the treatment arm after one year of follow-up.

Announced in October 2015, the pivotal study met its primary endpoint among the intent to treat (ITT) population, with a statistically significant improvement in the MLMT score seen in the treatment group as compared to the control group ($p = 0.001$). Excluding two patients who never received the gene therapy, the treated patients (n=20) achieved an average improvement of 1.9 lux levels, significantly greater than the 0.2 lux levels seen in the control patients (n=9) at year one. Importantly, 19 of these 20 patients responded to the treatment, with 13 being able to pass the MLMT at one lux level at year one, which was not observed in any of the control patients at year one (Exhibit 3). Of note, one lux level (equivalent to a moonless summer night or indoor nightlight) is the most difficult visual setting in the MLMT. A similar treatment effect was also achieved in these nine initial control patients who were then treated with LUXTURNA, with a mean MLMT improvement of 2.1 lux levels at year one. Notably, eight of these nine patients were able pass the maze test at one lux level one year post-treatment.

Besides delivering on the primary endpoint, the gene therapy also achieved statistically significant improvements in the first two secondary measures among the ITT population: mean FST ($p < 0.001$) and the MLMT score in the first injected eye ($p = 0.001$). Specifically, the mean FST averaged over both eyes among the initially treated 20 patients increased by more than a hundredfold, and a more significant FST effect (an average of ~two hundredfold improvement) was also seen in the nine crossed-over patients. Although the study missed the third secondary endpoint of visual acuity ($p = 0.17$), a mean improvement of approximately 9.0 (vs. 1.6 in the control patients) and 4.5 letters on the logMAR scale (a standard measure of visual acuity) were achieved among the 20 and nine treated patients, respectively. While the third secondary endpoint was missed, in our opinion, this should not be a significant concern given that the primary endpoint was met.

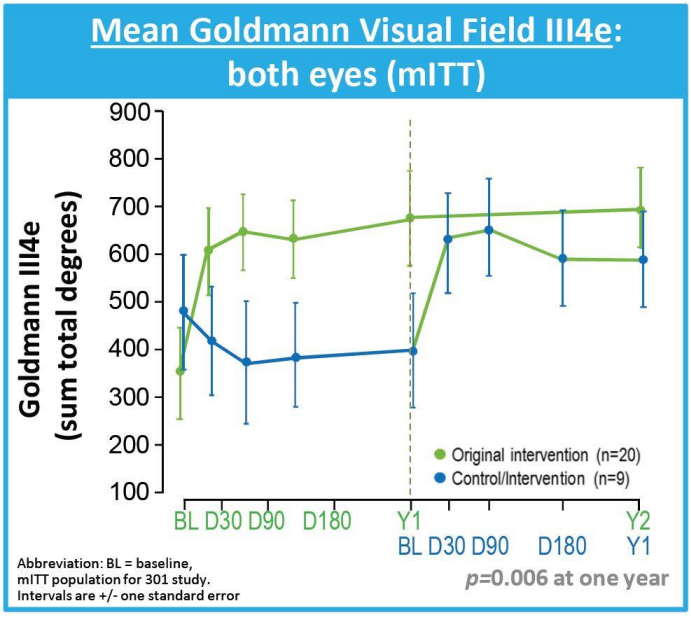
Exhibit 3: **Efficacy of LUXTURNA**



Source: Spark Therapeutics.

Additionally, visual field (VF), defined as the total field area of a person's retinal sensitivity that extends from a central fixation point to the periphery, was used as an additional endpoint in the Phase III study. Revealed in October 2016, the gene therapy achieved statistically significant improvement in VF among all treated patients as measured by both the Goldmann III4e test stimulus and the Humphrey macula threshold, demonstrating a mean difference of 387.7 sum total degrees (Goldmann, p=0.006) and 7.9 decibels (Humphrey, p<0.001) as compared to the control group.

Exhibit 4: **Goldmann III4e Test Stimulus Results From the Phase III Study**



Source: Spark Therapeutics.

In terms of safety, the gene therapy did not cause serious adverse events or deleterious immune responses in the Phase III study (Exhibit 5). The most common adverse events seen in the treated eyes were ocular adverse events caused by the surgical procedure. Of note, these ocular adverse events were largely resolved weeks after surgery. One surgical procedure-related SAE occurred in one patient in the 302 study, who experienced a reduction of VA after the procedure but achieved an improvement regarding the MLMT and FST testing.

Exhibit 5: **Safety Profile of LUXTURNA at Years 1 and 2**

Most common treatment-emergent ocular adverse events	Number of participants (n=29)
Increased intraocular pressure	5
Cataracts	4
Retinal tear	3
Retinal deposit*	3
Macular hole	2
Transient and mild eye inflammation	2
Eye pain	2
Eye pruritus	2

Procedure-related serious adverse event	Number of participants (n=29)
Loss of foveal function (visual acuity) – right eye	1

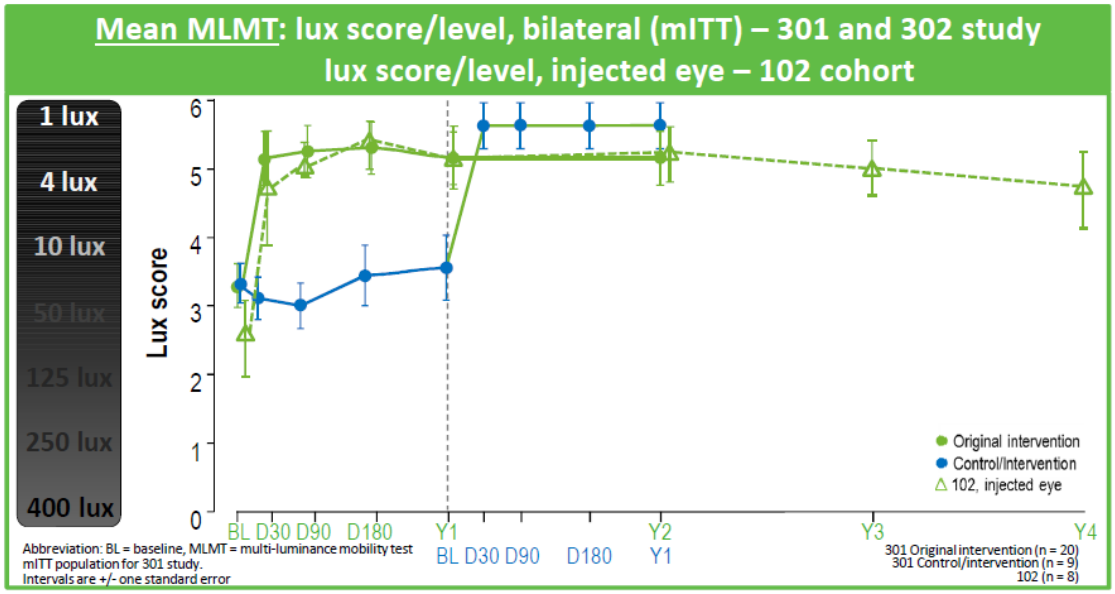
*Asymptomatic, self-limiting, subretinal precipitates

Source: Spark Therapeutics.

Long-Term Durability of the Treatment Effect

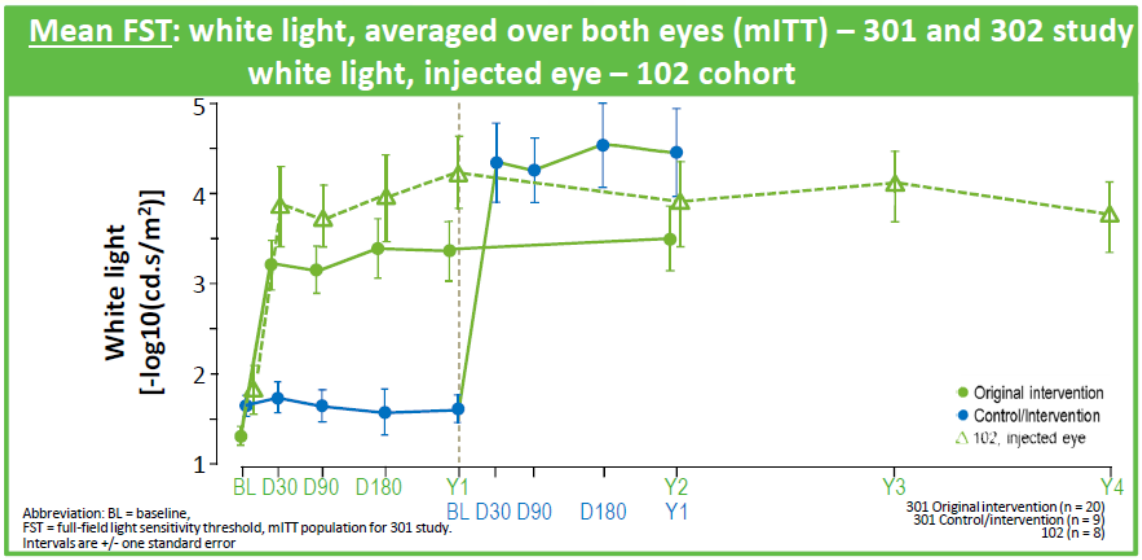
In terms of durability, the treatment effects of LUXTURNA appear to be long lasting as indicated by the mean MLMT (Exhibit 6) and FST (Exhibit 7) scores. The improvements achieved among the 19 patients in the initial treatment arm of the Phase III study were maintained at year two, with no sign of deterioration so far. In addition, the eight patients treated in the second Phase I study also experienced the long-lasting treatment benefit of the gene therapy over the course of four years. That said, the treatment effects as indicated by the MLMT score seen in these eight patients appear to gradually weaken in year three and year four.

Exhibit 6: **Long-Term Follow-Up of MLMT Scores**



Source: Spark Therapeutics.

Exhibit 7: **Long-Term Follow-Up of FST**



Source: Spark Therapeutics.

SPK-7001 for Choroideremia

Background of Choroideremia

Choroideremia (CHM) is an X-linked recessive eye disorder that is characterized by progressive degeneration of the choroid, retinal pigment epithelium (RPE), and neural retina. Clinically, CHM manifests in affected males as night blindness and progresses with a gradual loss of peripheral vision and legal blindness by middle age. The disease is caused by mutations to the *CHM* gene, most commonly due to the absence or deficiency of Rab escort protein-1 (REP1, encoded by *CHM*). The prevalence of Choroideremia is estimated at about 1:50,000 people, implying a total population of up to approximately 12,500 males in the United States and the five major European markets. Of all regions, northern Finland has the highest reported prevalence.

There is no current treatment or cure available for Choroideremia. However, nearly all reported cases of CHM have been attributed to functionally null mutations, which combined with slow rate of degeneration, make gene therapy an attractive therapeutic approach. Recently, Phase 1/2 clinical trials employing adeno-associated viral vector based approaches encoding REP1 have demonstrated clinical promise in restoring visual acuity (NightstaRx; 4D molecular therapeutics).

Clinical Development of SPK-7001

By leveraging the technology used for LUXTURNA, the company has developed a gene therapy product candidate SPK-CHM for the treatment of IRD caused by CHM gene mutations. SPK-CHM (SPK-7001) consists of the same vector (AAV2) used for LUXTURNA and a copy of CHM gene which has been shown to be able to restore REP1 production in preclinical models. Given the demonstrated efficacy data seen in the preclinical studies, the company has initiated a two-year Phase I/II study evaluating the safety and efficacy for subretinal administration of SPK-CHM at different dosage levels in 10 patients with late-stage IRD caused by CHM mutations.

To date, SPK-CHM has demonstrated a favorable safety profile with no observed product-related serious adverse events. In addition, the trial has moved to the higher dosage level without any safety issues raised by the data safety monitoring board. On the efficacy front, no meaningful efficacy endpoint has been achieved among four treated late-stage patients, as revealed in an interim analysis. Given a lack of efficacy in the treated late-stage patients seen to date, the company is expanding the study to include five additional patients with an earlier stage of disease.

The Competitive Landscape

Currently, there is no approved therapy for the treatment of Choroideremia. The most clinically advanced gene therapy candidate is NSR AAV-REP1, an AAV2 vector loaded with the CHM cDNA being developed by NightstaRx. In an ongoing Phase I/II study in six patients with Choroideremia, NSR AAV-REP1 treated patients achieved a 1.7 dB mean increase in retinal sensitivity as compared to a 0.8 dB mean decrease in sensitivity in controlled eyes in a six-month period, with the improvement correlated with the vector dose levels. In addition, a 3.8-letters mean increase in visual acuity was achieved among all treated patients, including two patients with advanced Choroideremia.

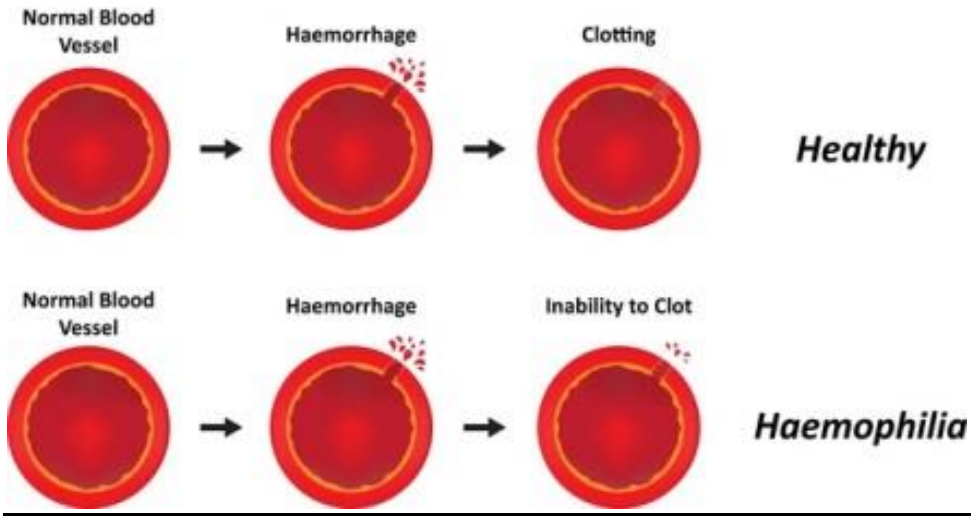
A long-term follow-up study of the Phase I/II trial is ongoing with the six treated patients being followed up for five years. In parallel, the company is conducting a 200+ patient, non-interventional, natural history study as well as a biomarker study for earlier disease progression with a goal to potentially treat younger patients before significant vision loss occurs.

The Hemophilia Franchise

Background of Hemophilia

Hemophilia is a rare, X-linked, genetic bleeding disorder that results in a deficiency in the clotting functionality of blood (Exhibit 8). Depending on which clotting factor the patient is deficient in, the disease is classified as hemophilia A (HA, deficiency in factor VIII) or hemophilia B (HB, deficiency in factor IX), in which the loss of function of either FVIII or FIX results in a deficiency of thrombin generation, an enzyme that is necessary for the intrinsic clotting cascade. The incidence rate of HA and HB is 1 in 5,000 and 1 in 25,000 - 30,000 male births, respectively, with a worldwide hemophilia population estimated to be 400,000 in total.

Exhibit 8: **What Is Hemophilia?**



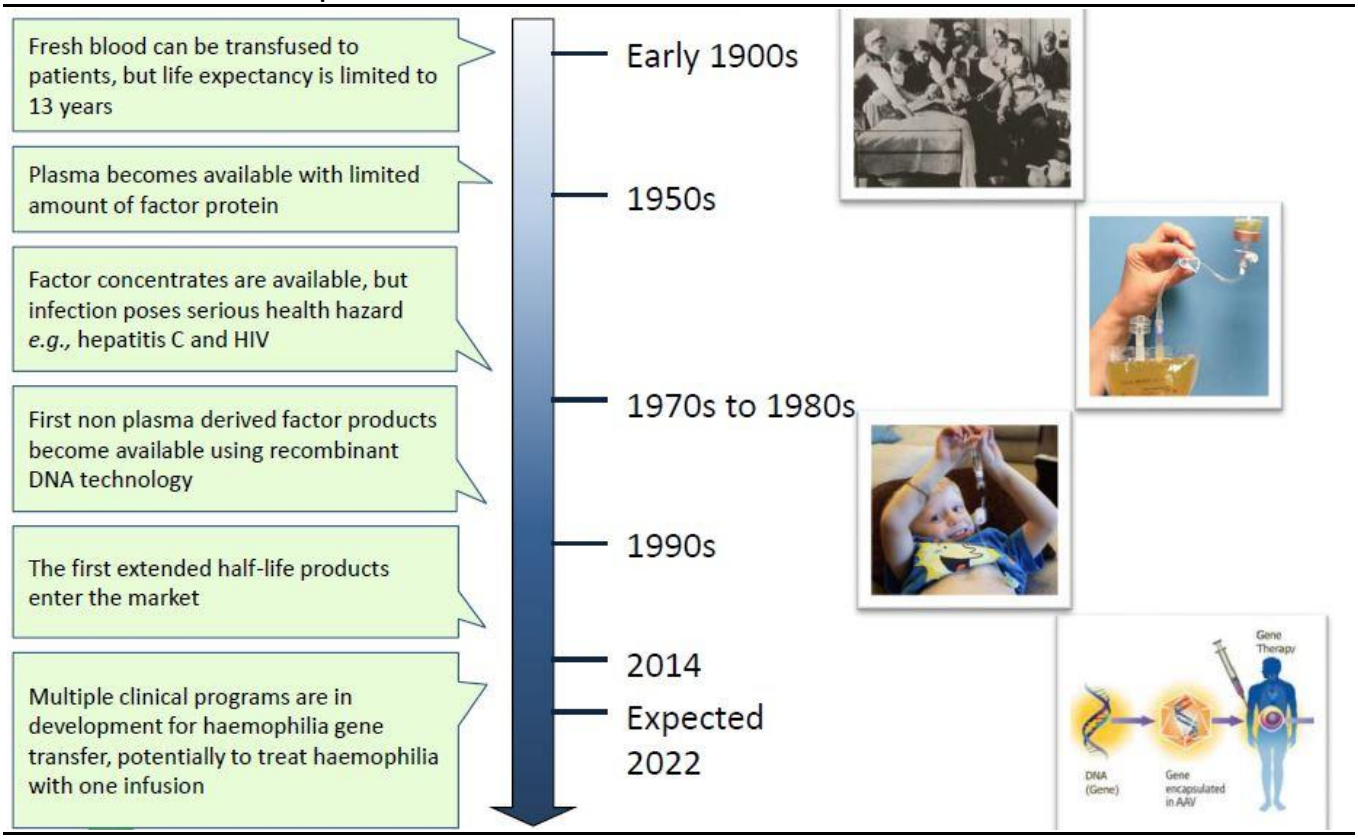
Source: https://ghr.nlm.nih.gov/condition/hemophilia.

While the diagnosis of which factor is deficient is important for treatment, the clinical symptoms of HA and HB are very similar. The severity of the disease is dependent on the level of functional clotting factor (50 - 150% being the normal range), which can be classified into three categories: severe (<1% activity), moderate (1-5% activity), and mild (6-49%). While patients with mild cases are typically asymptomatic outside of serious injury, trauma, or surgery, patients with moderate hemophilia are more susceptible and may experience prolonged bleeding even from minor injuries. Finally, patients with severe disease experience (in addition to difficulty responding to injury) frequent spontaneous bleeding episodes, often in joints and muscles, which leads to edema, inflammation, debilitating pain, as well as chronic deterioration of the joints over time.

The first treatment for hemophilia consisted of direct blood transfusion in the 1840s. In the 1950s and 1960s, the standard of care consisted of whole blood or fresh plasma transfusions. Although this improved a patient's quality of life significantly, for those with serious disease, the quantity of clotting factors was not sufficient to correct severe bleeding. Following the successful cloning of the FIX gene in 1984, the first commercially available recombinant FIX protein concentrates were made available in 1997 for patients with HB. Currently, various recombinant proteins or highly purified and inactivated plasma-derived factor concentrates have been made available and achieved widespread success in the clinic, with prophylactic protein replacement therapy being recommended as the standard of care (Exhibit 9).

In regard to the clinical outcome, 80% of uncontrolled bleeds have been effectively eliminated with a single dose of factors, and subsequent use increases the success rate to 90-95%. Importantly, when compared to episodic on-demand treatment, prophylactic treatment works well in terms of lowering the risk of having joint damage and developing chronic joint disorders, as well as reducing annual bleeding rate (ABR). That said, significant limitations with the current hemophilia treatment paradigm still persist, including: 1) the short half-lives (18-24 h) for protein concentrates, which introduces the need for frequent administrations (several times a week) and a high average cost of approximately $160,000 per year (of note, the cost for patients with severe hemophilia who receive prophylaxis treatment is even higher, with a median annual cost of approximately $300,000); and 2) the development of inhibitors (antibody developed against the factor protein) among 15% and 3% of HA and HB patients, respectively.

Exhibit 9: **Evolution of Hemophilia Treatment**



Source: National Hemophilia Foundation (hemophilia.org), American Society of Hematology, Spark Therapeutics.

One solution to the current protein replacement therapy is to increase the serum half-life of the recombinant proteins. Recently, bioengineering of recombinant coagulation proteins employing the IgG-Fc fusion strategy, pegylation, or fusion with recombinant albumin has achieved half-life extension, which permits a reduced dosing frequency and a reduced burden to patients (Exhibit 10). That said, a life-long factor administration is still required.

Exhibit 10: **Recently Approved and Late-Stage Protein Replacement Therapy for Hemophilia**

Product	Company	Key technique/feature	Mean half-life (hours)	Status
Hemophilia A				
Novoeight	Novo Nordisk		10.8	FDA approved
Eloctate	Bioverativ	Fc Fusion	19.7	FDA approved
Adynovate	Shire	PEGylated to target lysine residues	14.7	FDA approved
Nuwiq	Octapharma	Posttranslational modifications similar to those in pdFVIII	17.1	FDA approved
Kovaltry	Bayer	HSP70 to improve FVIII folding	14.3	FDA approved
Afstyla	CSL Behring		14.2	FDA approved
BAY 94-9027	Bayer	PEG linked to mutationally introduced surface cysteine residues	~19	Phase III
N8-GP	Novo Nordisk	PEGylated to the remaining 21 amino acid sequence of B-domain	~19	Phase III
Hemophilia B				
Rixubis	Shire		25.4	FDA approved
Alprolix	Bioverativ	Fc Fusion	86.5	FDA approved
Ixinity	Emergent	Thr-148 polymorphism	24	FDA approved
Idelvion	CSL Behring	cleavable linker rFIX with albumin moieties	104	FDA approved
N9-GP	Novo Nordisk	Pegylation	111	Phase III

Source: Company data, Raymond James research.

Spark's Solution to Hemophilia B

The short sequence of FIX gene (1,466 bp) renders HB an ideal target disease for gene therapy, particularly in the context of using AAV based vector due to its limited transgene capacity (~4.6 kbp). In addition, even an increase of 1% in circulating FIX levels would convert the HB disease phenotype from severe to moderate, with a further disease phenotype modifying effect from moderate to mild by achieving 5% of normal FIX levels.

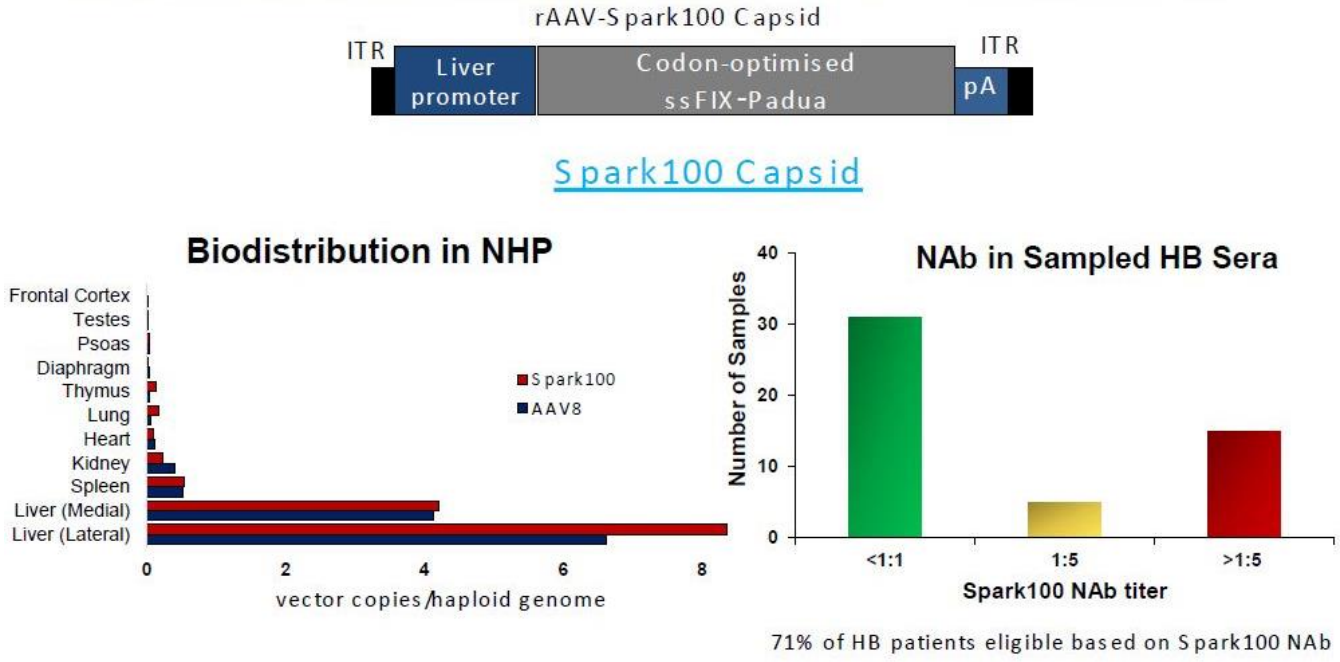
The concept of gene therapy for HB was validated by a dose-escalating, Phase I study (conducted by St. Jude Children's Research Hospital and the University College London) of an AAV8 vector packaged with a codon optimized human FIX transgene in patients with HB. Among six severe HB patients (FIX level <1%) treated with a single IV injection of 2x10^12 vg/kg transgene vectors, an approximately 5% mean FIX activity was achieved during a four year follow-up period. In addition, an 88% and 85% decrease in the annual bleeding rate (ABR) and the annual infusion rate (AIR) was achieved, respectively.

Safety wise, no serious adverse events were seen among all treated patients, with no generation of inhibitors (antibodies) to FIX during the entire follow-up period. Four patients developed a mild elevation in the liver transaminases ALT/AST between 7 and 11 weeks after gene transfer, which was concomitant with a decrease in the circulating FIX level. Importantly, a rescue of FIX expression was achieved among these patients when a short course of prednisolone (an immunosuppressant) was given, with the level of FIX maintained once prednisolone treatment was ended.

With a goal to enhance the efficiency of therapeutic FIX expression and simultaneously reduce the risk of side effects due to the immunogenicity against the gene transfer vector and its products, Spark has developed a transgene cassette known as SPK-9001 consisting of a bio-engineered AAV vector (Spark100 capsid) with a codon optimized, single stranded, high activity FIX transgene, known as FIX-Padua, to address the current limitations associated with AAV vector based gene therapy for HB (Exhibit 11).

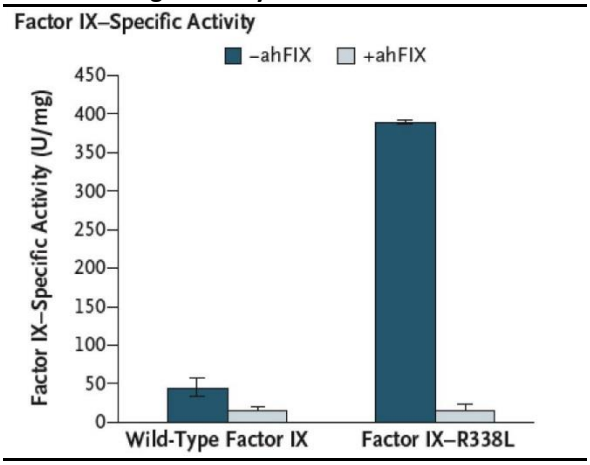
The Spark100 capsid confers two key advantages over other AAV vectors: 1) it has a comparable or maybe a better bio-distribution profile compared to AAV8 for the demonstrated liver tropism in preclinical models; and 2) there is a relatively low prevalence of pre-existing antibodies to this capsid within the human population, therefore potentially broadening the commercial addressable market. Additionally, the unique transgene cassette FIX-Padua consists of a naturally occurring FIX variant resulting from a gain-of-function mutation of leucine for arginine at position 338 (R338L). The Padua protein has a five- to ten-fold higher activity level compared with the wild-type FIX, and therefore could potentially achieve a high expression level of FIX with a much lower dose of viral vectors (Exhibit 12).

Exhibit 11: **SPK-9001 Construct**



Source: Spark Therapeutics.

Exhibit 12: **High Activity of FIX-Padua**



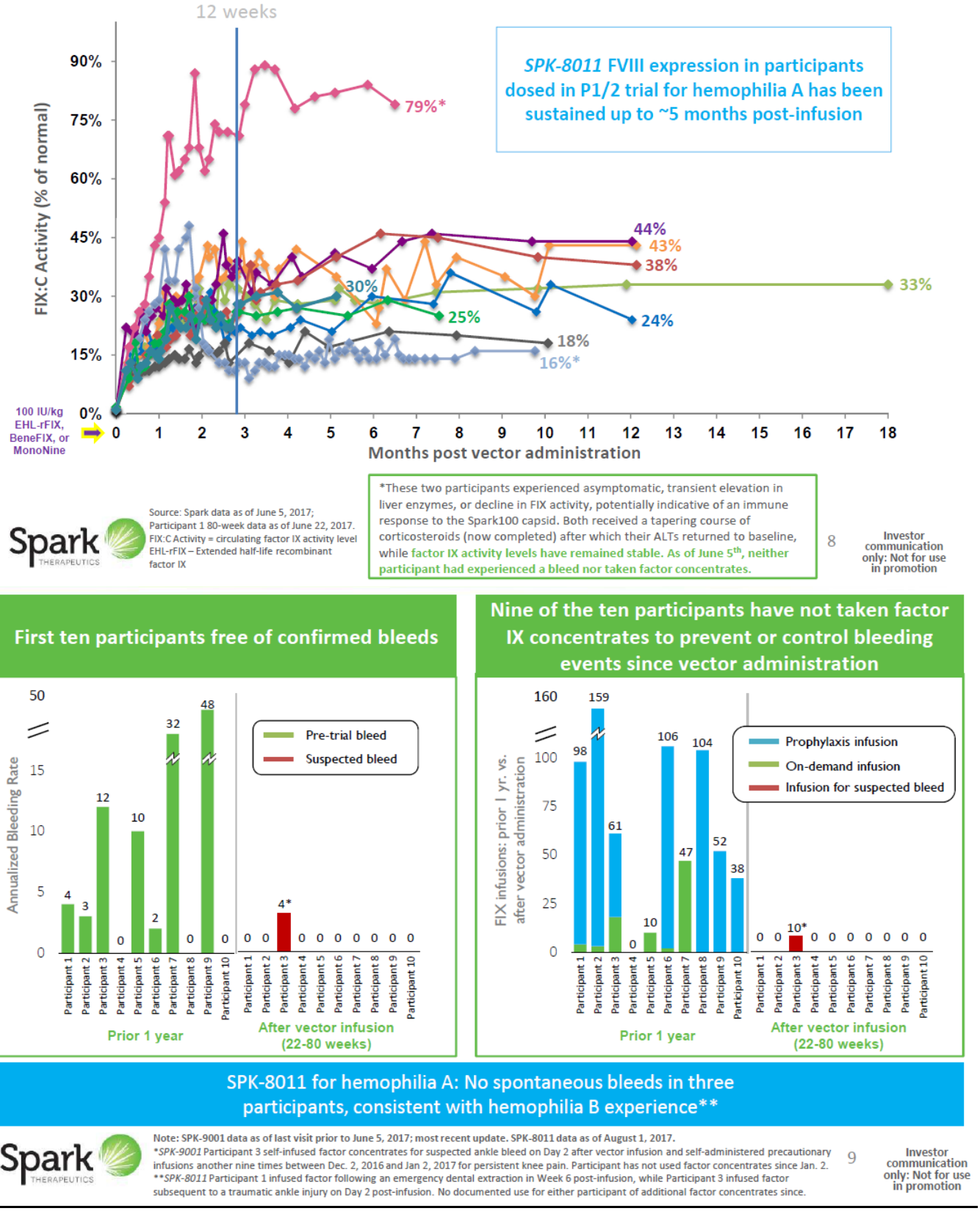
Source: Spark Therapeutics.

Clinical Study of SPK-9001

SPK-9001 which received the orphan product designation and the breakthrough therapy designation from the FDA, is currently being evaluated in an open-label, non-randomized, dose-escalating, Phase I/II study in patients with severe to moderate HB. While safety is the primary measurement of the study, a secondary endpoint includes changes of the circulating FIX activity (IU/dL or % from normal) from the baseline during a one-year follow-up period. Eligible participants for the study include patients with confirmed diagnosis of HB with a ≤2 IU/dL or ≤2% endogenous factor IX level, as well as having ≥50 days of exposure to factor IX products. The initial dose is 5x10^11 vg/kg with a potential to escalate up to two additional higher dose cohorts if efficacy profiles are inadequate.

Ten patients have received a single IV injection of SPK-9001 at a dose of 5x10^11 vg/kg. All treated patients achieved a steady-state FIX level 12 weeks after treatment, with a mean FIX level of 33% (14% to 81%), which translated into a 96% and 99% decrease in ABR and AIR, respectively (Exhibit 13). In addition, revealed at the 2017 International Society on Thrombosis and Haemostasis Congress (ISTH), FIX levels and reductions in ABR (96%) and AIR (99%) were maintained in these 10 treated patients as of the data cutoff in June 2017.

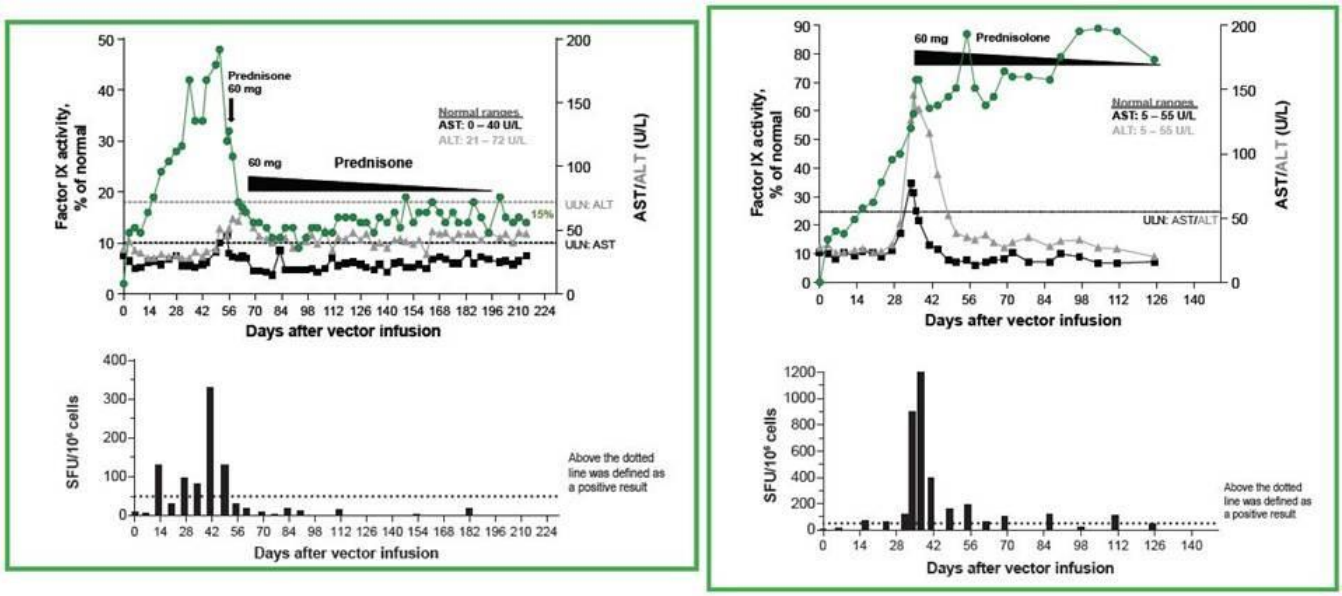
Exhibit 13: **Efficacy Data of SPK-9001 in Patients with Severe and Moderate HB**



Source: Spark Therapeutics.

On the safety side, SPK-9001 appears to be well tolerated with no serious adverse events reported to date. Of note, two patients had an asymptomatic elevation in liver enzymes (AST/ALT), which was concomitant with a decrease in the FIX level. Importantly, both patients received a tapering dose of oral prednisone, after which liver enzymes returned to baseline with the FIX level maintained at 15% and >70% after the steroid treatment (Exhibit 14). As of the data cutoff in June 2017, both patients continued to demonstrate stable FIX levels during an 18- and 12-week period post-steroids treatment, respectively.

Exhibit 14: **Effect of Steroids on Immune Response Patients Treated with SPK-9001**



Source: Spark Therapeutics.

Competitive Landscape of HB Gene Therapy

Beyond Spark Therapeutics, multiple companies have developed their own gene therapy products targeting HB with limited success (Exhibit 15). That said, we view Spark's SPK-9001 as the most promising and advanced gene therapy candidate for HB given its favorable safety and efficacy profile seen to date.

Exhibit 15: **Gene Therapy Product Candidates for HB**

Company	UCL/SJCRH	Baxalta/Shire	Spark/Pfizer	UniQure	Dimension
Product	scAAV2/8-LP1-hFIXco	BAX 335	SPK-9001	AMT-060	DTX101
Vector	AAV2/8	AAV8	AAVSpark100	AAV5	AAVrh10
Transgene Cassette	scAAV	scAAV	ssAAV	scAAV	scAAV
Promoter	LP1		Liver specific	LP1	
Transgene	Codon optimized hFIX	hFIX Padua	Codon optimized hFIX Padua	Codon-optimized wild type hFIX	wild type hFIX
Trial ID	NCT00979238	NCT01687608	NCT02484092	NCT02396342	NCT02618915
Phase	Phase I	Phase I/II (stopped)	Phase I/II	Phase I/II (completed)	Phase I/II)
Patient #	6 (high dose cohort)	7	10	10	6
Dose	2x10^12 vg/kg	2x10^11 vg/kg (2) 1x10^12 vg/kg (3) 3x10^12 vg/kg (2)	5x10^11 vg/kg	5x10^11 - 1.8x10^13 gc/kg	1.6x10^12 - 5x10^12 gc/kg
Delivery	IV infusion	IV infusion	IV infusion	IV infusion	
Efficacy					
Decrease in AIR	85.1%	NA	98.6%	85% (3 pts in cohort 1)	NA
Decrease in ABR	88%	NA	96.2%	76% (3 pts in cohort 2)	NA
Expression Persistence	~5% mean FIX lvl in 6/6 pts in 4 years	20 - 25% FIX lvl in 1/7 pt in 12 months	14 - 81% in a cumulative >380 weeks	6.9% FIX lvl in 5/10 pt at 5.5 months	3 - 8% in 5 pts
Mean FIX level	~5% (4 years after transfer)	NA	33% (12 weeks/3 months)	6.9%	NA
Safety					
Immune Suppression	Short course prednisolone	prednisolone	prednisone	2/10 received steroids	Yes
ALT/AST Increase	4/6	2/7 (highest dose)	0.2	0.2	5/6 (1 Grade 4)
Neutralizing Antibody	No	No	No	Yes	NA

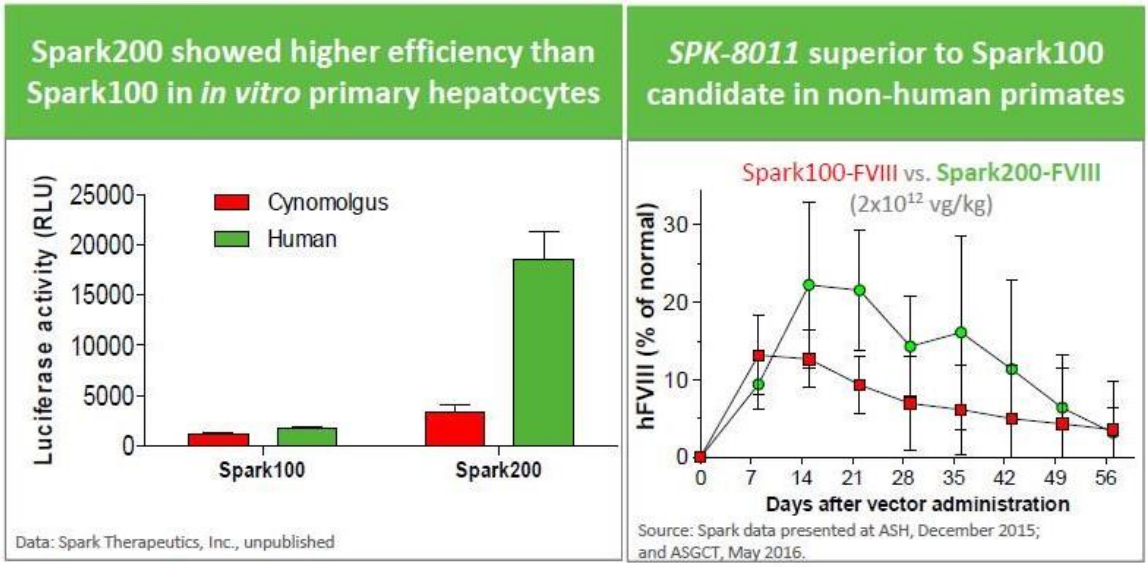
Source: Company data, Raymond James research.

Spark's Solution to Hemophilia A

As compared with FIX, the cDNA for human FVIII is much larger and exceeds the packaging capacity of a typical AAV vector (~4.6 kb). To date, various strategies have been developed to reduce the size of the FVIII cDNA, including deletion of the B domain sequence (BDD hFVIII) and replacement with a variety of amino acid linker sequences. Notably, Refacto, which is an FDA approved protein replacement therapy drug developed by Pfizer, consists of a recombinant BDD hFVIII. Spark has developed a transgene cassette known as SPK-8011, consisting of a bio-engineered, second generation AAV vector (Spark200 capsid) with a codon optimized, BDD hFVIII transgene.

In a preclinical study, Spark200 demonstrated a higher transduction efficiency for hepatocytes than Spark100 (Exhibit 16). In addition, SPK-8011 achieved superior FVIII expression levels in non-human primates relative to the first generation vector (Spark100-FVIII) during an approximately two-month follow-up period.

Exhibit 16: **Preclinical Data of SPK-8011**



Source: Spark Therapeutics.

Given the encouraging preclinical results seen to date, the company has initiated a dose-escalating Phase I/II study evaluating SPK-8011 for hemophilia A, with primary endpoints being the safety of SPK-8011 and changes in FVIII activity levels from baseline after receiving a single dose of SPK-8011. The initial dose of the study is 5x10^11 vg/kg, which is the same dose of SPK-9011 used in the ongoing Phase I study for HB.

Competitive Landscape of HA Gene Therapy

Including Spark, our analysis shows that five companies are currently developing gene therapies for hemophilia A, with BioMarin's molecule BMN-270 being the most advanced product candidate in the pipeline.

BMN-270, which consists of a BDD-FVIII transgene packaged in an AAV5 vector, is being evaluated in a dose-escalating Phase I/II study in patients with severe HA (<=1% of the FVIII level). Primary endpoints include the safety of a single IV injection of BMN-270 and changes of FVIII expression level from baseline

at 16 weeks after injection. Secondary endpoints include the impact of BMN-270 on the frequency of FVIII replacement therapy and the number of bleeding episodes requiring a factor treatment.

In August 2015, BioMarin started the Phase I/II study, with a total of 15 patients expected to be enrolled. After enrolling the first nine patients, increases in alanine aminotransferase (ALT) levels exceeded a pre-specified threshold, which triggered study suspension in June 2016. After protocol amendments, the study was reopened for enrollment in November 2016. According to ClinicalTrials.gov, the full enrollment of 15 patients was completed in June 2017.

In July 2017, BioMarin reported updated 52-week data for the first seven patients who received BMN-270 ($6x10^{13}$ vg/kg) as well as the initial 24-week data for patients who received a lower dose ($4x10^{13}$ vg/kg). As of the data cutoff in May 2017, BMN-270 ($6x10^{13}$ vg/kg) achieved a 97% reduction in ABR in six patients who received prophylaxis factor treatment before the study (Exhibit 18). More importantly, mean FVIII levels among treated patients were 104% with most patients in the normal range (50-150%) and one patient at 218%. In parallel, in the lower dose cohort, three patients achieved a mean of 32% FVIII level at 24 weeks (Exhibit 19).

Exhibit 17: **Factor VIII Levels (%) of $6x10^{13}$ vg/kg Dose Patients* by Visit (N=7)**

Week**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
N***	7	7	7	6	7	7	7	7	7
Median Factor VIII Level**** (%)	**97**	**101**	**122**	**99**	**99**	**111**	**105**	**105**	**89**
Mean Factor VIII Level**** (%)	**118**	**129**	**123**	**122**	**116**	**124**	**122**	**106**	**104**
Range (low, high)	(12, 254)	(12, 227)	(15, 257)	(26, 316)	(31, 273)	(17, 264)	(20,242)	(23,196)	(20, 218)

*All patients had severe hemophilia A, defined as less than 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood; **Weeks were windowed by +/- 2 weeks; *** For week 32, one patient had no Factor VIII reading; ****Bolded numbers are in the normal range of Factor VIII as defined by the World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of June 30, 2017). Factor VIII levels are determined by one-stage assay.
Source: BioMarin Pharmaceutical.

Exhibit 18: **Summary of Mean Annualized Bleeding Rate (ABR) and FVIII Infusions of 6x 10^{13} vg/kg Dose Patients Previously on Prophylaxis (N=6)***

	Before BMN-270 Infusion***	**After BMN-270 Infusion********
	Mean (median, SD)	**Mean (median, SD)**
Annualized Bleeding Rate(bleeding episodes per year per subject)**	16.3 (16.5, 15.7)	0.5 (0.0, 1.1)
Annualized FVIII Infusions (infusions per year per subject)**	136.7 (138.5, 22.4)	8.5 (0.0, 20.8)

Notes: *A 7th patient received Factor VIII on demand and was not included in analysis; **Post-infusion data were based on data after Factor VIII levels were above 5%; ***Obtained from medical records; ****5 of 6 patients had 0 bleeds requiring Factor VIII infusions and 0 Factor VIII infusions after Factor VIII levels were above 5%.
Source: BioMarin Pharmaceutical.

In August 2017, the company provided updated data from the $4x10^{13}$ vg/kg dose cohort, which demonstrated that the factor VIII activity levels continued to increase over time (Exhibit 19).

Exhibit 19: **Factor VIII Levels (%) of $4x10^{13}$ vg/kg Dose Patients* by Visit (N=6)**

Week**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
n	6	6	6	6	6	3	3	3
Median Factor VIII Level*** (%)	4	**15**	**21**	**29**	**34**	**29**	**41**	**51**
Mean Factor VIII Level*** (%)	**5**	**13**	**19**	**26**	**31**	**32**	**39**	**51**
Range (low, high)	(2,10)	(3,21)	(6,32)	(5,38)	(7,45)	(24,42)	(32,44)	(48,54)

Notes: *All patients had severe hemophilia A, defined as less than 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood, **Weeks were windowed by +/- 2 weeks, *** Bolded numbers are in the mild to normal range of Factor VIII activity as defined by the World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of July 31, 2017). Factor VIII levels are determined by one-stage assay.
Source: BioMarin Pharmaceutical.

Exhibit 20: **Summary of Mean Annualized Bleeding Rate (ABR) and FVIII Infusions of $4x10^{13}$ vg/kg Dose Patients Previously on Prophylaxis (N=6) up to 32 Weeks**

	Before BMN-270 Infusion**	**After BMN-270 Infusion*****
	Mean (median, SD)	**Mean (median, SD)**
Annualized Bleeding Rate* (bleeding episodes per year per subject)	12.2 (8.0, 15.4)	1.0 (0.0, 2.3)
Annualized FVIII Infusions* (infusions per year per subject)	144.2 (155.5, 43.3)	4.8 (0.0, 11.6)

Notes: * Post-infusion data were based on data after Factor VIII levels were above 5%; **Obtained from medical records; ***5 of 6 patients had 0 bleeds requiring Factor VIII infusions after Factor VIII levels were above 5%.
Source: BioMarin Pharmaceutical.

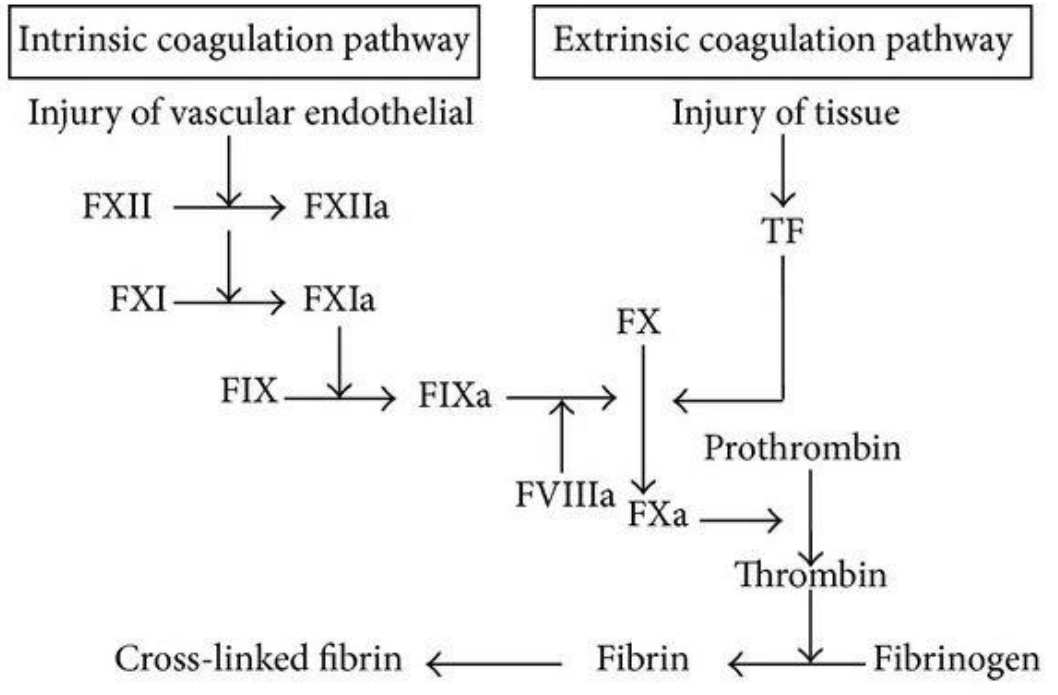
On the safety front, BMN-270 appeared to be well tolerated across all doses (including two patients tested at the lowest doses of $6x10^{12}$ vg/kg and $2x10^{13}$ vg/kg), with no patients having developed inhibitors to date and withdrawing from the study. In addition, none of the patients treated with a high dose of BMN-270 remained on steroid treatment. That said, there were two SAEs, with ALT and AST elevations seen in 73% (all Grade 1) and 47% of the patients, respectively.

Based on the updated results, BioMarin now plans to initiate two Phase III registrational studies evaluating two doses ($6x10^{13}$ vg/kg and $4x10^{13}$ vg/kg) of BMN-270 in 4Q17, respectively. While the design of this study has not been finalized, BioMarin indicated that each of the pivotal studies is likely to enroll <100 patients, with data collection no longer than one year after treatment.

Emicizumab – A Promising Drug Candidate for HA

Another notable drug candidate for HA that could be a potential competitor outside the gene therapy arena is emicizumab (Roche), a FIXa x FX bi-specific agonistic antibody designed to mimic FVIIIa to facilitate FIXa catalyzed FX activation (Exhibit 21). One important feature of emicizumab is that it cannot be neutralized by FVIII inhibitors due to its structural difference relative to FVIII. In a Phase III study (HAVEN 1) evaluating a prophylactic treatment of emicizumab dosed once per week in adults and teens with HA and inhibitors to FVIII, emicizumab successfully met the primary endpoint with a statistically significant reduction in ABR (87%, p<0.0001) compared with patients treated with on-demand bypassing agents (BPAs). In addition, emicizumab aced all the secondary endpoints including a statistically significant reduction in all bleeds (89%, p<0.0001), treated spontaneous bleeds (92%, p<0.0001), treated joint bleeds (89%, p=0.005), and treated target joint bleeds (95%, p=0.0002).

Exhibit 21: **The Coagulation Pathway**



Source: International Journal of Endocrinology; 2014; 2014: 731498; Ying Huang et al.; Changes in Coagulation and Fibrinolytic Indices in Women with Polycystic Ovarian Syndrome Undergoing Controlled Ovarian Hyperstimulation; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4211182/

Of note, 62.9% of patients who received emicizumab had no treated bleeds, which compared favorably with those (only 5.6%) who received on-demand BPAs during a median 31-week follow-up period. In a separate arm in this study, which enrolled patients who had prior prophylactic BPA treatment, emicizumab achieved a 79% reduction in ABR (p=0.0003) as compared to the prior prophylaxis with BPAs. Revealed from an interim analysis of a parallel Phase III study (HAVEN 2) evaluating a similar dose regimen and dosing schedule of emicizumab in children with HA and inhibitors to FVIII, only one child had a treated bleed among 19 emicizumab treated children during a median 12-week follow-up period. Additionally, no joint or muscle bleeds were seen among emicizumab treated children. Moreover, among eight children who received prior prophylaxis with BPAs or had prior on-demand BPAs, a 100% reduction in treated bleeds was achieved following the emicizumab treatment.

That said, one concern surrounding emicizumab is its safety profile. During the study, serious thromboembolic events and thrombotic microangiopathy (TMA) were seen in two and three patients, respectively. Additionally, one death occurred due to TMA, albeit the investigator concluded that it was not related to emicizumab.

Fitusiran – Targeting Hemophilia Through Rebalancing the Coagulation System

Fitusiran (ALN-AT3), developed by Alnylam Pharmaceuticals and currently in a Phase III study (ATLAS) for hemophilia, is a subcutaneously administered RNAi therapeutic consisting of a small interfering RNA-GalNAc conjugate targeting antithrombin (AT). Given that hemophilia is characterized by a genetic deficiency in clotting factors (FVIII for HA and FIX for HB) that ultimately leads to an inadequate thrombin generation, fitusiran could potentially correct the hemostatic imbalance in hemophilia by knocking down the endogenous anticoagulant AT, therefore adding weight to the other side of the equation, which leads to an increase in thrombin generation and a reduction in disease burden.

In an ongoing Phase II study evaluating the safety and efficacy of fitusiran in patients with hemophilia A (n=27, 13 have inhibitors) and hemophilia B (n=6, one has inhibitors), a monthly injection of fitusiran achieved a 95% and 100% reduction in the median ABR in all treated patients and patients with inhibitors, respectively. In addition, 48% and 67% of all treated patients (n=33) remained bleed-free and experienced zero spontaneous bleeds in the study seen to date. On the safety front, the majority of adverse events were mild or moderate in severity, with the most common adverse events being injection site reaction (18%). Asymptomatic and greater than 3x the upper limit of normal (ULN) increases in ALT occurred in 11 patients (33%), which resolved subsequently (10 of the 11 patients). Two possibly drug-related SAEs occurred: asymptomatic ALT elevation occurred in one patient who had a chronic HCV infection and discontinued the study, and a seizure with confusion occurred in one patient who had a prior history of seizure disorder.

Financial and Market Analysis

Revenues

IRD Due to RPE65 Mutation

IRD due to biallelic RPE65 mutations, US		2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with LCA		6,512	6,558	6,604	6,650	6,697	6,744	6,791	6,837	6,884	6,931	6,978	7,026	7,073	7,122	7,170	7,219	7,268	7,318
# of prevalent patients with RPE65 mutation related LCA		521	525	528	532	536	539	543	547	551	554	558	562	566	570	574	578	581	585
LCA incidence	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%
# of new LCA patients	100	100	101	102	102	103	104	105	105	106	107	107	108	109	110	110	111	112	113
% RPE65 mutation among LCA patients	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%
# of new patients with RPE65 mutation related LCA	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9
# of patients with RP		65,125	65,581	66,040	66,502	66,968	67,436	67,908	68,371	68,838	69,307	69,779	70,255	70,734	71,216	71,702	72,191	72,683	73,178
# of prevalent patients with RPE65 mutation related RP		1,302	1,312	1,321	1,330	1,339	1,349	1,358	1,367	1,377	1,386	1,396	1,405	1,415	1,424	1,434	1,444	1,454	1,464
RP incidence	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%
# of new RP patients	1,000	1,003	1,010	1,017	1,024	1,031	1,038	1,045	1,053	1,060	1,067	1,074	1,082	1,089	1,096	1,104	1,111	1,119	1,127
% RPE65 mutation among new RP patients	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
# of new patients with RPE65 mutation related RP	20	20	20	20	20	21	21	21	21	21	21	21	22	22	22	22	22	22	23
Total # of new patients with RPE65 mutation associated IRDs (LCA and RP)		28	28	28	29	29	29	29	29	30	30	30	30	30	31	31	31	31	32
Total # of prevalent patients with RPE65 mutation associated IRDs (LCA and RP)		1,823	1,836	1,849	1,862	1,875	1,888	1,901	1,914	1,927	1,941	1,954	1,967	1,981	1,994	2,008	2,021	2,035	2,049
Total # of prevalent patients eligible for LUXTURNA		1,459	1,469	1,479	1,490	1,500	1,511	1,521	1,532	1,542	1,552	1,563	1,574	1,584	1,595	1,606	1,617	1,628	1,639
# of patients for LUXTURNA at peak		1,021	1,028	1,036	1,043	1,050	1,057	1,065	1,072	1,079	1,087	1,094	1,102	1,109	1,117	1,124	1,132	1,140	1,147
# of treated new patients			105	210	315	420	20	20	21	21	21	21	21	21	21	22	22	22	22
Accumulated # of treated patients			105	315	630	1,050	1,070	1,091	1,112	1,132	1,153	1,174	1,195	1,217	1,238	1,260	1,282	1,304	1,326
Market penetration of prevalence			7%	21%	42%	70%	71%												
Total market opportunity ('000)		$ 1,458,798	$ 1,469,009	$ 1,479,292	$ 1,489,647	$ 1,500,075	$ 1,510,575	$ 1,521,149	$ 1,531,520	$ 1,541,961	$ 1,552,473	$ 1,563,056	$ 1,573,712	$ 1,584,441	$ 1,595,243	$ 1,606,118	$ 1,617,067	$ 1,628,092	$ 1,639,191
Peak market opportunity ('000)	70%	$ 1,021,158	$ 1,028,306	$ 1,035,505	$ 1,042,753	$ 1,050,052	$ 1,057,403	$ 1,064,805	$ 1,072,064	$ 1,079,372	$ 1,086,731	$ 1,094,140	$ 1,101,599	$ 1,109,109	$ 1,116,670	$ 1,124,283	$ 1,131,947	$ 1,139,664	$ 1,147,434
sales of LUXTURNA ('000)			$ 105,005	$ 210,010	$ 315,016	$ 420,021	$ 20,349	$ 20,491	$ 20,632	$ 20,773	$ 20,915	$ 21,057	$ 21,201	$ 21,345	$ 21,491	$ 21,637	$ 21,785	$ 21,933	$ 22,083
Risk adjusted US revenues from LUXTURNA ('000)			90,725	181,449	272,174	362,898	17,581	17,704	17,826	17,948	18,070	18,193	18,317	18,442	18,568	18,695	18,822	18,950	19,080

IRD due to biallelic RPE65 mutations, EU		2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with LCA		10,240	10,271	10,302	10,332	10,363	10,395	10,426	10,455	10,484	10,514	10,543	10,573	10,602	10,632	10,632	10,632	10,632	10,632
# of prevalent patients with RPE65 mutation related LCA		819	822	824	827	829	832	834	836	839	841	843	846	848	851	851	851	851	851
LCA incidence	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%	0.000031%
# of new LCA patients	158	158	158	159	159	160	160	161	161	162	162	163	163	163	164	164	164	164	164
% RPE65 mutation among LCA patients	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%
# of new patients with RPE65 mutation related LCA	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
# of patients with RP		102,400	102,707	103,015	103,324	103,634	103,945	104,257	104,549	104,842	105,136	105,431	105,727	106,023	106,320	106,320	106,320	106,320	106,320
# of prevalent patients with RPE65 mutation related RP		2,048	2,054	2,060	2,066	2,073	2,079	2,085	2,091	2,097	2,103	2,109	2,115	2,120	2,126	2,126	2,126	2,126	2,126
RP incidence	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%	0.00031%
# of new RP patients	1,577	1,579	1,584	1,588	1,593	1,598	1,603	1,607	1,612	1,617	1,621	1,626	1,630	1,635	1,639	1,641	1,641	1,641	1,641
% RPE65 mutation among new RP patients	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
# of new patients with RPE65 mutation related RP	32	32	32	32	32	32	32	32	32	32	32	33	33	33	33	33	33	33	33
Total # of new patients with RPE65 mutation associated IRDs (LCA and RP)		44	44	44	45	45	45	45	45	45	45	46	46	46	46	46	46	46	46
Total # of prevalent patients with RPE65 mutation associated IRDs (LCA and RP)		2,867	2,876	2,884	2,893	2,902	2,910	2,919	2,927	2,936	2,944	2,952	2,960	2,969	2,977	2,977	2,977	2,977	2,977
Total # of prevalent patients eligible for LUXTURNA		2,294	2,301	2,308	2,314	2,321	2,328	2,335	2,342	2,348	2,355	2,362	2,368	2,375	2,382	2,382	2,382	2,382	2,382
# of patients for LUXTURNA at peak		1,606	1,610	1,615	1,620	1,625	1,630	1,635	1,639	1,644	1,649	1,653	1,658	1,662	1,667	1,667	1,667	1,667	1,667
# of treated new patients			20	143	326	489	652	32	32	32	32	32	32	32	32	32	32	32	32
Accumulated # of treated patients			20	163	489	978	1,630	1,661	1,693	1,725	1,756	1,788	1,820	1,852	1,884	1,917	1,949	1,981	2,013
Market penetration of prevalence			1%	7%	21%	42%	70%	71%	72%	73%	75%	76%	77%	78%	79%	80%	82%	83%	85%
Total market opportunity ('000)		$ 1,835,010	$ 1,840,515	$ 1,846,036	$ 1,851,574	$ 1,857,129	$ 1,862,701	$ 1,868,289	$ 1,873,525	$ 1,878,777	$ 1,884,043	$ 1,889,324	$ 1,894,619	$ 1,899,930	$ 1,905,255	$ 1,905,255	$ 1,905,255	$ 1,905,255	$ 1,905,255
Peak market opportunity ('000)		$ 1,284,507	$ 1,288,360	$ 1,292,225	$ 1,296,102	$ 1,299,990	$ 1,303,890	$ 1,307,802	$ 1,311,468	$ 1,315,144	$ 1,318,830	$ 1,322,527	$ 1,326,234	$ 1,329,951	$ 1,333,679	$ 1,333,679	$ 1,333,679	$ 1,333,679	$ 1,333,679
sales of LUXTURNA ('000)			$ 16,000	$ 114,389	$ 260,778	$ 391,167	$ 521,556	$ 25,205	$ 25,278	$ 25,348	$ 25,419	$ 25,491	$ 25,562	$ 25,634	$ 25,706	$ 25,733	$ 25,733	$ 25,733	$ 25,733
Risk adjusted EU revenues from LUXTURNA ('000)			13,824	98,832	225,312	337,968	450,625	21,777	21,840	21,901	21,962	22,024	22,086	22,148	22,210	22,233	22,233	22,233	22,233
Total risk adjusted Revenue for LUXTURNA (U.S. and EU) ('000)			104,549	280,281	497,486	700,867	468,206	39,482	39,666	39,849	40,033	40,217	40,403	40,590	40,778	40,928	41,055	41,183	41,313

IRD due to RPE65 mutation	Key assumptions	Rationale
LCA prevalence	0.002%	Literature review
LCA incidence rate	2.5/100,000	Literature review
Portion of LCA patients with RPE65 mutation	8%	Literature review
RP prevalence	0.02%	Literature review
Portion of RP patients with RPE65 mutation	2%	Company guidance
Portion of patients who have required photoreceptors to potentially benefit from LUXTURNA	80%	According to the company, about 80% of patients who have the required viable photoreceptors can benefit from this gene therapy
Total number of eligible patients for LUXTURNA in 2017 (US and EU)	3,753	Patients with RPE65 mutation caused LCA and RP who also have a required level of photoreceptors
Pricing of LUXTURNA	$1 million (US), $0.8 million (EU)	One-time upfront payment; based on the price of Glybera of ~$1 million in Germany and the price of Strimvelis of ~$665K in Europe
Market share at peak	70%	No approved therapeutics so far; MeiraGTx is currently conducting a Phase I study of RPE65 gene therapy for LCA2. Given that Spark's LUXTURNA is in a far more advanced stage, we assign a higher market share to LUXTURNA
Drug Risk	90%	BLA submitted, given the totality of the efficacy and safety profile of LUXTURNA seen to date, we are confident about its approval and thereby assign a high probability of success
Commercialization time	2Q18 (US), 3Q18 (EU)	Company guidance and our estimate
Commercial rights	worldwide	We assume Spark will be in charge of a worldwide commercialization of LUXTURNA given the ultra-orphan status of the disease (very few number of patients)

Source: Raymond James research.

Choroideremia

Choroideremia, US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with choroideremia	4,342	4,372	4,403	4,433	4,465	4,496	4,527	4,558	4,589	4,620	4,652	4,684	4,716	4,748	4,780	4,813	4,846	4,879
Total # of prevalent patients eligible for SPK-7001	3,473	3,498	3,522	3,547	3,572	3,597	3,622	3,646	3,671	3,696	3,722	3,747	3,772	3,798	3,824	3,850	3,876	3,903
Total # of new patients eligible for SPK-7001	52	52	53	53	53	54	54	55	55	55	56	56	56	57	57	58	58	58
# of patients for SPK-7001 at peak	1,389	1,399	1,409	1,419	1,429	1,439	1,449	1,459	1,469	1,479	1,489	1,499	1,509	1,519	1,530	1,540	1,551	1,561
# of treated new patients							5	144	298	447	595	22	23	23	23	23	23	23
Accumulated # of treated patients							5	149	447	893	1,489	1,511	1,534	1,556	1,579	1,602	1,625	1,649
Total market opportunity ('000)	$ 3,473,328	$ 3,497,641	$ 3,522,125	$ 3,546,780	$ 3,571,607	$ 3,596,608	$ 3,621,784	$ 3,646,475	$ 3,671,335	$ 3,696,364	$ 3,721,563	$ 3,746,934	$ 3,772,478	$ 3,798,197	$ 3,824,091	$ 3,850,161	$ 3,876,409	$ 3,902,836
Peak market opportunity ('000)	$ 1,389,331	$ 1,399,056	$ 1,408,850	$ 1,418,712	$ 1,428,643	$ 1,438,643	$ 1,448,714	$ 1,458,590	$ 1,468,534	$ 1,478,545	$ 1,488,625	$ 1,498,774	$ 1,508,991	$ 1,519,279	$ 1,529,636	$ 1,540,064	$ 1,550,563	$ 1,561,134
sales of SPK-7001 ('000)							$ 5,000	$ 143,863	$ 297,725	$ 446,588	$ 595,450	$ 22,424	$ 22,577	$ 22,731	$ 22,886	$ 23,042	$ 23,199	$ 23,357
Market penetration of prevalence							0.1%	4%	12%									
Risk adjusted US revenues from SPK-7001 ('000)							1,200	34,527	71,454	107,181	142,908	5,382	5,419	5,455	5,493	5,530	5,568	5,606

Choroideremia, EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with choroideremia	6,827	6,847	6,868	6,888	6,909	6,930	6,950	6,970	6,989	7,009	7,029	7,048	7,068	7,088	7,088	7,088	7,088	7,088
Total # of prevalent patients eligible for SPK-7001	5,461	5,478	5,494	5,511	5,527	5,544	5,560	5,576	5,592	5,607	5,623	5,639	5,655	5,670	5,670	5,670	5,670	5,670
Total # of new patients eligible for SPK-7001	82	82	82	83	83	83	83	84	84	84	84	84	85	85	85	85	85	85
# of patients for SPK-7001 at peak	2,185	2,191	2,198	2,204	2,211	2,218	2,224	2,230	2,237	2,243	2,249	2,255	2,262	2,268	2,268	2,268	2,268	2,268
# of treated new patients								5	221	451	677	902	34	34	34	34	34	34
Accumulated # of treated patients							0	5	226	677	1,353	2,255	2,289	2,323	2,357	2,391	2,425	2,459
Total market opportunity ('000)	$ 4,369,071	$ 4,382,178	$ 4,395,325	$ 4,408,511	$ 4,421,736	$ 4,435,001	$ 4,448,306	$ 4,460,775	$ 4,473,278	$ 4,485,816	$ 4,498,390	$ 4,510,999	$ 4,523,643	$ 4,536,322	$ 4,536,322	$ 4,536,322	$ 4,536,322	$ 4,536,322
Peak market opportunity ('000)	$ 1,747,628	$ 1,752,871	$ 1,758,130	$ 1,763,404	$ 1,768,694	$ 1,774,001	$ 1,779,323	$ 1,784,310	$ 1,789,311	$ 1,794,327	$ 1,799,356	$ 1,804,399	$ 1,809,457	$ 1,814,529	$ 1,814,529	$ 1,814,529	$ 1,814,529	$ 1,814,529
sales of SPK-7001 ('000)								$ 4,000	$ 176,440	$ 360,880	$ 541,320	$ 721,760	$ 27,113	$ 27,189	$ 27,218	$ 27,218	$ 27,218	$ 27,218
Market penetration of prevalence								0%	4%	12%								
Risk adjusted EU revenues from SPK-7001 ('000)								960	42,346	86,611	129,917	173,222	6,507	6,525	6,532	6,532	6,532	6,532
Total risk adjusted revenues from SPK-7011 (U.S. and EU)							1,200	35,487	113,800	193,792	272,825	178,604	11,926	11,981	12,025	12,062	12,100	12,138
Total risk adjusted revenues from the IRD franchise (U.S. and EU)		$ 104,549	$ 280,281	$ 497,486	$ 700,867	$ 468,206	$ 40,682	$ 75,153	$ 153,648	$ 233,825	$ 313,042	$ 219,007	$ 52,516	$ 52,759	$ 52,953	$ 53,118	$ 53,284	$ 53,451

Choroideremia	Key assumptions	Rationale
Choroideremia prevalence	0.0013%	Literature review
Portion of patients who have required photoreceptors to potentially benefit from SPK-7001	80%	Similar to the rationale of LUXTURNA
Total number of eligible patients for SPK-7001 in 2017 (US and EU)	8,935	Patients with REP-1 mutation caused Choroideremia who also have a required level of photoreceptors
Pricing of SPK-7001	$1 million (US), $0.8 million (EU)	Similar to the rationale of LUXTURNA
Market share at peak	40%	NightstaRx plans to initiate a Phase III study of a gene therapy (NSR AAV-REP1) for the same indication. Given that Spark's SPK-7001 is in an early clinical stage, we assign a lower market share to SPK-7001
Drug risk	25%	Given the early stage of the program and a lack of efficacy in late stage Choroideremia seen to date, assuming 25% chance of success
Commercialization time	4Q23 (US), 4Q24 (EU)	Company guidance and our estimate
Commercial rights	worldwide	We assume Spark will be in charge of a worldwide commercialization of SPK-7001 given the ultra-orphan status of the disease (very few number of patients)

Source: Raymond James research.

Hemophilia A

SPK-8011 for Hemophilia A, US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with HA	20,105	20,246	20,387	20,530	20,674	20,818	20,964	21,107	21,251	21,396	21,542	21,689	21,836	21,985	22,135	22,286	22,438	22,591
# of patients with severe and moderate HA	10,052	10,123	10,194	10,265	10,337	10,409	10,482	10,554	10,625	10,698	10,771	10,844.27	10,918.20	10,992.64	11,067.58	11,143.03	11,218.99	11,295.48
# of patients without inhibitor to FVIII	8,545	8,604	8,665	8,725	8,786	8,848	8,910	8,970	9,032	9,093	9,155	9,218	9,280	9,344	9,407	9,472	9,536	9,601
# of patients without or with mild antibody to the vector	5,981	6,023	6,065	6,108	6,150	6,193	6,237	6,279	6,322	6,365	6,409	6,452	6,496	6,541	6,585	6,630	6,675	6,721
% market share							2%	6%	13%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Accumulated # of patients on therapy							125	376.76	822	1,591	1,602	1,613	1,624	1,635	1,646	1,658	1,669	1,680
Total market opportunity ('000)	$ 2,392,473	$ 2,409,220	$ 2,426,085	$ 2,443,068	$ 2,460,169	$ 2,477,390	$ 2,494,732	$ 2,511,739	$ 2,528,863	$ 2,546,103	$ 2,563,461	$ 2,580,937	$ 2,598,532	$ 2,616,247	$ 2,634,083	$ 2,652,041	$ 2,670,120	$ 2,688,324
Peak market opportunity ('000)	$ 598,118	$ 602,305	$ 606,521	$ 610,767	$ 615,042	$ 619,348	$ 623,683	$ 627,935	$ 632,216	$ 636,526	$ 640,865	$ 645,234	$ 649,633	$ 654,062	$ 658,521	$ 663,010	$ 667,530	$ 672,081
Sales of SPK-8011 ('000)							$ 49,895	$ 150,704	$ 328,752	$ 636,526	$ 640,865	$ 645,234	$ 649,633	$ 654,062	$ 658,521	$ 663,010	$ 667,530	$ 672,081
Market penetration							2%	6%	13%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Risk adjusted US revenues from SPK-8011 ('000)	0	0	0	0	0	0	29,937	90,423	197,251	381,915	384,519	387,141	389,780	392,437	395,112	397,806	400,518	403,249

SPK-8011 for Hemophilia A, EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with HA	40,960	41,083	41,206	41,330	41,454	41,578	41,703	41,820	41,937	42,055	42,172	42,291	42,409	42,528	42,528	42,528	42,528	42,528
# of patients with severe and moderate HA	20,480	20,541	20,603	20,665	20,727	20,789	20,851	20,910	20,968	21,027	21,086	21,145	21,205	21,264	21,264	21,264	21,264	21,264
# of patients without inhibitor to FVIII	17,408	17,460	17,513	17,565	17,618	17,671	17,724	17,773	17,823	17,873	17,923	17,974	18,024	18,074	18,074	18,074	18,074	18,074
# of patients without or with mild antibody to the vector	12,186	12,222	12,259	12,296	12,332	12,369	12,407	12,441	12,476	12,511	12,546	12,581	12,617	12,652	12,652	12,652	12,652	12,652
% market share								2%	6%	13%	25%	25%	25%	25%	25%	25%	25%	25%
Accumulated # of patients on therapy								249	748.58	1,626.46	3,137	3,145	3,154	3,163	3,163	3,163	3,163	3,163
Total market opportunity ('000)	$ 4,874,245	$ 4,888,867	$ 4,903,534	$ 4,918,245	$ 4,932,999	$ 4,947,798	$ 4,962,642	$ 4,976,552	$ 4,990,501	$ 5,004,489	$ 5,018,516	$ 5,032,583	$ 5,046,689	$ 5,060,834	$ 5,060,834	$ 5,060,834	$ 5,060,834	$ 5,060,834
Peak market opportunity ('000)	$ 1,218,561	$ 1,222,217	$ 1,225,884	$ 1,229,561	$ 1,233,250	$ 1,236,950	$ 1,240,660	$ 1,244,138	$ 1,247,625	$ 1,251,122	$ 1,254,629	$ 1,258,146	$ 1,261,672	$ 1,265,209	$ 1,265,209	$ 1,265,209	$ 1,265,209	$ 1,265,209
Sales of SPK-8011 ('000)								$ 99,531	$ 299,430	$ 650,584	$ 1,254,629	$ 1,258,146	$ 1,261,672	$ 1,265,209	$ 1,265,209	$ 1,265,209	$ 1,265,209	$ 1,265,209
Market penetration								2%	6%	13%	25%	25%	25%	25%	25%	25%	25%	25%
Risk adjusted EU revenues from SPK-8011 ('000)								59,719	179,658	390,350	752,777	754,887	757,003	759,125	759,125	759,125	759,125	759,125
Total risk adjusted revenues from SPK-8011 for HA ('000)							29,937	150,141	376,909	772,266	1,137,297	1,142,028	1,146,783	1,151,562	1,154,238	1,156,931	1,159,643	1,162,374

Hemophilia A (HA)	Key assumptions	Rationale
HA prevalence	0.0062%	Literature review
Portion of patients with moderate to severe HA	50%	Literature review
Portion patients without inhibitors to Factor VIII	85%	Literature review
Portion patients without or with mild neutralizing antibodies to Spark's vector	70%	Company guidance
Total number of eligible patients for SPK-8011 in 2017 (US and EU)	18,167	Based on our calculation after considering the previously mentioned statistics of HA subpopulations.
Pricing of SPK-8011	$0.4 million (U.S.) $0.32 million (EU)	Annuity payment; Based on our literature search an annual cost of $301,392 was required for patients with severe hemophilia receiving prophylaxis (without inhibitors).
Market share at peak	25%	Multiple factor products are on the market as well as multiple gene therapy candidates are in the pipeline
Drug risk	60%	Given the safety and efficacy data of SPK-8011 seen to date
Commercialization time	1Q23 (US), 1Q24 (EU)	Based on company guidance, BMN-270's development timeline, and our estimate
Commercial rights	worldwide	We assume Spark will be in charge of a worldwide commercialization of SPK-8011 given the orphan status of the subpopulation of HA patients whom the company expects to target

Source: Raymond James research.

Hemophilia B

SPK-9001 for Hemophilia B, US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with HB	5,026	5,061	5,097	5,132	5,168	5,205	5,241	5,277	5,313	5,349	5,385	5,422	5,459	5,496	5,534	5,572	5,609	5,648
# of eligible patients with severe and moderate HB	2,513	2,531	2,548	2,566	2,584	2,602	2,621	2,638	2,656	2,674	2,693	2,711	2,730	2,748	2,767	2,786	2,805	2,824
# of patients without inhibitor to FIX	2,136	2,151	2,166	2,181	2,197	2,212	2,227	2,243	2,258	2,273	2,289	2,304	2,320	2,336	2,352	2,368	2,384	2,400
# of patients without or with mild antibody to the vector	1,495	1,506	1,516	1,527	1,538	1,548	1,559	1,570	1,581	1,591	1,602	1,613	1,624	1,635	1,646	1,658	1,669	1,680
% market share					10%	20%	35%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%
Accumulated # of patients on therapy					154	310	546	942	948	955	961	968	974	981	988	995	1,001	1,008
Total market opportunity ('000)	$ 598,118	$ 602,305	$ 606,521	$ 610,767	$ 615,042	$ 619,348	$ 623,683	$ 627,935	$ 632,216	$ 636,526	$ 640,865	$ 645,234	$ 649,633	$ 654,062	$ 658,521	$ 663,010	$ 667,530	$ 672,081
Peak market opportunity ('000)	$ 358,871	$ 361,383	$ 363,913	$ 366,460	$ 369,025	$ 371,609	$ 374,210	$ 376,761	$ 379,329	$ 381,915	$ 384,519	$ 387,141	$ 389,780	$ 392,437	$ 395,112	$ 397,806	$ 400,518	$ 403,249
Sales of SPK-9001 ('000)					$ 61,504	$ 123,870	$ 218,289	$ 376,761	$ 379,329	$ 381,915	$ 384,519	$ 387,141	$ 389,780	$ 392,437	$ 395,112	$ 397,806	$ 400,518	$ 403,249
Market penetration					10%	20%	35%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%
Risk adjusted US revenues from SPK-9001 ('000)					43,053	86,709	152,802	263,733	265,531	267,341	269,163	270,998	272,846	274,706	276,579	278,464	280,363	282,274
Risk adjusted US royalty revenues from SPK-9001 ('000)					5,166	10,405	18,336	31,648	31,864	32,081	32,300	32,520	32,742	32,965	33,189	33,416	33,644	33,873

SPK-9001 for Hemophilia B, EU	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
# of patients with HB	7,903	7,927	7,951	7,974	7,998	8,022	8,046	8,069	8,092	8,114	8,137	8,160	8,183	8,206	8,206	8,206	8,206	8,206
# of eligible patients with severe and moderate HB	3,952	3,963	3,975	3,987	3,999	4,011	4,023	4,034	4,046	4,057	4,068	4,080	4,091	4,103	4,103	4,103	4,103	4,103
# of patients without inhibitor to FIX	3,833	3,369	3,379	3,389	3,399	3,409	3,420	3,429	3,439	3,449	3,458	3,468	3,478	3,487	3,487	3,487	3,487	3,487
# of patients without or with mild antibody to the vector	2,683	2,358	2,365	2,372	2,379	2,387	2,394	2,400	2,407	2,414	2,421	2,428	2,434	2,441	2,441	2,441	2,441	2,441
% market share						10%	20%	35%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%
Accumulated # of patients on therapy						239	479	840	1,444	1,448	1,452	1,457	1,461	1,465	1,465	1,465	1,465	1,465
Total market opportunity ('000)	$ 858,585	$ 754,625	$ 756,889	$ 759,160	$ 761,437	$ 763,722	$ 766,013	$ 768,160	$ 770,313	$ 772,472	$ 774,637	$ 776,809	$ 778,986	$ 781,169	$ 781,169	$ 781,169	$ 781,169	$ 781,169
Peak market opportunity ('000)	$ 515,151	$ 452,775	$ 454,133	$ 455,496	$ 456,862	$ 458,233	$ 459,608	$ 460,896	$ 462,188	$ 463,483	$ 464,782	$ 466,085	$ 467,392	$ 468,702	$ 468,702	$ 468,702	$ 468,702	$ 468,702
Sales of SPK-9001 ('000)						$ 76,372	$ 153,203	$ 268,856	$ 462,188	$ 463,483	$ 464,782	$ 466,085	$ 467,392	$ 468,702	$ 468,702	$ 468,702	$ 468,702	$ 468,702
Market penetration						10%	20%	35%	60%	60%	60%	60%	60%	60%	60%	60%	60%	60%
Risk adjusted EU revenues from SPK-9001 ('000)						53,461	107,242	188,199	323,531	324,438	325,348	326,260	327,174	328,091	328,091	328,091	328,091	328,091
Risk adjusted EU royalty revenues from SPK-9001 ('000)						6,415	12,869	22,584	38,824	38,933	39,042	39,151	39,261	39,371	39,371	39,371	39,371	39,371
Total risk adjusted royalties from SPK-9001 in HB ('000)					5,166	16,820	31,205	54,232	70,687	71,013	71,341	71,671	72,002	72,336	72,560	72,787	73,014	73,244

Hemophilia B (HB)	Key assumptions	Rationale
HB prevalence	0.0015%	Literature review
Portion of patients with moderate to severe HB	50%	Literature review
Portion patients without inhibitors to Factor IX	97%	Literature review
Portion patients without or with mild neutralizing antibodies to Spark's vector	70%	Company estimation
Total number of eligible patients for SPK-9011 in 2017 (US and EU)	4,178	Based on our calculation after considering the previously mentioned statistics of HB subpopulations.
Pricing of SPK-9001	$0.4 million (U.S.) $0.32 million (EU)	Similar to the rationale of SPK-8011 for hemophilia A
Market share at peak	60%	Multiple factor products are on the market; SPK-9001 has demonstrated a better safety and efficacy profile than UniQure's product candidate
Drug Risk	70%	Given the safety and efficacy data of SPK-9001 seen to date
Commercialization time	1Q21 (US), 1Q22 (EU)	Based on company guidance and our estimate
Commercial rights	Pfizer (a 12% royalty rate to Spark)	Company deal terms

Source: Raymond James research.

Operating Expenses

Building off of the R&D expense reported for 2Q17, we are projecting R&D expenses of $137 million for 2017, increasing to $379 million for 2021. The R&D assumptions from 2017 to 2021 take into account continued expenditure for the clinical trials associated with the company's retinal diseases and hemophilia franchise.

Based on the SG&A expense reported for 2Q17, we are projecting SG&A expenses of $103 million for 2017, increasing to $131 million for 2021. These estimates reflect a ramp in the growth associated with the assumption of hiring a 20-person sales force starting in 2H17 ahead of the potential U.S. commercial launch of LUXTURNA in 2018.

The COGS for LUXTURNA, SPK-8011, and SPK-7001 are expected to be 5% of the revenues from the corresponding product.

Net Income and EPS

The net income for 2Q17 was $(74.4) million, or $(2.40) per share. We are projecting net income of $(252.7) million or $(7.51) per diluted share in 2017, increasing to $267.8 million or $6.24 per diluted share in 2021.

Cash

Based on our estimates, we expect a cash burn rate of approximately $47.6 million to $51.0 million per quarter for the full-year 2017, and we believe the current cash position is sufficient to fund operations into the year of profitability (2019).

Valuation and Price Target Analysis

Valuation

We value Spark Therapeutics using a sum-of-the-parts analysis of four programs: 1) LUXTURNA for RPE65-mediated IRDs; 2) SPK-8011 for hemophilia A; 3) SPK-7001 for Choroideremia; and 4) SPK-9001 for hemophilia B (royalties only). To derive a value for each of these programs, we conduct a risk-adjusted net present value (rNPV) analysis, which utilizes the net income as a proxy of the free cash flow (FCF). The revenues for each product are derived from our market models (see pages 166-170 for more detail), whereas the R&D and SG&A expenses are estimated largely based on the number of patients on clinical trials and the size of a sales force, respectively. To calculate the NPV, the approximate FCF based on the net income for any given year is discounted at a rate of 10% back to the present time. To account for the clinical/regulatory risk, the NPV is further multiplied by a probability of success assigned to each program. Using this methodology, we derive a risk-adjusted per share NPV of $30.17, $42.30, $5.09, and $4.99 for LUXTURNA, SPK-8011, SPK-7001, and SPK-9001, respectively. Combining these values with the cash value of $13.76 per share, we derive a price target of $96.32, which we round to $96.

Exhibit 22: **Valuation Analysis**

Product	POS	Per share value	Weighting
LUXTURNA for RPE65 mediated IRDs	90%	30.17	31%
SPK-8011 for hemophilia A	60%	42.30	44%
SPK-7001 for Choroideremia	25%	5.09	5%
SPK-9001 for hemophilia B (royalties only)	70%	4.99	5%
Cash	N/A	13.76	14%
Total		96.32	

Key assumptions

Discount rate	10%
Fully diluted shares outstanding (‘000)	41,515

Source: Raymond James research.

Exhibit 23: **rNPV of LUXTURNA**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034
Revenues (risk-unadjusted, '000)	$ -	$ 114,605	$ 330,800	$ 575,794	$ 811,188	$ 541,905	$ 45,696	$ 45,910	$ 46,121	$ 46,334	$ 46,548	$ 46,763	$ 46,979	$ 47,196	$ 47,370	$ 47,517	$ 47,666	$ 47,815
COGS (including royalties to be paid)	-	5,730	16,540	28,790	40,559	27,095	2,285	2,295	2,306	2,317	2,327	2,338	2,349	2,360	2,368	2,376	2,383	2,391
R&D	12,131	8,460	16,540	28,790	40,559	27,095	2,285	2,295	2,306	2,317	2,327	2,338	2,349	2,360	2,368	2,376	2,383	2,391
SGA	21,236	45,884	50,341	52,847	54,993	33,742	11,417	11,647	11,882	12,121	12,365	12,614	12,869	13,128	13,264	13,305	13,346	13,388
Income before tax	(33,367)	54,531	247,379	465,367	675,077	453,973	29,710	29,672	29,628	29,580	29,528	29,472	29,413	29,349	29,369	29,461	29,553	29,646
Tax	-	-	-	-	-	-	-	-	-	5,916	5,906	5,894	5,883	5,870	5,874	5,892	5,911	5,929
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Approximate FCF (net income)	(33,367)	54,531	247,379	465,367	675,077	453,973	29,710	29,672	29,628	23,664	23,622	23,578	23,530	23,479	23,495	23,569	23,642	23,716
Present time	10/9/2017																	
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23
Discount rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
NPV	(32,650)	48,509	200,055	342,129	451,184	275,828	16,410	14,899	13,525	9,820	8,912	8,086	7,336	6,655	6,054	5,521	5,035	4,591
Total NPV ('000)	1,391,900																	
Fully diluted shares outstanding ('000)	41,515																	
Per share value	33.53																	
Probability of success	90%																	
Risk-adjusted per share value	**30.17**																	

Source: Raymond James research.

Exhibit 24: **rNPV of SPK-8011**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ -	$ 49,895	$ 250,235	$ 628,182	$ 1,287,109	$ 1,895,494	$ 1,903,380	$ 1,911,305	$ 1,919,270	$ 1,923,729	$ 1,928,219	$ 1,932,739	$ 1,937,289
COGS (including royalties to be paid)	-	-	-	-	-	-	2,495	12,512	31,409	64,355	94,775	95,169	95,565	95,964	96,186	96,411	96,637	96,864
R&D	21,447	81,739	92,089	156,897	209,326	64,701	67,328	70,062	72,906	75,867	78,947	82,153	85,488	88,960	89,166	89,374	89,584	89,795
SGA	6,402	13,193	13,729	14,287	16,406	25,285	54,419	97,770	117,790	122,573	75,772	76,135	76,452	76,771	76,949	77,129	77,310	77,492
Income before tax	(27,849)	(94,933)	(105,818)	(171,184)	(225,732)	(89,986)	(74,347)	69,892	406,077	1,024,315	1,646,000	1,649,923	1,653,799	1,657,576	1,661,427	1,665,305	1,669,208	1,673,139
Tax	-	-	-	-	-	-	-	-	-	204,863	329,200	329,985	330,760	331,515	332,285	333,061	333,842	334,628
Tax rate	0%	0%	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Approximate FCF (net income)	(27,849)	(94,933)	(105,818)	(171,184)	(225,732)	(89,986)	(74,347)	69,892	406,077	819,452	1,316,800	1,319,938	1,323,039	1,326,061	1,329,142	1,332,244	1,335,367	1,338,511
Present time	10/9/2017																	
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23
Discount rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
NPV	(27,251)	(84,449)	(85,575)	(125,851)	(150,867)	(54,674)	(41,066)	35,096	185,370	340,064	496,781	452,695	412,508	375,864	342,488	312,079	284,374	259,130
Total NPV ('000)	2,926,715																	
Fully diluted shares outstanding ('000)	41,515																	
Per share value	70.50																	
Probability of success	60%																	
Risk-adjusted per share value	**42.30**																	

Source: Raymond James research.

Exhibit 25: **rNPV of SPK-7001**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ -	$ 5,000	$ 147,863	$ 474,165	$ 807,467	$ 1,136,770	$ 744,184	$ 49,691	$ 49,921	$ 50,104	$ 50,260	$ 50,417	$ 50,575
COGS (including royalties to be paid)	-	-	-	-	-	-	250	7,393	23,708	40,373	56,838	37,209	2,485	2,496	2,505	2,513	2,521	2,529
R&D	4,530	9,335	9,221	28,404	42,075	43,783	2,256	2,030	2,050	2,133	2,219	2,310	2,403	2,501	2,505	2,513	2,521	2,529
SGA	3,426	7,059	7,346	7,644	7,954	9,134	14,994	36,754	58,100	70,969	70,117	39,691	16,148	16,473	16,534	16,585	16,637	16,689
Income before tax	(7,956)	(16,394)	(16,567)	(36,048)	(50,029)	(52,918)	(12,499)	101,686	390,307	693,993	1,007,595	664,975	28,655	28,450	28,560	28,649	28,738	28,828
Tax	-	-	-	-	-	-	-	-	-	138,799	201,519	132,995	5,731	5,690	5,712	5,730	5,748	5,766
Tax rate	0%	0%	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Approximate FCF (net income)	(7,956)	(16,394)	(16,567)	(36,048)	(50,029)	(52,918)	(12,499)	101,686	390,307	555,194	806,076	531,980	22,924	22,760	22,848	22,919	22,991	23,063
Present time	10/9/2017																	
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23
Discount rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
NPV	(7,785)	(14,584)	(13,397)	(26,502)	(33,437)	(32,152)	(6,904)	51,060	178,171	230,400	304,103	182,451	7,147	6,451	5,887	5,369	4,896	4,465
Total NPV ('000)	845,640																	
Fully diluted shares outstanding ('000)	41,515																	
Per share value	20.37																	
Probability of success	25%																	
Risk-adjusted per share value	**5.09**																	

Source: Raymond James research.

Exhibit 26: **rNPV of SPK-9001**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ 7,381	$ 24,029	$ 44,579	$ 77,474	$ 100,982	$ 101,448	$ 101,916	$ 102,387	$ 102,861	$ 103,337	$ 103,658	$ 103,981	$ 104,306	$ 104,634
COGS (including royalties to be paid)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R&D	12,374.12	21,948	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SGA	7,709	11,855	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Income before tax	(20,083)	(33,804)	-	-	7,381	24,029	44,579	77,474	100,982	101,448	101,916	102,387	102,861	103,337	103,658	103,981	104,306	104,634
Tax	-	-	-	-	-	-	-	-	-	20,290	20,383	20,477	20,572	20,667	20,732	20,796	20,861	20,927
Tax rate	0%	0%	0%	0%	0%	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Approximate FCF (net income)	(20,083)	(33,804)	-	-	7,381	24,029	44,579	77,474	100,982	81,158	81,533	81,910	82,288	82,669	82,926	83,185	83,445	83,707
Present time	10/9/2017																	
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23
Discount rate	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
NPV	(19,652)	(30,071)	-	-	4,933	14,600	24,623	38,903	46,097	33,680	30,759	28,092	25,657	23,432	21,368	19,486	17,770	16,205
Total NPV ('000)	295,883																	
Fully diluted shares outstanding ('000)	41,515																	
Per share value	7.13																	
Probability of success	70%																	
Risk-adjusted per share value	**4.99**																	

Source: Raymond James research.

Bull/Bear Analysis

In our bull case, we assume higher probability of success for the company's four programs, which results in a value of about $118 per share, indicating a 38% return from the current level. In our bear case, we decrease the probability of success and derive a value of about $62, suggesting downside risk of 28%.

Exhibit 27: **Bull/Bear Analysis**

Probability of success of each program	Bull	Base	Bear
LUXTURNA for RPE65-mediated IRDs	100%	90%	70%
SPK-8011 for hemophilia A	80%	60%	30%
SPK-7001 for Choroideremia	40%	25%	0%
SPK-9001 for hemophilia B (royalties only)	90%	70%	50%
Valuation	$118	$96	$62
Return	38%	12%	-28%

Note: The closing price of 10/9/17 was used to calculate the potential returns
Source: Raymond James research.

Management

Jeffrey D. Marrazzo, Co-Founder and Chief Executive Officer

Jeff Marrazzo has led the creation and growth of Spark Therapeutics from a research center within the Children's Hospital of Philadelphia to a fully integrated gene therapy company. Mr. Marrazzo has led Spark in raising $1 billion in capital, establishing a global collaboration with Pfizer, and advancing multiple clinical programs including the successful Phase III trial of LUXTURNA and the subsequent BLA submission (accepted by the FDA). Prior to Spark, he helped build and sell the first genetic testing benefit management and pharmacogenomics medicines company to CVS Caremark. Previously, he served as an advisor to former Pennsylvania Governor Edward G. Rendell. Mr. Marrazzo is a member of the board of directors of BIO. He received a B.A. in economics and B.S.E. in systems science and engineering from the University of Pennsylvania. He also holds a dual MBA/MPA from The Wharton School of the University of Pennsylvania and Harvard University, a program which he founded.

Katherine A. High, M.D., President and Head of Research and Development

Dr. Kathy High is an accomplished hematologist with a longstanding interest and significant experience in gene therapy for genetic disease. Prior to Spark, she was the director of the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia and a member of the faculty at the University of Pennsylvania and of the medical staff at CHOP, where she was also an Investigator of the Howard Hughes Medical Institute. She served a five-year term on the FDA Advisory Committee on Cell, Tissue and Gene Therapies and is a past president of the American Society of Gene & Cell Therapy (ASGCT). She received her A.B. in chemistry from Harvard University, an M.D. from the University of North Carolina School of Medicine, a business certification from the University of North Carolina Business School Management Institute for Hospital Administrators and an M.A. from the University of Pennsylvania.

Federico Mingozzi, Ph.D., Chief Scientific Officer

Dr. Federico Mingozzi is the chief scientific officer at Spark Therapeutics, bringing two decades of experience in gene therapy, immunology, as well as biochemistry and molecular biology in both industry and academic settings. Dr. Mingozzi currently serves as faculty at the Pierre and Marie Curie University in Paris, France, and Universitat Autonoma de Barcelona, Spain. He received his bachelor's degree in biology and his Ph.D. in biochemistry and molecular biology from the University of Ferrara in Italy, and his MBA from Drexel University. Throughout his distinguished career, Dr. Mingozzi has received several awards and has contributed to more than 90 publications, including seminal findings in the field of AAV gene therapy.

Stephen Webster, Chief Financial Officer

Stephen Webster has nearly 30 years of experience as a financial professional in the life sciences industry. Prior to Spark Therapeutics, Mr. Webster was senior vice president of finance and chief financial officer at Optimer Pharmaceuticals, Inc., a commercial-stage company in the antibiotic field. Before that, he served in the same capacity at Adolor Corporation, a commercial-stage company in the gastrointestinal space. Mr. Webster played an integral role in the sale of both Optimer and Adolor to Cubist Pharmaceuticals, Inc. Prior to taking his first operating role, Mr. Webster spent 15 years as an investment banker to life sciences companies, raising more than $3 billion in financings and advising clients on more than $3 billion in aggregate mergers and acquisitions value. He received his A.B. in economics from Dartmouth College and his MBA in finance from The Wharton School of the University of Pennsylvania.

Daniel R. Faga, Chief Business Officer

Dan Faga has 15 years of biopharma industry experience. Prior to joining Spark Therapeutics, he was a managing director at Centerview Partners, where he served as a founding member of Centerview's healthcare advisory practice. Primarily focused in the life sciences sector, Mr. Faga has extensive expertise in corporate strategy, mergers and acquisitions, and partnering, and he has advised on more than $50 billion in biopharma transactions. Prior to Centerview, Mr. Faga worked at Merrill Lynch in its healthcare investment banking group and as a management consultant in the life sciences practice at PRTM. Mr. Faga earned a B.S. in engineering from Cornell University and an MBA in healthcare management from The Wharton School of the University of Pennsylvania.

John Furey, Chief Operating Officer

John Furey is responsible for global commercial operations, medical affairs, technology development, and technical operations at Spark Therapeutics. He has 25 years of experience in developing and implementing operational strategies and leading commercial and technical teams. Prior to Spark, Mr. Furey was senior vice president and head of global operations for Baxalta, where he directed manufacturing, quality, engineering, and process development. He actively managed a $2.5 billion production budget across Baxalta's global network and led a first-in-class supply chain organization for rare diseases. Mr. Furey led the team that coordinated and delivered the successful establishment of Baxalta through a spin-out from Baxter and led the Baxter Vaccine inline business to realize significant top line and bottom line growth. He also spent two years in China as general manager of Pfizer’s vaccine business unit following a role with responsibility for global pricing and reimbursement at Pfizer Vaccines. Earlier in his career, he held both commercial and operations positions of increasing scope and responsibility with Pfizer and Wyeth Pharmaceuticals. Mr. Furey has an executive MBA from St. Joseph’s University, Philadelphia, a B.S. from Trinity College, Dublin, and a diploma in environmental health from the Dublin Institute of Technology.

Joseph La Barge, J.D., Chief Legal Officer

Joe La Barge is an executive and legal advisor with more than 15 years of experience counseling life science companies and healthcare institutions. Before joining Spark Therapeutics, Mr. La Barge was vice president, general counsel and chief compliance officer at Tengion, Inc., a clinical-stage regenerative medicine company, where he oversaw legal affairs, compliance and quality assurance. While at Tengion, Mr. La Barge helped lead the company’s initial public offering in 2010. He also played an integral role in developing Tengion’s intellectual property strategies for its novel, first-in-class, cell-based therapies. Mr. La Barge was previously of counsel at Ballard Spahr LLP in Philadelphia, where he advised biotechnology companies in private and public financings, mergers and acquisitions, and collaboration and licensing transactions. He also served as deputy general counsel to the Kennedy Health System in New Jersey. Mr. La Barge received his J.D. from Temple University and a B.A. from Bucknell University.

Spark Income Statement

All figures in thousands ($), except per share data

	FY16A	1Q17A	2Q17A	3Q17E	4Q17E	FY17E	1Q18E	2Q18E	3Q18E	4Q18E	FY18E
Risk-unadjusted Product Revenues											
LUXTURNA for RPE65 associated IRDs		-	-	-	-	-	-	26,251	36,752	51,602	114,605
SPK-7001 for Choroideremia		-	-	-	-	-	-	-	-	-	-
SPK-8011 for Hemophilia A		-	-	-	-	-	-	-	-	-	-
SPK-9001 for Hemophila B		-	-	-	-	-	-	-	-	-	-
Total risk-unadjusted product revenues	-	-	-	-	-	-	-	26,251	36,752	51,602	114,605
License and collaboration revenues	20,183	1,274	1,483								
Total revenues	**20,183**	**1,274**	**1,483**	**-**	**-**	**2,758**	**-**	**26,251**	**36,752**	**51,602**	**114,605**
Operating expenses:											
Cost of sales	-	-	-	-	-	-	-	1,313	1,838	2,580	5,730
Research and development	86,379	32,735	32,989	34,123	37,219	137,065	40,636	44,047	45,470	39,681	169,834
Acquired in process research and development	11,132	-	3,070			3,070					-
Impairment of acquired in-process research and development			15,696								
Selling, general, and administrative	48,070	21,414	26,729	27,146	27,567	102,856	27,993	28,423	29,007	25,416	110,839
Total operating expenses	145,582	54,149	78,484	61,269	64,786	258,688	68,629	73,782	76,315	67,677	286,404
Operating income (loss)	**(125,399)**	**(52,874)**	**(77,001)**	**(61,269)**	**(64,786)**	**(255,930)**	**(68,629)**	**(47,531)**	**(39,563)**	**(16,075)**	**(171,799)**
Other income (expense):											
Interest income	1,747	585	533			1,118					-
Total other income (expense)	1,747	585	533	-	-	1,118	-	-	-	-	-
Income (loss) before taxes	**(123,653)**	**(52,289)**	**(76,469)**	**(61,269)**	**(64,786)**	**(254,812)**	**(68,629)**	**(47,531)**	**(39,563)**	**(16,075)**	**(171,799)**
Income tax expense (benefit)	-	-	(2,109)	-	-	(2,109)	-	-	-	-	-
Net income (loss)	**(123,653)**	**(52,289)**	**(74,360)**	**(61,269)**	**(64,786)**	**(252,704)**	**(68,629)**	**(47,531)**	**(39,563)**	**(16,075)**	**(171,799)**
Net (loss) per share, basic	**(4.29)**	**(1.70)**	**(2.40)**	**(1.68)**	**(1.78)**	**(7.51)**	**(1.88)**	**(1.30)**	**(1.08)**	**(0.44)**	**(4.68)**
Net (loss) per share, diluted	**(4.29)**	**(1.70)**	**(2.40)**	**(1.68)**	**(1.78)**	**(7.51)**	**(1.88)**	**(1.30)**	**(1.08)**	**(0.44)**	**(4.68)**
Weighted average shares outstanding, basic	28,804	30,772	30,968	36,365	36,465	33,642	36,565	36,665	36,765	36,865	36,715
Weighted average shares outstanding, diluted	28,804	30,772	30,968	36,365	36,465	33,642	36,565	36,665	36,765	36,865	36,715

Spark Income Statement

All figures in thousands ($), except per share data

	FY16A	FY17E	FY18E	FY19E	FY20E	FY21E
Risk-unadjusted Product Revenues						
LUXTURNA for RPE65 associated IRDs		-	114,605	330,800	575,794	811,188
SPK-7001 for Choroideremia		-	-	-	-	-
SPK-8011 for Hemophilia A		-	-	-	-	-
SPK-9001 for Hemophila B		-	-	-	-	7,381
Total risk-unadjusted product revenues	-	-	114,605	330,800	575,794	818,569
License and collaboration revenues	20,183					
Total revenues	**20,183**	**2,758**	**114,605**	**330,800**	**575,794**	**818,569**
Operating expenses:						
Cost of sales	-	-	5,730	16,540	28,790	40,559
Research and development	86,379	137,065	169,834	176,623	285,529	378,795
Acquired in process research and development	11,132	3,070	-	-	-	-
Impairment of acquired in-process research and development						
Selling, general, and administrative	48,070	102,856	110,839	113,966	124,822	131,430
Total operating expenses	145,582	258,688	286,404	307,129	439,141	550,784
Operating income (loss)	**(125,399)**	**(255,930)**	**(171,799)**	**23,671**	**136,652**	**267,785**
Other income (expense):						
Interest income	1,747	1,118	-	-	-	-
Total other income (expense)	1,747	1,118	-	-	-	-
Income (loss) before taxes	**(123,653)**	**(254,812)**	**(171,799)**	**23,671**	**136,652**	**267,785**
Income tax expense (benefit)	-	(2,109)	-	-	-	-
Net income (loss)	**(123,653)**	**(252,704)**	**(171,799)**	**23,671**	**136,652**	**267,785**
Net (loss) per share, basic	**(4.29)**	**(7.51)**	**(4.68)**	**0.64**	**3.64**	**7.06**
Net (loss) per share, diluted	**(4.29)**	**(7.51)**	**(4.68)**	**0.56**	**3.22**	**6.24**
Weighted average shares outstanding, basic	28,804	33,642	36,715	37,115	37,515	37,915
Weighted average shares outstanding, diluted	28,804	33,642	36,715	42,084	42,484	42,884

Spark Balance Sheet

Figures in $ thousands except per share data

ASSETS	3Q16	4Q16	1Q17	2Q17
Current assets:				
Cash and cash equivalents	90,616	58,923	27,495	36,812
Marketable securities	216,033	237,243	226,200	178,983
Other receivable	1,021	16,781	5,947	5,010
Prepaid expenses and other current assets	1,565	1,647	3,714	5,520
Total current assets	309,235	314,594	263,355	226,324
Marketable securities	51,921	21,900	31,701	22,768
Property and equipment, net	19,788	19,794	23,098	25,530
Acquired-in-process research and development	15,490	15,490	14,951	-
Goodwill	2,096	1,160	1,120	1,196
Other assets	1,005	925	854	814
TOTAL ASSETS	399,536	373,863	335,078	276,632
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current liabilities:				
Accounts payable	8,629	9,929	14,021	15,104
Accrued expenses and other	9,279	13,827	9,098	14,433
Current portion of long-term debt	275	302	304	307
Current portion of deferred rent	761	771	1,141	1,033
Current portion of deferred revenue	5,169	5,169	5,169	6,277
Total current liabilities	24,113	29,998	29,733	37,154
Long-term debt	1,300	1,224	1,147	1,069
Long-term deferred rent	7,496	7,498	11,086	10,250
Long-term deferred revenue	5,169	3,866	2,591	-
Deferred tax liability	1,936	1,000	965	-
TOTAL LIABILITIES	40,015	43,586	45,523	48,473
STOCKHOLDERS' EQUITY				
Common stock	31	31	31	31
Additional paid-in-capital	575,640	583,974	596,436	607,530
Accumulated or other comprehensive (loss) income	(54)	(794)	(1,690)	651
Treasury stock	(553)	(553)	(553)	(1,023)
Accumulated deficit	(215,544)	(252,381)	(304,670)	(379,030)
TOTAL STOCKHOLDERS' EQUITY	359,521	330,277	289,555	228,159
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	399,536	373,863	335,078	276,632

Spark Statement of Cash Flows

Figures in thousands ($) except per share data

	3Q16	4Q16	1Q17	2Q17
Operating Activities:				
Net loss	(32,562)	(36,837)	(52,289)	(74,360)
Adjustments to reconcile net loss to net cash used in operating activities:				
Noncash rent expense	(181)	12	303	230
Depreciation expense	958	1,021	1,031	1,195
Loss on disposal of property and equipment	-	101	-	-
Acquired in-process research and development	-	11,132	387	3,070
Stock-based compensation expense	5,788	7,236	9,029	9,361
Impairment of acquired in-process research and development	-	-	-	15,696
Noncash income tax benefit	-	-	-	(2,109)
Changes in Operating Assets and Liabilities:				
Prepaid expenses and other assests	338	(2)	(1,969)	(1,699)
Other receivables	(37)	(15,752)	10,701	982
Accounts payable and accrued expenses	6,208	5,796	(2,690)	7,531
Deferred rent	-	-	3,654	(1,174)
Deferred revenue	(1,303)	(1,303)	(1,274)	(1,483)
Net cash used in operating activities	(20,791)	(28,596)	(33,118)	(42,760)
Cash flows from investing activities				
Purchase of acquired in-process research and development	0	(11,132)		(3,457)
Payment for acquisition, net of cash acquired	-	-	-	-
Purchases of marketable securities	(119,056)	(6,934)	(24,225)	(42,312)
Proceeds from maturities of marketable securities	5,000	15,000	24,780	101,587
Purchases of property and equipment	(1,814)	(1,066)	(2,230)	(4,991)
Net cash used in investing activities	(115,869)	(4,133)	(1,676)	50,827
Cash flows from financing activities				
Proceeds from exercise of options	790	758	3,434	1,734
Purchase of treasury stock	-	-		(471)
Purchase from public offerings of common stock, net	(116)	-	-	-
Payments on long-term debt	(25)	-	(75)	(75)
Proceeds from issuance of common stock under ESPP	-	340	-	-
Proceeds from long-term debt	1,600	(49)	-	-
Net cash provided by (used in) financing activities	2,250	1,048	3,359	1,188
Effect of exchange rate changes on cash and cash equivalents	-	(12)	6	62
Net change in cash and cash equivalents	(134,411)	(31,692)	(31,428)	9,317
Cash and cash equivalents at beginning of period	225,027	90,616	58,923	27,495
Cash and cash equivalents at end of period	90,616	58,923	27,495	36,812

Voyager Therapeutics, Inc. (VYGR-NASDAQ)

Biotechnology

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Intrepid Voyagers Looking to Transform the CNS Space; Initiating at Outperform

Recommendation: We are initiating coverage of Voyager Therapeutics with an **Outperform** rating and a price target of $35 (High Risk/Speculation suitability, given the stage of clinical development). In our opinion, Voyager is an undervalued gene therapy company, with six product candidates addressing the unmet medical needs for patients with central nervous system (CNS) disorders. Given that the lead asset, VY-AADC01, has achieved clinically meaningful improvements on multiple efficacy endpoints among patients with Parkinson's disease (PD) in a Phase Ib study, we believe the product has the potential to transform the treatment paradigm of this disease. With VY-AADC01 poised to continue to showcase its therapeutic potential in an upcoming pivotal program, a pipeline with multiple shots on goal addressing multi-billion dollar market opportunities, and a cash position of ~$121 million (pro forma), we recommend Voyager shares to risk-tolerant investors.

Keeping Parkinson's disease treatable. Voyager's VY-AADC01, which utilizes an AAV2 vector to deliver a functional copy of the aromatic amino acid decarboxylase (AADC) gene, has been evaluated in Phase I studies. Based on our analysis of the clinical results, we believe VY-AADC01 is an active drug with a good safety profile, having achieved dose and time dependent improvements on multiple endpoints including the diary on- and off-time, the Unified Parkinson Disease Rating Scale (UPDRS) scores, and reductions in the doses of oral medications (e.g., levodopa). Based on the data seen to date, we believe the upcoming placebo-controlled Phase II/III pivotal program (which is slated to start in 4Q17) has a greater-than-average chance of success. If approved, we do not expect VY-AADC01 to face significant direct competition from existing therapies given that this gene therapy is likely to be positioned as an add-on therapy. Assuming a U.S. approval in 2022, we estimate VY-AADC01 to generate peak sales of $1.4 billion by 2026.

Multiple ponies in the stable. With an additional five product candidates, Voyager is not a one-trick pony in the gene therapy space. While early, these assets, which aim to address the significant unmet needs in multiple CNS indications including amyotrophic lateral sclerosis (ALS) and Huntington's disease, could start creating value in late 2018 or early 2019. Although each of these indications represents significant market opportunities, given the early stage of development, we have opted to value these programs as upside to our current valuation.

Valuation: Using the risk-adjusted net present value (NPV) analysis of VY-AADC01, we derive a target price of $35 (see page 208 for more detail). While our target price represents a significant potential upside, our **Outperform** rating balances the risks associated with the company's clinical programs with the upside potential of the company's short- and long-term catalysts.

GAAP EPS	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Full Year	Revenues (mil.)
2016A	(0.29)	(0.37)	(0.35)	(0.57)	$(1.59)	$14
New 2017E	**(0.65)A**	**(0.73)A**	**(0.82)**	**(0.89)**	**(3.09)**	**3**
New 2018E	**(0.90)**	**(0.92)**	**(0.81)**	**(0.85)**	**(3.47)**	**0**

Rows may not add due to rounding.

Rating
Outperform 2

Current and Target Price

Current Price (Oct-09-17)	$20.24
Target Price:	$35.00
52-Week Range	$22.95 - $8.10
Suitability	High Risk/Speculation

Market Data

Shares Out. (mil.)	26.9
Market Cap. (mil.)	$544
Avg. Daily Vol. (10 day)	408,420
Dividend/Yield	$0.00/0.0%
BVPS (Jun-17)	$4.05
LT Debt (mil.)/% Cap.	$0/0%

Earnings & Valuation Metrics

	2016A	2017E	2018E
P/E Ratios (GAAP)	NM	NM	NM

Voyager Therapeutics, headquartered in Cambridge, Massachusetts, is a clinical-stage gene therapy company focusing on diseases of the central nervous system (CNS). Currently, the company has six product candidates, with VY-AADC01 being the most advanced. VY-AADC01, which consists of an AAV2 vector and the AADC gene, is being developed for advanced Parkinson's disease (PD), with promising clinical results demonstrated in a Phase I study and the potential to initiate a pivotal Phase II/III program later this year. Besides VY-AADC01, there are five other preclinical-stage assets addressing the unmet needs in different types of CNS indications, including the monogenic form of amyotrophic lateral sclerosis (ALS), Huntington's disease, Friedreich's ataxia, frontotemporal dementia, and severe chronic pain. Based on our estimates, VY-AADC01 alone is tackling a U.S. market opportunity of $14 billion.

Source: FactSet.

Company Description

Voyager Therapeutics, headquartered in Cambridge, Massachusetts, is a clinical-stage gene therapy company focusing on diseases of the central nervous system (CNS). Currently, the company has six product candidates, with VY-AADC01 being the most advanced. VY-AADC01, which consists of an AAV2 vector and the AADC gene, is being developed for advanced Parkinson's disease, with promising clinical results demonstrated in a Phase I study and the potential to initiate a pivotal Phase II/III program later this year. Besides VY-AADC01, there are five other preclinical-stage assets addressing the unmet needs in different types of CNS indications, including the monogenic form of amyotrophic lateral sclerosis (ALS), Huntington's disease, Friedreich's ataxia, frontotemporal dementia, and severe chronic pain. Based on our estimates, VY-AADC01 alone is tackling a U.S. market opportunity of $14 billion.

Newsworthy Catalysts

Product	Timing	Description
VY-AADC01 for Advanced Parkinson's disease	4Q17	Potential for Sanofi to make an opt-in decision
	4Q17	Begin the pivotal Phase II/III program
	1Q18	Long-term data from cohorts 1-3 (e.g., 12-month results from cohort 3) of the Phase Ib study
	1Q18	Results from the Phase I posterior trial
	1H18	Dose the first patient in the pivotal Phase II/III program
VY-SOD101 for monogenic form of ALS	Late 2017/ early 2018	File IND
	2H18	Biomarker data
VY-FXN01 for Friedreich's ataxia	4Q17	Lead candidate selection
N/A	November, 2017	R&D Day

Source: Voyager Therapeutics, Raymond James research.

Voyager's Portfolio

Product	Status	Market	Rights
VY-AADC01	Phase I	Advanced Parkinson's disease	Voyager (Sanofi has ex-U.S. options)
VY-SOD101	Lead candidate selection	Monogenic form of ALS	Voyager
VY-HTT01	Lead candidate selection	Huntington's disease	Voyager (Sanofi has ex-U.S. options and option to co-promote in the U.S.)
VY-FXN01	Preclinical	Friedreich's ataxia	Voyager (Sanofi has ex-U.S. options)
VY-TAU01	Preclinical	FTD/ Alzheimer's disease	Voyager
VY-NAV01	Preclinical	Severe chronic pain	Voyager

Notes: ALS -- Amyotrophic Lateral Sclerosis , FTD -- Frontotemporal Dementia
Source: Voyager Therapeutics, Raymond James research.

Summary of Investment Risks

Clinical and Regulatory Risk

While promising, the clinical results seen with VY-AADC01 were derived from a small number of patients, which may not be replicated in larger studies. As for the pipeline of product candidates, no clinical data has been reported to date. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk

There are multiple existing and development-stage products for PD. While we do not believe they would pose significant direct competition for VY-AADC01, the commercial adoption of this gene therapy may still face some pressure and take time.

In addition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Voyager cannot secure a reasonable price for VY-AADC01, the economics of this product may not meet expectations.

Financing Risk

Voyager currently has no product revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Summary of Investment Highlights

Tackling Parkinson's Disease With a Unique Approach

The Unmet Medical Need

Parkinson's disease (PD) is a chronic, progressive and debilitating disease of the nervous system. While the root cause of PD is largely unknown, the abnormalities in motor functions are recognized to be caused by the loss or degeneration of dopamine producing neurons in the brain. As the second most common neurodegenerative disorder, PD currently affects approximately one million Americans, with ~70,000 new patients every year in the U.S. Depending on the severity of the disease, PD is categorized into three types: mild, moderate, and advanced. According to our literature review, there are approximately 130,000 advanced PD patients in the U.S., with about 10,000 such cases expected every year.

There are five main treatment options with different mechanisms of action (MOAs) for PD: 1) levodopa (or L-DOPA), a precursor of dopamine, which is the current standard of care; 2) the combination of an aromatic amino acid decarboxylase (AADC) or catechol-*O*-methyltransferase (COMT) inhibitor with L-DOPA. An AADC or COMT inhibitor can prevent the conversion of L-DOPA into downstream metabolites

before L-DOPA crosses the blood-brain barrier (BBB) and reaches the target location inside the brain; 3) inhibitors of the dopamine oxidation enzyme (monoamine oxidase type B [MAOB]) that are capable of delaying the clearance of dopamine in the synapse (a junction between two nerve cells); 4) dopamine agonists, which can mimic dopamine and activate dopamine receptors; and 5) deep brain stimulation (DBS), a surgical procedure that utilizes electrical stimulation to improve PD symptoms. Despite these existing interventions, currently there are no treatments that can cure the disease or even reverse or slow down the progression of the disease. In addition, PD patients become less responsive to these therapies as the disease progresses, resulting in limited treatment options for patients with advanced PD. Given the prevalence and sub-optimal options, in our opinion, there is a need to develop a therapy that is more efficacious or at least can enhance the performance of these existing interventions.

Voyager's Solution

To tackle the unmet medical need in advanced PD, Voyager has been developing a unique product (VY-AADC01), a gene therapy that utilizes an AAV2 vector to deliver a copy of the AADC transgene into the putamen (a region in the brain where neurons can use the AADC enzyme to convert L-DOPA to dopamine). Of note, in PD patients, many such neurons along with the AADC enzyme are gone, resulting in the putamen incapable of efficiently converting L-DOPA to dopamine. While there are a number of existing interventions for PD, none of them are an AADC enzyme therapy, suggesting that Voyager's approach could be synergistic with these products.

VY-AADC01 Has Achieved Dose and Time-Dependent Improvements on Multiple Efficacy Endpoints

Voyager is conducting a Phase Ib study evaluating VY-AADC01 delivered via a transfrontal (top of the head) surgical procedure in patients with advanced PD. A total of 15 patients, who had similar characteristics as compared to those typical advanced PD patients, were equally split and treated in three dosing cohorts: cohort 1 – 7.5x10^11 vg , cohort 2 – 1.5x10^12 vg, and cohort 3 – 4.5x10^12 vg. Of note, at baseline, these patients were on high doses (~1,400 to 1,700 mg) of PD medications, including L-DOPA and other medications. In our opinion, the one-time administration of the gene therapy demonstrated dose and time dependent therapeutic effects on multiple measurements:

Enhanced AADC activity correlated with reduced need of oral PD medications. A mean increase of 13%, 56%, and 79% in the AADC enzyme activity from baseline to six months as measured by PET scans was seen in cohorts 1, 2, and 3, respectively. More importantly, the enhanced AADC activity appeared to result in reduced need of the background oral PD medications, as evidenced by a mean decrease of 14%, 34%, and 42% in the doses of these medications from baseline to six months for cohorts 1, 2, and 3, respectively. In our opinion, these results suggest that VY-AADC01 was delivered to the right location and able to express functional AADC enzyme, resulting in increased conversions of L-DOPA to dopamine.

Improved motor functions indicated by patient-reported diary "on" and "off" time. Diary on-time and off-time are the gold-standard, patient-reported endpoints. "Off-time" refers to the periods during which a medication is not working well, resulting in worsening of PD symptoms, whereas "on-time" refers to the time of adequate control of the symptoms. Dose and time dependent improvements on both endpoints were achieved. Specifically, the average increase in diary on-time without troublesome dyskinesia achieved in cohort 2 was 2.2 hours at six months, which further improved to 3.3 hours at 12 months, both of which were greater than those seen in cohort 1 (a lower dose cohort) at the same time points. Similar patterns were also observed in the diary off-time, with cohort 2 achieving a mean reduction of 1.1 hours at six months and 2.3 hours at 12 months vs. 0.8 hours at six months and 1.4 hours at 12 months seen in cohort 1. Interestingly, the improvements on these endpoints appeared to continue to improve over time.

Improved motor functions and daily living activities measured by physician rated UPDRS scores. The Unified Parkinson Disease Rating Scale (UPDRS) is a physician-monitored evaluation of a patient's performance, including motor functions (measured by UPDRS-III) and activities of daily living (UPDRS-II). Notably, an approximate 55% reduction (reduction is improvement) in the UPDRS-III on-medication scores were seen in both cohorts 2 and 3 at either 6 months or 12 months, whereas there were no improvements over the course of 24 months seen in cohort 1. The activities of daily living as measured by the UPDRS-II scores also improved in both cohorts 2 and 3 at either 6 months or 12 months.

Key takeaways from the clinical results:

- VY-AADC01 appears to be an active therapy, delivering clinically meaningful improvements on FDA acceptable endpoints. If cohort 1 were to serve as a placebo control, in our opinion, the results seen in cohorts 2 and 3 suggest that the gene therapy delivered therapeutic effects beyond what placebo could generate.
- The improvements on these measurements appear to be consistent (e.g., enhanced AADC activity correlated with improved clinical outcomes).
- Both doses tested in cohorts 2 and 3 appeared to be active. While there were some slight differences, overall, the two doses were largely comparable in terms of efficacy.

Pivotal Testing on the Horizon

Given the encouraging results seen in the Phase Ib study, the company plans to initiate a pivotal Phase II/III program evaluating VY-AADC01 in late 2017, with the first patient expected to be dosed in 1H18. This pivotal program consists of a double-blind, placebo-controlled Phase II study assessing VY-AADC01 in 30-42 patients as well as a global, double-blind, placebo-controlled Phase III trial evaluating the gene therapy in 100-120 patients. The primary endpoint for the Phase II portion is likely to be the diary on-time at 12 months, with key secondary endpoints being the diary off-time, UPDRS-I, II and III scores, and PDQ-39. Of note, the Phase III study is likely to start shortly after Phase II enrollment is completed. More guidance regarding the pivotal program will be provided at the upcoming R&D Day.

Based on our discussions with management, there are a couple of reasons why there is a Phase II portion of the pivotal program: 1) the Phase II study could help select appropriate endpoints for a larger-scale Phase III trial; and 2) if the Phase II trial is successful, the company may be able to file for an accelerated approval for VY-AADC01, with the Phase III study serving as a confirmatory trial.

The Competitive Landscape – Limited Direct Competition Is Expected

While there are multiple interventions available for PD (e.g., AbbVie's DUOPA, Newron Pharmaceuticals' Xadago, and deep brain stimulation devices marketed by medical device companies such as Medtronic and Abbott), in our opinion, these treatments are not likely to be direct competitors of Voyager's VY-AADC01. Given the different MOA, we believe VY-AADC01 is likely to be positioned as an add-on therapy to existing oral/IV medications. To the best of our knowledge, VY-AADC01 is the only therapy that can deliver the AADC enzyme in the brain. With respect to the potential competition from deep brain stimulation, in our opinion, VY-AADC01 is likely to be used before this surgical intervention. Currently, deep brain stimulation is utilized only when a patient has had PD symptoms for at least five years, with inadequate control of the symptoms by other medications.

Besides the existing options, there are also a slew of product candidates being developed for advanced PD. All of the non-gene therapy products have different MOAs as compared to VY-AADC01 (Exhibit 13). In the gene therapy world, Oxford BioMedica's OXB-102 appears to be the only other product in

development. OXB-102, which is in a Phase I/IIa preparation stage, utilizes a lentiviral vector to deliver three genes to encode AADC, tyrosine hydroxylase, and cyclohydrolase, respectively. While no clinical data has been reported for OXB-102, an earlier generation of this gene therapy, OXB-101 (also known as ProSavin), had been tested in a Phase I/II trial. In this study, which enrolled 15 patients, OXB-101 achieved a significant improvement in the UPDRS III off-medication scores but not in the UPDRS III on-medication measures. Given the results, Oxford generated OXB-102, which is supposed to be a more potent formulation of OXB-101. Given that OXB-102 uses a lentiviral vector, in our opinion, the safety of this gene therapy could be an issue in the long term.

Market Opportunity

Assuming a U.S. approval in 2022 with a probability of success of 50%, a one-time annual payment of approximately $100,000, and 10% market penetration, we expect VY-AADC01 to generate peak sales of $1.4 billion by 2026.

Voyager's Portfolio

Product	Status	Market	Rights
VY-AADC01	Phase I	Advanced Parkinson's Disease	Voyager (Sanofi has ex-U.S. options)
VY-SOD101	Lead candidate selection	Monogenic form of ALS	Voyager
VY-HTT01	Lead candidate selection	Huntington's Disease	Voyager (Sanofi has ex-U.S. options and option to co-promote in the U.S.)
VY-FXN01	Preclinical	Friedreich's Ataxia	Voyager (Sanofi has ex-U.S. options)
VY-TAU01	Preclinical	FTD/ Alzheimer's Disease	Voyager
VY-NAV01	Preclinical	Severe chronic pain	Voyager

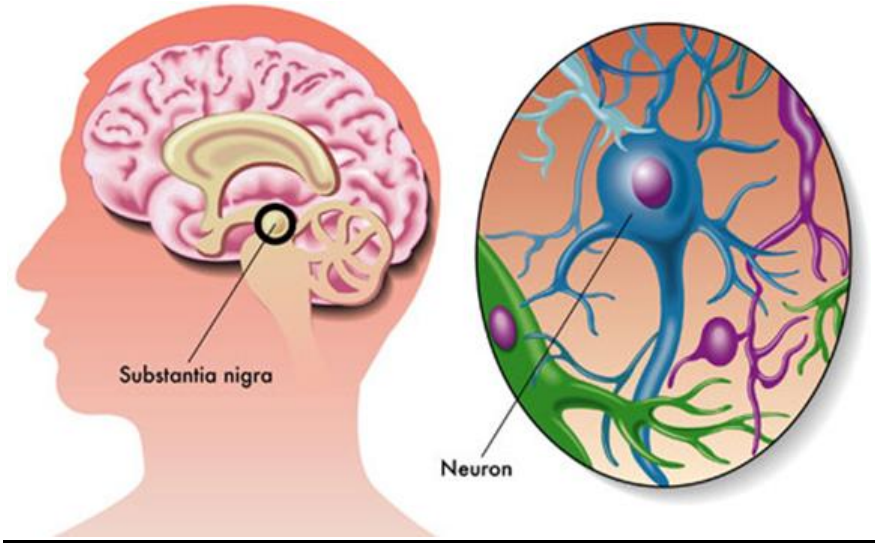
Notes: ALS -- Amyotrophic Lateral Sclerosis , FTD -- Frontotemporal Dementia
Source: Voyager Therapeutics, Raymond James research.

The Parkinson's Disease Franchise

Background of Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive and debilitating disease of the nervous system that is due to the loss or degeneration of dopamine producing neurons in the area of the midbrain called substantia nigra (Exhibit 1). This preferential loss of dopamine producing neurons in the "motor control center" in the brain leads to the motor symptoms including rigidity, impaired posture and balance, tremors, and slowed movement (bradykinesia). At the advanced stages, patients frequently require the daily assistance of a nurse as they experience more severe motor symptoms including falling, "freezing of gait," and difficulty with speech and swallowing. In addition, a majority of patients with PD also develop non-motor symptoms including disorders of sleep-wake cycle regulation, cognitive impairment, disorders of mood, autonomic dysfunction, sensory symptoms (such as hyposmia), and pain, which is another major determinant of the quality of life (QOL) for these patients.

Exhibit 1:
Parkinson's Disease — Loss of Dopamine-Producing Neurons in the Substantia Nigra



Source: DesMD.

PD is the second most common neurodegenerative disorder, which affects as many as one million Americans and an estimated 7 to 10 million people worldwide. It is estimated that there are between 5 to 35 new cases per 100,000 individuals each year worldwide, with an estimated yearly incidence of 21 per 100,000 persons in the U.S.

Clinically, PD is classified into three main stages: mild, moderate, and advanced (see below), with the late stage patients (moderate and advanced) constituting approximately 60% of the total PD population.

Mild PD: Patients in this stage may experience minor shaking, slowness in movements, and stiffness in the muscles. That said, the brain is still producing a basal level of dopamine. Therefore, medications are able to mitigate symptoms.

Moderate PD: The moderate stage is characterized by more advanced motor complications and daily "off" episodes, in which motor symptoms cannot be controlled with medication. Patients typically advance into the moderate stage 2-5 years after diagnosis.

Advanced PD: Severe PD patients have significant "off" time and dyskinesia, causing a small percentage of patients to become bedridden or require a wheelchair. At this stage, patients respond minimally to oral medication and often undergo invasive surgical procedures.

In addition, a rating system (1 – 5) developed by Hoehn and Yahr (Hoehn and Yahr scale) and a recently modified version are commonly used to track how the symptoms of PD progress, with stage 4 and 5 being commonly defined by clinicians as advanced PD (Exhibit 2). Lastly, another well-accepted classification for advanced PD includes patients who have developed motor fluctuations.

Exhibit 2: **Original and Modified Hoehn and Yahr Scale System**

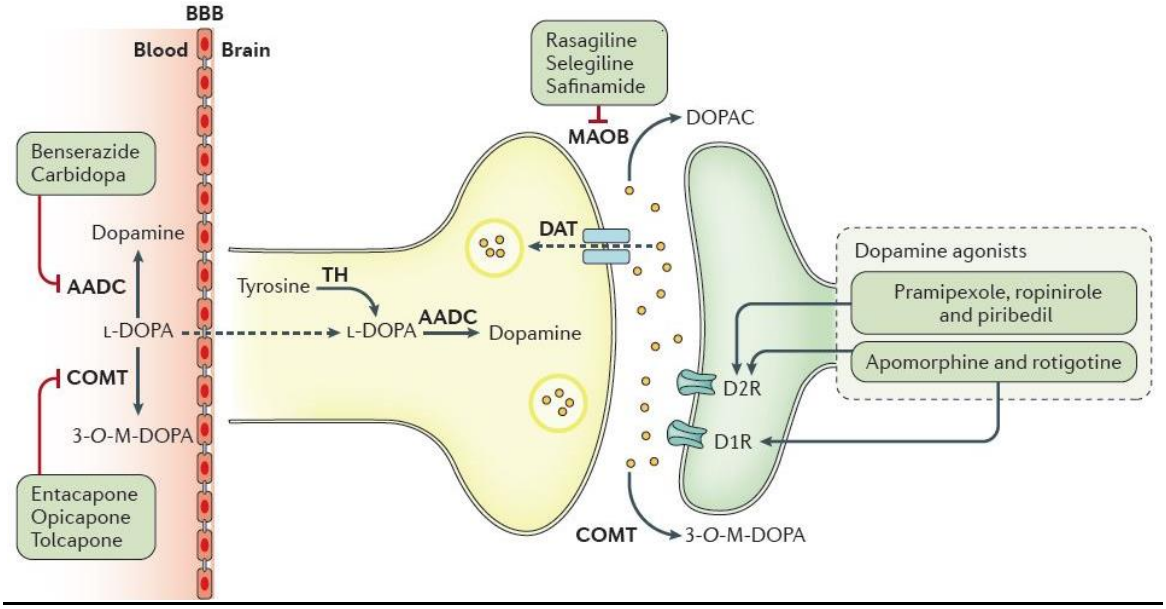
Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral disease
1.5	*Not defined*	Unilateral plus axial involvement
2	Bilateral involvement without impairment of balance	Bilateral disease, without impairment of balance
2.5	*Not defined*	Mild bilateral disease, with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided	Wheelchair bound or bedridden unless aided

Source: Raymond James research.

Current Treatment Options

Given that striatal dopamine depletion due to the loss of dopamine neurons is the main culprit of motor symptoms in PD, replenishing dopamine through the administration of levodopa, or L-DOPA (the precursor of dopamine) marked a breakthrough in the treatment of PD and is the current standard of care for PD. Over time, practically all patients with PD will be treated with this agent. In addition, a slew of dopaminergic pharmacological agents capable of prolonging the half-life of L-DOPA are frequently used as a combination therapy with L-DOPA given L-DOPA's short half-life (Exhibit 3). One strategy is to increase the serum half-life of L-DOPA before it crosses the BBB through the inhibition of L-DOPA metabolic enzymes, including aromatic amino acid decarboxylase (AADC) and catechol-*O*-methyltransferase (COMT). For example, the current gold-standard treatment regimen is the oral administration of the combination of carbidopa (AADC inhibitor) and L-DOPA (LD/CD treatment), which has demonstrated favorable and consistent therapeutic benefit in patients with PD. Another method is to postpone the synaptic clearance of dopamine through the inhibition of the dopamine oxidation enzyme monoamine oxidase type B (MAOB). Lastly, dopamine agonists that are able to activate dopamine receptors (D1R and D2R) and mimic the effect of dopamine are used as an alternative therapy to control motor complications.

Exhibit 3: **Dopaminergic Drug Targets in Parkinson Disease**



Source: Nature Reviews Disease Primers 3, doi:10.1038/nrdp.2017.13.

Current Therapies for Advanced PD

While patients are generally well responsive to L-DOPA treatments in the early stages of the disease, they become less responsive as the disease progresses. In addition, advanced patients experience an enhanced sensitivity to small changes in plasma L-DOPA levels, which leads to a narrowing therapeutic window of dopaminergic therapies. Therefore, a general strategy for the treatment of advanced PD focuses on maintaining a steady and therapeutic level of L-DOPA through optimization of a range of factors including absorption, timing of administration, dosage, and delivery route. That said, only limited treatment options exist for patients with advanced PD.

DUOPA, developed by AbbVie and approved by the FDA for the treatment of advanced PD in January 2015, is a re-formulated LD/CD that is in a suspension format and placed into the intestine in a tube through a surgical procedure called percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). This special delivery approach of LD/CD is able to bypass the stomach as well as avoid an erratic gastric emptying movement, therefore improving the intestinal absorption of LD/CD. In a randomized, double-blinded, double-dummy, active-controlled pivotal study of DUOPA in 66 patients with advanced PD, DUOPA significantly prolonged patients' "on" time compared to baseline. During a 12-week study period, DUOPA achieved a 4-hour decrease in "off" time (p=0.0015) as well as a 4.1-hour increase in "on" time as compared to a 2.1-hour decrease and a 2.2-hour increase in the control group. Notably, it appears that a clear and durable delta in the change of "off" time between DUOPA and the active control was evident starting at four weeks after the treatment. On the safety front, DUOPA is well tolerated with a comparable safety profile relative to the active control.

Xadago (safinamide), an MAOB inhibitor, was approved by the FDA in March 2017 as an add-on therapy to L-DOPA to treat patients with middle and late stages of PD who experience "off" episodes. In a double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of Xadago as an adjunct agent to L-DOPA for the treatment of patients with PD and motor fluctuations, the combination therapy met the primary endpoint with a statistically significant improvement in "on" time compared to placebo. Specifically, a mean of 1.36 hours and 1.37 hours increase in total "on" time with no or non-troublesome dyskinesia was achieved in patients who had 100 mg/day (n=224) and 50 mg/day (n=223) of Xadago

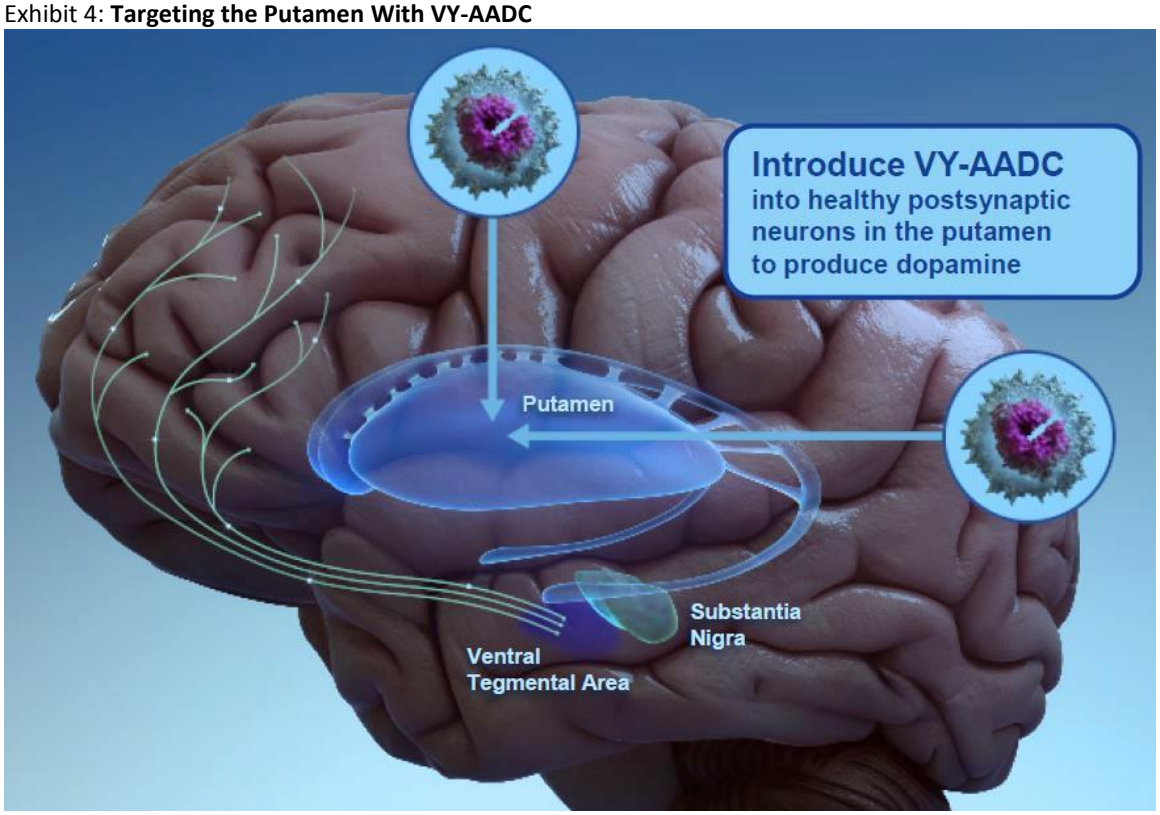
compared to a mean of 0.97 hours increase in the placebo group (n=222) at week 24. In addition, improvements in secondary endpoints including "off time," UPDRS-III, and CGI-C were all significantly greater in both Xadago groups relative to placebo. On the safety front, no significant differences for the incidences of treatment emergent adverse events (TEAEs) or discontinuations due to TEAEs were seen between Xadago groups and placebo.

Another treatment option for advanced PD is deep brain stimulation (DBS), which requires surgical implantation of an electrode in certain regions of the brain known to be associated with motor functions. By delivering electrical stimulation to these areas to block abnormal nerve signals, DBS is able to alleviate certain motor symptoms associated with PD.

Voyager's Solution

Given that striatal dopamine depletion due to the loss of dopaminergic neurons in the substantia nigra is the core mechanism underlying the motor symptoms of PD, in our opinion, a therapeutic approach capable of supplying dopamine directly to the downstream mediators of the dopaminergic pathway could potentially lead to the rescue of dopamine function (Exhibit 4).

Exhibit 4: **Targeting the Putamen With VY-AADC**

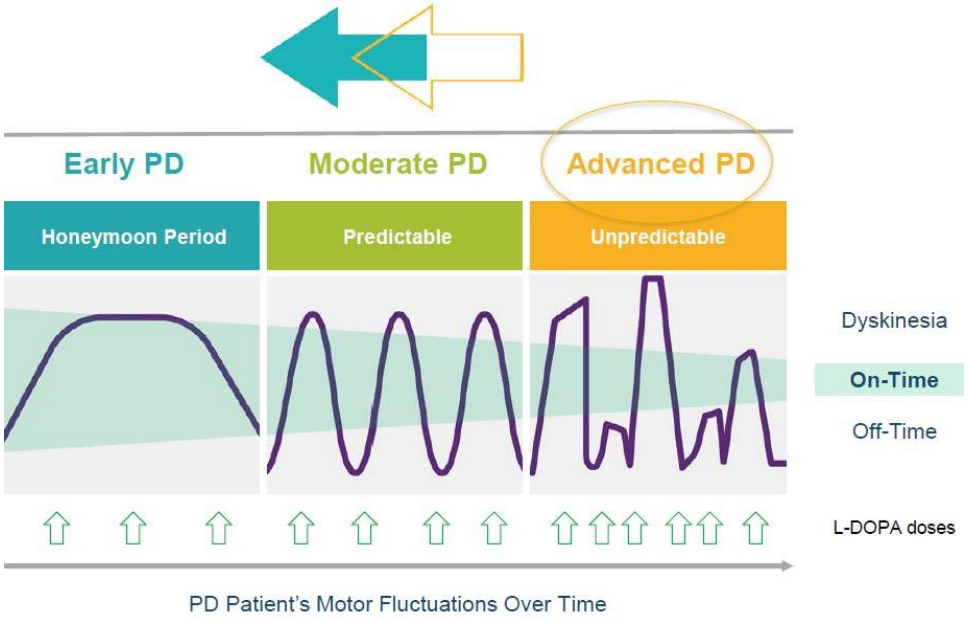


Source: Voyager Therapeutics.

With a goal to restore the responsiveness to L-DOPA in patients with advanced PD, the company has developed gene therapy product candidate VY-AADC01, which consists of a cytomegalovirus promoter fused with an AADC transgene that is packaged by the AAV2 capsid. Importantly, an intrathecal delivery method has been developed that enables the target delivery of the AADC gene into the putamen region,

an indispensable region in the dopaminergic pathway that receives information from the substantia nigra. Therefore, a sustained AADC enzyme activity in the putamen region should lead to an increased and durable dopamine level in the synaptic area, which could potentially result in a clinically meaningful improvement in motor functions (Exhibit 5).

Exhibit 5: **Goal of VY-AADC Gene Therapy – Restore Function**



Source: Voyager Therapeutics.

Endpoints Used in Clinical Trials

While there is a host of clinical endpoints being utilized to assess the motor and non-motor symptoms of patients with PD, the following endpoints are well established and have been accepted by the FDA to evaluate the therapeutic benefit of drug candidates for PD:

Changes in Diary "On" and "Off" Time

Changes in "on" and "off" time measured by Patient Hauser Diaries are the current gold-standard efficacy measurements for drug candidates seeking regulatory approval for symptomatic treatment of PD. "Off-time" refers to the periods during which a medication is not working well, resulting in worsening of PD symptoms, whereas "on-time" refers to the time of adequate control of the symptoms. These diaries are designed to record patients' motor state for half-hour intervals over a 24-hour period. In order to qualify for the diary study in the clinical setting, patients are trained by certified instructors and are required to reach a certain degree of diary concordance before the study enrollment. The most commonly used primary efficacy endpoints in PD clinical studies include: 1) the change from baseline in "off" time during waking hours; 2) the change in "on" time without troublesome dyskinesia (good "on" time) during waking hours; and 3) changes in total "on" time or "on" time according to other dyskinesia categories. In general, a one hour reduction in "off" time or a one hour increase in "on" time may be considered clinically significant, and has been used as an assumption in clinical studies to date.

Unified Parkinson Disease Rating Scale (UPDRS)

The UPDRS is a rating tool (scale) that was developed to provide a comprehensive monitoring system for PD-related disability and impairment. It consists of four components to measure patients' 1) mentation, behavior, and mood (UPDRS-I); 2) activities of daily living (UPDRS-II); 3) motor sections (UPDRS-III); and 4) complications of therapy (UPDRS-IV). Specifically, patients' disability status are evaluated by interviews with a total of 199 possible points to be assigned, where more points represent a worse disability. For UPDRS-I, the scale is given based on patients' intellectual impairment, thought disorder, depression, and motivation. For UPDRS-II, 13 qualifiers are included to gauge patients' activities of daily living, including: speech, salivation, swallowing, handwriting, cutting food/handing utensils, dressing, hygiene, turning in bed/adjusting bed clothes, falling that is unrelated to freezing, freezing when walking, walking, tremor, and sensory complaints related to parkinsonism. Lastly for UPDRS-III, motor exams are given, which include speech, facial expression, tremor at rest, rigidity, finger taps, hand movements, rapid alternating movements, leg agility, arising from chair, posture, gait, postural stability, and hypokinesia.

Parkinson's Disease Questionnaire – 39 (PDQ-39)

PDQ-39 is a questionnaire created to assess patients' quality of life by evaluating 39 parameters in eight groups of issues, including mobility, activities of daily living, emotional well-being, stigma of the disease, social support, cognitive, communication, and bodily discomfort. Participants in the questionnaire need to choose one of five possible answers in 3 – 10 parameters in each of the eight groups.

Clinical Development of VY-AADC01

Phase I UCSF Trial

The first in-human study of VY-AADC01 was conducted at the University of California, San Francisco (UCSF) in 10 patients with advanced PD. In the Phase I trial, two dose levels of VY-AADC01 (9x10^10 vg in 100uL and 3x10^11 vg in 200uL) were delivered directly to the putamen region through stereotactic injections. While no gene therapy-related SAEs occurred during the study, three patients had a surgical procedure related minor hemorrhages. On the efficacy front, improvements in motor functions were seen in all treated patients. Specifically, an approximately three-hour reduction in "off" time as well as an increase in "on" time without dyskinesia were achieved at six months following the treatment. In addition, an improvement in both motor and non-motor functions in the "on" and "off" medication period was seen as measured by the UPDRS score (Exhibit 6).

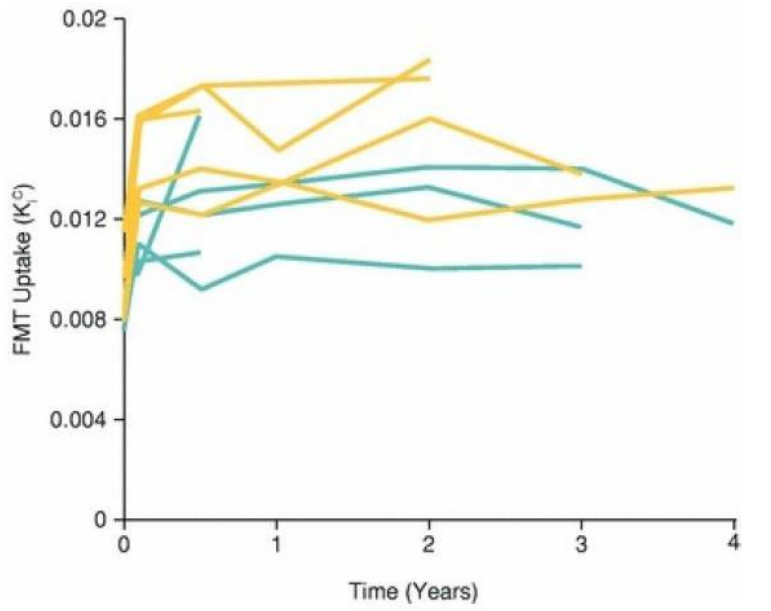
Exhibit 6: **Summary of UPDRS Results From the Phase 1 UCSF Study**

	Off medications				On medications			
	Baseline	6 months	% Change	*p* Value	Baseline	6 months	% Change	*p* Value
Total UPDRS								
Low-dose cohort	69.6	49.6	–28	0.04	32.6	21.8	–33	0.024
High-dose cohort	62.4	41.3	–33	0.001	29.7	20.5	–31	0.08
Combined cohorts	66	45.5	–31	0.0008	31.2	21.2	–32	0.004

Source: Voyager Therapeutics.

During a long-term follow-up study (four years) for the 10 treated patients, dose-dependent AADC expression in the brain was seen in the positron emission tomography (PET) scan (FMT uptake), which suggests a one-time treatment of VY-AADC01 could lead to a long-term AADC expression for up to four years (Exhibit 7).

Exhibit 7: **Long-Term AADC Expression as Measured by PET Imaging**



Source: Voyager Therapeutics.

Phase I JMU Trial

Another phase I study of VY-AADC01 in patients with advanced PD was conducted at Jichi Medical University (JMU) in Japan with the primary endpoints being safety and tolerability of the treatment. Among the six treated patients, an enhanced PET signal was observed in patients during a 96-week follow-up period. On the safety side, the treatment was well tolerated without treatment-related SAEs.

VY-AADC01 Phase Ib Trial

Given the favorable safety profile of VY-AADC01, UCSF initiated an open-label Phase Ib trial (NCT01973543) in patients with advanced PD with a goal to optimize the dose level of VY-AADC01. The primary endpoints of the study were safety and tolerability of the treatment, with functional secondary endpoints being the UPDRS score, AADC PET imaging, daily requirements for levodopa and related medications, and changes in patients' sensitivity to L-DOPA. Patients are allowed to continue to take PD medications, including levodopa. In October 2015, the IND for the Phase Ib trial was transferred to the company, which initiated a second clinical site at the University of Pittsburgh Medical Center (UPMC) in December 2015. In addition, three modifications were incorporated into the Phase Ib trial compared to the previously completed Phase I studies, including: 1) With a goal to reduce the risk of hemorrhages seen in the previously finished Phase I UCSF trial, the intrathecal delivery of VY-AADC01 was guided under a real-time intra-operative MRI system to avoid procedure associated injury to specific blood vessels. 2) Higher doses of VY-AADC01 were used as compared to the previously finished Phase I UCSF trial.

Specifically, patients were enrolled in three cohorts and dosed with 7.5x10^11 vg (cohort 1), 1.5x10^12 vg (cohort 2), and 4.5x10^12 vg (cohort 3) of VY-AADC01. 3) Larger infusion volumes were used to potentially increase the coverage of VY-AADC01 in the putamen (450 uL for cohort 1, and up to 900 uL for both cohort 2 and cohort 3).

In September 2017, the company provided a most recent update on this Phase Ib trial, which included data from cohort 1 at 24 months, cohort 2 at 12 months, and cohort 3 at six months. The study has enrolled a total of 15 patients, with five for each dose cohort (Exhibit 8). According to the company, the profiles of these 15 patients are representative of typical patients with advanced Parkinson's disease. Of note, at baseline, these patients were on high doses (~1,400 to 1,700 mg) of PD medications, including levodopa and other medications. It is worth noting that all these 15 patients were also candidates for DBS.

Exhibit 8: **Baseline Characteristics of the 15 Patients Enrolled Into the Phase Ib Study**

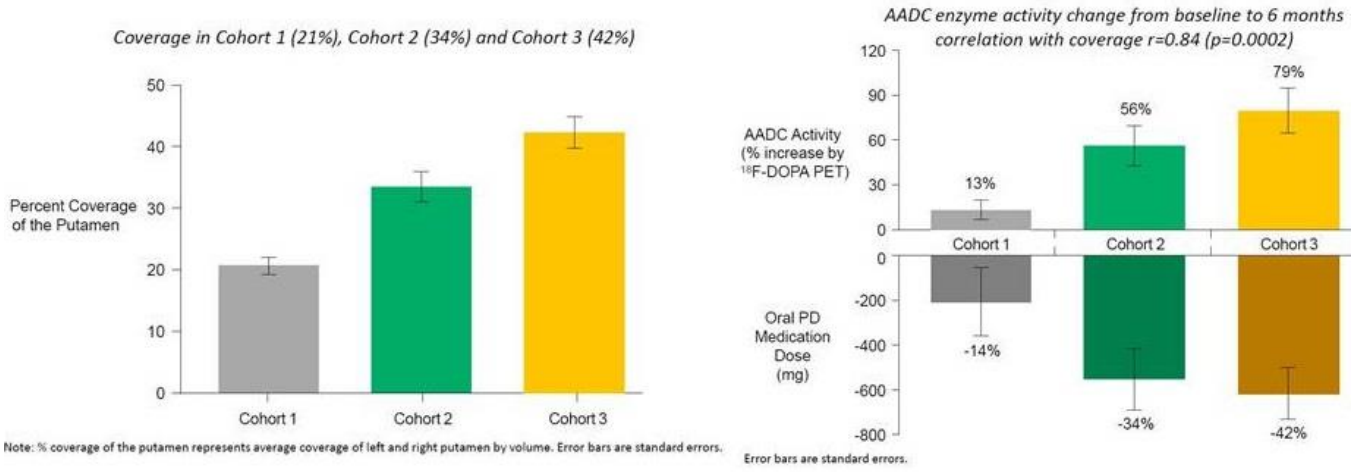
	Cohort 1	Cohort 2	Cohort 3
Age	57.4 (7.2)	58.4 (8.6)	57.4 (4.5)
Sex	1 Female, 4 Male	5 Male	1 Female, 4 Male
PD Duration (years)	9.9 (4.6)	10.1 (1.6)	8.5 (3.6)
UPDRS II off	13.6 (2.1)	16.0 (1.7)	19.8 (7.8)
UPDRS II on	3.0 (2.9)	3.6 (1.7)	5.0 (3.9)
UPDRS III off	37.2 (5.9)	35.8 (7.6)	38.2 (9.7)
UPDRS III on	7.6 (5.1)	17.0 (3.8)	16.0 (3.1)
Avg. Diary off-time (hrs)	4.9 (1.7)	4.2 (1.4)	4.7 (1.2)
Avg. Diary on-time (hrs)	10.5 (2.1)	10.7 (1.8)	10.3 (1.6)
Hoehn and Yahr Stage	3.0 (0.0)	3.0 (0.0)	3.4 (0.49)
LED(1) mg	1467.5 (615.0)	1635.5 (687.3)	1476.5 (429.1)

Mean (standard deviation)
(1) Levodopa Equivalent Dose

Source: Voyager Therapeutics.

In this Phase Ib study, VY-AADC01 delivered under the real-time intra-operative MRI-guidance achieved a 21%, 34%, and 42% mean coverage of the putamen in cohort 1 (n=5), cohort 2 (n=5), and cohort 3 (n=5), respectively. Of note, the percent coverage of the putamen refers to the average coverage of both left and right putamen by volume. In addition, these three cohorts achieved a 13%, 56%, and 79% mean increase in the AADC enzyme activity at six months relative to baseline as measured by the ^{18}F-DOPA PET scans (Exhibit 9), respectively, which appeared to correlate with decreased usage of oral PD medications including L-DOPA (a decrease of 14%, 34%, and 42% for cohorts 1, 2, and 3, respectively). According to the company, one patient in cohort 3 had a significant reduction in the dose of L-DOPA. Excluding this patient, the reductions in oral medications for other patients in cohort 3 were similar to those in cohort 2. This phenomenon of reduced need of L-DOPA appears to be unprecedented. In our opinion, these results suggest VY-AADC01 reached the target location and expressed AADC, resulting in increased conversion of L-DOPA to dopamine.

Exhibit 9: **Correlation of Putamen Coverage of VY-AADC01 With AADC Activity and Decrease in Oral Medications**



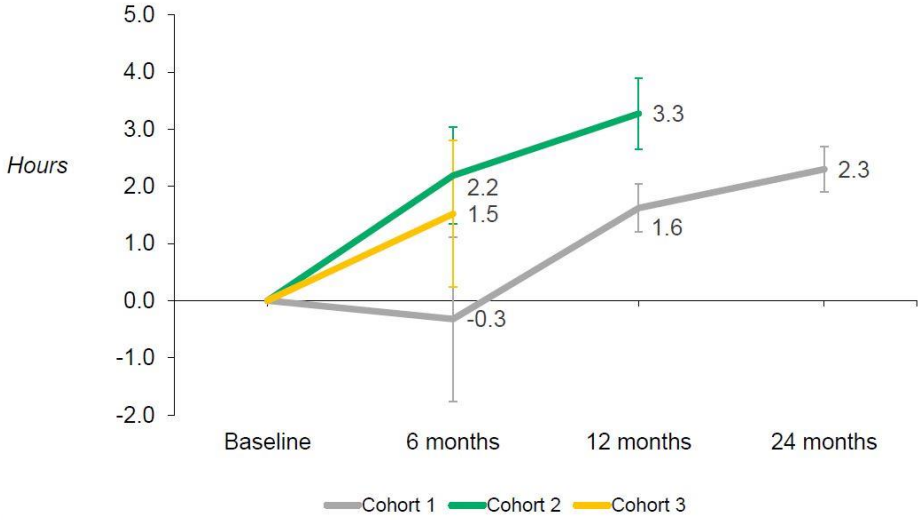
Source: Voyager Therapeutics.

Moreover, it appears that VY-AADC01 was able to achieve time-dependent motion function improvements as measured by the diary "on" and "off" time, which are well-established clinical endpoints acceptable by the FDA. While no placebo was included in the study, in our opinion, VY-AADC01 at higher doses delivered results that placebo would not be able to generate given the dose-dependent effects. Specifically, a 2.2-hour increase in "on" time without troublesome dyskinesia was seen in cohort 2 at six months after the treatment, which was further improved to a more than 3-hour increase at 12 months (placebo is expected to generate a 1-1.5 hour improvement at 12 months, according to the company). In addition, a 1.5-hour increase in "on" time without troublesome dyskinesia was seen in cohort 3 at six months. According to the company, one patient in cohort 3 experienced a significant reduction in the dose of L-DOPA due to dyskinesia, which could have affected the average "on" time of this cohort. Lastly, a similar trend was seen in cohort 1, albeit at a lower efficacy level. Notably, it appears that a trend of continued increase in "on" time without dyskinesia was seen in both cohorts 1 and 2 (2.3-hour vs. 1.6-hour increase at 24 and 12 months in cohort 1) (Exhibit 10).

According to the company, the time-dependent effects most likely resulted from changes in the plasticity of dopamine receptors as well as the circuits involved in controlling motor functions, which were also seen in the preclinical non-human primate studies.

Exhibit 10: **Diary "On" Time in Patients Treated With VY-AADC01**

>3-hour increase in diary on-time (w/o troublesome dyskinesia), including 4.0 hours of diary on-time w/o dyskinesia (data not shown) at 12 months in Cohort 2

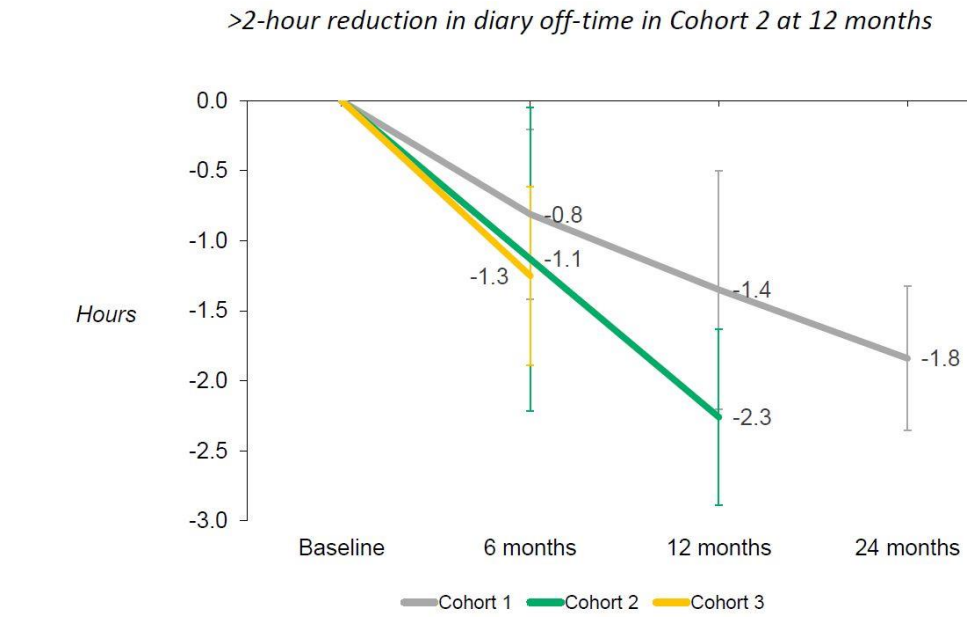


Note: Error bars represent standard errors. Hour change from baseline.

Source: Voyager Therapeutics.

With respect to "off" time in the diary, a 1.1 hour decrease in "off" time was seen in cohort 2 at six months post-treatment, which was further improved to a 2.2 hour decrease at 12 months (Exhibit 11). In addition, such effect was also seen in cohort 1 (a 0.8, 1.4, and 1.8 hour decrease at 6, 12, and 24 months, respectively) and cohort 3 (1.3 hour decrease at six months). Recall, in the registrational study of DUOPA (approved by the FDA in 2015) in patients with advanced PD, DUOPA achieved a statistically significant 4 hour decrease in "off" time as well as a 4.1 hour increase in "on" time at 12 weeks after the treatment. Given the promising results of VY-AADC01 seen to date, in our opinion, we are cautiously optimistic that the AAV-based AADC gene therapy could potentially achieve a similar clinical benefit, if not better, in the upcoming pivotal study.

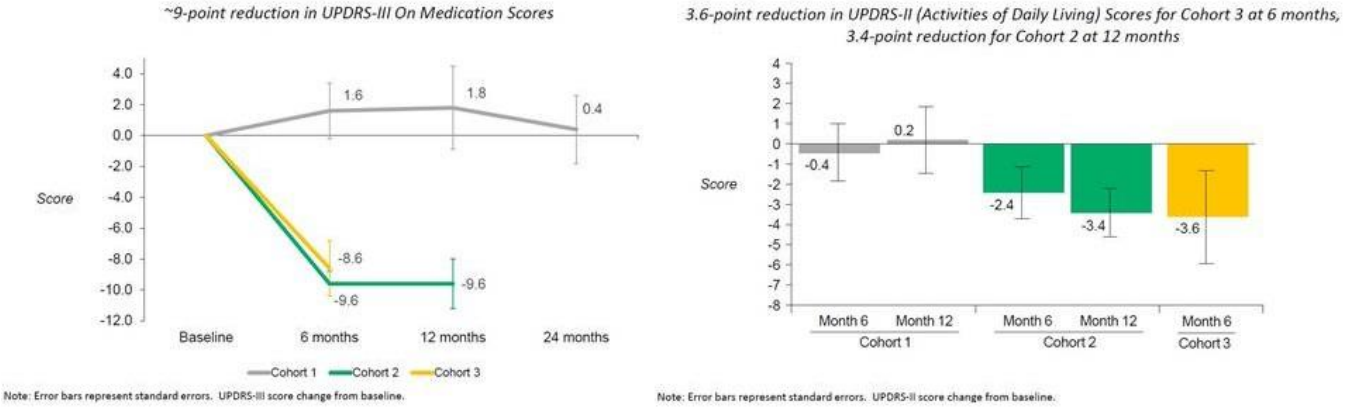
Exhibit 11: **Diary "Off" Time in Patients Treated With VY-AADC01**



Source: Voyager Therapeutics.

Lastly, VY-AADC01 also demonstrated clinical benefit to improve patients' quality of life (QOL) measured by a range of endpoints following the treatment, including 1) an 8.6 and 9.6 point reduction in the UPDRS-III on medication was seen in cohorts 3 and 2 at six months, respectively, which was maintained at 12 months in cohort 2; and 2) a 3.6 and 2.4 point improvement in the UPDRS-II off medication was achieved in cohorts 3 and 2, with a further improvement of 3.4 points seen in cohort 2 at 12 months (Exhibit 12).

Exhibit 12: **Change in UPDRS-III on medication and UPDRS-II off medication**



Source: Voyager Therapeutics.

On the safety side, VY-AADC01 was well tolerated with no vector-related serious adverse events (SAEs). In addition, the surgical procedure for the delivery of vectors was successfully completed in all 15 treated patients, with 14 of them being discharged from the hospital within two days following the surgery. One patient had a pulmonary embolism in the lung and a related heart arrhythmia, which was likely related to immobility during the surgical procedure and the subsequent formation of a blood clot. The SAE was resolved following the anti-coagulant treatment with the deep vein thrombosis (DVT) prophylaxis being subsequently included in the surgical protocol.

Future Timeline of the VY-AADC01 Franchise

Given the demonstrated efficacy and safety profile of VY-AADC01 seen to date, the company plans to initiate a Phase II/III pivotal study of VY-AADC01 in 4Q17 with the goal to dose the first patient in 1H18. In parallel, the Phase Ib study is ongoing with the long-term follow-up data from cohorts 1 – 3 slated to deliver in 1Q18. In addition, the company has initiated a route of administration Phase I study (NCT03065192) in which the vector is delivered through a posterior trajectory (back of the head) surgical procedure as compared to the previously used transfrontal (top of the head) surgical procedure. As of the most recent update in September 2017, three patients were dosed through the posterior delivery approach and discharged from the hospital the day after surgery. So far, a better putaminal coverage (approximately 50%) was achieved in these treated patients as compared to those seen in the ongoing Phase Ib study. In addition, the procedure time appeared to be reduced from 4-5 hours to 2-3 hours as only one injection was needed with this approach as compared to two with the transfrontal method. On the safety front, no SAEs were reported in the procedure.

Of note, the company is evaluating a different manufacturing procedure that uses the baculovirus/Sf9 cells as compared to the HEK293 cells to produce the gene therapy product candidate. The new product candidate VY-AADC02 uses the same vector as VY-AADC01 and can be produced in a more scalable manufacturing system. That said, as required by the FDA, the company needs to demonstrate a comparable quality and activity between VY-AADC02 and VY-AADC01 before conducting further clinical studies for VY-AADC02. According to our discussion with management, the company has received guidance from the FDA regarding the required in vitro and preclinical data needed to demonstrate a comparability between the new and old version of vectors used for the transgene delivery.

Competitive Landscape for Advanced PD

Besides the existing interventions (e.g., DUOPA, Xadago, and deep brain stimulation), there are a slew of drug candidates in clinical development for advanced PD (Exhibit 13). Among these products, four are at the Phase III or NDA stage including CVT-301 and Tozadenant (Acorda Therapeutics), Accordion Pill CD/LD (AP-CD/LD, Intec Pharma/Biogen), and ND0612 (NeuroDerm).

Exhibit 13: **Select Approved and Clinical-Stage Products for Advanced PD**

Drug	Company	MOA	Route of Administration	Phase	Trial ID
DUOPA (carbidopa and levodopa)	AbbVie	**Levodopa** (L-DOPA) can cross the blood-brain barrier and get converted to dopamine; **Carbidopa**, an AADC inhibitor, prevents the conversion of L-DOPA to dopamine before L-DOPA enters the brain	Percutaneous endoscopic gastrostomy guided infusion	Approved	N/A
CVT-301	Acorda Therapeutics	Inhaled LD/CD	Inhalation	NDA	
AP-CD/LD	Intec Pharma/Biogen	AADC inhibitors	Oral	III	NCT02605434
ND0612H	NeuroDerm	AADC inhibitors	Subcutaneous	III	NCT02782481
Tozadenant	Acorda Therapeutics	Adenosine A2a receptor	Oral	III	NCT03051607/ NCT02453386
IPX203	Impax Laboratories	AADC inhibitors	Oral	II	NCT03007888
PF-06649751	Pfizer Inc.	Dopamine	Oral	II	NCT02687542/ NCT03185481
Foliglurax (PXT002331)	Prexton Therapeutics	Metabotropic glutamate receptor subtype 4 (mGluR4)	Oral	I	NCT03162874
ISC-hpNSC	International Stem Cell Corporation	Stem cells	Intracerebral	I	NCT02452723
SER-214	Serina Therapeutics	D1R, D2R, D3R	Subcutaneous	I	NCT02579473
VY-AADC01	Voyager Therapeutics	AADC	Intracerebral	I	NCT03065192

Source: Raymond James research.

After conducting a comparative analysis of these late stage candidates, we noticed all of these therapeutic options have demonstrated clinically meaningful improvement in advanced PD patients with motor fluctuations in the context of increasing the good “on” time, decreasing the diary “off” time, as well as reducing UPDRS-III scores, all of which are FDA accepted endpoints (Exhibit 14). That said, given the different MOAs, in our opinion, these product candidates are not likely to pose significant direct competition to Voyager’s gene therapy.

Exhibit 14: **Safety and Efficacy Profile of Selected Therapeutic Candidates**

	AP-CD/LD		ND0612H		Tozadenant (120 mg)	CVT-301	VY-AADC01	
Study	Phase II		Phase IIa (006 study)		Phase IIb	SPAN-PD	Phase Ib	
Patient population	Advanced PD		Advanced PD		Advanced PD	PD with motor fluctuations	Advanced PD	
Dosing	50/375 mg, BID, 21 days	50/500 mg, BID, 21 days	24 hrs	ND0612H, 14 hrs; oral LD in the morning	120 mg, BID, 12 weeks	84 mg	cohort 1 7.5x10^11 vg	cohort 2 1.5x10^12 vg
Patient number	16	18	<19	<19	82	271	5	5
Control	CD/LD	CD/LD	N/A, baseline	N/A, baseline	Placebo	Placebo	NA, baseline	
Data readout	data readout from day 18 through day 20		change from baseline to Day 28		change from baseline to week 12	change from control at week 12	change from baseline at 12 months	
Efficacy								
Mean "Off" time at baseline (hrs)	NA	NA	5.5	5	about 6 hrs			
Mean "Off" time in treatment group (hrs)	2.4	2.8	2.7	3.7	NA			
Mean "Off" time in placebo (hrs)	4.3	5.1	NA	NA	NA			
Mean "Off" time reduction compared to baseline	NA	NA	-2.8 (p=0.004)	-1.3 (p=0.158)	-1.857		1.4 (3 pts only)	2.2
Mean "Off" time reduction vs control (hrs)	-1.9 (-44%, p<0.0001)	-2.3 (-45%, p<0.0001)	NA	NA	-1.094 (p<0.01)			
Mean good "On" time at baseline (hrs)	NA	NA	9.2	8.5	NA			
Mean good "On" time in treatment group (hrs)	13.4	12.4	12.9	11.3	NA			
Mean good "On" time in placebo (hrs)	11.3	9.7	NA	NA	NA			
Mean good "On" time increase compared to baseline	NA	NA	3.7 (p<0.001)	2.8 (p=0.003)	2.05		1.6 (3 pts only)	4.1
Mean good "On" time increase vs control (hrs)	2.1 (19%, p<0.0001)	2.7 (28%, p<0.0001)	NA	NA	1.19 (p<0.01)			
Complete reduction of "Off" time to zero	NA	NA	42% (n=19)	11%				
Daily IR L-DOPA frequency besides treatment	1.5	2	2.3	NA				
UPDRS-III decrease from baseline	NA	NA	NA	NA	-3.2	-9.83		
UPDRS-III decrease from baseline in control group					-0.994	-5.91		
UPDRS-III reduction vs control (hrs)						-3.92 (p=0.009)		
UPDRS-III decrease from baseline at 8 am	NA	NA	17.1 (from 37.4)	NA				
UPDRS-III decrease from baseline at 12 pm	NA	NA	7.2 (from 22.5)	NA				
UPDRS-III decrease from baseline at 4 pm	NA	NA	7 (from 28.8)	NA				
QOL change from baseline (PDQ39)	NA	NA	-7.5 (p=0.008)	3.6 (p=0.161)	-2.372 (-4.043 in placebo)		-1.9	-9.2
Safety	NO SAE and other significant toxicity compared to L-DOPA treatment		Infusion site reactions (nodules, bruising and erythema)		6 deaths, no relationship between the death and treatment was identified by IDMC	Cough in CVT-301 vs control: 12.9% vs 0.8%	One patient had a pulmonary embolism, likely due to surgical procedure, resolved	

Source: Raymond James research.

Exhibit 15: **Gene Therapy Products for PD**

Product	Company	Status	Vector	Transgene
VY-AADC01	Voyager	Phase I	AAV2	AADC
OXB-102 (a more potent formulation of OXB-101)	Oxford BioMedica	Phase I/IIa in preparation	Lentivirus	Tyrosine hydroxylase, AADC, and GTP cyclohydrolase
OXB-101 (ProSavin)	Oxford BioMedica	Terminated	Lentivirus	Tyrosine hydroxylase, AADC, and GTP cyclohydrolase
AMT-090 (AAV2-GDNF)	uniQure N.V.	Terminated	AAV2	glial-derived neurotrophic factor (GDNF)

Source: Company data, Raymond James research.

The ALS Franchise

Background of ALS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that is characterized by degeneration of motor neurons in the brain and spinal cord. The onset of the disease is usually around mid to late 50s as presented by limb weakness, difficulty chewing, speaking, swallowing, or breathing, with 15-20% of patients having progressive cognitive abnormalities marked by behavioral changes and, ultimately, dementia. Patients with ALS have a median survival rate of three to five years from the disease onset, with a more rapid progression and reduced survival among individuals who have a cognitive impairment. In regard to the etiology of ALS, a variety of genetic mutations due to inheritance (familial) or environmental exposures are known to contribute to the disease (Exhibit 16), with SOD1 (superoxide dismutase 1) being the first identified ALS gene in 1993. SOD1 encodes a protein whose function is to catalyze the conversion of superoxide anion (O_2-) to hydrogen peroxide (H_2O_2) and oxygen (O_2). Mutations in the SOD1 gene have been demonstrated to cause the accumulation of toxic aggregates of the SOD1 protein, leading to the mal- or dysfunction and death of motor neurons.

Exhibit 16: **Identified and Selected Genes Associated With ALS**

Locus	Gene symbol	Gene name	Chromosome
ALS 1	*SOD1*	Superoxide dismutase 1, soluble	21q22.11
ALS 2	*ALS2*	Amyotrophic lateral sclerosis 2 (juvenile)	2q33.2
ALS 3	Unknown	Unknown	18q21
ALS 4	*SETX*	Senataxin	9q34.13
ALS 5	*SPAST*	Spastin	2p24
ALS 6	*FUS*	Fused in sarcoma	16p11.2
ALS 7	Unknown	Unknown	20p13
ALS 8	*VAPB*	VAMP (vesicle-associated membrane protein)-associated protein B and C	20q13.33
ALS 9	*ANG*	Angiogenin, ribonuclease, RNase A family, 5	14q11.1
ALS 10	*TARDBP*	TAR DNA-binding protein	1p36.22
ALS 11	*FIG4*	FIG4 homologue, SAC1 lipid phosphatase domain containing (*Saccharomyces cerevisiae*)	6q21
ALS 12	*OPTN*	Optineurin	10p13
ALS 13	*ATXN2*	Ataxin 2	12q23–q24.1
ALS 14	*VCP*	Valosin-containing protein	9p13
ALS 15	*UBQLN2*	Ubiquilin 2	Xp11.21
ALS 16	*SIGMAR1*	Sigma non-opioid intracellular receptor 1	9p13
ALS 17	Unknown	Unknown	3p11.2
ALS 18	*PFN1*	Profilin 1	17p13.3
ALS–FTD 1	Unknown	Unknown	9q21–q22
ALS–FTD 2	*C9orf72*	Chromosome 9 open reading frame 72	9p21.2
ALS–FTD 3	*CHMP2B*	Charged multivesicular body protein 2B	3p12.1
ALS	*UNC13A*	Unc-13 homologue A (*Caenorhabditis elegans*)	19p13.12
ALS	*DAO*	D-amino-acid oxidase	12q24
ALS	*DCTN1*	Dynactin 1	2p13
ALS	*NEFH*	Neurofilament, heavy polypeptide	22q12.1–q13.1
ALS	*PRPH*	Peripherin	12q12
ALS	*SQSTM1*	Sequestosome 1	5q35
ALS	*TAF15*	TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68 kDa	17q11.1–q11.2
ALS	*SPG11*	Spastic paraplegia 11 (autosomal recessive)	15q14
ALS	*ELP3*	Elongator acetyltransferase complex subunit 3	8p21.1

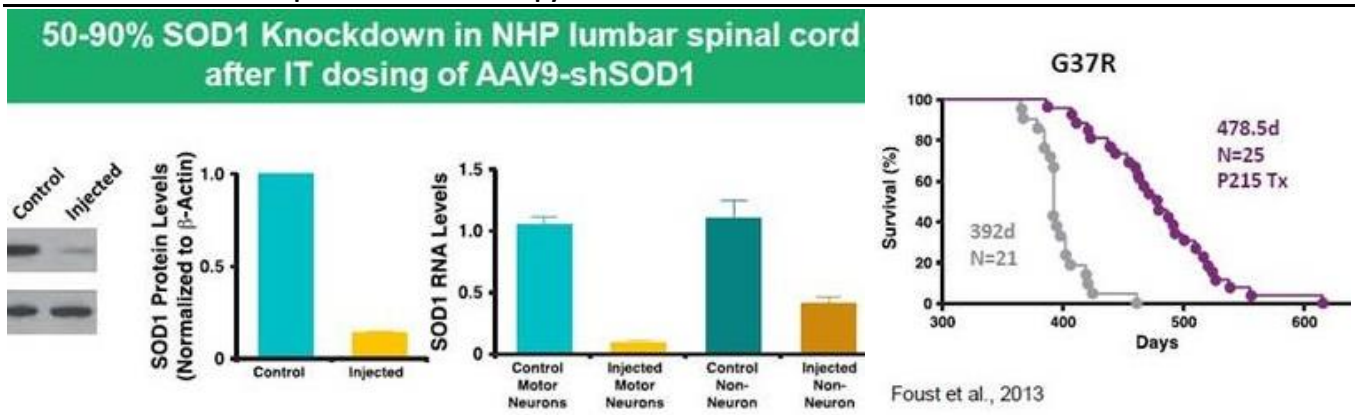
Source: Nat Rev Neurol. 2013 Nov;9(11):617-28.

The incidence of ALS in the U.S. and EU is about 1 to 2 per 100,000 people in a year, with an estimated prevalence being approximately 3 to 5 per 100,000. It is estimated that about 90% of ALS patients are sporadic (occurring without a family history), with the remaining 10% being familial, among whom an estimated 13-20% have an ALS that is caused by mutations in the SOD1 gene. Despite the poor prognosis and lethality of the disease, the current stand of care for ALS is primarily symptom management, including ventilatory support, nasogastric feeding, and prevention of aspiration (control of saliva secretion and cough assisting). In addition, Rilutek (Concordia/Sanofi) and Radicava (Mitsubishi Tanabe Pharma) are the only two drugs that are approved by the FDA for the treatment of ALS. While Rilutek acts by suppressing excessive motor neuron firing, Radicava is an antioxidant that is able to suppress oxidative stress. That said, none of these drugs were able to achieve a significant survival benefit.

VY-SOD101

With the goal to slow the functional decline and prolong survival without ventilatory support for patients with ALS caused by mutations in the SOD1 gene, Voyager is developing a gene therapy called VY-SOD101, which employs an AAV9 encapsulated RNAi sequence to knock down SOD1 expressed in motor neurons in the spinal cord through an intrathecal injection. Previous results from multiple proof-of-principle studies have shown that a significant knockdown of SOD1 in lumbar spinal cord can be achieved in a non-human primate model following an intrathecal injection of an AAV9 vector encapsulated SOD1-RNAi (Exhibit 17). Additionally, knockdown of SOD1 by an AAV vector delivered RNAi in mouse models has achieved an extension of median survival by 87 days compared to the control group.

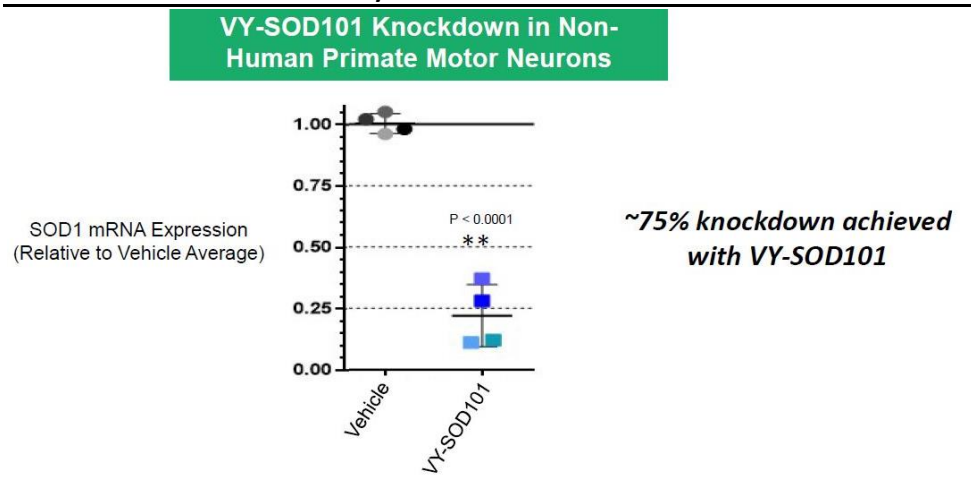
Exhibit 17: **Proof-of-Concept of AAV Gene Therapy for ALS With SOD1 Mutations**



Source: Voyager Therapeutics.

Employing a screening strategy towards over 100 RNAi sequences, the company has identified multiple highly potent RNAi sequences capable of knocking down SOD1, which were subsequently evaluated and optimized in different AAV capsids, microRNA expression cassettes, vector genome configurations, as well as doses and sites for the intrathecal injection. The selected candidate VY-SOD101 has demonstrated early activity as evidenced by an average of ~75% knockdown of the SOD1 mRNA in non-human primate motor neurons (Exhibit 18). Now the company is conducting IND-enabling studies for VY-SOD101 with a goal to file an IND in 4Q17/1Q18. Given the demonstrated SOD1 knockdown associated survival benefit in preclinical studies, we believe such results could potentially translate into clinical studies to provide a meaningful benefit for ALS patients with SOD1 mutations in their motor neurons.

Exhibit 18: **Knockdown of SOD1 by VY-SOD101 in Preclinical Models**



Source: Voyager Therapeutics.

The Huntington's Franchise

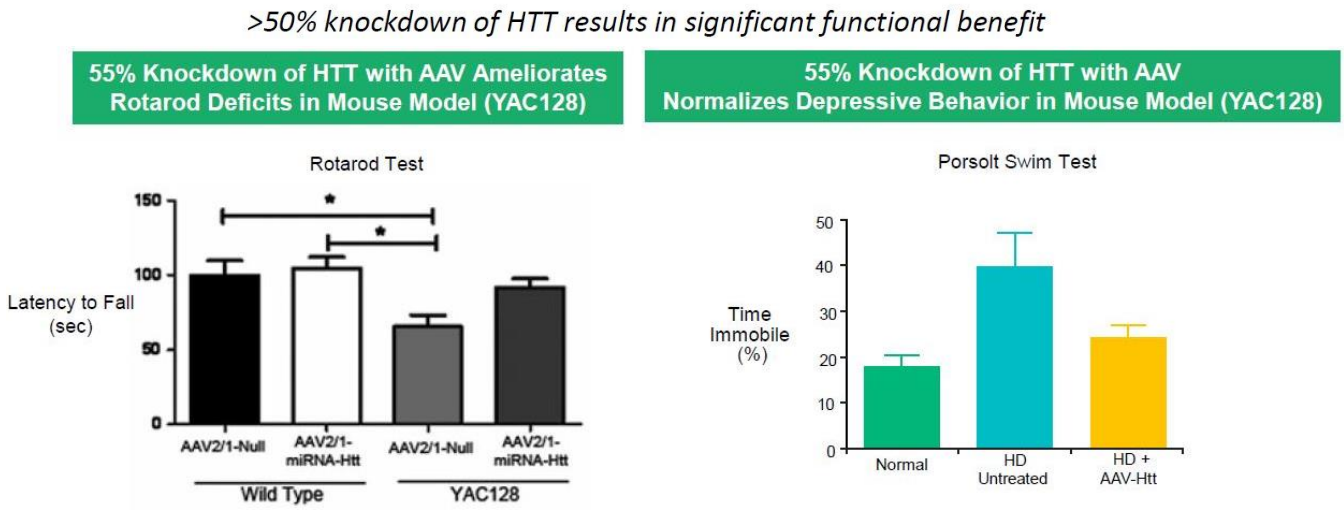
Huntington's Disease Overview

Huntington's disease (HD) is an inherited autosomal dominant genetic disorder that causes the progressive loss of nerve cells in the brain, resulting in a decline of motor and cognitive functions as well as a range of behavioral and psychiatric symptoms. HD is caused by mutations in the huntingtin (HTT) gene that leads to the accumulation of abnormal intracellular huntingtin protein and the subsequent neuronal cell death. The disease onset usually starts between the ages of 30 to 50 with symptom presentations including mood swings, impaired judgement, chorea (unsteady gait and involuntary movements), slurred speech, and weight loss. Based on the progression of the disease, HD can be generally divided into three stages across a 15- to 20-year period (early, middle, and late), with patients at the late stage eventually succumbing to pneumonia, heart failure, or other complications not caused by the disease itself. According to the Huntington's Disease Society of America, approximately 30,000 individuals in the United States have HD, with no approved disease modifying treatment. To date, only one drug, called tetrabenazine, has been approved by the FDA for the treatment of chorea associated with HD.

VY-HTT01

Voyager's gene therapy candidate is designed deliver an AAV vector encapsulated RNAi to the striatum and cortex region in the brain to specifically knock down the HTT expression and therefore could potentially slow down the progression of cognitive and motor dysfunction. Data from early preclinical studies has shown that an AAV vector consisting of HTT targeting RNAi delivered to the CNS in a mouse model was able to achieve a 55% HTT knockdown, which was successfully translated into a functional benefit (motor and behavior) (Exhibit 19). Through a range of screening and optimization processes, the company has selected a candidate called VY-HTT01, which has demonstrated an average of above 50% knockdown of HTT in non-human primates. Now the company is conducting IND-enabling studies for VY-HTT01 with a goal to file an IND in 2018.

Exhibit 19: **Functional Improvement by Targeting HTT in Preclinical Studies**



Source: Voyager Therapeutics.

In addition to the aforementioned product candidates, Voyager has multiple gene therapy programs in the early preclinical stages including: VY-FXN01 for Friedreich's ataxia, VY-TAU01 for frontotemporal dementia/Alzheimer's disease, and VY-NAV01 for severe, chronic pain, which could potentially provide additional meaningful data and add further upside.

Financial and Market Analysis

Revenues

Exhibit 20: **Market Model for Parkinson's Disease**

US	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
PD prevalence																			
PD incidence																			
# of patients with PD ('000)	1,000	1,007	1,014	1,021	1,028	1,035	1,043	1,050	1,057	1,065	1,072	1,080	1,087	1,095	1,103	1,110	1,118	1,126	1,134
# of new patients with PD annually ('000)	68	69	69	70	70	71	71	72	72	73	73	74	74	75	75	76	76	77	78
% of patients with advanced PD																			
# of patients with advanced PD ('000)	130	131	132	133	134	135	136	137	137	138	139	140	141	142	143	144	145	146	147
# of new patients with advanced PD annually ('000)	9	9	9	9	9	9	9	9	9	9	10	10	10	10	10	10	10	10	10
Market share for VY-AADC																			
# of patients eligible for VY-AADC at peak ('000)	13	13	13	13	13	13	14	14	14	14	14	14	14	14	14	14	15	15	15
# of new patients eligible for VY-AADC at peak ('000)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
WAC of VY-AADC	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000	$ 100,000
Total addressable market opportunity ('000)	$13,000,000	$13,091,000	$13,182,637	$13,274,915	$13,367,840	$13,461,415	$13,555,645	$13,650,534	$13,746,088	$13,842,311	$13,939,207	$14,036,781	$14,135,039	$14,233,984	$14,333,622	$14,433,957	$ 14,534,995	$14,636,740	$14,739,197
Peak market opportunity ('000)	$ 1,300,000	$ 1,309,100	$ 1,318,264	$ 1,327,492	$ 1,336,784	$ 1,346,141	$ 1,355,564	$ 1,365,053	$ 1,374,609	$ 1,384,231	$ 1,393,921	$ 1,403,678	$ 1,413,504	$ 1,423,398	$ 1,433,362	$ 1,443,396	$ 1,453,499	$ 1,463,674	$ 1,473,920
# of VY-AADC treated patients ('000)						1	4	8	11	14	14	14	14	14	14	14	15	15	15
Accumulated # of VY-AADC treated patients ('000)						1	5	14	25	38	52	66	81	95	109	124	138	153	167
sales of VY-AADC ('000)						$ 134,614	$ 406,669	$ 819,032	$ 1,099,687	$ 1,384,231	$ 1,393,921	$ 1,403,678	$ 1,413,504	$ 1,423,398	$ 1,433,362	$ 1,443,396	$ 1,453,499	$ 1,463,674	$ 1,473,920
Market penetration						1.0%	3.0%	6.0%	8.0%	10.0%	10.0%	10%	10%	10%	10%	10%	10%	10%	10%

Advanced Parkinson's disease (PD)	Key assumptions	Rationale
PD prevalence	0.307%	Literature review
PD incidence	0.021%	Literature review
% of patients with advanced PD	13%	Literature review
Total number of addressable patients with advanced PD for VY-AADC in 2017 (US)	~130,000	Calculated based on aforementioned assumptions
Number of new patients with advanced PD every year	~9,000	Calculated based on aforementioned assumptions
Pricing of VY-AADC	$100,000	Upfront one-time payment; A deep brain stimulation procedure for advanced PD can cost up to $100,000 per patient; The annual cost of DUOPA is approximately $67,824 (based on a WAC cost of $5,652/month)
Market share at peak	10%	While there are many existing therapies, we believe VY-AADC is likely to be positioned as an add-on therapy. Conservatively, we assume a 10% market share at this moment
Drug Risk	50%	VY-AADC has demonstrated a promising safety and efficacy profile in early stage clinical studies
Commercialization time	1Q22 (US)	Company guidance and our estimate;
Commercial rights	US only	We assume Sanofi-Genzyme will take the ex-U.S. commercial rights

Source: Raymond James research.

Operating Expenses

Building off of the R&D expense reported for 2Q17, we are projecting R&D expenses of $65 million for 2017, increasing to $103 million for 2020. The R&D assumptions from 2017 to 2020 take into account continued expenditure for the clinical trials associated with the company's VY-AADC franchise as well as other early stage programs.

Based on the SG&A expense reported for 2Q17, we are projecting SG&A expenses of $19 million for 2017, increasing to $22 million for 2020.

The COGS for VY-AADC is expected to be 5% of the revenues.

Net Income and EPS

The net income for 2Q17 was $(18.9) million, or $(0.73) per share. We are projecting net income of $(80.3) million or $(3.09) per diluted share in 2017, decreasing to $(124.4) million or $(3.28) per diluted share in 2020.

Cash

Based on our estimates, we expect a cash burn rate of approximately $20 million per quarter for the remainder of 2017, and we believe the current cash position is sufficient to fund operations into 2019. However, we have modeled two capital raises into our estimates. We expect the company to raise approximately $150 million in early 2019 and $150 million in 2020. We have included these raises into our model as a necessity for the company to sustain operations until it can potentially reach profitability.

Valuation and Price Target Analysis

Valuation

We value Voyager Therapeutics using a sum-of-the-parts analysis of the company's Parkinson's disease (PD) program as well as its current cash levels. To derive a value for the PD program, we conduct a risk-adjusted net present value (rNPV) analysis, which utilizes the net income as a proxy of the free cash flow (FCF). The revenues for VY-AADC are derived from our market model (see page 207 for more detail), whereas the R&D and SG&A expenses are estimated largely based on the number of patients on clinical trials and the size of a sales force, respectively. To calculate the NPV, the approximate FCF based on the net income for any given year is discounted at a rate of 15% back to the present time. To account for the clinical/regulatory risk, the NPV is further multiplied by a probability of success assigned to each program. Using this methodology, we derive a risk-adjusted per share NPV of $30.53 for VY-AADC. Combining this value with the cash value of $4.07 per share, we derive a price target of $34.60, which we round to $35.

Exhibit 21: **Valuation Analysis**

Product	POS	Per share value	Weighting
VY-AADC for Parkinson's disease	50%	$30.53	88%
Cash	N/A	$4.07	12%
Total		$34.60	

Key assumptions

Discount rate	15%
Fully diluted shares outstanding ('000)	29,811

Source: Raymond James research.

Exhibit 22: **rNPV of VY-AADC**

Year	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034	12/31/2035
Revenues (risk-unadjusted, '000)	$ -	$ -	$ -	$ -	$ -	$ 134,614	$ 406,669	$ 819,032	$ 1,099,687	$ 1,384,231	$ 1,393,921	$ 1,403,678	$ 1,413,504	$ 1,423,398	$ 1,433,362	$ 1,443,396	$ 1,453,499	$ 1,463,674	$ 1,473,920
COGS						6,731	20,333	40,952	54,984	69,212	69,696	70,184	70,675	71,170	71,668	72,170	72,675	73,184	73,696
R&D	35,793	78,751	97,688.29	102,573	61,544	30,772	15,386	15,539.76	15,695	15,852	16,011	16,171	16,332	16,496	16,661	16,827	16,996	17,166	17,337
SGA	9,443	19,816	20,807	21,847	37,940	54,837	63,578	66,757	70,095	73,600	77,280	81,144	85,201	89,461	93,934	98,631	103,563	108,741	114,178
Income before tax	(45,236)	(98,567)	(118,495)	(124,420)	(99,483)	42,275	307,372	695,783	958,912	1,225,567	1,230,934	1,236,179	1,241,295	1,246,271	1,251,099	1,255,768	1,260,266	1,264,584	1,268,709
Tax	-	-	-	-	-	-	15,369	139,157	191,782	245,113	246,187	247,236	248,259	249,254	250,220	251,154	252,053	252,917	253,742
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Net income	(45,236)	(98,567)	(118,495)	(124,420)	(99,483)	42,275	292,003	556,627	767,130	980,454	984,747	988,944	993,036	997,017	1,000,879	1,004,614	1,008,213	1,011,667	1,014,967
Present time	10/9/2017																		
Discount period	0.23	1.23	2.23	3.23	4.23	5.23	6.23	7.23	8.23	9.23	10.23	11.23	12.23	13.23	14.23	15.23	16.23	17.23	18.23
Discount rate	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
NPV	(43,818)	(83,025)	(86,792)	(79,245)	(55,098)	20,360	122,285	202,700	242,918	269,973	235,787	205,906	179,790	156,966	137,021	119,593	104,367	91,064	79,445
NPV of net income (2017-2035)	1,820,198																		
Fully diluted shares outstanding ('000)	29,811																		
Per share value	61.06																		
Probability of success	50%																		
Risk-adjusted per share value	**30.53**																		

Source: Raymond James research.

Bull/Bear Analysis

In our bull case, we assume a higher probability of success for the company's Parkinson's disease program, which results in a value of about $47 per share, indicating a 132% return from the current level. In our bear case, we assume a 10% chance of success for the PD program and derive a value of about $10, suggesting downside risk of 51% from the current level.

Exhibit 23: **Bull/Bear Analysis**

Probability of success	Bull	Base	Bear
VY-AADC for Parkinson's disease	70%	50%	10%
Valuation	$47	$35	$10
Return	132%	73%	-51%

Note: The closing price of 10/9/17 was used to calculate the potential returns
Source: Raymond James research.

Management

Steven Paul, M.D., President and Chief Executive Officer

Dr. Steven Paul, a member of the board of directors and a venture partner at Third Rock Ventures, brings to Voyager more than 35 years of neuroscience expertise and an extensive track record in CNS drug discovery and development. As a venture partner at Third Rock, he helps lead the ideation and development of new companies, including Voyager. Before joining Voyager, Dr. Paul was the founding director of the Appel Alzheimer's Disease Research Institute, where he was the principal investigator of the institute's novel adeno-associated virus (AAV) gene therapy program for Alzheimer's disease, as well as professor of neuroscience, psychiatry, and pharmacology at Weill Cornell Medical College. Preceding his appointment at Weill Cornell, Dr. Paul spent 17 years at Eli Lilly, during which time he held several key leadership roles, including president of the Lilly Research Laboratories, and vice president of discovery research and neuroscience research. As president of the Lilly Research Laboratories, he was responsible for the company's overall R&D strategy, expanding its efforts in oncology and biotechnology and resulting in a pipeline of approximately 70 new molecular entities. Prior to Lilly, Dr. Paul served as scientific director of the National Institute of Mental Health. He has also served as medical director in the Commissioned Corps of the United States Public Health Service. Dr. Paul currently serves on the board of Sage Therapeutics and Alnylam Pharmaceuticals, and is a chairman of the board for the Foundation for the National Institutes of Health. He previously served on the board of Sigma-Aldrich, which was acquired by Merck KGaA. Dr. Paul holds a Bachelor of Arts in biology and psychology from Tulane University and a Master of Science and Doctor of Medicine from the Tulane University School of Medicine.

Jane Pritchett Henderson, Chief Financial Officer and Senior Vice President of Corporate Development

Jane Pritchett Henderson has more than 28 years of life sciences industry and banking experience and leadership. Prior to Voyager, Ms. Henderson served as chief financial and business officer of Kolltan Pharmaceuticals, Inc., having joined the privately held biopharmaceutical company in 2013 and leading the sale of Kolltan to Celldex Pharmaceuticals, Inc., in late 2016. Previously, Ms. Henderson served as vice president of business development at ISTA Pharmaceuticals, Inc., when ISTA Pharmaceuticals was acquired by Bausch + Lomb. Prior to ISTA Pharmaceuticals, Ms. Henderson served as chief financial officer and head of business development at Axerion Pharmaceuticals, Inc., and as chief financial officer and chief business officer at Panacos Pharmaceuticals, Inc. In addition to her industry experience, Ms. Henderson's extensive

healthcare investment banking experience includes the execution of more than 95 mergers and acquisitions, advisory and financing deals as managing director and other senior roles at HSBC Holdings plc, Canadian Imperial Bank of Commerce, Lehman Brothers, and Salomon Brothers. Ms. Henderson currently serves on the board of directors of Eleven Biotherapeutics, Inc. Ms. Henderson holds a Bachelor of Science in psychology from Duke University.

Bernard Ravina, M.D., M.S., Chief Medical Officer

Dr. Bernard Ravina has deep expertise across a number of CNS diseases and more than 15 years of clinical research experience in both academia and industry. Prior to Voyager, Dr. Ravina was medical director in clinical development at Biogen Idec. There, he worked on both small molecule drugs and biologics for the treatment of neurological disorders and was responsible for biomarker and clinical development plans in Parkinson's disease, stroke, and neuropathic pain. Before joining Biogen Idec, Dr. Ravina was associate professor of neurology, director of the movement and inherited neurological disorders unit, and associate chair of neurology at the University of Rochester School of Medicine. Dr. Ravina holds a Doctor of Medicine from Johns Hopkins University School of Medicine and a Master of Science in clinical epidemiology and biostatistics from the University of Pennsylvania. He completed residency training in neurology and a fellowship in Parkinson's disease and movement disorders at the University of Pennsylvania.

Dinah Sah, Ph.D., Chief Science Officer

Dr. Dinah Sah has more than 20 years of experience in research and drug development in the biotechnology industry, focused on neurodegenerative diseases. Dr. Sah has led multiple programs from early research through Phase I clinical trials, as well as discovering novel therapeutic targets and drug candidates that have advanced into clinical development. Before joining Voyager, Dr. Sah was at Alnylam Pharmaceuticals, where she was most recently vice president of research, providing scientific leadership and administrative oversight of discovery research and multiple research and development programs. At Alnylam, her leadership of several RNAi therapeutics R&D programs resulted in the landmark demonstration of human proof-of-mechanism for this novel class of drugs. Prior to Alnylam, Dr. Sah was associate director of research at Biogen, where she led neuroscience research and strategic planning for neurobiology, and before that, she headed neuroscience research at Signal Pharmaceuticals, where she also led multiple corporate partnerships and projects. Dr. Sah is an inventor on more than 25 patents, and her publications across diverse research areas include 18 articles in the New England Journal of Medicine, Nature Medicine, Nature Biotechnology, Nature Neuroscience, Nature Chemical Biology, Nature Reviews Drug Discovery, Molecular Therapeutics, Neuron, PNAS, and EMBO Journal. Dr. Sah received a Bachelor of Science in biology from the Massachusetts Institute of Technology, a Doctor of Philosophy in neurobiology from Harvard University, and completed her postdoctoral training at Harvard Medical School.

Matthew P. Ottmer, Chief Operating Officer

Matthew Ottmer has more than 18 years of biotechnology industry experience, including executive leadership of business operations, product development, and commercialization across multiple therapeutic areas and all stages of development. Mr. Ottmer joins Voyager most recently from Momenta Pharmaceuticals, Inc., where he was chief operating officer, responsible for program and alliance management, research, clinical development, pharmaceutical sciences, and commercial activities since late 2015. Prior to this role, he spent 16 years at Biogen, Inc., in a variety of leadership roles, including as senior vice president of strategy and emerging businesses, head of Tysabri business, chief of staff to the chief executive officer, president of Syntonix Pharmaceuticals, Inc. (a wholly owned subsidiary of Biogen, now Bioverativ, Inc.), and vice president of global operations. Mr. Ottmer received a Bachelor of Arts in political science from the University of Michigan and an MBA from Northwestern University's Kellogg School of Management.

Voyager Income Statement

All figures in thousands ($), except per share data

	FY16A	1Q17A	2Q17A	3Q17E	4Q17E	FY17E	1Q18E	2Q18E	3Q18E	4Q18E	FY18E
Revenues											
VY-AADC for Parkinson's disease					-	-	-	-	-	-	-
Collaboration revenues		1,464	1,177			2,641					-
Total revenues	14,220	1,464	1,177	-	-	2,641	-	-	-	-	-
Operating expenses:											
Cost of sales						-					-
Research and development	42,249	14,072	15,300	16,830	18,513	64,715	18,883	19,261	19,646	20,960	78,751
General and administrative	13,270	4,914	4,516	4,651	4,791	18,873	4,863	4,935	4,984	5,034	19,816
Total operating expenses	55,519	18,986	19,816	21,481	23,304	83,588	23,746	24,196	24,630	25,995	98,567
Operating income	**(41,299)**	**(17,522)**	**(18,639)**	**(21,481)**	**(23,304)**	**(80,947)**	**(23,746)**	**(24,196)**	**(24,630)**	**(25,995)**	**(98,567)**
Other income (expense):											
Interest income	976	253	255			508					-
Other income (expense):	182	395	(297)			98					-
Total other income (expense)	1,158	648	(42)	-	-	508	-	-	-	-	-
Income (loss) before taxes	**(40,141)**	**(16,874)**	**(18,681)**	**(21,481)**	**(23,304)**	**(80,439)**	**(23,746)**	**(24,196)**	**(24,630)**	**(25,995)**	**(98,567)**
Income tax provision	52	226	(195)	-	-	31	-	-	-	-	-
Net income (loss)	**(40,193)**	**(16,648)**	**(18,876)**	**(21,481)**	**(23,304)**	**(80,310)**	**(23,746)**	**(24,196)**	**(24,630)**	**(25,995)**	**(98,567)**
Net (loss) per share, basic	**(1.59)**	**(0.65)**	**(0.73)**	**(0.82)**	**(0.89)**	**(3.09)**	**(0.90)**	**(0.92)**	**(0.81)**	**(0.85)**	**(3.47)**
Net (loss) per share, diluted	**(1.59)**	**(0.65)**	**(0.73)**	**(0.82)**	**(0.89)**	**(3.09)**	**(0.90)**	**(0.92)**	**(0.81)**	**(0.85)**	**(3.47)**
Weighted average shares outstanding, basic	25,302	25,792	25,946	26,046	26,146	25,983	26,246	26,346	30,446	30,546	28,396
Weighted average shares outstanding, diluted	25,302	25,792	25,946	26,046	26,146	25,983	26,246	26,346	30,446	30,546	28,396

Voyager Income Statement

All figures in thousands ($), except per share data

	FY16A	FY17E	FY18E	FY19E	FY20E
Revenues					
VY-AADC for Parkinson's disease		-	-	-	-
Collaboration revenues		2,641	-		
Total revenues	14,220	2,641	-	-	-
Operating expenses:					
Cost of sales		-	-		
Research and development	42,249	64,715	78,751	97,688	102,573
General and administrative	13,270	18,873	19,816	20,807	21,847
Total operating expenses	55,519	83,588	98,567	118,495	124,420
Operating income	**(41,299)**	**(80,947)**	**(98,567)**	**(118,495)**	**(124,420)**
Other income (expense):					
Interest income	976	508	-		
Other income (expense):	182	98	-		
Total other income (expense)	1,158	508	-	-	-
Income (loss) before taxes	**(40,141)**	**(80,439)**	**(98,567)**	**(118,495)**	**(124,420)**
Income tax provision	52	31	-		
Net income (loss)	**(40,193)**	**(80,310)**	**(98,567)**	**(118,495)**	**(124,420)**
Net (loss) per share, basic	**(1.59)**	**(3.09)**	**(3.47)**	**(3.51)**	**(3.28)**
Net (loss) per share, diluted	**(1.59)**	**(3.09)**	**(3.47)**	**(3.51)**	**(3.28)**
Weighted average shares outstanding, basic	25,302	25,983	28,396	33,796	37,946
Weighted average shares outstanding, diluted	25,302	25,983	28,396	33,796	37,946

Voyager Balance Sheet

Figures in $ thousands except per share data

ASSETS	3Q16	4Q16	1Q17	2Q17
Current Assets:				
Cash and cash equivalents	63,507	36,641	43,604	66,300
Marketable securities, current	127,646	137,777	114,066	75,023
Prepaid expenses and other current assets	1,868	4,368	3,410	3,403
Total Current Assets	193,021	178,786	161,080	144,726
Property and equipment, net	4,253	7,893	10,134	10,674
Deposits and other non-current assets	2,294	1,527	1,876	1,534
Marketable securities, non-current	2,416	1,360	2,000	1,480
TOTAL ASSETS	201,984	189,566	175,090	158,414
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current Liabilities:				
Accounts payable	787	550	557	307
Accrued expenses	6,304	6,488	5,593	7,314
Deferred revenue, current portion	12,296	6,764	4,914	4,215
Total Current Liabilities	19,387	13,802	11,064	11,836
Deferred rent	1,988	4,999	5,058	5,430
Deferred revenue, net of current portion	31,456	34,818	35,248	34,838
Other non-current liabilities	29	25	1,023	1,019
TOTAL LIABILITIES	52,860	53,644	52,393	53,123
STOCKHOLDERS' EQUITY				
Common stock	25	26	26	26
Additional paid-in capital	223,811	225,963	229,009	230,773
Accumulated other comprehensive income (loss)	630	(52)	325	30
Accumulated deficit	(75,342)	(90,015)	(106,663)	(125,538)
TOTAL STOCKHOLDERS' EQUITY	149,124	135,922	122,697	105,291
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	201,984	189,566	175,090	158,414

Voyager Statement of Cash Flows

Figures in thousands ($) except per share data

	3Q16	4Q16	1Q17	2Q17
Operating Activities:				
Net Loss	(8,997)	(14,673)	(16,648)	(18,875)
Adjustments to Reconcile Net Loss to Net Cash Used:				
Stock-based compensation expense	1,789	1,782	2,165	1,539
Depreciation	160	164	317	409
Amortization of premiums and discounts on marketable securities	144	125	92	77
In-kind research and development expenses	237	193	44	69
Other non-cash items	(484)	1,118	855	(999)
Changes in Operating Assets and Liabilities:				
Prepaid expenses and other current assets	(384)	(536)	958	7
Other non-current assets	-	(50)	(1,490)	1,490
Deferred revenue	(3,669)	(2,363)	(1,464)	(1,178)
Accounts payable	333	(237)	280	(523)
Accrued expenses	682	335	(504)	1,235
Other non-current liabilities	-	-	1,000	-
Lease incentive benefit	-	1,050	101	414
Net Cash Provided (Used) in Operating Activities	(10,189)	(13,092)	(14,294)	(16,335)
Investing Activities:				
Purchases of property and equipment	(503)	(3,869)	(2,945)	(467)
Change in restricted cash	-	50	-	-
Purchases of marketable securities	(54,586)	(45,723)	-	-
Proceeds from maturities of marketable securities	61,700	35,400	23,600	39,000
Net Cash Provided (Used) in Investing Activities	6,611	(14,142)	20,655	38,533
Financing Activities:				
Proceeds from the exercise of stock options	53	368	602	498
Net Cash Provided (Used) in Financing Activities	53	368	602	498
Net Decrease in Cash and Cash Equivalents	(3,525)	(26,866)	6,963	22,696
Cash and Cash Equivalents at Beginning of Period	67,032	63,507	36,641	43,604
Cash and Cash Equivalents at End of Period	63,507	36,641	43,604	66,300

Appendix —Description of Select Gene Therapy Companies

The following company descriptions were obtained from the companies via their websites and/or company filings. Any opinions or forward looking statements within the appendix are not those of the covering analyst or Raymond James and Associates and should not be used to make investment decisions.

Abeona Therapeutics Inc. (NASDAQ: ABEO)

3333 Lee Parkway, Suite 600, Dallas, TX 75219

(216) 346-7405

Abeona Therapeutics Inc. is a clinical-stage biopharmaceutical company focused on developing novel therapies for life-threatening rare genetic diseases. Developing therapies for rare disease requires new approaches and strong collaboration between researchers, industry, regulators and patient groups. Abeona was forged from the company's close collaborations with key stakeholders all dedicated to transforming new biotechnology insights into breakthrough treatments for rare diseases. Abeona Therapeutics is working on a number of exciting technologies (including gene therapies) and products aimed at curing various rare diseases. In many disorders, particularly genetic diseases caused by a single genetic defect, gene therapy aims to treat a disease by delivering the correct copy of DNA into a patient's cells.

Agilis Biotherapeutics (Private)

Kendall Square, 245 First St #1800, Cambridge, MA 02142

(510) 673-7809

Agilis Biotherapeutics is advancing innovative DNA therapeutics designed to provide long-term efficacy for patients with debilitating, often fatal, rare genetic diseases that affect the central nervous system. The company's therapies are engineered to impart sustainable clinical benefit, and potentially a functional cure, by inducing persistent expression of a therapeutic gene. Its technology enables precise targeting and restoration of lost gene function, while avoiding unintended off-target effects. Agilis' integrated strategy increases the efficiency of developing DNA therapeutics to more rapidly advance safe, targeted gene therapies that achieve long-term efficacy and enable patients to remain asymptomatic without continuous invasive treatment.

Initially, Agilis is developing DNA therapeutics for patients with rare diseases of the central nervous system (CNS) that are caused by single-gene defects. Its lead programs are focused on Aromatic L-Amino Acid Decarboxylase Deficiency (AADC-D), Friedreich's ataxia (FA) and Angelman syndrome (AS). AADC deficiency arises from mutations in the DDC gene and in its profound form results in severe developmental failures, global muscular hypotonia, severe long-lasting seizures, and premature death. FA is a rare inherited neurodegenerative disease that results in a physically debilitating, life-shortening condition. AS is a rare disorder characterized by a severe cognitive disability. Agilis Biotherapeutics is also pursuing development work in the rare CNS disease Fragile X syndrome.

Its longer-term goal is to engineer, develop, and commercialize a robust pipeline of pioneering DNA therapeutics that address a broad range of rare CNS diseases for which there are no or limited therapies, and for which the basis for biomedical intervention is clear. The diseases it targets usually appear during childhood, creating significant illness and long-term quality-of-life consequences that often include premature mortality.

American Gene Technologies International Inc. (Private)

15010 Broschart Rd #110, Rockville, MD 20850

(301) 337-2100

AGT is developing and commercializing genetic medicines targeting major diseases, including HIV/AIDS, Phenylketonuria (PKU) and Hepatocellular carcinoma (liver cancer, or HCC). The company's drug candidates have achieved initial proof of concept in preclinical studies and have potential to deliver cost-effective therapies that are better targeted and more potent with fewer side effects. AGT's drugs will treat symptomatic disease, but are intended to provide durable cures that extend the length and improve the quality of patients' lives.

AGT anticipates becoming a clinical stage company in 2017 with a Phase I human trial for its HIV functional cure. AGT has three lead candidate drugs in its pipeline – all based on its proven drug-delivery platform — a proprietary vector with broad applicability in immuno-oncology and thousands of additional diseases. Curing even just one of the diseases will be a remarkable success for patients, society and researchers.

Currently, AGT has lead drug candidates for the following indications:

- HIV/AIDS
- Phenylketonuria (PKU)
- Hepatocellular carcinoma (liver cancer, or HCC)

In addition to its lead programs, AGT has research and drug development in:

- Familial dysautonomia
- Parkinson's disease

Applied Genetic Technologies Corporation (NASDAQ: AGTC)

14193 NW 119th Terrace Suite 10, Alachua, Florida 32615

(386) 462-2204

AGTC is a clinical-stage biotechnology company that uses its proprietary gene therapy platform to develop products designed to transform the lives of patients with severe diseases, with an initial focus in ophthalmology. AGTC's lead product candidates focus on inherited orphan diseases of the eye, caused by mutations in single genes that significantly affect visual function and currently lack effective medical treatments.

AGTC's product pipeline includes six named ophthalmology development programs across five targets (X-linked retinoschisis (XLRS), X-linked retinitis pigmentosa (XLRP), achromatopsia, wet age-related macular degeneration and blue cone monochromacy), one non-ophthalmology program (alpha-1 antitrypsin deficiency) and proof-of-concept data in multiple additional indications. AGTC employs a highly targeted approach to selecting and designing its product candidates, choosing to develop therapies for indications having high unmet medical need, clinical feasibility and commercial potential. AGTC has a significant intellectual property portfolio and expertise in the design of gene therapy products including capsids, promoters and expression cassettes, as well as expertise in the formulation, manufacture and physical delivery of gene therapy products.

Asklepios BioPharmaceutical, Inc. (Private)

870 Martin Luther King, Jr. Blvd., Chapel Hill, NC 27514

919-968-2727

Asklepios BioPharmaceutical, Inc. (AskBio) was founded in 2003 by Richard Jude Samulski, PhD and Sheila Mikhail in Chapel Hill, NC to take advantage of the deep gene therapy resources in the Research Triangle Park area. AskBio has since set the standard for gene therapy clinical development including a deep portfolio of intellectual property in gene therapy for multiple diseases and an advanced manufacturing process. AskBio has established and formed industry alliances for multiple spin out companies and continues to pursue new gene therapy technologies and treatments

AveXis Inc. (NASDAQ: AVXS)

2275 Half Day Rd, Suite 200, Bannockburn, IL 60015

(847) 572-8280

AveXis is committed to moving gene therapies into the clinical setting for patients and families devastated by rare and orphan neurological genetic diseases. With the support of industry and academic alliances, the company is advancing cutting-edge science in order to treat rare and life-threatening genetic diseases—starting with its clinical-stage, proprietary gene therapy candidate, AVXS‑101.

Its proprietary gene therapy candidate, AVXS-101, has been granted Orphan Drug Designation for the treatment of all types of spinal muscular atrophy (SMA) and Breakthrough Therapy Designation, as well as Fast Track Designation for the treatment of SMA Type 1—one of the most life-threatening neurological genetic disorders.

AVROBIO Inc. (Private)

700 Technology Square, Suite 101, Cambridge, MA 02139

781-962-6030

AVROBIO, Inc., a leader in lentiviral-based gene therapies, is a clinical stage company developing disruptive therapies that have the potential to transform patients' lives in a single dose. The aim of AVROBIO's gene therapy programs is to deliver lasting and meaningful benefits for patients with genetic diseases by restoring normal gene function and enzyme/protein production.

AVROBIO's Gene Therapy for Fabry Disease (AVR-RD-01): A Phase 1 trial is currently enrolling patients in Canada. The primary objective of this trial is to evaluate the safety and tolerability of infusing the patient's own genetically modified stem cells that express the enzyme α-galactosidase A (α-Gal A). A phase 2 trial will be initiated in early 2018; the primary objective of that trial is to assess the safety and efficacy of AVR-RD-01.

AVROBIO's Gene Therapy for Gaucher Disease (AVR-RD-02): The primary objective of the upcoming Phase 1/2 trial is to evaluate the safety and efficacy of AVR-RD-02, the patient's own genetically modified stem cells that will express glucocerebrosidase (GCase), the enzyme that is deficient in Gaucher Disease.

AVROBIO's Gene Therapy for Pompe Disease (AVR-RD-03): Pre-clinical experiments using its gene therapy platform and proprietary lysosomal targeting sequence demonstrated safety and efficacy in Pompe disease mice. Preclinical studies are underway to enable a future Phase 1/2 trial.

AVROBIO's Gene Therapy for Cystinosis (AVR-RD-04): The primary objective of the upcoming Phase 1/2 trial is to evaluate the safety and efficacy of using the patient's own stem cells, which are genetically modified to express the CTNS protein, to treat the underlying disease.

BioMarin Pharmaceutical Inc. (NASDAQ: BMRN)

770 Lindaro Street, San Rafael, CA 94901

(415) 506-6700

BioMarin is a world leader in developing and commercializing innovative biopharmaceuticals for rare diseases driven by genetic causes.

BioMarin focuses on developing first-in-class and best-in-class therapeutics that provide meaningful advances to patients who live with serious and life-threatening rare genetic diseases. BioMarin remains steadfast to its original mission—to bring new treatments to market that will make a big impact on small patient populations. These patient populations are mostly children, suffering from diseases so rare, that the entire patient population can number as few as 1,000 people worldwide. These conditions are often inherited, difficult to diagnose, progressively debilitating, have few, if any, treatment options, and are usually ignored.

Time is critical to patients with rare diseases, and BioMarin strives to quickly develop important therapies for them. The efficiency and speed of its research, development, manufacturing, and commercial efforts is at the heart of its ability to urgently deliver therapies. BioMarin track record of developing and commercializing new treatments has been significantly faster than the industry average and is ingrained in its culture. CenterWatch, a leading source for global clinical trial information, has named it one of the fastest drug developers in the industry. BioMarin was also ranked tenth on Forbes list of innovative companies in 2015.

As a biopharmaceutical company, its success stems from its focus on science and the hope its therapies can bring to patients. BioMarin are world leaders in metabolic disease innovation with multiple products commercialized and a growing pipeline of product candidates to address unmet medical needs. It continues to fuel its R&D engine by looking for opportunities that align with its strengths and competencies. And BioMarin relentlessly pursue exciting, early-stage science that has the potential to change the course of disease.

A constant in BioMarin's culture is how patients continue to drive it. The passion and dedication that its employees bring to work each day is a testament to the inspiration its patients provide, and the knowledge of the impact BioMarin can make in their lives.

Bioverativ Inc. (NASDAQ: BIVV)

225 Second Avenue, Waltham, MA 02451

(781) 663-4400

Leaders in their fields, the scientists at Bioverativ are deeply committed to the discovery and development of new medicines to address areas of serious need for patients. Leveraging its deep understanding of the biology of hemostasis gained over 15 years of research, the company plans to accelerate the development of its innovative pipeline of programs in hemophilia, cold agglutinin disease, sickle cell disease, beta thalassemia, and other blood disorders.

The company's pipeline includes hemophilia programs that have been designed to provide less-frequent prophylactic dosing for hemophilia A and subcutaneous dosing for hemophilia B, and gene therapy programs for hemophilia A and B.

It also includes programs to address cold agglutinin disease, a rare and chronic autoimmune hemolytic condition for which there are no approved therapies. BIVV009 (formerly TNT009) is the only therapy in development that is designed to selectively inhibit the classical complement pathway of the immune system. BIVV009 targets C1s, thereby impacting the central mechanism of this disease.

Bioverative is also pursuing several approaches that seek to target the root cause of sickle cell disease, a profoundly debilitating disease that is linked to a shorter life expectancy and has few treatment options.

Just as it has done in hemophilia, Bioverativ hopes to bring forward new medicines that meaningfully advance the treatment of people with sickle cell disease.

Bluebird Bio (NASDAQ: BLUE)

150 Second Street, Cambridge, MA 02141

(399) 499-9300

Originally named Genetix Pharmaceuticals after being founded in 1992, the company changed its name in 2010 to bluebird bio and has since emerged as a leading player in the gene therapy space. Through its extensive knowledge base of genetics, the company has been able to integrate three different, but related platforms into the goals of the company: gene therapy, gene editing, and cancer immunotherapy. The company's gene therapy vertical is largely focused on addressing severe inherited diseases and mitigating the effects of genetic mutations and defects in hopes of treating the disease. The gene editing platform is closely linked to gene therapy, although gene editing involves the actual correction of genetic mutations that may cause various types of disorders, which could potentially serve as curative, single-administration treatments. Lastly, the cancer immunotherapy platform encompasses bluebird bio's autologous CAR-T program, which utilizes the company's own gene therapy technology to engineer modified T cells to target and eliminate tumor cells, especially within hematologic cancers.

The CAR-T program takes advantage of bluebird's internal lentiviral vector asset to deliver the necessary genetic constructs into a patient's harvested T cells which are then reinfused into the patient. The company's lead CAR-T product candidate, bb2121, which targets B-cell maturation agent (BCMA) in multiple myeloma, is partnered with Celgene and is currently being studied in a Phase I clinical trial in patients with relapsed/refractory multiple myeloma. Also in preclinical stages in the pipeline are a "next-gen" BCMA targeting CAR-T therapy, HPV-16 E6 TCR therapy partnered with Kite Pharma (the first program to which bluebird has said they will apply their genome editing technology) and targeted therapies licensed from Five Prime Therapeutics and ViroMed in addition to other programs.

B-MoGen Biotechnologies Inc. (Private)

614 McKinley Place NE, Minneapolis, MN 55413

(612) 656-4576

B-MoGen provides cutting edge tools for gene delivery and gene editing which provide unique and powerful solutions to basic and applied research problems. Its founders have developed and licensed innovative new methods that use transposons and targeted nucleases to study human diseases and genetics in ways that are otherwise impossible. Providing tools and custom services, B-MoGen can accelerate customer's research and achieve what others cannot: targeting a favorite gene in a favorite cell.

B-MoGen offer gene delivery solutions that enhance gene delivery for hard to transfect cells, including primary cells, and improve the duration of gene expression. Its gene editing approaches are useful for antibody validation, enhancing protein production, human disease research, and mitochondrial DNA editing.

Caribou Biosciences, Inc. (Private)

2929 Seventh Street #105, Berkeley, CA 94710

(510) 982-6030

Caribou Biosciences is a pioneer in the revolutionary field of CRISPR-Cas genome editing. Its proprietary technology puts it at the forefront of the development of new medical therapies and bio-based products, which offer benefits to both human health and society as a whole.

The company's singular focus is on the advancement of new applications for CRISPR-Cas gene editing that will help bring the tremendous promise this technology holds for patients and consumers to reality.

Caribou Biosciences is a rapidly growing leader in one of the most revolutionary developments in science this century – CRISPR-Cas gene editing.

It is applying Caribou's transformational technology platform and discoveries in four priority markets:

- Therapeutics
- Agricultural biotechnology
- Biological research
- Industrial biotechnology

Through the formation of alliances with industry leaders in each of these markets as well as internal technology and product development, Caribou is driving the creation and adoption of innovative new medical therapies and bio-based products.

The Caribou CRISPR-Cas technology platform enables simple, flexible targeting of any site in a genome with applications in:

- Human and animal therapeutics
- New disease models
- Genomics
- Bioproduction cell lines and fermentation strains
- Functional genomic screens
- Plants with enhanced traits

Caribou currently counts among its key collaborators Novartis and Intellia Therapeutics.

Casebia Therapeutics (Private)

610 Main St, Cambridge, MA 02139

(857) 270-5100

Pioneering a new field of medicine requires more than vision. It takes a long-term commitment, sufficient resources and a collaborative approach to seize on the emerging breakthroughs that will define the future.

Casebia Therapeutics, a 50-50 joint venture between CRISPR Therapeutics and Bayer, was created to accelerate the field of gene editing therapeutics today, and for the long haul. Drawing on CRISPR/Cas9 technology and expertise from CRISPR Therapeutics and the distinctive disease know-how and protein engineering capabilities of Bayer, Casebia is working to redefine what is possible for patients with a wide range of inherited diseases.

Casebia is dedicated to leading the gene editing and genetic engineering revolution today, and over the long term, advancing the CRISPR technologies of tomorrow. Together with its partners, Casebia is working to optimize gene editing across multiple disciplines and create the therapies that will unlock the full potential of gene editing for patients:

Cas9 protein: Modification of multiple characteristics of the Cas9 protein to improve specificity, efficiency, and ease of deliverability.

Guide RNA selection: Combining bioinformatics and experimental assays to identify guide RNAs with high efficiency and no off-target cutting.

Delivery of CRISPR/Cas9 to target cells: Developing next-generation delivery technologies to increase delivery efficiency and access additional organ systems.

Efficiency of correction: Achieving high efficiency of correction across all cell types and enable new therapeutic strategies.

Cellular engineering: Improving the ex vivo cell collection, manipulation and administration process for a variety of stem and hematopoietic cell types.

Crispr Therapeutics AG (NASDAQ: CRSP)

Aeschenvorstadt 36, 4051 Basel, Switzerland

+41 61 228 7800

CRISPR Therapeutics is a leading gene-editing company focused on the development of transformative medicines using its proprietary CRISPR/Cas9 gene-editing platform. CRISPR/Cas9 is a revolutionary technology that allows for precise, directed changes to genomic DNA. Its multi-disciplinary team of world-class researchers and drug developers is working to translate this technology into breakthrough human therapeutics in a number of serious diseases. Its lead programs in beta-thalassemia and sickle cell disease have advanced to IND/CTA-enabling studies with a CTA filing planned by the end of 2017, and CRISPR is advancing additional programs in ex vivo and in vivo disease areas. In addition to the company's fully-owned programs, CRISPR's strategic collaborations with Bayer AG and Vertex Pharmaceuticals expand its portfolio and enable CRISPR with unique capabilities. Through the company's private financings, partnerships, and IPO CRISPR has raised >$400M to fund and accelerate its portfolio. CRISPR has licensed the foundational CRISPR/Cas9 patent estate for human therapeutic use from the company's scientific founder, Dr. Emmanuelle Charpentier, who co-invented the application of CRISPR/Cas9 for gene editing. CRISPR is headquartered in Zug, Switzerland with R&D operations in Cambridge, Massachusetts, and some business operations in London, UK.

CRISPR Therapeutics' mission is to develop transformative gene-based medicines for patients with serious diseases. Its therapeutic approach is to cure diseases at the molecular level using the breakthrough gene editing technology called CRISPR/Cas9. The company is focused on the treatment of somatic (non-germline) cells, analogous to the approach taken by more traditional and established gene therapy methods. It is not using human germline modifications and its support the current recommendations of the International Society for Stem Cell Research in this regard. Together with other Gene Editing Companies, CRISPR has issued a Joint Statement - Position Regarding Human Germline Gene Editing. Its development of transformative new medicines will involve working closely with patients and families, healthcare professionals, regulatory agencies and other groups dedicated to improving healthcare.

CRISPR is building a portfolio of therapeutic candidates based on several important criteria that include among others the seriousness of the condition, the unmet medical need, and a clear link between the underlying genetic abnormality and the respective disease. The company is evaluating both in vivo treatments, administering CRISPR/Cas9 technology in cells inside the human body, and ex vivo treatments, removing specific cells from the body, editing the gene causing the disease(s) and delivering the modified cells back to the patient. Therapeutic indications with potential for ex vivo treatment include hemoglobinopathies, such as sickle cell disease and beta thalassemia, certain types of immunodeficiencies, and specific approaches to immune therapies for cancer. In vivo treatment approaches using CRISPR/Cas9 gene editing may be used for diseases of the liver, eye and lung among others, for which delivery mechanisms have been established.

Dimension Therapeutics, Inc. (NASDAQ: DMTX)

840 Memorial Drive, Cambridge, MA 02139

(617) 401-0011

Dimension Therapeutics, Inc. is a leader in discovering and developing new therapeutic products for people living with devastating rare and metabolic diseases associated with the liver, based on the most advanced mammalian adeno-associated virus (AAV) gene delivery technology. Dimension is actively

progressing its broad pipeline, which features programs addressing unmet needs for patients suffering from inherited metabolic diseases, including OTC deficiency and GSDIa, and a collaboration with Bayer in hemophilia A. Dimension has initiated a phase 1/2 clinical trial with DTX301 for the treatment of OTC deficiency. The company targets diseases with readily identifiable patient populations, highly predictive preclinical models, and well-described, and often clinically validated, biomarkers. Founded in 2013, Dimension maintains headquarters in Cambridge, Massachusetts.

Editas Medicine Inc. (NASDAQ: EDIT)

11 Hurley Street, Cambridge, MA 02141

(617) 401‑9000

Editas Medicine is building a leading genome editing company dedicated to treating patients with genetically defined diseases.

Editas Medicine believes it has entered a new era in genomic medicine as the growth of genomic information in recent years has significantly expanded its understanding of genetically defined diseases. Furthermore, a new technology known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has the potential to achieve accurate, directed changes in DNA and fulfill the promise that started with the sequencing of the human genome – the potential to treat diseases at their source, at the DNA level.

Editas Medicine has developed a proprietary genome editing platform consisting of four interrelated components that are designed to meet these goals. Each component is underpinned by several specific technologies and capabilities. With its platform, Editas is able to design and optimize each element of the company's products necessary to achieve the desired edit, including the type of Cas9 or Cpf1, the sequence and structure of the guide RNA(s), the delivery vector, and elements to control expression in cells and drive the desired repair mechanism.

Cpf1 complements Editas' expanding toolbox of CRISPR enzymes, increasing its ability to target additional disease mutations. This new enzyme uses a smaller, simpler guide-RNA, does not include a tracrRNA, and produces a different type of cut at the target DNA.

Errant Gene Therapeutics (Private)

218 North Jefferson Street, Suite 300, Chicago, IL 60661

(312) 441-1800

Errant Gene Therapeutics, LLC was established in October 2003 by Patrick Girondi to develop treatments for life-threatening diseases, in particular those recognized as rare disorders or orphan diseases.

EGT's primary strategy is to address the unmet medical needs of patients with orphan diseases through the development of its technology and treatments. In addition, the company maintains a constant search for new therapeutic advancements that have the potential to be developed into future treatments. The company's strong intellectual property position is the result of world-wide exclusive licensing agreements from prominent academic laboratories and the acquisition of proprietary technology.

The EGT lead product candidates, Thalagen and CG-1521, target the treatment of the blood disorder thalassemia and refractory prostate cancer, respectively. These products are based on pharmacological technology which corrects the errant gene expression causing each disorder. EGT is currently developing two technologies which can be rapidly introduced into human clinical trials, studied and made available to patients. Thalagen is a treatment for thalassemia based on the technology of gene therapy; CG-1521 is an inhibitor of histone deacetylase and represents a new treatment paradigm for therapy resistant prostate cancer.

Additional product candidates in development target pulmonary and neurodegenerative disorders.

Fibrocell Science Inc (NASDAQ: FCSC)

405 Eagleview Boulevard, Exton, PA 19341

(484) 713-6000

Fibrocell, a cell and gene therapy company, is focused on diseases affecting the skin and connective tissue. The company's approach to personalized biologics is distinctive based on its proprietary autologous fibroblast technology. By extracting fibroblast cells from a patient's own skin, Fibrocell creates localized gene therapies that are compatible with the unique biology of each patient and have the potential to address the underlying cause of disease.

Fibrocell's autologous fibroblast technology uses its patented manufacturing process, which involves collecting small skin biopsies from patients, isolating cells and expanding them in culture, transducing the fibroblast cells with an integrative lentiviral vector to express a targeted protein, followed by continued expansion of the gene-modified cells in culture. In this manner, each patient is treated with cells that were cultivated from his or her own dermal tissue (i.e., autologous). Fibrocell is developing its gene-therapy product candidates in collaboration with Intrexon Corporation (NYSE: XON), a leader in synthetic biology.

Freeline Therapeutics (Private)

UCL Royal Free Medical School, Pond Street, London, NW3 2QG, UK

+44 (0)20 7794 4227

Freeline's mission is to become a leading biopharmaceutical company founded on the successful development and commercialization of liver directed gene therapies for bleeding disorders and other severe diseases.

These therapies are based on Freeline's next-generation proprietary AAV vector platform, with its lead program being a gene therapy to treat hemophilia B. This gene therapy treatment, pioneered by Professor Amit Nathwani, Professor of Hematology at UCL and CSO of Freeline Therapeutics, has transformed the lives of patients by providing a safe, reliable source of the blood clotting protein Factor IX (Ref to NEJM papers 2011 and 2014; links are mentioned below). Clinical relevant blood levels of Factor IX have been obtained in ten out of ten treated patients and long-term sustained levels have been observed following a single gene therapy treatment.

The success seen to date gives it a solid platform for developing a gene therapy approach for the treatment of Hemophilia B and other conditions.

Genethon (Private)

1 Rue de l'internationale , 91000 Évry, France

+33 1 69 47 28 28

Genethon's mission is to design gene therapy products for rare diseases, and to ensure their pre-clinical and clinical development in order to provide patients with access to these innovative treatments. These projects, which are being developed either internally at Genethon or as part of partnerships, involve neuromuscular diseases, pathologies of the immune system, of the eye, and other rare diseases.

Gensight Biologics SA (EPA: SIGHT)

74, rue du Faubourg Saint-Antoine, 75012 Paris, France

+33 1 76 21 72 20

Created in 2013, GenSight Biologics is a Phase III clinical-stage biotechnology company discovering and developing novel therapies for mitochondrial and neurodegenerative diseases of the eye and central nervous system. To address these therapeutic areas, it leverages the company's integrated development platform by combining a gene therapy-based approach with its core technology platforms of mitochondrial targeting sequence, or MTS, and optogenetics.

Gensight's initial focus has been on developing therapies for severe retinal diseases, with the goal of preserving or restoring vision in patients suffering from sight-threatening ophthalmic diseases. Using its gene-therapy based approach, its product candidates are designed to be administered in a single treatment to each eye by intravitreal or subretinal injection in order to provide patients with a long-lasting functional cure.

Gensight's pipeline currently comprises two lead product candidates for the treatment of sight-threatening retinal degenerative diseases, together with products in preclinical development targeting ophthalmic and neurodegenerative diseases.

Gensight sequentially raised €20 M in a Series A round in March 2013 and €32 M in a Series B round in July 2015, from European and U.S. blue-chip investors, followed by an IPO on Euronext in July 2016, raising an additional €46 M. More recently, it raised €22.5 M from leading investors in the U.S. and Europe in June 2017.

Homology Medicines, Inc. (Private)

45 Wiggins Ave, Bedford, MA 01730

(781) 301-7277

Homology is using its proprietary technology platform to design and develop treatments to address rare diseases at the genetic level, ushering in a new era where cures for devastating diseases are possible.

Homology is based on groundbreaking science that harnesses the naturally occurring process of homologous recombination, the cells' natural mechanism for gene repair. This non-nuclease-based approach offers substantial benefits over current gene editing and gene therapy approaches, utilizing proprietary vectors that allow for precise and efficient in vivo and ex vivo gene editing and superior bio-distribution across many tissue types for gene therapy.

Two advanced approaches to curing genetic diseases are gene editing and gene therapy. Homology Medicines' technology offers the option to pursue both approaches and can provide important advantages over current methods. Homology's proprietary technology is based on the discovery of a novel class of human-derived adeno-associated virus (AAV) vectors that can be used to achieve precise and efficient in vivo and ex vivo gene editing, as well as gene therapy.

Homology's AAV technology is based on the pioneering research of Saswati Chatterjee, Ph.D., Professor of Virology at the Beckman Research Institute at the City of Hope in California. Dr. Chatterjee and her team led the first AAV vector-mediated gene transfer studies into human hematopoietic stem cells (HSCs) and subsequently identified and isolated a series of naturally-occurring AAVHSCs from human CD34+ cells. These vectors have many unique properties, including high efficiency and precise gene editing, plus the ability to deliver to the central nervous system (CNS), which can be bolstered by technology Homology licensed from the California Institute of Technology.

HORAMA S.A. (Private)

27 rue du Faubourg Saint-Jacques, 75014 Paris, France

HORAMA is developing new gene therapies in the field of rare ophthalmological diseases to restore patients' autonomy and reduce costs for the community. The aim of gene therapy for the treatment of rare genetic diseases is to provide a healthy copy of the disease-causing mutated gene in order to restore the missing function and hence stop disease evolution.

HORAMA is developing its own gene therapy approach based on vector technology using non-pathogenic, recombinant adeno-associated viruses (rAAV). The rAAV bearing the therapeutic gene of interest is administered into retinal cells where it expresses its encoded healthy protein, thus restoring normal function and preventing further deterioration of the retina.

The company has its proprietary manufacturing processes set up with its academic partners. The companys platform develops a solid pipeline of innovative gene therapy medicinal products for several applications in the field of retinal diseases.

HORAMA benefits from exclusive licensing agreements on several patent applications relating to either rAAV technologies or to results obtained from preclinical or clinical (Phase 1/2) results. HORAMA specific patented know-how, added to its Orphan Drug Designations, confirms its ability to bring new drugs to the market.

Intellia Therapeutics (NASDAQ: NTLA)

40 Erie Street, Suite 130, Cambridge, MA 02139

(857) 285-6200

Intellia is a leading genome editing company, focused on the development of proprietary, potentially curative therapeutics using a recently developed biological tool known as the CRISPR/Cas9 system. Intellia believes the CRISPR/Cas9 technology has the potential to transform medicine by permanently editing disease-associated genes in the human body with a single treatment course.

Intellia's combination of deep scientific expertise and clinical development experience, along with its leading intellectual property portfolio, puts Intellia in a unique position to unlock broad therapeutic applications of the CRISPR/Cas9 technology and create a new class of therapeutic products.

Juventas Therapeutics (Private)

3615 Superior Avenue Suite 4403B, Cleveland, OH 44114

(216) 273-4000

Juventas Therapeutics is a private, clinical stage biotechnology company developing novel non-viral gene therapies that activate natural processes to repair the body. Product candidate JVS-100 is a non-viral gene therapy that expresses stromal cell-derived factor-1, or SDF-1, a naturally occurring signaling protein that has been shown to recruit the body's own stem cells and promote tissue repair in a broad range of disease states. This therapeutic approach is based on research originating at the Cleveland Clinic. Juventas is currently completing a Phase 2b study in patients with advanced peripheral artery disease.

Krystal Biotech Inc. (NASDAQ: KRYS)

2100 Wharton St. #701, Pittsburgh, PA 15203

(412) 586-5830

Krystal Biotech has developed a proprietary gene therapy platform, the Skin TARgeted Delivery platform, or STAR-D platform, that consists of a patent pending engineered viral vector and skin-optimized gene

transfer technology, to develop off-the-shelf treatments for dermatological diseases for which it believes there are no known effective treatments.

Krystal's modified HSV-1 is a replication-deficient, non-integrating viral vector that can efficiently penetrate a broad range of skin cells. Krystal's high payload capacity to accommodate large or multiple genes and low immunogenicity makes it a suitable choice for direct and repeat delivery to the skin.

The company's lead product candidate, KB103, is currently in preclinical development and seeks to use gene therapy to treat RDEB. KB103 is a replication-defective, non-integrating viral vector that has been engineered employing its STAR platform to deliver functional human COL7A1 genes directly to the patients' dividing and non-dividing skin cells. Other indications in the current pipeline include Netherton Syndrome, Ichthyosis Vulgaris, and Atopic Dermatitis.

Lysogene SA (EPA: LYS)

18-20 rue Jacques Dulud , 92 200 Neuilly-sur-Seine, France

+ 33 1 41 43 03 90

Lysogene was founded in 2009, by Karen Aiach and Olivier Danos, with a focused scientific development plan, pragmatic approach and bold mission. The company has been built on a comprehensive understanding of the impact of neurodegenerative diseases on patients and families.

Lysogene's development strategy focusses on diseases with neurological involvement. The company's first programs are for neuropathic Lysosomal Storage Disorders (LSD), which are particularly good candidates for gene therapy as the genetic correction of a small subset of neural cells should be sufficient to target large regions of the central nervous system (CNS) as secreted lysosomal enzymes can diffuse and be captured by adjacent and distal cells. Moreover, tight regulation of produced enzyme levels is not required because low levels (about 10%) of enzyme activity are anticipated as sufficient for a therapeutic effect. Furthermore supraphysiological levels of many acidic hydrolases have no deleterious effect.

Lysogene is developing adeno-associated viral (AAV) vectors that have demonstrated their effectiveness in safely delivering genetic material to the CNS. These vectors have been developed from non-pathogenic and replication deficient viruses. They have been used in clinical trials since the mid-1990s treating hundreds of subjects with currently no known related serious adverse events. AAV gene therapy vectors are emerging as the gene transfer vehicle with high potential for use in the CNS as they transduce post mitotic cells that mediate the sustained, long term gene expression required in chronic progressive diseases.

Lysogene's gene therapy route of administration is direct delivery of the vector to the CNS. This may be one of the most efficient methods to treat neurological pathologies of LSDs. The structure of the CNS provides advantages for direct delivery in that vectors can be transported along neuronal connections to distal sites and secreted enzymes can be transported anterograde and retrograde to cross correct cells distal from the injection site. This delivery approach has shown to be safe in several clinical trials in LSDs (Batten's disease, Canavan disease, MPS IIIA and MPS IIIB), in Parkinson and Alzheimer diseases. Furthermore, direct injection in this small and immunologically privileged site can potentially overcome limitations linked to systemic injection which would require a very high dose to target the CNS and can be neutralized by anti AAV antibodies or may trigger the activation of CD8+ T cell response.

MeiraGTx (Private)

450 East 29th Street, 15th Floor, New York, NY 10016

(646) 490-2965

MeiraGTx is pioneering the use of gene therapy to treat devastating neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). The company is developing innovative gene therapies for ocular diseases, including rare inherited blindness and age-

related macular degeneration (AMD). MeiraGTx is also establishing treatments for xerostomia, a frequent and debilitating side effect of radiation treatment used in head and neck cancers. The company's revolutionary gene regulation technologies promise to transform the way gene therapy can be applied and create new paradigms for biologic therapeutics.

The delivery of biologics directly to cells and tissues where they are needed using gene therapy promises to revolutionize medicine. One critical piece of this therapeutic strategy will be the ability to modulate the levels of transduced proteins – tuning them on or off, up or down – to maximize therapeutic effect. MeiraGTx has developed a suite of genetic switches that allow the regulation of expression of any linked gene therapeutic. This new technology will enable the correct levels of any transduced protein to be maintained in patients by the simple oral administration of a specific small molecule. In this way, MeiraGTx is harnessing the power of next generation gene therapies through precision dosing.

Milo Biotechnology (Private)

2322 Delaware Drive, Cleveland Heights, OH 44106

(216) 212-3211

Milo Biotechnology is a Cleveland, Ohio based company developing therapies to increase muscle strength and prevent muscle atrophy. The company's lead program is a skeletal muscle specific transgene of the protein follistatin. The follistatin 344 transgene is delivered via an adeno-associated virus to achieve long lasting and potent expression in muscle. Milo is currently engaged in three clinical studies for rare muscular dystrophies.

Milo Biotechnology's therapy is based on adeno-associated virus (AAV) delivery of follistatin. AAVs are small, non-pathogenic carriers that can be tailored to deliver sustained administration of follistatin via a single dose.

Follistatin is a protein that increases muscle function and prevents fibrosis. Follistatin functions primarily by blocking the TGF-β family ligands, proteins that activate signalling pathways that lead to reduced muscle mass and strength. Compared to other drugs Milo's therapy has the advantage of targeting not one, but many of the TGF-β family ligands that suppress muscle growth.

Milo's follistatin therapy has been successfully tested in mice, macaques and in a Phase I/II clinical study in Becker muscular dystrophy.

Nightstar Therapeutics (Private)

215 Euston Road, Gibbs Building, London, NW1 2BE, UK

44 20 7611 2077

Nightstar Therapeutics is a clinical-stage company focused on developing and commercializing a pipeline of novel and potentially curative, one-time retinal gene therapies for patients suffering from rare inherited retinal diseases that would otherwise progress to blindness, and, for which, there are no currently approved treatments.

The company's lead retinal gene therapy product candidate, NSR-REP1, is being developed for the treatment of choroideremia (CHM), a rare, degenerative, X-linked genetic retinal disorder primarily affecting males that is caused by a mutation in the CHM gene.

Nightstar is currently conducting a prospective, natural history study, known as the NIGHT study, across multiple clinical sites in the United States, Europe and Canada. Nightstar plans to initiate a Phase 3 registrational clinical study, the STAR study, of NSR-REP1 for CHM in the first half of 2018. NSR-REP1 has been granted orphan drug designation for the treatment of CHM from both the U.S. Food and Drug Administration and the European Medicines Agency.

Nightstar is developing NSR-RPGR for the treatment of X-linked retinitis pigmentosa (XLRP), an inherited X-linked recessive retinal disease characterized by mutations in the RPGR gene, leading to a lack of protein transport and a loss of photoreceptors, the specialized cells in the eye that convert light into visual signals. NSR-RPGR is currently being evaluated in a dose-ranging Phase 1/2 clinical trial for the treatment of XLRP. The company plans to initiate a natural history trial across multiple clinical sites by the end of 2018. Nightstars' NSR-BEST1 gene therapy product candidate is being developed for the treatment of Best vitelliform macular dystrophy and is currently in preclinical development.

The company has licensed three additional retinal gene therapy preclinical programs and are evaluating other in-licensing opportunities to broaden its pipeline and drive future growth.

Oxford BioMedica plc (LON: OXB)

Windrush Court, Transport Way, Oxford OX4 6LT, UK

+44 (0) 1865 783 000

Using its unique LentiVector delivery platform, Oxford has created a valuable portfolio of gene and cell therapy product candidates in the areas of oncology, ophthalmology and CNS disorders. The company has strong partnerships with Novartis, Immune Design and Orchard Therapeutics, providing them with access to its intellectual property, state-of-the-art production facilities and expertise, and, in addition, Oxford has licensed products and technology rights to Sanofi and technology rights to GSK. These partnerships provide Oxford with multiple income streams, consisting of upfront milestone payments, development and production fees and potential royalties on future product sales. Oxford plan to progress its wholly-owned products via spin-outs and out-licensing opportunities, while continuing to invest in its LentiVector platform. Oxford plans to continue its preclinical R&D to discover new potential products.

The LentiVector platform is applicable in many therapeutic areas, and has a number of specific advantages. Lentiviral vectors can genetically modify dividing cells, such as T-cells, as well as non- or rarely dividing cells, such as neurons or early progenitor/stem cells, making it a delivery system of choice in gene and cell therapy. The platform can also integrate genes into non-dividing cells, including in the brain and retina, with ground-breaking long-term studies suggesting gene expression may be maintained indefinitely, offering the prospect of permanent therapeutic benefit following a single administration. The LentiVector platform is also used as valuable research tool, with applications in transgenesis, stem cell manipulation, somatic disease models, target validation and gene discovery.

Poseida Therapeutics, Inc. (Private)

4242 Campus Point Ct #700, San Diego, CA 92121

(858) 779-3100

Poseida Therapeutics is a spin out of Transposagen Biopharmaceuticals that utilizes best-in-class, proprietary genome editing technologies to develop targeted, life-saving therapeutics in areas of high unmet medical need. Poseida has demonstrated proof-of-principle that validates the potential of its differentiated genome engineering technologies and their therapeutic applications. Poseida technology platforms have broad applicability and Poseida's long-term goal is to apply its proprietary gene editing technologies to a broad range of human diseases. The initial applications of Poseida's technologies will be in gene therapy and CAR-T product candidates for liver disorders and cancer, respectively.

Precision BioSciences, Inc. (Private)

302 East Pettigrew St., Dibrell Building, Suite A-100, Durham, NC 27701

(919) 314-5512

Precision, utilizes a proprietary genome editing method called ARCUS, combined with a team made up of some of the leading minds and pioneers in genome editing in an effort to overcome cancers, cure genetic diseases, and enable the development of safer, more productive food sources.

The backbone of the ARCUS technology is the ARC Nuclease – a fully synthetic enzyme that is very similar to a homing endonuclease but is modified to be a better starting point for the development of new gene editing reagents. ARC Nuclease shares many of the positive attributes of a homing endonuclease, such as small size and unparalleled sequence specificity, but it can more easily be evolved into a custom gene editing tool that recognizes a DNA sequence of its choosing. Each ARCUS reagent is optimized using a set of proprietary in silico and lab-based techniques to ensure maximum gene editing efficiency with minimum off-target activity.

Rocket Pharmaceuticals Ltd. (Private)

430 E 29th St, New York, NY 10016

(646) 440-9100

Rocket's pipeline is comprised of first-in-class gene therapies for rare and devastating inherited diseases.

Designed in collaboration with leading academic and industry partners, Rocket lentiviral-based programs aim to enable transduction of patients' stem cells by means of third generation, self-inactivating lentiviral vectors to optimize the potential for gene-correction and stem cell engraftment such that the functional deficits of each disorder are corrected, with sufficient quantities of healthy protein manufactured by patients' own hematopoietic cells. The AAV-based program involves direct injection of the therapeutic vector, which has displayed substantial tropism for the organs most afflicted by the underlying disorder, ultimately enabling sufficient quantities of healthy protein to restore homeostasis.

Each program is intended to be transformative, enabling not only reversal of the disorder at molecular and cellular levels, but sustained relief from debilitating and potentially life-threatening symptoms.

Sangamo Therapeutics Inc (NASDAQ: SGMO)

501 Canal Boulevard, Richmond, CA 94804

(510) 970-6000

Sangamo was founded in 1995 as Sangamo BioSciences, Inc. in order to research new technologies for genome editing. Over two decades, Sangamo's scientists developed the most advanced, flexible and precise technologies available for gene-based therapies. In 2017, Sangamo is conducting new human clinical trials, including the first ever in vivo human genome editing studies. Reflecting this focus on the clinical development of new genomic therapies, in 2017 the Company announced a new name, Sangamo Therapeutics.

Sangamo has developed a range of capabilities that enable it to address serious and life-threatening genetic diseases with the appropriate therapeutic approach. These include best-in-class capabilities in gene therapy and genome editing, which are being deployed to produce therapeutic proteins from the liver and to generate new types of cell-based therapies. Sangamo can also regulate genes for therapeutic benefit.

Selecta Biosciences Inc. (NASDAQ: SELB)

480 Arsenal Way, Watertown, MA 02472

(617) 923-1400

Selecta Biosciences, Inc. is a clinical-stage biopharmaceutical company that is seeking to unlock the full potential of biologic therapies by avoiding unwanted immune responses. Selecta's tolerogenic Synthetic

Vaccine Particles (SVP) technology platform is designed to enable a range of novel biologics for rare and serious diseases that require new treatment options. The company's current proprietary pipeline includes SVP-enabled enzyme, oncology and gene therapies. SEL-212, the company's lead candidate in Phase 2, is being developed to treat severe gout patients and resolve their debilitating symptoms, including flares and gouty arthritis. Selecta's clinical oncology candidate, LMB-100, is in a Phase 1 program targeting pancreatic cancer and mesothelioma. Its two proprietary gene therapy product candidates are being developed for rare inborn errors of metabolism and have the potential to enable repeat administration. The use of SVP is also being explored in the development of vaccines and treatments for allergies and autoimmune diseases. Selecta is based in Watertown, Massachusetts.

Solid BioSciences (Private)

161 First St, Cambridge, MA 02142

(617) 337-4680

Solid Biosciences is focused on solving Duchenne muscular dystrophy and meeting the diverse needs of patients, from addressing the underlying cause of the disease to managing its multiple manifestations. Its mandate is to accelerate the discovery and development of multiple scientific approaches in parallel as quickly and safely as possible. Solid has established collaborations with industry, academia and non-profits – all with the goal of moving closer to effective therapies. The company is building a diversified portfolio of targeted therapeutic candidates. All assets go through an extensive diligence process, culminating with a commitment to identify a path forward.

Solid's lead program is an adeno-associated virus (AAV) microdystrophin gene transfer candidate, which aims to enable the systemic delivery of a synthetic, functional version of the dystrophin gene. The company is also actively exploring other potential gene therapy candidates that could be beneficial for Duchenne muscular dystrophy (DMD).

Solid chose to pursue its microdystrophin because of its potential to restore the expression of a modified but functional dystrophin regardless of a patient's specific mutation. Results from two preclinical studies have demonstrated that a single administration of SGT-001 led to long-term expression of the microdystrophin protein in muscle, as well as improvements in muscle histology and function.

Currently, Solid is conducting a number of key studies that are intended to enable it to enter the clinic in the second half of 2017. Solid is performing this research in collaboration with the University of Missouri, the University of Washington, the University of Florida and Texas A&M University.

Synpromics Ltd (Private)

9 Little France Rd, Edinburgh EH16 4UX, UK

+44 131 651 9662

Synpromics was founded in 2010 to commercialize proprietary and patent-pending technology, developed by Dr. Michael L Roberts, in the emerging field of synthetic biology. This is a highly disruptive technology putting the power to control gene expression in almost any condition of interest into the hands of scientists developing next generation technologies, therapeutics and diagnostics.

Traditionally, promoters tend to be based on viral or gene specific endogenous promoters and have a number of constraints that create a bottleneck in the development of tools and products in the Biotech industry. This is not surprising as natural promoters have evolved over millennia to regulate gene expression to the precise levels required to elicit a specific physiological function, in a particular cellular environment. Consequently, natural promoters are not best suited to control the expression of genes in the industrial setting of a bioreactor, nor in the environs of a diseased cell, where a particular degree of specificity and optimal therapeutic expression is required.

Synpromics' designs and develops patentable synthetic promoters that are designed to regulate genes in a highly specific manner. Given that these promoters greatly improve upon the natural promoters on which the entire biotech industry currently relies, there is enormous potential for the company to drive the Biotech industry forward and transform the entire sector.

Synpromics' business model is to create libraries of synthetic promoters in collaboration with partners and in return generate revenue through license fees, milestone payments and ongoing royalties subsequent to their integration into commercial applications.

Transposagen Biopharmaceuticals, Inc. (Private)

535 W 2nd St, Lexington, KY 40508

(859) 428-8561

Transposagen, Inc. is a privately-held biotechnology company founded in 2005 to commercialize early gene editing technology for the construction of rodent models of disease. Since then, Transposagen has significantly increased its scientific offerings to include a suite of gene editing technologies and services that address the research needs of both academic and drug discovery investigators.

The company is headquartered in Kentucky.

Transposagen's growing success and the unique piggyBac technology have yielded two spin-off companies, Poseida Therapeutics and Hera BioLabs, which focus on therapeutic development and toxicology testing, respectively.

The Footprint-Free gene editing system combines the piggyBac excision-only transposase with the utility of the latest site-specific nucleases technologies, including CRISPR and XTN TALENs. This process allows researchers to surgically alter a single nucleotide without creating unwanted mutations and select for very rare events.

UniQure N.V. (NASDAQ: QURE)

Meibergdreef 61, 1105BA , Amsterdam, The Netherlands

+31-20-566-7394

UniQure is delivering on the promise of gene therapy, single treatments with potentially curative results. The company has developed a modular technology platform to rapidly bring new disease-modifying therapies to patients with severe genetic diseases.

UniQure is advancing a focused pipeline of innovative gene therapies and have established clinical proof-of-concept in its lead indication, hemophilia B, and preclinical proof-of-concept in Huntington's disease. UniQure's pipeline of adeno-associated virus (AAV)-based gene therapies has been developed using an innovative technology platform, supported by industry-leading proprietary commercial-grade manufacturing capabilities. Through recent collaborations and its strategic partnership with Bristol-Myers Squibb to develop gene therapies for cardiovascular diseases, the company has taken the next steps toward developing gene therapies targeting chronic and degenerative diseases that affect larger populations.

Universal Cells Inc. (Private)

3005 1st Ave, Seattle, WA 98121

(425) 246-5454

Universal Cells Inc. is a private Seattle-based biotechnology company developing nuclease-free genome editing technologies that accurately and efficiently edit any gene, without off-target cutting.

Universal Cells uses recombinant adeno-associated virus (rAAV)-mediated gene editing to efficiently edit chromosomal genes without the use of genotoxic nucleases. rAAV vectors are effective and safe, and have been used in numerous clinical trials. Universal has licensed a stem cell-tropic rAAV vector serotype for engineering human pluripotent stem cells. Its technology allows Universal to produce customized stem cells that contain deletions, insertions, or point mutations at any genomic position.

Unlike nuclease-based genome editing, Universal's approach is not genotoxic. It does not require a double strand break, generate off-target alterations to the genome, or produce unwanted mutations at the target site. It also does not introduce nuclease genes into the cell that may have unintended effects.

Vivet Therapeutics (Private)

29 rue Tronchet, Paris 75008, France

+33 6 84 75 50 87

Vivet Therapeutics is dedicated to developing innovative gene therapy treatments for orphan diseases. Vivet Therapeutics is focused on optimizing gene therapy through collaborating with the Fundacion para la Investigacion Medica Aplicada (CIMA, Universidad de Navarra) to develop new AAV vectors specifically targeting the liver and generating new technologies to optimize gene delivery and long term expression.

The company's development strategy is to target the liver using a novel synthetic adeno associated virus (AAV-ANC80) to introduce therapeutic genes to hepatocytes, correcting the genetic disorder.

Vivet's keys to success are its exclusive license rights and access to know how granted by its strategic partners, FIMA and MEE, enabling it to address various inherited disorders such as Wilson's disease, Progressive Familiar Intrahepatic Cholestasis (PFIC) and Citrullinemia type I in close collaboration with the Center for Applied Medical Research (CIMA) in Pamplona, Spain.

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Outperform (MO2) Expected to appreciate and outperform the S&P 500 over the next 12-18 months. For higher yielding and more conservative equities, such as REITs and certain MLPs, an Outperform rating is used for securities where we are comfortable with the relative safety of the dividend and expect a total return modestly exceeding the dividend yield over the next 12-18 months.
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Market Perform (MP3) The stock is expected to perform generally in line with the S&P/TSX Composite Index over the next twelve months and is potentially a source of funds for more highly rated securities.
Underperform (MU4) The stock is expected to underperform the S&P/TSX Composite Index or its sector over the next six to twelve months and should be sold.

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	Coverage Universe Rating Distribution*			Investment Banking Distribution		
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Market Perform (Hold)	42%	28%	33%	12%	27%	0%
Underperform (Sell)	5%	2%	12%	11%	25%	0%

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High Risk/Growth (H/GRW) Medium to higher risk equities of companies in fast growing and competitive industries, with less predictable earnings (or losses), more leveraged balance sheets, rapidly changing market dynamics, financial or legal issues, higher price volatility (beta), and potential risk of principal.

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Valuation Methodology: The Raymond James methodology for assigning ratings and target prices includes a number of qualitative and quantitative factors including an assessment of industry size, structure, business trends and overall attractiveness; management effectiveness; competition; visibility; financial condition, and expected total return, among other factors. These factors are subject to change depending on overall economic conditions or industry- or company-specific occurrences. Only stocks rated Strong Buy (SB1) or Outperform (MO2) have target prices and thus valuation methodologies.

Valuation Methodology: We value Adverum Biotechnologies, Inc. using a sum-of-the-parts analysis.
Valuation Methodology: We value Spark Therapeutics using a sum-of-the-parts analysis of four programs: 1) LUXTURNA for RPE65-mediated IRDs; 2) SPK-8011 for hemophilia A; 3) SPK-7001 for Choroideremia; and 4) SPK-9001 for hemophilia B (royalties only).
Valuation Methodology: We value REGENXBIO Inc. using a sum-of-the-parts analysis.
Valuation Methodology: We value Voyager Therapeutics, Inc. using a sum-of-the-parts analysis.

Risk Factors

General Risk Factors: Following are some general risk factors that pertain to the businesses of the subject companies and the projected target prices and recommendations included on Raymond James research: (1) Industry fundamentals with respect to customer demand or product / service pricing could change and adversely impact expected revenues and earnings; (2) Issues relating to major competitors or market shares or new product expectations could change investor attitudes toward the sector or this stock; (3) Unforeseen developments with respect to the management, financial condition or accounting policies or practices could alter the prospective valuation; or (4) External factors that affect the U.S. economy, interest rates, the U.S. dollar or major segments of the economy could alter investor confidence and investment prospects. International investments involve additional risks such as currency fluctuations, differing financial accounting standards, and possible political and economic instability.

Specific Investment Risks Related to the Industry or Issuer

Biotechnology Industry Risk Factors
Risks include various policy and government regulatory risk, intellectual property risk, and potential health care reform initiatives that could impact demand, availability, and/or reimbursement of key products within the U.S. (or other foreign) markets.

Healthcare Sector General Risks
Potential risks such as reimbursement cuts, acquisition integration, and higher-than-expected operating costs (we note continued cyclical pressure on labor, supply and malpractice costs), as well as a slowing managed care pricing cycle, could negatively impact the healthcare sector.

Company-Specific Risks for Adverum Biotechnologies, Inc.

Clinical and Regulatory Risk
The clinical development of Adverum's products bears risk given that these products are not in the clinic yet. In addition, the failures of other companies' gene therapy products for wet AMD and A1AT deficiency would result in additional scrutiny of Adverum's product candidate for the same indications although Adverum's approaches are differentiated. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk
If approved, Adverum's products are likely to face competition from existing therapies. For example, in the wet AMD space, the approved anti-VEGF therapies (e.g. Regeneron's Eylea and Roche/Novartis' Lucentis) have demonstrated effectiveness (although there are some compliance issues), resulting in challenges associated with changing physicians' prescribing behaviors. With respect to A1AT deficiency and HAE for which two other gene therapy products are being developed, respectively, a number of existing enzyme replacement therapies could also pose competition. Aside from competition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Adverum

cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercial viable.

Financing Risk
Adverum currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Company-Specific Risks for Audentes Therapeutics, Inc.

Clinical and Regulatory Risk
The clinical development of Audentes' products bears risk given that no clinical data has been reported for these products. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk
In general, the commercial success of a gene therapy is dependent on pricing/reimbursement. If Audentes cannot secure a reasonable price to compensate for the ultra-rare nature of most of the diseases being evaluated, the company's products may not be commercially viable. In addition, Audentes' products could face competition from existing therapies. For example, in the Pompe disease space, the approved enzyme replacement therapy (Sanofi's Lumizyme) has demonstrated effectiveness, which could result in pressure on the adoption of Audentes' gene therapy if/when it is commercialized.

Financing Risk
Audentes currently has no product revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Company-Specific Risks for REGENXBIO Inc.

Clinical and Regulatory Risk
The clinical development of REGENXBIO's wholly owned products bears risk given that we have not seen any clinical data to date. In addition, the failures of other companies' gene therapy products for wet AMD would result in additional scrutiny of REGENXBIO's product candidate for the same indication although REGENXBIO's approach is differentiated. While a broad pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk
If approved, REGENXBIO's products are likely to face competition from existing therapies. For example, in the wet AMD space, the approved anti-VEGF therapies (e.g., Regeneron's Eylea and Roche/Novartis' Lucentis) have demonstrated effectiveness (although there are some compliance issues), resulting in challenges associated with changing physicians' prescribing behaviors. With respect to HoFH, for which another gene therapy product (RGX-501) is being evaluated, a number of existing interventions could also pose competition. That said, RGX-501 has the potential to be used in conjunction with some of these therapies.

Aside from competition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If REGENXBIO cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercially viable.

Financing Risk
REGENXBIO currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Company-Specific Risks for Spark Therapeutics, Inc.

Clinical and Regulatory Risk
While we believe LUXTURNA is likely to be approved given the clinical data seen to date, there are uncertainties (e.g., the advisory committee's view on the novel primary endpoint and manufacturing) that could derail the current regulatory path.
Except for LUXTURNA, other clinical/preclinical product candidates may not deliver clinically meaningful results in the ongoing/future studies.

Commercial Risk
The commercial rollout of LUXTURNA could face challenges in identifying patients and obtaining insurance coverage. With respect to SPK-8011, there are multiple gene therapy products in development for hemophilia A, resulting in potentially fierce competition if all products exhibit comparable efficacy and safety profiles.

In general, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Spark cannot secure a reasonable price to compensate for the rare nature of most of the diseases being evaluated, the company's products may not be commercially viable.

Financing Risk
Spark currently has limited revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

Company-Specific Risks for Voyager Therapeutics, Inc.

Clinical and Regulatory Risk
While promising, the clinical results seen with VY-AADC01 were derived from a small number of patients, which may not be replicated in larger studies. As for the pipeline of product candidates, no clinical data has been reported to date. While a diversified pipeline creates multiple shots on goal, a setback in any of these programs could negatively impact shares.

Commercial Risk
There are multiple existing and development-stage products for PD. While we do not believe they would pose significant direct competition for VY-AADC01, the commercial adoption of this gene therapy may still face some pressure and take time. In addition, the commercial success of a gene therapy is also dependent on pricing/reimbursement. If Voyager cannot secure a reasonable price for VY-AADC01, the economics of this product may not meet expectations.

Financing Risk
Voyager currently has no product revenues and will likely need to raise capital periodically in order to sustain operations. The ability of the company to raise sufficient capital on time is vital for operations and could occur through both dilutive and non-dilutive means.

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