



**Astellas Pharma Inc.**

R&D Meeting

March 9, 2022

## Event Summary

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<b>[Company Name]</b>	Astellas Pharma Inc.	
<b>[Company ID]</b>	4503-QCODE	
<b>[Event Language]</b>	JPN	
<b>[Event Type]</b>	Investor Conference	
<b>[Event Name]</b>	R&D Meeting	
<b>[Date]</b>	March 9, 2022	
<b>[Time]</b>	09:30 – 11:05 (Total: 95 minutes, Presentation: 58 minutes, Q&A: 37 minutes)	
<b>[Venue]</b>	Webcast	
<b>[Number of Speakers]</b>	5	
	Kenji Yasukawa	Representative Director, President and CEO
	Mathew Pletcher	Division Head of GT-RTO
	Bernhardt Zeiher	Chief Medical Officer
	Naoki Okamura	Chief Strategy Officer (CStO), Chief Business Officer (CBO)
	Yoshitsugu Shitaka	Corporate Executive, Chief Scientific Officer
<b>[Participant Names]</b>	Hidemaru Yamaguchi	Citigroup Global Markets Japan Inc.
	Kazuaki Hashiguchi	Daiwa Securities Co. Ltd.
	Motoya Kohtani	Nomura Securities Co., Ltd.
	Madoka Sato	Schroder Investment Management (Japan) Limited

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## Presentation

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**Yasukawa:** Good morning, everyone. I'm Kenji Yasukawa of Astellas Pharma Inc. Thank you very much for joining our R&D Meeting despite your very busy schedule today. In our R&D Meeting today, we are going to explain Astellas' initiatives for gene therapy.

### CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION

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In this material, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas Pharma. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this material is not intended to constitute an advertisement or medical advice.



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This is a cautionary statement regarding forward-looking information on page two. I'm not going to read it.

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**I Introduction**

Kenji Yasukawa, Ph.D.  
President and Chief Executive Officer

**II Building Leadership in Gene Therapy**

Mathew Pletcher, Ph.D.  
Division Head of Gene Therapy Research & Technical Operations

**III Update on Clinical Programs in Gene Therapy**

Bernhardt (Bernie) Zeiher, M.D.  
Chief Medical Officer



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Page 3. This is the agenda for today.

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# INTRODUCTION



**Kenji Yasukawa, Ph.D.**  
President and Chief Executive Officer

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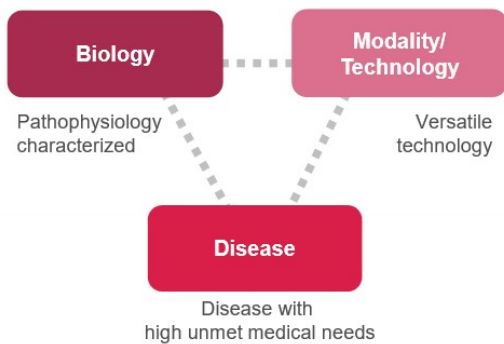
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Gene therapy has the potential to be transformative for patients, their families and society by addressing the root cause of disease, which provides a variety of VALUES

## FOCUS AREA APPROACH



Primary Focus Genetic Regulation has been selected based on;

- Scientific validity
- Feasibility
- Identified lead program and potential follow-on programs

## ASTELLAS' COMMITMENT TO GENE THERAPY



1. Scheduled to be operational and GMP-ready by mid-2022



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And the next page. First, I'd like to explain the background why we work on gene therapy.

Needless to explain to you during this meeting, our focus area approach is our R&D strategy. We are aiming to identify disease-causing biology so that the most appropriate corresponding modality or technology to continuously create new drug candidates for diseases with high unmet medical needs, also based on development possibilities. These three points will be combined. An R&D technology platform will be established, and we can create new research fees and the leading compound or project will enter the clinical stage.

Our R&D data package will be accepted by the regulatory authorities to allow us to proceed into the clinical stage. That's what we call Primary Focus. Once it's identified as a Primary Focus, we will use our management resources intensively. And genetic regulation is one of our Primary Focuses.

Looking at the scientific validity, gene therapy is a treatment approach to address the root causes of genetic diseases that occur due to gene mutation or deficiency, and it can target diseases with a clear association between the cause and how to address the situation.

Next on feasibility. We have high capabilities in research to leverage AAV technology platforms and continuously create programs in development to ensure appropriate patient selection, study design development, and conduct clinical studies in the field of rare diseases, and in manufacturing, to supply high-quality products end-to-end from clinical trial through commercial stages.

Astellas has high capabilities in all these areas.

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It's not just AT132, which was already in the clinical stage for XLMTM at the time of acquisition of Audentes; we also obtained multiple follow-on programs for various diseases with high unmet medical needs, such as AT845 for Pompe disease and Duchenne muscular dystrophy programs as well.

At the bottom of this page, you can find a simple chart on the history of our initiatives by now.

In Tsukuba, before the acquisition of Audentes, we had been conducting exploratory research on gene therapy from before. At that time, we were facing challenges of manufacturing high-quality products for gene therapy. But through our acquisition of Audentes in 2020, we successfully brought in high manufacturing capabilities in-house, which substantially accelerated our initiatives for gene therapies.

Since then, we also have made investments actively. In April last year, we launched Astellas Gene Therapies, AGT, as a gene therapy center of excellence and build end-to-end capabilities, incorporating R&D, manufacturing, and commercialization.

Furthermore, in May this year, we are planning to have the grand opening of a new large-scale manufacturing facility in Sanford, North Carolina, which is scheduled to be operational and GMP ready. We can cover commercial-scale manufacturing as well. We will leverage and develop our capabilities. We have acquired and nurtured to the maximum and continue our commitment to gene therapy going forward as well.

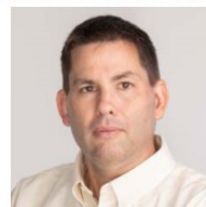
## OVERVIEW OF TODAY'S PRESENTATIONS

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### Building Leadership in Gene Therapy

- Basics of gene therapy
- Astellas' capabilities in gene therapy

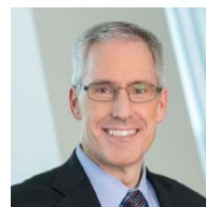
Mathew Pletcher, Ph.D.  
Division Head of GT-RTO



### Update on Clinical Programs in Gene Therapy

- AT132: Status update and next steps
- AT845: Program summary and latest data of FORTIS study

Bernhardt (Bernie) Zeiher, M.D.  
Chief Medical Officer



GT-RTO: Gene Therapy Research & Technical Operations

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Page 6. Let me give you a brief overview of today's presentations from now by two speakers on research and development.

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Today, on behalf of AGT, Mathew Pletcher, Head of Gene Therapy Research and Technical Operations, will present on our gene therapy research and manufacturing; then Astellas' capabilities, strengths in the field, and our future direction will be explained, as well as the basics of gene therapy.

And then Bernhardt Zeiher will give you an update on the current status of our ongoing clinical development programs, AT132 and AT845.

Now I'd like to hand over to Mat. Mat, please start your presentation.

**Pletcher\***: Thank you, Kenji. I'm Mat Pletcher, Division Head of Gene Therapy Research and Technical Operations at Astellas. I'm pleased to be here today to talk about the gene therapy landscape and Astellas' unique approach and capabilities in the field.

At Astellas, our goal is to boldly push the boundaries of what is possible to **discover, develop and deliver** breakthrough, first-of-their-kind gene therapies with **life-changing value for patients across many disease areas**



Please move to slide 8.

I've worked in gene therapy in rare disease for most of my career and have been personally touched by their impact to my daughter with a rare genetic condition that is causing her to lose her sight. I believe quite passionately that gene therapy holds a promise to transform how we treat many diseases and provide truly life-changing value to patients.

At Astellas, we are deeply committed to the disruptive potential of this groundbreaking area of research, which requires us to think differently and continually enhance our capabilities to be a leading player in the field. As we are developing our leadership in genetic medicine, I'm excited to talk to you today about how we are building the necessary capabilities to ensure that we are uniquely placed to navigate this complex field.

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## WHAT IS A GENETIC DISEASE?

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Genetic diseases are often **rare and complex to treat** with **limited** or no **therapeutic options** and **significantly reduce quality of life and life expectancy**<sup>1</sup>

There are **300 million** people living with rare diseases worldwide, **70%** of which have a genetic basis and are mostly present from birth<sup>2</sup>

**Genetic disorders** can be caused by<sup>3</sup>:



A **mutation in one gene**  
(monogenic disorder)



**Multiple genes**  
(multifactorial  
inheritance disorder)



**A combination of gene  
mutations and  
environmental factors**



**Damage to  
chromosomes** that  
carry genes



1. Cohen, J. & Biesecker, B. *American Journal of Medical Genetics Part A* 152A, 1136-1156 (2010)., 2. Nguengang Wakap, S. et al. *European Journal of Human Genetics* 28, 165-173 (2019)., 3. *National Human Genome Research Institute* (2022). at <https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders>.

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Please move to slide 9. What do we mean when we talk about genetic disease?

Genetic disease is caused by changes in a person's DNA. DNA provides the code for making protein and molecules that perform most of the functions in the body. Sometimes when a section of DNA has changed, the protein it codes for is also affected and may no longer be able to carry out its normal function. This may profoundly alter the biology of cells in the body resulting in a genetic disorder.

Rare monogenic diseases are often life limiting with few or no effective treatment options. This is especially true for the diseases we are aiming to address in our clinical programs, such as X-linked myotubular myopathy in pompe disease.

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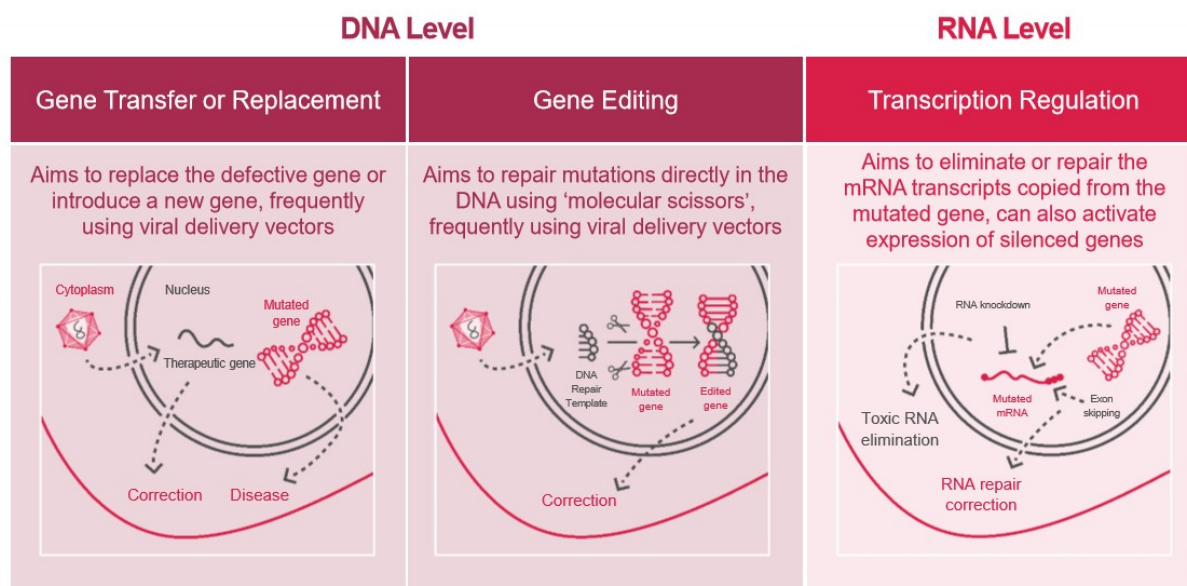
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# GENE THERAPY IS THE DELIVERY OF GENETIC MATERIAL INTO CELLS TO CORRECT DISEASE

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Approaches include<sup>1</sup>:



DNA: Deoxyribonucleic acid, mRNA: Messenger RNA, RNA: Ribonucleic acid.  
1. Wang, D. & Gao, G. *Discovery Medicine* 18, 151-156 (2014).



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Please move to slide 10. The identification of disease commutations is the first step in creating new gene-based treatments.

After identifying disease-associated mutation, we can study how the function of the corresponding gene product, the protein, is altered and determine if a genetic medicine approach might be appropriate for treating a disease.

There are three primary approaches that are typically used for gene-based therapeutics. Gene transfer or replacement introduces a wild-type or nonmutated copy of mutated gene into the dysfunctional cell. This approach is based on the concept that if a disease is due to a recessive loss of function mutation in a single gene, then adding back the wild-type gene should restore normal function and alleviate the disease phenotype.

Gene editing is performed using enzymes, particularly nuclease, that have been engineered to target a specific DNA sequence where they induce cuts into the DNA strands, enabling either the removal of existing DNA insertion, a replacement DNA, or the purposeful disruption of existing DNA in order to create a therapeutic effect. This editing mechanism could also be targeted to RNA as well as DNA.

Finally, gene therapy can be used to turn the expression of a gene on or off through transcription regulation. This approach is useful when a disease is caused by the expression of a toxic protein or when a potentially therapeutic gene already exists in the genome that have been silenced as part of the normal developmental process.

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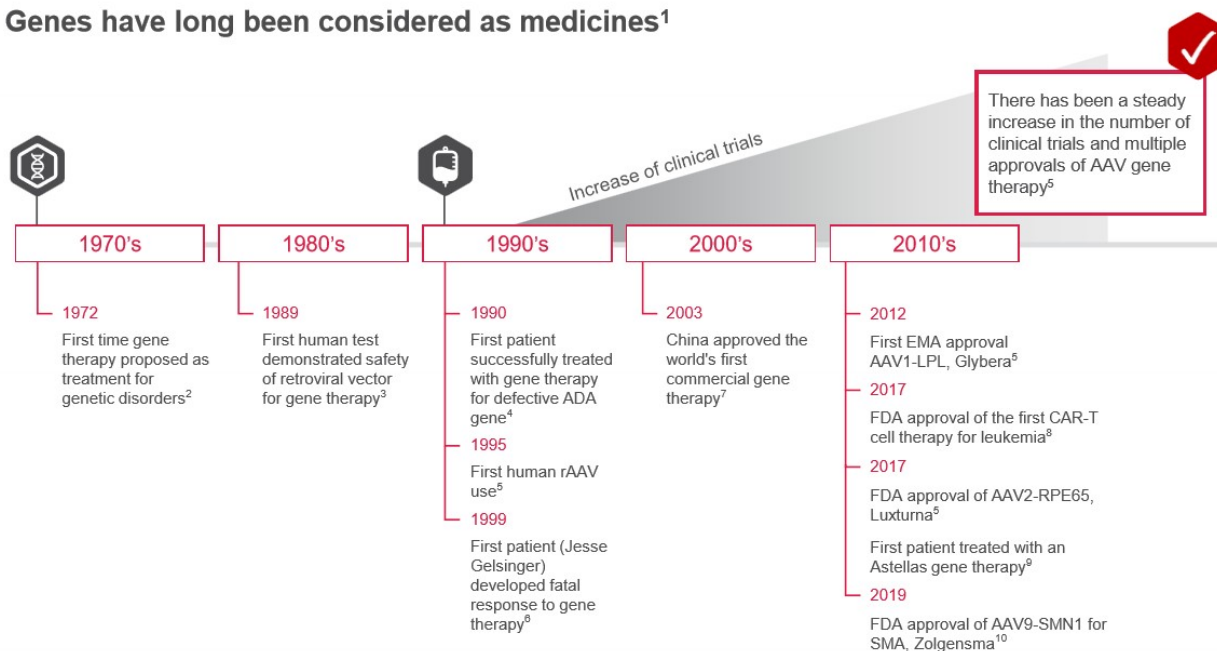
Gene therapy has an immense potential for targeting a broad spectrum of diseases given the incredible flexibility of the platform. It can address the underlying cause of disorder, tackling it at the source, which can bring substantial, positive, long-term health benefits to patients and reduce the need for chronic care.

This could mean considerable medical, economic, and social value. It's particularly apparent when looking at X-linked myotubular myopathy, where up to 90% of patients require a ventilator and long-term round-the-clock care.

## GENE THERAPY DEVELOPMENT IS RAPIDLY PROGRESSING BUT WE ARE LEARNING AS WE GO

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Genes have long been considered as medicines<sup>1</sup>



AAV: Adeno-associated virus, ADA: Adenosine deaminase, rAAV: Recombinant adeno-associated virus, EMA: European Medicines Agency, FDA: Food and Drug Administration, CAR: Chimeric antigen receptor.

1. Wang D, Gao G. *Discov Med* 2014;18:67-77. 2. Wirth T, et al. *Gene* 2013; 525(2):162. 3. Cornetta K, et al. *Nature Gene Therapy* 2005;12:S28-S35. 4. Blaese RM, et al. *Science* 1995;270(5235):475-80. 5. Wang D, et al. *Nat Rev Drug Discov* 2019;18:358-78. 6. Sibbald B. *CMAJ* 2001;164(11):1612. 7. Pearson S, et al. *Nature Biotechnology* 2004;22:3-4. 8. [www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm](http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm); accessed July 2020. 9. Audentes Therapeutics Announces Dosing of First Patient in ASPIRO, a Phase 1/2 Clinical Trial of AT132 for the Treatment of X-Linked Myotubular Myopathy. 10. [www.fda.gov/vaccines-blood-biologics/Zolgensma](http://www.fda.gov/vaccines-blood-biologics/Zolgensma); accessed July 2020.

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Please move to slide 11. We have come a long way since 1972 when the first gene therapy was proposed and the significant increase in the number of clinical trials and approval demonstrates the industry's focus on realizing the promise of gene therapies for patients.

In 20 years, we have moved from theory to proven application in treating human disease. In the last two decades, we have seen an accelerated rate of approvals with the delivery of the first commercial gene therapy in China in 2003, and the first approvals for CAR T-cell therapy for leukemia in 2017, for vision loss with Luxturna in 2017, and the treatment of spinal muscular atrophy in children under two with the approval of Zolgensma by the FDA in 2019.

There have been successes, but this is still a research field in its infancy. The journey has not been without its challenges and setbacks. In 1999, the gene therapy community faced a tragic loss with the death of Jesse Gelsinger in a trial with an adenovirus-based gene therapy.

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What will our progress look like in another 20 years? We recognize that there are still barriers to overcome. And in the spirit of innovation, the field is collectively learning as we go. At Astellas, we are committed to playing our part in delivering many more life-changing therapies in the future.

## AAVS ARE ONE OF THE MOST PROMISING AND VERSATILE VIRAL VECTORS FOR DELIVERY OF GENETIC MEDICINES

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**Adeno-associated viruses (AAV)** are **naturally occurring viruses** that are able to infect and enter into human cells but are **not currently known to cause disease**, making them an attractive and efficient vector to deliver gene therapy<sup>1</sup>



- The genome of AAV can be **easily removed and replaced** with the desired transgene, a therapeutic gene<sup>1</sup>
- Broad tissue tropism and high transduction efficiency
- rAAVs deliver genes without genomic integration, with little risk of insertional mutagenesis<sup>2</sup>
- Potential long-term stability and able to continuously produce protein in non-dividing cells<sup>1</sup>



AAV: Adeno-associated virus, rAAV: Recombinant adeno-associated virus

1. Wang, D., Tai, P. & Gao, G. *Nature Reviews Drug Discovery* 18, 358-378 (2019). 2. Naso, M., Tomkowicz, B., Perry, W. & Strohl, W. *BioDrugs* 31, 317-334 (2017).

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Please move to slide 12. Key to unlocking the potential of gene therapy was a discovery of adeno-associated virus or AAV vectors.

AAV is currently the leading platform for *in vivo* gene delivery for the treatment of a variety of human diseases. They are found in multiple species, including human and nonhuman primates. The current consensus is that AAV itself does not cause any human disease, making them an efficient vector for delivery of gene therapy.

AAV vector-delivered DNA is incredibly stable, demonstrating durable expression over years, but does not generally integrate into the cells' DNA, limiting the potential for insertional mutagenesis. In addition, these vectors can affect a variety of dividing and nondividing cells and have been found to be much less immunogenic than earlier generations of gene therapy vectors like adenoviruses.

Other advantages include an ability to transduce a broad range of cell types and a relatively high transduction efficiency, which refers to their ability to transfer genetic material into cells. It is for these reasons that Astellas is focused on AAV technology for our gene therapy platform, working to optimize current generation AAV while investing in the exploration of next-generation technology.

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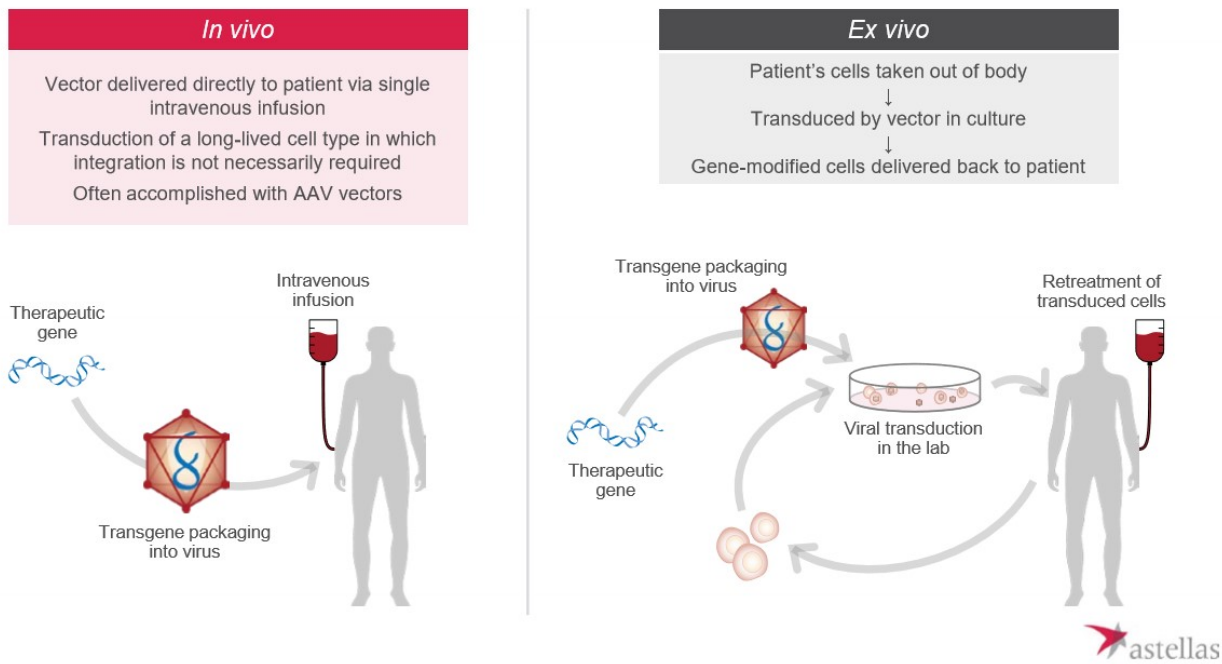
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## TWO PRIMARY STRATEGIES OF GENE THERAPY ADMINISTRATION

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### Two primary strategies: *in vivo* vs. *ex vivo* delivery



AAV: Adeno-associated virus.

1. Wang, D., Tai, P. & Gao, G. *Nature Reviews Drug Discovery* 18, 358-378 (2019); 2. Naso, M., Tomkowicz, B., Perry, W. & Strohl, W. *BioDrugs* 31, 317-334 (2017).

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Please move to slide 13. There are two main approaches for how gene therapy is administered, *in vivo* and *ex vivo*.

*In vivo* gene therapy involves the infusion of a virus carrying the therapeutic gene directly into the patient's body. Since DNAs delivered by AAV vectors can exist for the entire lifespan of a given cell, they are commonly used for *in vivo* experiments requiring long-term expression.

Conversely, *ex vivo* gene therapy involves the harvesting of cells from a patient, followed by subsequent viral transduction *ex vivo* in a laboratory setting, bio-virus carrying the therapeutic gene. The transduced cells are then returned back to the patient.

Astellas' main area of focus is *in vivo* gene therapy administration.

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# OUR PIPELINE OF GENE-BASED THERAPIES IS ONE OF THE BROADEST IN THE INDUSTRY

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Broad portfolio including systemically delivered programs targeting neuromuscular disorders, and locally delivered programs for CNS and ocular disorders

 In the clinic

\*Currently on clinical hold

CNS: Central nervous system, XLMTM: X-linked myotubular myopathy. The listed treatments are investigational agents. The safety and efficacy of these agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval or become commercially available for uses being investigated.

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 Neuromuscular disease programs	 CNS disorders	 Ocular programs	 Other
AT132* for XLMTM	AT808 for Friedreich's Ataxia	A1015 for Primary open angle glaucoma	ADR for Hepatitis D virus infection
AT845 for Pompe disease	HUB for Huntington's disease	TFB for Dry age-related macular degeneration, Stargardt macular dystrophy	
AT753 for Duchenne muscular dystrophy	DAD for Angelman syndrome	GTSG for Stargardt macular dystrophy	
AT702 for Duchenne muscular dystrophy	GTFX for Fragile X syndrome		
AT751 for Duchenne muscular dystrophy			
AT466 for Myotonic dystrophy			
MDL-201			
MDL-202			

Please move to slide 14. Our goal is to successfully deliver to patients a series of transformative gene therapies over the coming decade.

At Astellas, our broad, differentiated pipeline is enhanced by our deep knowledge and expertise in AAV-based gene delivery technology and guided by the Astellas focus area approach. This is designed to build sustainable, expandable drug discovery capabilities that can deliver new treatment platforms and innovative products with transformative value for patients.

We have two candidates in clinical development, AT132, which is currently on clinical hold for X-linked myotubular myopathy, and AT845 for Pompe disease. In addition, we are working at the research stage to build a sustainable portfolio across a number of areas, including other rare neuromuscular diseases, central nervous system, and ocular disorders. Our goal is to expand to more common diseases in larger patient populations in the near future.

Shortly, I will go into more detail on two key programs: DAD for Angelman syndrome, and AT808 for Friedreich's Ataxia and some of their initial data. We look forward to providing updates on the wider pipeline at a later stage.

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## DISEASE BACKGROUND



AS is a neurodevelopmental disorder characterized by **severe cognitive disability, ataxia, seizures and autistic behaviors**. Patients have a **normal lifespan** but require **lifelong care**<sup>1</sup>



Prevalence is estimated to be **~60,000 – 100,000** (EU, US, Japan)<sup>1</sup>



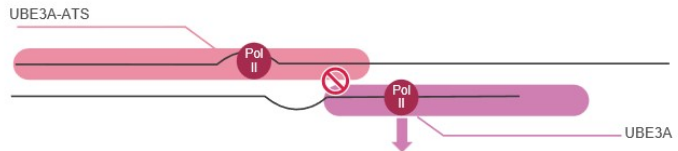
It is caused by **de novo loss of or coding mutations in maternal UBE3A**. Paternal UBE3A is **imprinted** in neurons by UBE3A-ATS and silenced, resulting in expression of faulty maternal UBE3A<sup>2</sup>



Treatment approaches aim to **unsilence** paternal UBE3A by downregulating UBE3A-ATS

## INVESTIGATIONAL DAD – Three vector approaches

The mechanism of UBE3A imprinting



### 1. ZFP binds to UBE3A-ATS to prevent its transcription

AAV-delivered transgene encodes zinc finger protein (ZFP) that de-represses paternal UBE3A

### 2. miRNA cleaves UBE3A-ATS and causes Pol II release

MicroRNA (miRNA) cleaves UBE3A-ATS and causes RNA Polymerase II (Pol II) release, allowing expression of paternal UBE3A

### 3. MsgRNA (targeting poly A signal) degrades UBE3A-ATS

Modified single guide RNA (MsgRNA) targets the Poly(A) site of UBE3A-ATS, terminating its transcription



AAV: Adeno-associated virus, AS: Angelman syndrome, Pol II: RNA polymerase II, ZFP: Zinc finger protein, miRNA: MicroRNA, MsgRNA: Modified single guide RNA.  
1. NORD (National Organization for Rare Disorders) (2022) at <https://rarediseases.org/rare-diseases/angelman-syndrome/>. 2. Khatri, N. & Man, H. *Frontiers in Molecular Neuroscience* 12, (2019).

Please move to slide 15. I'd like to take this opportunity to spotlight two of our key investigational programs: DAD for Angelman syndrome; and AT808 for Friedreich's ataxia.

First, let's take a look at DAD for Angelman syndrome. Angelman syndrome is a rare genetic and neurological disorder caused by the deletion or loss of function of the maternal copy of UBE3A. It is characterized by a severe developmental delay and learning disabilities, absence or near absence of speech, inability to coordinate voluntary movements, fingerlessness with jerky movements of the arms and legs, and distinct behavioral patterns. Additional symptoms may occur, including seizures, sleep disorders, and feeding difficulties.

Currently, therapies for Angelman syndrome are symptomatic and supportive, with no approved medication that significantly impacts the core disease manifestations. Advances in neuroscience and in gene therapy techniques, however, hold potential providing meaningful treatment for the syndrome. Astellas is investigating ways to restore UBE3A expression by multiple vectorized approaches. Normally, only the maternal copy of UBE3A is expressed. That means in most Angelman patients, there exists a healthy but silent paternal copy of the gene.

All of the approaches we are currently pursuing look to activate the functional paternal UBE3A through disruption of the UBE3A antisense long noncoding RNA. This multifaceted exploration demonstrates the versatility of AAV and our approach to identifying a treatment for this devastating disease.

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## SPOTLIGHT ON AT808 FOR FRIEDREICH'S ATAXIA (FA)

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### DISEASE BACKGROUND



FA is a **progressive, neurodegenerative movement disorder** with a typical age of onset between 10 and 15 years. It is caused by **loss of function mutation in the frataxin** (gene FXN)<sup>1</sup>



The most common form of inherited ataxia has an estimated prevalence of **~15,000 – 20,000 worldwide**<sup>2</sup>



Characterized by unsteady posture, frequent falling, and progressive difficulty in walking due to **impaired ability to coordinate voluntary movements**<sup>2</sup>



**No approved disease-modifying treatments**



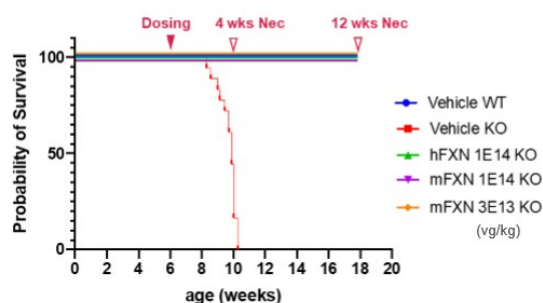
Common cause of death is due to the FA-associated **cardiomyopathy**<sup>3</sup>

### INVESTIGATIONAL AT808

– AAV gene therapy to express FXN in affected tissues



Heart POC mouse study showed **reversal of phenotype**<sup>4</sup>



- FXN transgene protein expression was detected by IHC and WB in heart
- AT808 rescued the mortality, improved ejection fraction, and fibrosis in heart



FA: Friedreich's ataxia, FXN: Frataxin gene, AAV: Adeno-associated virus, bp: Base pairs, ITR: Inverted terminal repeat, hPGK: Human phosphoglycerate kinase, hFXNco: Codon-optimized human Frataxin, SV40: Simian virus 40, LpA: late polyadenylation, POC: Proof of concept, IHC: Immunohistochemistry, WB: Western blotting, Nec: Necropsy, WT: Wild type, KO: Knock out, hFXN: Human frataxin, mFXN: Mouse frataxin.  
 1. Koeppen, A. *Journal of the Neurological Sciences* 303, 1-12 (2011). 2. *NORD* (2022) at <https://rarediseases.org/rare-diseases/friedreichs-ataxia/>.  
 3. Weidemann, F. et al. *Journal of Neurochemistry* 126, 88-93 (2013). 4. Astellas data on file.

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Please move to slide 16. Let's look now at our investigational treatment for Friedreich's ataxia.

Friedreich's ataxia is a genetic, progressive neurodegenerative movement disorder with a typical age of onset between 10 and 15 years. It is caused by the loss of expression of the gene, frataxin. The disease is characterized by impaired ability to coordinate voluntary movements. Friedreich's is also associated with cardiomyopathy and 60% of Friedreich's ataxia patients die of cardiac dysfunction.

There are no approved treatments, although surgery and physical, occupational, and speech therapy are aimed at keeping the disease in check for as long as possible. Astellas is investigating AT808 as an AAV vector-based gene therapy to express the frataxin gene in affected tissues. The construct was selected to reduce potential toxicity from high levels of frataxin expression. The human PGK promoter was selected for its ubiquitous and lower expression compared to other commonly used options.

We initially conducted a proof-of-concept study in a severe mouse model of the disease. As you can see in the figure on this slide, these mice typically die within 8 to 10 weeks of age due to heart failure. We were able to demonstrate rescued mortality as well as improved ejection fraction and reduction of fibrosis in the heart with our frataxin construct. Frataxin transgene protein expression was also detected by amino histochemistry and western blot in the heart.

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**The pioneering field of gene therapy is uniquely complex** and cannot be navigated alone

We are often working in **unchartered territory** with rare diseases that are not well understood, and we are all learning as we go

There is a need for **cross-industry collaboration and information-sharing** in our quest to bring these therapies to patients

Please move to slide 17. While it's important to consider how far we've come with rapid advancements in the field, this is still a relatively new space and the whole community is continually learning and growing as we navigate often completely uncharted territory.

At Astellas, we recognize the inherent challenge and higher risk of delivering transformative therapies to patients, and are committed to learning from the expected setbacks as part of advancing groundbreaking science.

In order to enable innovation and to push the boundaries of what is possible for patients, Astellas has built a long-term strategy, allowing time to understand the science, build and enhance necessary expertise and capability, and work in close partnership with our stakeholder communities, patients, advocacy, healthcare professionals, regulatory authorities, and our developmental partners.

We believe we are entering a new frontier of hope in gene therapy. With the knowledge and expertise of our team, combined with cutting-edge capabilities, we have the potential to truly transform the promise of gene therapy.

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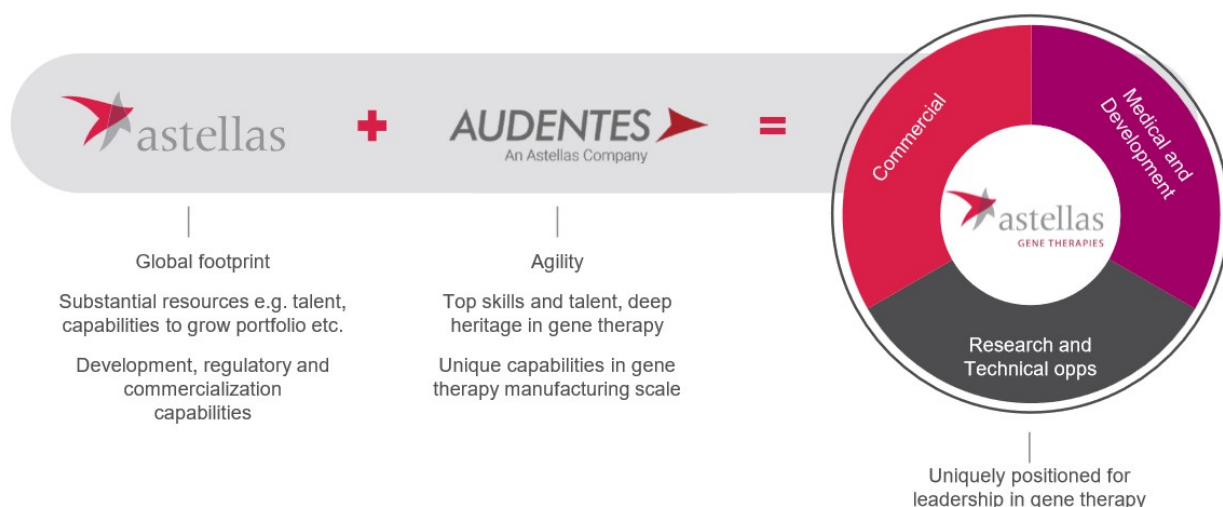
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LAUNCHED IN APRIL 2021, **ASTELLAS GENE THERAPIES**  
**COMBINES THE BEST OF BIOTECH AND PHARMA**



Astellas Proprietary Information

Please move to slide 18. The acquisition of Audentes was a testament to our active partnering in gene therapy, an important strategic move in our ambition to become an established leader in the space. Moreover, the capability to make and deliver gene therapies to patients who need them is central.

Astellas Gene Therapies was established by combining Audentes' industry-leading in-house gene therapy manufacturing capability, innovative scientific approach, and know-how in gene therapy with Astellas' global footprint, resources, and leading development, regulatory, and commercialization capabilities. In addition, the acquisition enabled us to convene a team of over 400 passionate, dedicated, and specialist scientists, researchers, and operational experts grouped into development, research, and technical operations, and commercialization functions in an incredibly competitive field.

Finally, by combining the Audentes pipeline with that of Astellas, and including our other Primary Focuses, we are able to explore new therapeutic options in more common diseases and larger patient populations. With all of that, we believe that we are firmly positioned to deliver transformative therapies for patients with genetic diseases.

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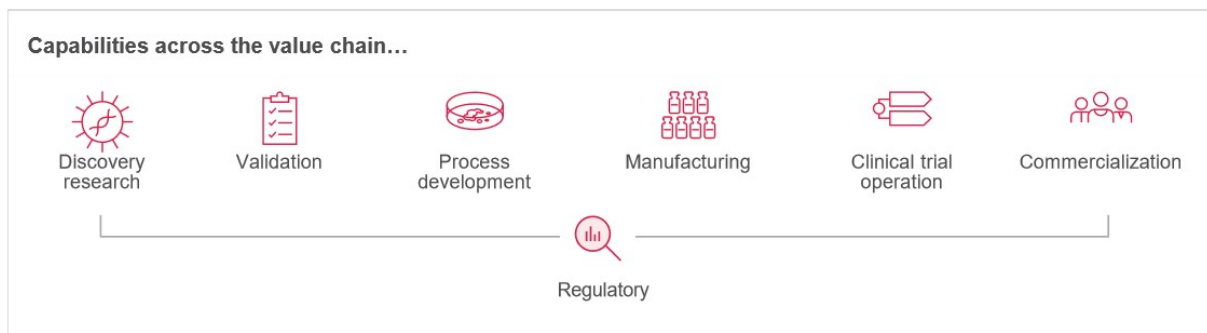


## TRANSFORMING GROUND-BREAKING SCIENCE INTO A SCALABLE OPERATION, DELIVERING FOR PATIENTS WORLDWIDE

19

**Long-term commitment** to advancing gene therapy with significant ongoing investment to build a portfolio of medicines and **a series of launches across multiple diseases** over the coming years

**One of the broadest early pipelines in the industry**, capacity to produce high-quality gene therapy products to meet anticipated demand, and an aligned commercial team already working to optimize our in-market potential



Astellas Proprietary Information

Please move to slide 19. The end-to-end capabilities Astellas now has in-house is a key competitive advantage for us. It enables us to mobilize our diverse and expansive portfolio.

Having the capabilities to manufacture and scale gene therapies is important for the success in this field. Many sponsors rely on external partners for this part of their operation. Given the heightened activity in the gene therapy space right now, there is a high demand on outsourced support. Having those in-house capabilities is essential to being competitive.

It also means that we can integrate new technologies and respond to regulatory requirements with speed and agility, working with our global quality and assurance and pharmacovigilance teams to ensure the highest standards of quality and safety.

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Gene therapies are manufactured through a **complex process in which living cells insert a functional gene into a virus**

The process requires **advanced technology** and facilities

Despite significant progress, producing therapeutic genetic material and viral vector delivery systems **efficiently, economically** and at **scale** remains a **critical challenge**



AAV: Adeno-associated virus, RCB: Research cell bank

Astellas Proprietary Information

Please move to slide 20. Let's have a closer look at the manufacturing specifically.

There has been significant progress in research and recent regulatory approvals, but scalability and manufacturing costs remain critical challenges for fully realizing potential gene therapy. I won't go through this workflow in detail, but you can see the complexity with multiple steps involved. Each of them requires significant optimization.

To illustrate the challenges of AAV manufacturing, let's take the example of empty capsids which lack the vector genome and, therefore, unable to provide a therapeutic benefit. As such, we seek to remove the majority of these capsids from the final drug product as part of the manufacturing process in order to lower the total viral exposure to the patient. But this step removes some full capsids as well, thus reducing the overall productivity of the process.

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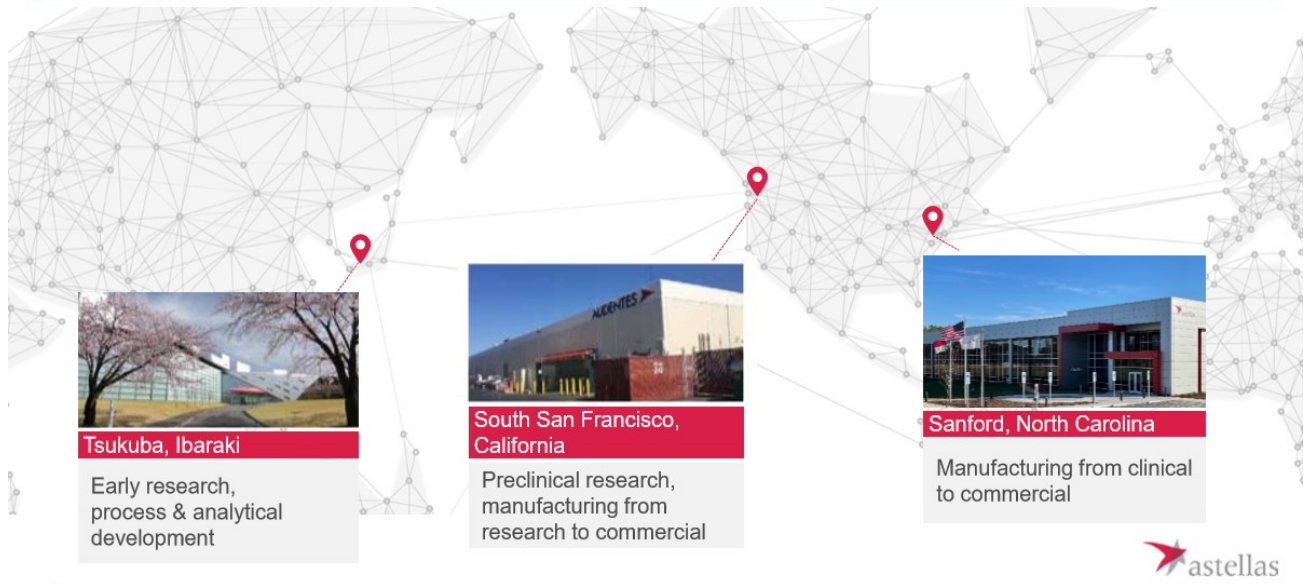




## EARLY INVESTMENT IN AAV MANUFACTURING TO SUPPORT A GROWING PORTFOLIO OF GENE THERAPIES

21

Our unique manufacturing infrastructure is a **key competitive advantage** in helping us to overcome these industry challenges, with research and manufacturing **co-located as agile organizations**, enabling **flexible collaboration and knowledge-sharing**



AAV: Adeno-associated virus.

Astellas Proprietary Information

Please move to slide 21. Our integrated global manufacturing infrastructure is an important way in which we are overcoming these industry challenges of complexity, manufacturing process, and scalability. It allows us to combine research and manufacturing, which enables continual learning and knowledge sharing as we go.

We are particularly excited to be further expanding our capabilities with a new cutting-edge gene therapy manufacturing facility opening in Sanford, North Carolina in May this year, which builds on our existing network of facilities in Tsukuba, Japan and South San Francisco, California.

This is an important strategic step for Astellas as it gives us the flexibility to produce material for multiple programs and studies in parallel as opposed to in sequence. This means we can advance our programs more rapidly. We never want manufacturing to be the rate-limiting step in advancing these programs for patients.

### Support

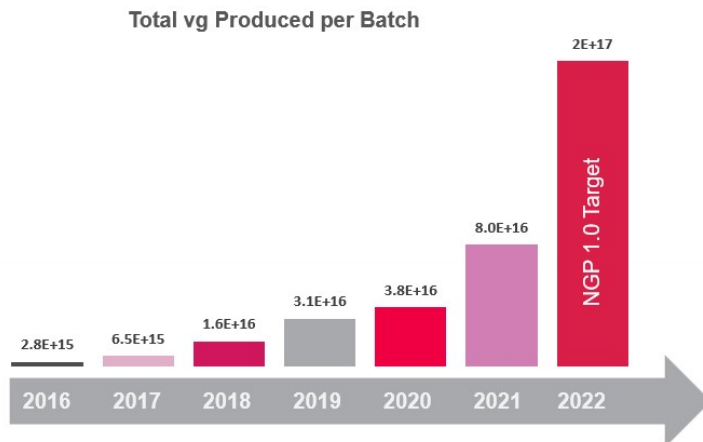
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**SCRIPTS**  
Asia's Meetings, Globally

20

**Audentes / AGT Progress in productivity and yield<sup>1</sup>:**



Dramatic increases in both productivity and yield are seen over time with process improvements and additional knowledge and experience; further improvements planned to continue trajectory



AAV: Adeno-associated virus, AGT: Astellas Gene Therapies, vg: vector genome.  
 1. NGP 1.0: Next Generation AAV Process 1.0, for AAV8/9; current goal is to develop and lock process by end of Q3 FY22.

Astellas Proprietary Information

Please move to slide 22. We are already able to see the impact of the investments in innovation of Astellas Gene Therapies on the overall productivity of our manufacturing process.

Through the introduction of new technology and process improvements created by our scientists, we have seen an increase in the amount of AAV vector genomes we can produce from a single production run. As we move into our next-generation process in 2022, we anticipate another substantial jump in our AAV manufacturing capabilities.

This evolution in productivity has a direct relationship to the cost of goods of gene therapies. By improving manufacturing productivity, we will hopefully be able to increase the access of patients to these transformative medicines.

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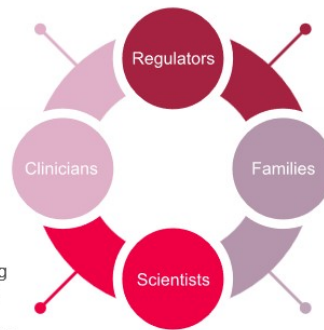


We are actively seeking partnerships that enhance our research-to-Investigational New Drug application stage portfolio and solve fundamental issues such as novel gene constructs, better delivery vectors, and re-administration technologies

Due to intense competition for an often limited patient pool, there is **increasing pressure to be first-to-market**

With multiple elements required for successful gene therapy development, **collaboration among industry, academia, regulators, clinician and patient communities is critical**

**Clinicians:** design and implementation of an effective, clinically feasible development program



**Regulators:** alignment on CMC and nonclinical requirements, clinical program design elements, endpoint selection

**Scientists:** understanding disease pathophysiology, AAV vector biology, immune responses to AAV treatments

**Patients and families:** essential to understand the patient experience to deliver true VALUE in areas of highest unmet need



AAV: Adeno-associated virus, CMC: Chemistry, manufacturing and controls.

Astellas Proprietary Information

Please move to slide 23. The pace and innovation and the highly competitive landscape in gene therapy requires strong collaboration and cross-industry partnership.

The majority of genetic diseases are rare and have limited or no other available therapy options. As such, there is pressure to work quickly to meet the patient needs and achieve first-to-market status.

To do this, we must ensure our candidates have the highest possible chance of success every step of the way. This means partnering and collaborating with academic groups and leading-edge biotechnology companies, clinicians, and scientific experts in the field, regulatory authority, and importantly, the patient communities we serve to ensure we have the expertise to overcome complex challenges across all stages of research and development.

Astellas prides itself by continually pushing the boundaries of current research and knowledge. We continue to seek further partnerships and collaborations help us fulfill the potential of Astellas' plans and aspirations in gene therapy.

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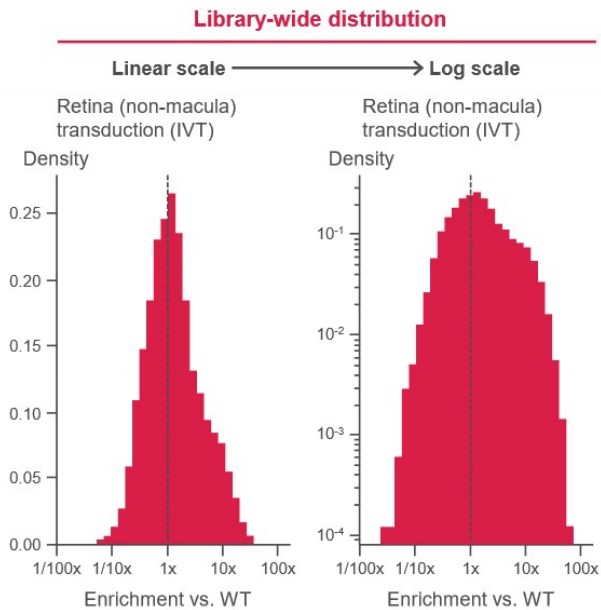
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In our ambition to remain at the forefront of gene therapy innovation and reach more patients, Astellas has entered into a research collaboration with Dyno Therapeutics<sup>1</sup>

Dyno's CapsidMap™ Platform applies experimental data and machine learning to create **novel AAV capsids** designed to **optimize tissue targeting** and **immune-evading properties**

Unlike traditional approaches, CapsidMap™ is uniquely well-suited for delivery across multiple organs, with the goal of enabling more effective **whole-body treatment for many diseases**



**Capsids with altered and improved transduction in the non-macular retina: Results pooled from non-macula retinal samples<sup>2</sup>**

AAV: Adeno-associated virus, IVT: Intravitreal, WT: Wild-type capsid.  
1. Astellas Press Release, December 2, 2021. 2. Dyno Therapeutics data on file.

Astellas Proprietary Information

Please move to slide 24. One of the collaborations we are particularly excited about is our recently announced research collaboration with Dyno Therapeutics and AAV optimization.

We believe we have the capabilities and know-how to be successful with today's AAV technology, particularly in core areas of biology like neuromuscular, central nervous systems, and ophthalmology. And this is driving our shorter-term activity. But having said that, even in these spaces, we know there are opportunities to increase our capabilities with improved AAV, and that's why we pursued the research collaboration with Dyno Therapeutics. Ultimately, we believe we can deliver a next-generation capsid that can improve safety and efficacy even in areas where we already see benefit with our current generation AAV.

One of the key limitations of AAV is that a large proportion of the therapeutic load is taken up by the liver. We are looking at shifting the balance to enable more enhanced and efficient delivery to target cells and tissues. As seen on the figure on the right, for Dyno's program to identify improved vectors for delivery to the back of the eye, early data indicates that their CapsidMap platform was able to identify novel capsids that substantially outperform the current generation of AAV.

Ultimately, our long-term ambition is to move beyond the core areas we are exploring, bringing gene therapy out of the rare disease space and into more common diseases. We're going to need different kinds of technologies to do that, and that includes evolving to next-generation capsids.

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## STAYING AT THE FOREFRONT OF SCIENTIFIC INNOVATION IN GENE THERAPY – OUR FUTURE FOCUS OF INTEREST

25

Capabilities	Portfolio assets	Partnerships
<ul style="list-style-type: none"> <li>• Novel improved AAV capsids</li> <li>• Technologies to manage pre-existing immunity and the possible need for redosing</li> <li>• Technologies to further improve efficiency and quality of manufacturing of viral vectors</li> <li>• Technologies for efficient delivery and expression in target organs</li> <li>• Non-viral gene delivery technologies</li> </ul>	<p>Novel AAV based projects targeting serious diseases with a strong link between biology/modality and disease</p> <ul style="list-style-type: none"> <li>• Neuromuscular Diseases</li> <li>• Central Nervous System</li> <li>• Ophthalmology</li> </ul>	<p>Partnerships with synergistic capabilities to maximizing global development value of project assets</p> <ul style="list-style-type: none"> <li>• Manufacturing</li> <li>• Global reach, including Japan and Asia</li> </ul>

AAV: Adeno-associated virus



Astellas Proprietary Information

Please move to slide 25. In order to continue to grow into a leadership position in gene therapy and tackle some of the biggest challenges in gene therapy today, we are always looking to further build and optimize our capabilities and portfolio assets.

From a capability perspective, our key focus areas include: novel improved AAV capsids, for which the Dyno Therapeutics collaboration is a key component; technologies to manage preexisting immunity and the possible need to redo; technologies to further improve efficiency and quality of manufacturing of viral vectors, the launch of the new Sanford site is a key step in this journey; technologies for efficient delivery and regulated expression in target organs; and nonviral gene delivery technologies.

Our broad and exciting pipeline is what positions us for leadership in gene therapy. From a portfolio perspective, we are looking at novel AAV-based projects targeting serious diseases with a strong link between biology, modality, and disease. Our current focus areas are neuromuscular and CNS diseases alongside ophthalmology. As such, we are actively pursuing external clinical and clinic-ready assets that complement this focus.

Finally, we are always looking for partners with synergistic capabilities to help us maximize the value of our assets and technology. This includes leveraging our own manufacturing capabilities, increasing our global reach, including Japan and Asia.

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## ASTELLAS IS FIRMLY POSITIONED TO DELIVER TRANSFORMATIVE THERAPIES FOR GENETIC DISEASES

26

The breadth and depth of our Gene Therapies pipeline marks Astellas as one of the leading developers of gene therapies worldwide



Highly-skilled scientists, researchers and operational experts



Strategic partnerships and investments with world-renowned academic groups and leading-edge biotechnology companies



Unique, industry-leading, scalable in-house manufacturing infrastructure



Deeply committed to partnering with and delivering for the patient communities that we serve



Full value chain capabilities, globally consistent standards and processes



Astellas Proprietary Information

Please move to slide 26.

To summarize, Astellas Gene Therapies is at the very leading edge of innovation in gene therapy. We are investing with a goal of remaining at the forefront of genetic medicines for the long term. Alongside our industry-leading pipeline, our unique culture combines the agile, rapid, and flexible biotech mentality with the solid foundations and reach of a global manufacturing company.

Our innovative manufacturing, regulatory, and commercial infrastructure are unique to the industry, strengthened by global standards and processes. We continually pursue new areas of gene therapy science across Astellas. And with our external partners, are always on the lookout for new partnerships that can help advance and enhance our portfolio.

Our dedication to bringing a better tomorrow for our patient community is resolute. We believe our knowledge, passion, and resilience, combined with our bold trailblazing approach will lead to innovations in gene therapy that will provide transformational value for patients across many diseases.

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One of the most active preclinical developers, with

**16** 

gene therapy candidates in development

**3** 

cutting-edge laboratory and manufacturing facilities



**400+**

Passionate, highly skilled scientists, researchers and operational experts



## END-TO-END CAPABILITIES

incorporating research, development, manufacturing and commercialization



Active partnerships with leading industry and academia, including Dyno Therapeutics to develop next-generation (AAV) vectors

## BOLD APPROACH

and

## PATIENT FIRST

CULTURE



AAV: Adeno-associated virus.

Astellas Proprietary Information

Please move to slide 27.

Thank you very much for your time today. I will leave you with a by-the-numbers overview of Astellas Gene Therapies, as I now hand you over to our Chief Medical Officer, Bernie Zeiher. I look forward to answering your comments and questions later.

**Zeiher\***: Thank you, Mat, and good morning. My name is Bernie Zeiher, and I'm the Chief Medical Officer at Astellas, and I'm pleased to provide you an update on the clinical stage assets in our gene therapy pipeline.

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# OUR PIPELINE OF GENE-BASED THERAPIES IS ONE OF THE BROADEST IN THE INDUSTRY

Broad portfolio including systemically delivered programs targeting neuromuscular disorders, and locally administered programs for CNS and ocular disorders

	 Neuromuscular disease programs	 CNS disorders	 Ocular programs	 Other
	AT132* for XLMTM	AT808 for Friedreich's ataxia	A1015 for Primary open angle glaucoma	ADR for Hepatitis D virus infection
	AT845 for Pompe disease	HUB for Huntington's disease	TFB for Dry age-related macular degeneration, Stargardt macular dystrophy	
	AT753 for Duchenne muscular dystrophy	DAD for Angelman syndrome	GTSG for Stargardt macular dystrophy	
	AT702 for Duchenne muscular dystrophy	GTFX for Fragile X syndrome		
	AT751 for Duchenne muscular dystrophy			
	AT466 for Myotonic dystrophy			
	MDL-201			
	MDL-202			

 In the clinic

\*Currently on clinical hold

CNS: Central nervous system, XLMTM: X-linked myotubular myopathy.

The listed treatments are investigational agents. The safety and efficacy of these agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval or become commercially available for uses being investigated.



Astellas Proprietary Information

Please move to slide 29.

Today, I'll be providing an update on the AT132 program, which is currently on clinical hold, and the AT845 program in Pompe disease.

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A close-up photograph of a young child with dark hair and eyes, looking downwards. The child is wearing a grey long-sleeved shirt. A medical device, possibly a nebulizer or respiratory support, is attached to their chest. The background is a soft, out-of-focus white.

## UPDATE ON AT132 FOR THE TREATMENT OF XLMTM

Next slide.

Let me start with the AT132 program, which is being evaluated as a treatment for X-linked myotubular myopathy or XLMTM.

---

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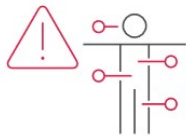
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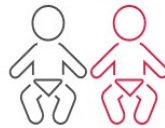
# XLMTM – A DEVASTATING DISEASE WITH NO EFFECTIVE TREATMENT OPTIONS

31

Half of XLMTM patients do not survive past 18 months<sup>1</sup>



XLMTM is a **life-threatening neuromuscular disease** characterized by extreme muscle weakness and respiratory failure<sup>1</sup>



XLMTM affects approximately **1 in 40,000 to 50,000 newborn males**<sup>2</sup>



Motor milestones are **substantially delayed or not achieved**<sup>3,5</sup>



**90% require respiratory support at birth**, continuing to demonstrate chronic, life-long ventilator dependence up to 24 hours per day<sup>1,2</sup>



**> 70% require feeding tubes**<sup>3,4</sup>



XLMTM: X-linked myotubular myopathy.

1. Graham, R. et al. *Archives of Disease in Childhood* 105, 332-338 (2019). 2. Beggs, A. et al. *Neuromuscular Disorders* 27, S172 (2017). 3. Amburgey, K. et al. *Neurology* 89, 1355-1364 (2017). 4. Lawlor, M. & Dowling, J. *Neuromuscular Disorders* 31, 1004-1012 (2021). 5. Molera, C. et al. *Journal of Neuromuscular Diseases* 9, 73-82 (2022).

Astellas Proprietary Information

Please move to slide 31. As a brief reminder, XLMTM is a rare disorder affecting 1 in 40,000 to 50,000 newborn males.

90% of boys born with XLMTM require respiratory support at birth and most demonstrate lifelong ventilatory dependence. Most also will require feeding tubes for nutritional support. They do not achieve typical motor milestones like sitting unaided, standing independently, or walking. Available treatment is supportive, and there's little hope for these boys or their parents who need to provide near round-the-clock monitoring.

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XLMTM is a monogenic disease due to mutations of the MTM1 gene which encodes myotubularin

Myotubularin is required for normal muscle development, cellular organization and function

AT132 delivers the full-length human MTM1 gene which is controlled by a desmin promoter – this restricts the transcription of MTM1 to the muscle cells where it is delivered

Systemic gene replacement therapy with muscle-specific desmin promoter

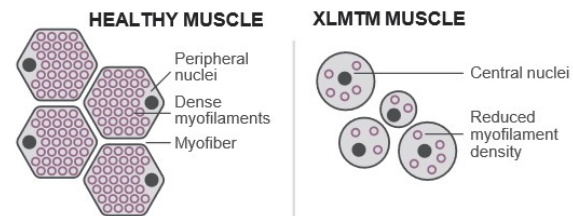


Figure 1a. Astellas proprietary image.

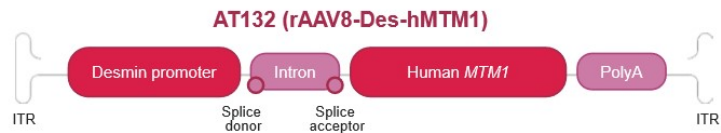


Figure 1b. Adapted from Astellas InVivo Gene Editing Summit Presentation November 2021.



ITR: Inverted terminal repeat; MTM1: Myotubularin 1; PolyA: Polyadenylation signal; XLMTM: X-linked myotubular myopathy.

Astellas Proprietary Information

Please move to slide 32. XLMTM is caused by mutations in the MTM1 gene, which encodes a protein noted myotubularin.

As depicted in the top-right figure, lack of or dysfunction of myotubularin alters the structure and function of skeletal muscle cells. AT132 uses a serotype 8 AAV to deliver the vector genome depicted in the lower-right figure. The vector includes a full-length human MTM1 gene with a muscle-specific Desmin promoter.

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## PRIMARY ENDPOINTS

- Safety
- Change from baseline in daily hours of ventilator support at 24 weeks after treatment

## ELIGIBILITY CRITERIA

- Males under five years old or enrolled in INCEPTUS natural history study
- Genetically confirmed XLMTM
- Require ventilator support
- Liver related exclusion: over 5x ULN of ALT or AST; or hepatic peliosis by ultrasound

## AS OF JANUARY 2021

- 1.3 x 10<sup>14</sup> vg/kg cohort: n=6 dosed
- 3.5 x 10<sup>14</sup> vg/kg cohort: n=17 dosed
- Control<sup>2</sup>: n=15

## KEY EFFICACY ASSESSMENTS

### Neuromuscular

- CHOP INTEND
- Motor milestones

### Respiratory

- Ventilator support
- Maximal inspiratory pressure

### Muscle biopsy

- Protein expression
- Histology / pathology

ASPIRO, NCT03199469; INCEPTUS, NCT02704273.

\*ASPIRO trial currently on clinical hold



ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ULN: Upper limit of normal; vg: vector genome; XLMTM: X-linked myotubular myopathy.

1. ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy: Update on Preliminary Clinical Trial Results. InVivo Gene Editing Summit.

2. Clinicaltrials.gov (2022) at <https://clinicaltrials.gov/ct2/show/NCT02704273> Clinical Protocol INCEPTUS.

Astellas Proprietary Information

Please move to slide 33. ASPIRO is our two-part, multinational randomized, open-label ascending dose trial to evaluate the safety and efficacy of AT132 in young boys with XLMTM.

The primary endpoints in the study include safety and efficacy, with respiratory impact measured by evaluating the change in hours of daily ventilator support from baseline. Participants received a single dose of either 1.3 x 10<sup>14</sup> vector genome per kilogram or a higher dose of 3.5 x 10<sup>14</sup> vector genome per kilogram.

## Support

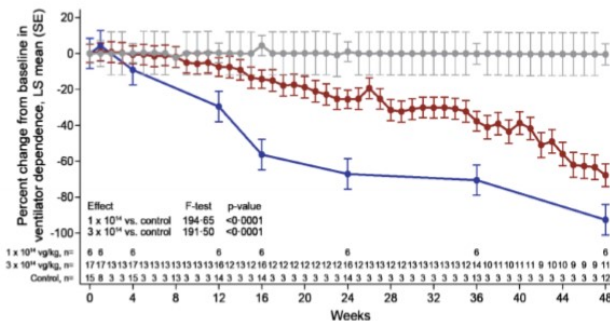
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# AT132 HAS DEMONSTRATED SIGNIFICANT IMPROVEMENTS IN RESPIRATORY FUNCTION AT 48 WEEKS

**Reduction in ventilator dependence** including ventilator independence in several participants<sup>1</sup>



Dose (vg/kg)	Baseline	Week 48	Change
1.3 x 10 <sup>14</sup> (n=6)	20.5 ± 2.0	1.3 ± 2.0	-19.2
3.5 x 10 <sup>14</sup> (n=17)	23.6 ± 1.2	7.7 ± 1.5	-16.1
Control (n=15)	20.2 ± 1.3	21.5 ± 1.4	-0.3



LSM: Least square mean; SE: Standard error; vg: vector genome.  
 1. ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy: Update on Preliminary Clinical Trial Results. InVivo Gene Editing Summit.

Astellas Proprietary Information

Please move to slide 34. This slide depicts the January 2021 cutoff of ventilator dependence data from the ASPIRO study.

As shown in the table on the right, at baseline, participants required mechanical ventilation for 20 to 23 hours on average. While there was no significant change in the control group, participants treated with AT132 required 19 hours less than mechanical ventilation in the low-dose group and 16 hours less in the high-dose group. Of note, the observed differences between the two dose groups is most likely explained by a more conservative ventilator weaning protocol that was instituted at the time the 3.5 x 10<sup>14</sup> dose was introduced.

Reduction in ventilatory support and especially full independence from mechanical ventilation is clinically meaningful and associated with improvements of quality of life and reduced risk of respiratory infection.

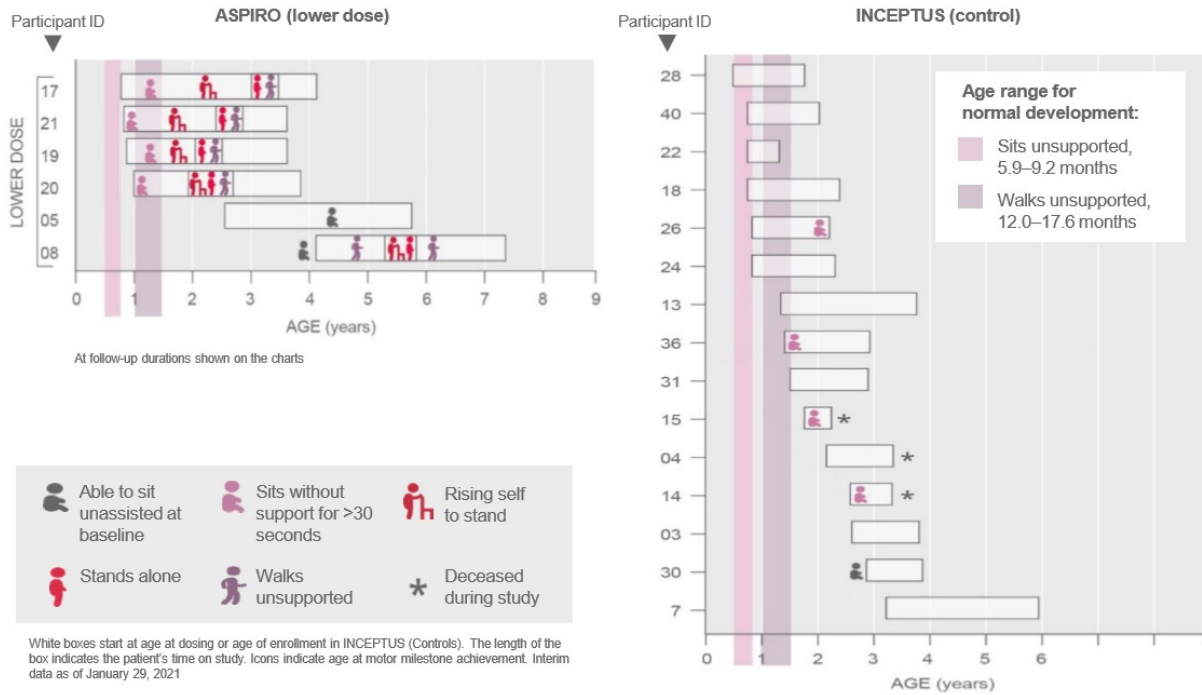
Thus far, 14 treated participants, five in the lower dose group and nine in the higher dose group, have achieved and maintained ventilator independence beginning at a median of 51 weeks following dosing. In contrast, no control participants achieved ventilator independence.

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# AT132 ALSO DEMONSTRATED CLINICALLY MEANINGFUL IMPROVEMENT IN MOTOR MILESTONE ACQUISITION IN LOWER DOSE COHORT



ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy: Update on Preliminary Clinical Trial Results. InVivo Gene Editing Summit.

Astellas Proprietary Information

Please move to slide 35. This slide depicts the motor milestone acquisition of participants in the control and AT132 lower-dose cohorts.

Normally, children can sit unsupported from six to nine months of age and walk unsupported from 12 to 17 months of age. The control participant data in the figure on the right demonstrates that only five of the 15 boys are able to sit unassisted. None of the 15 rise to standing or are able to walk independently.

This contrasts with the lower-dose cohort shown in the upper-left figure. All of the boys acquired the ability to sit independently. Five of the six can rise to standing and five of the six acquired the ability to walk independently.

Long-term monitoring of the study participants beyond the January 2021 data snapshot used for these figures show that treated subjects continue to achieve and maintain major motor milestones. These are really unprecedented and clinically meaningful improvements in physical function.

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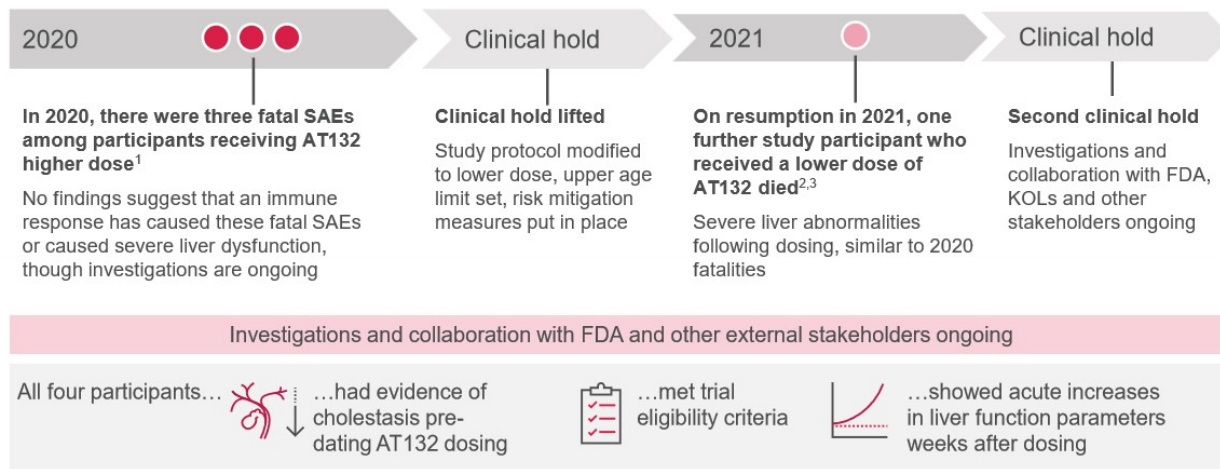




## ASPIRO IS CURRENTLY ON CLINICAL HOLD PENDING FURTHER INVESTIGATIONS

36

Four ASPIRO participants have died following serious hepatic adverse events



This clinical picture has not been observed with other systemically administered AAV gene therapies<sup>4</sup>



AAV: Adeno-associated virus; KOL: Key opinion leader; SAE: Serious adverse event.  
 1. ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy: Update on Preliminary Clinical Trial Results. InVivo Gene Editing Summit, 2. Astellas Press Release. September 14, 2021. 3. Astellas Press Release. September 1, 2021. 4. FDA, Cellular, Tissue, and Gene Therapies Advisory Committee September 2-3, 2021 Meeting Presentation.

Astellas Proprietary Information

Please move to slide 36. While the clinical improvements observed to date in the ASPIRO study have been truly remarkable, four ASPIRO participants dosed with AT132 died following serious hepatic adverse events.

The first death occurred in May 2020, after which the program was placed on clinical hold. Two subsequent deaths occurred in participants dosed prior to the clinical hold.

Extensive evaluation of the clinical data identified older age at heavier weight, prior cholestatic disease, and higher-dose treatment as risk factors. Our analyses were provided to FDA along with an amended protocol that restricted the upper age limit, reverted to the lower dose of  $1.3 \times 10^{14}$  vector genome per kilogram, and included other risk-mitigation measures.

The clinical hold was lifted in December 2020 and dosing resumed in 2021. Despite these measures, a fourth participant died after receiving a lower dose. As with the other three participants, he showed acute severe hepatic dysfunction, which showed a cholestatic pattern. He later died of a septic event.

Given these tragic series adverse events, the program was placed on a second clinical hold in September 2021, and we are currently undertaking not only a reevaluation of the clinical data, but also potential mechanisms and ways to reduce the risk of these severe hepatic events.

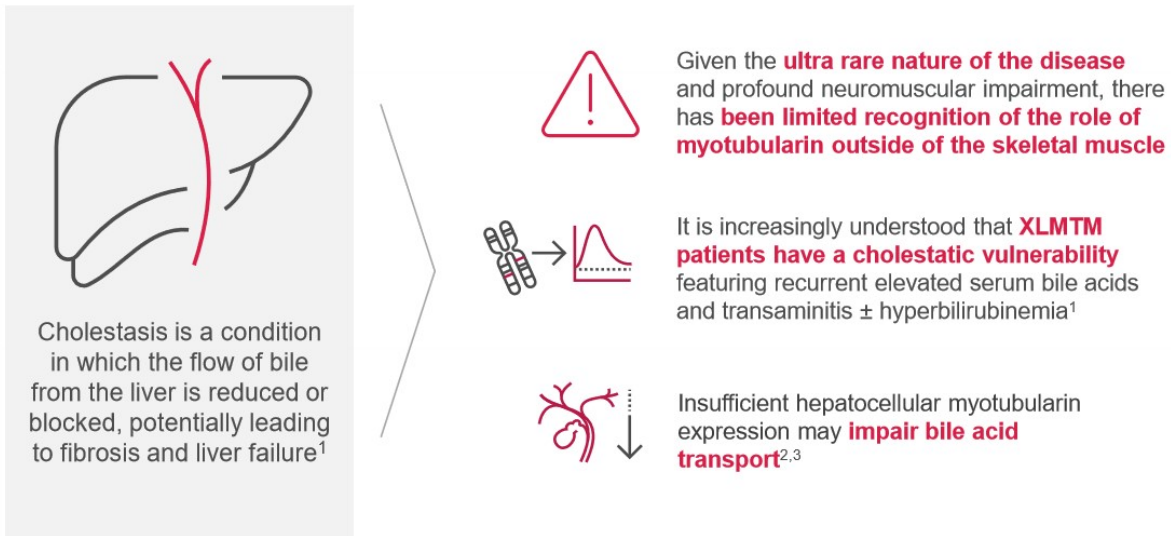
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## INTRAHEPATIC CHOLESTASIS IS INCREASINGLY RECOGNIZED AS PART OF THE NATURAL HISTORY OF XLMTM

37



We hypothesize the combination of AAV gene therapy which is taken up by the liver, together with this underlying risk for cholestasis, may lead to the severe liver impairment in some participants



XLMTM: X-linked myotubular myopathy.

1. Molera, C. et al. *Journal of Neuromuscular Diseases* 9, 73-82 (2022). 2. Hnia, K. et al. Myotubularin phosphoinositide phosphatases: Cellular functions and disease pathophysiology. *Trends Mol Med.* 2012;18(6):317-270

3. Trauner, M. Bile salt transporters: Molecular characterization, function, and regulation. *Physiol Rev.* 2003;83(2):633-71.

Astellas Proprietary Information

Please move to slide 37. As part of our investigation and in collaboration with external experts, we've learned that intrahepatic cholestasis is part of the natural history of XLMTM.

Boys have been found to have recurrent episodes of elevated serum bile acid, at times associated with elevations in transaminases, with or without bilirubin elevation. Additionally, boys have been reported to present with severe hepatic dysfunction related to their cholestasis without having received prior AAV gene therapy.

Taken together, we hypothesized that myotubularin plays an important role in hepatocellular function. Absence or defective myotubularin seems to be associated with the risk of intrahepatic cholestasis. Based on the available data from our ongoing investigations, we hypothesized that the combination of AAV gene therapy, which is taken up by the liver, together with this underlying risk for cholestasis, may lead to the severe liver impairment in some participants.

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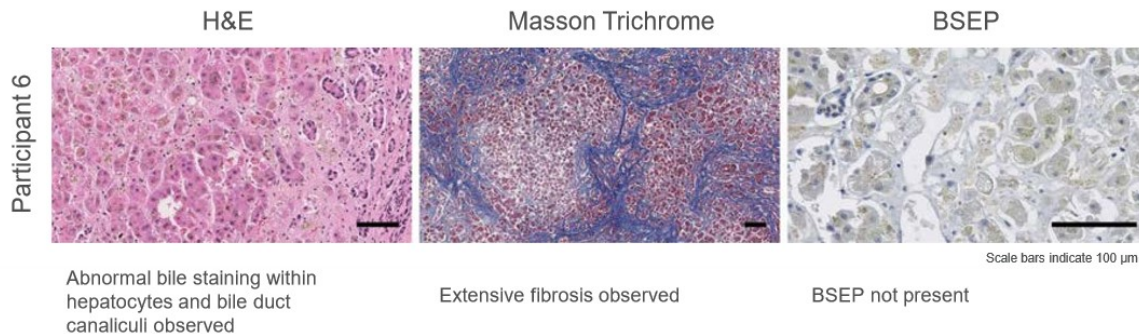




## LIVER HISTOPATHOLOGY CONSISTENT ACROSS DECEASED SUBJECTS AND WITHOUT INFLAMMATORY INFILTRATES

38

### Liver histopathology in deceased participants



### Commonly observed pathology among participants<sup>1</sup>

- Pattern of intracellular and extracellular bile accumulation, hepatocyte ballooning and giant cell formation
- Liver histopathology findings similar to what is seen in **progressive familial intrahepatic cholestasis (PFIC) disorders**
- No significant inflammatory cell infiltrates



BSEP: Bile salt export pump; H&E: Hematoxylin and eosin; PFIC: Progressive familial intrahepatic cholestasis.  
1. ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy: Update on Preliminary Clinical Trial Results. InVivo Gene Editing Summit.

Astellas Proprietary Information

Please move to slide 38. I would now like to look more closely at the liver histopathology using participant six as an example.

The hematoxylin and eosin-stained image on the left shows the diffuse pattern of intracellular and extracellular bile accumulation, hepatocyte ballooning, and giant cell formation. Importantly, there's no significant inflammatory cell infiltrates noted in this case or in the other three fatal cases.

The trichrome stain in the center panel shows extensive liver fibrosis in blue. And the final image on the right is liver tissue stained for BSEP, or bile salt export pump protein. BSEP is a major mechanism for bile acid export from hepatocytes and was found to be missing in this participant as well as the other three boys.

Mutations in the gene encoding BSEP caused one form of progressive familial intrahepatic cholestasis, or PFIC, which has very similar histopathologic and laboratory features for those observed in these four boys.

We hypothesized that the absence of BSEP played a key role in the pathophysiology of cholestasis and liver failure in these participants. But we do not currently understand what about XLMTM and AT132 may have led to the disappearance of BSEP in these individuals.

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**SAFETY IS OUR KEY PRIORITY: RESUMPTION OF CLINICAL DOSING PUSHED TO FY2023, WITH BLA SUBMISSION OUTSIDE OF CSP2021**

 <p><i>In vivo</i> and <i>in vitro</i> experiments to understand the mechanism of cholestasis in XLMTM and how this may be exacerbated by AAV</p>	 <p>Product enrichment – reduction of empty capsids to enable a lower total capsid dose</p>	 <p>Modification of participant eligibility criteria to reduce risk of hepatic toxicities</p>	 <p>Engagement with external experts and the patient advocacy community</p>	 <p>Discussions with Regulatory Authorities to address clinical hold</p>
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AAV: Adeno-associated virus; BLA: Biologics license applications; XLMTM: X-linked myotubular myopathy.

Astellas Proprietary Information

Please move to slide 39. The AT132 program has a large number of ongoing activities, but it's important to note that we do not anticipate resuming clinical dosing until FY2023, due to the need to create a new investigational drug product and provide comparability information to regulatory agencies.

In turn, this would push the filing of a BLA beyond FY2025 outside of the timeline for CSP2021. The ongoing and planned activities include *in vivo* and *in vitro* experiments attempting to identify the pathogenic mechanisms, which may account for why the combination of XLMTM and AAV may lead to absence of BSEP, severe cholestasis and hepatic failure.

Investigational product enrichment. In line with the industry trends and a desire to constantly improve product quality, we wish to take this moment to further remove empty capsids from our investigational product. This will reduce the overall dose of AAV capsids delivered to each participant. As I mentioned, generating and ensuring the comparability of this enriched investigational drug product will mean that dosing XLMTM subjects will not incur until FY2025.

Next, we'll be modifying the protocol. We'll be reviewing nonclinical and clinical data and anticipate further modifying the protocol to identify a study population with a lower risk of cholestatic events after AAV therapy.

Engagement has been critical throughout our program, and we will continue to consult with external experts to help us confirm and pressure test our hypotheses and data interpretation. Plus, we will continue to communicate our findings to our most important stakeholders, our patients and their families.

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And likewise, it is critical for us to engage with regulatory authorities to address the clinical hold, and we anticipate submitting our responses to the FDA clinical hold in the second quarter of FY2022.

As I have discussed, despite these devastating events, the remarkable clinical improvements we have seen to date with AT132 drives us to do everything we possibly can to find a path forward for this program and bring hope to the XLMTM community. We very much look forward to providing updates on our progress in due course.



Please move to slide 40. We'll now take a look at our most recent program to enter the clinic, AT845, which is in clinical development for the treatment of Pompe disease.

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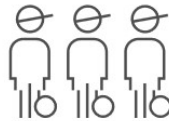
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Pompe disease is a **lysosomal storage disease caused by a deficiency in acid alpha-glucosidase (GAA)** – GAA deficiency leads to accumulation of glycogen in lysosomes



**Overall incidence** for infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) is estimated to be approximately **1 in 40,000**<sup>1</sup>



IOPD is **rapidly progressive** and characterized by cardiomegaly, hepatomegaly, weakness and hypotonia<sup>2</sup>

**Our initial target for treatment:**

LOPD is **characterized by slowly progressive myopathy** involving skeletal muscle



GAA: Acid alpha-glucosidase; IOPD: Infantile-onset Pompe disease; LOPD: Late-onset Pompe disease.

1. NORD (National Organization for Rare Disorders) (2022) at <https://rarediseases.org/rare-diseases/pompe-disease/>. 2. Kishnani, P. & Howell, R. *The Journal of Pediatrics* 144, S35-S43 (2004).

Astellas Proprietary Information

Please move to slide 41. Pompe disease is a rare, severe autosomal recessive metabolic disease characterized by progressive muscular degeneration.

It is caused by mutations in the acid alpha-glucosidase, also known as GAA. Lysosomal GAA is responsible for metabolizing glycogen, and dysfunction or absence of this protein results in the accumulation of glycogen primarily in skeletal and cardiac muscles where it causes damage to tissue structure and function.

The infantile form, or IOPD, is rapidly progressive and characterized by cardiomegaly, hepatomegaly, weakness, and hypotonia. If left untreated, many children with IOPD do not live past the first year of life.

Meanwhile, late-onset Pompe disease, or LOPD, is characterized by a slowly progressive myopathy, primarily involving skeletal muscles, including the diaphragm, which subsequently leads to respiratory insufficiency.

We are initially targeting LLPD, which has a more well-established regulatory pathway to approval.

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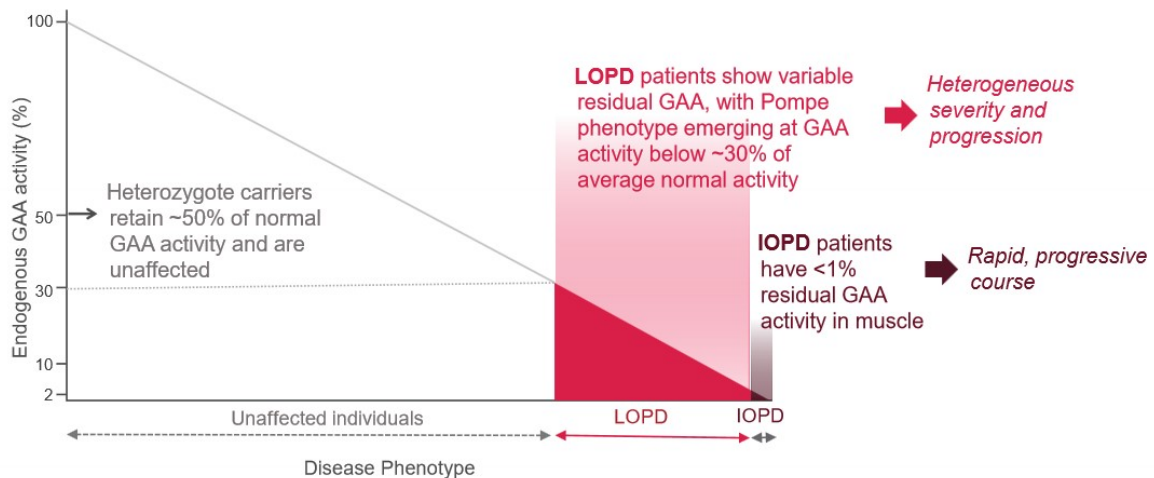


## REDUCED GAA ACTIVITY IS A HALLMARK OF SYMPTOMATIC POMPE DISEASE

42

Improved GAA activity is a key biomarker for evidence of AT845 efficacy

"NORMAL" LEVELS OF MUSCLE GAA ACTIVITY LIKELY NOT REQUIRED TO DRAMATICALLY IMPACT POMPE



GAA: Acid alpha-glucosidase, IOPD: Infantile-onset Pompe disease; LOPD: Late-onset Pompe disease.  
1. van der Ploeg, A. & Reuser, A. The Lancet 372, 1342-1353 (2008). 2. Ripolone, M. et al. *Neuropathology and Applied Neurobiology* 44, 449-462 (2017).

Astellas Proprietary Information

Please move to slide 42. Reduced GAA activity is a hallmark of Pompe disease and levels of endogenous GAA activity correlate with the disease phenotype.

As shown in the figure, patients with IOPD have less than 1% endogenous GAA activity, whereas those with LOPD have a spectrum of up to 30% endogenous GAA activity. Importantly, heterozygote carriers may have as little as 50% activity and are unaffected. Thus, GAA activity can serve as a key biomarker for evidence of AT845 efficacy and help support our dosing decisions. Knowing that heterozygous may have as little as 50% GAA activity allows us to set this minimum level as our target for dosing.

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## LIMITATIONS OF CURRENT STANDARD-OF-CARE: ENZYME REPLACEMENT THERAPY (ERT)

43



Currently approved ERTs replace the enzyme through **chronic, repeated infusions**



Long-term studies of LOPD patients on ERT show an **initial positive effect** followed by stabilization and **then decline in functional measures**<sup>1,2</sup>



**ERT is known to be immunogenic** and can elicit antibodies that further impact effectiveness<sup>3</sup>



Pompe clinician experts and patients highlight that **a significant unmet need remains** given disease progression despite ERT<sup>4,5</sup>



ERT: Enzyme replacement therapy; LOPD: Late-onset Pompe disease.

1. Papadimas, G. et al. *Neuromuscular Disorders* 31, 91-100 (2021). 2. Gutschmidt, K. et al. *Journal of Neurology* 268, 2482-2492 (2021). 3. Patel, T. et al. *Molecular Genetics and Metabolism* 106, 301-309 (2012). 4. Schoser, B. et al. *BMC Neurology* 17, (2017). 5. Hahn, A. & Schänzer, A. *Annals of Translational Medicine* 7, 283-283 (2019).

Astellas Proprietary Information

Please move to slide 43. The standard of care for Pompe disease is enzyme replacement therapy, or ERT.

ERT is delivered via intravenous infusions every two weeks for life. If the treatment is stopped, glycogen will once again build up in the body's cells. But real-world evidence has confirmed that patients using ERT see an initial improvement in the first years of therapy, but this is followed by a secondary sustained decline in multiple outcome measures.

In addition, antibody responses to ERT can cause hypersensitivity reactions, which further impede efficacy. Experts believe that there's a significant unmet need due to the short half-life, inefficient uptake in key tissues affected by the disease, and the immunogenicity of ERT.

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# AT845 IS INTENDED TO DIRECTLY DELIVER GENETIC MATERIAL FOR GAA EXPRESSION IN THE MUSCLE

Pompe disease is a monogenic disease due to deficiency of GAA, affecting both skeletal and cardiac muscle and leading to **lysosomal glycogen build-up and injury to the muscle cells**

AT845 is a recombinant AAV vector serotype 8 **expressing the human acid alpha-glucosidase (hGAA) gene specifically in the muscle**

Muscle-directed gene therapy addresses uptake challenges by ***in situ* expression of GAA in muscles<sup>1</sup>, avoiding the need for repeated infusions**

## Systemic gene replacement therapy with muscle-specific promoter

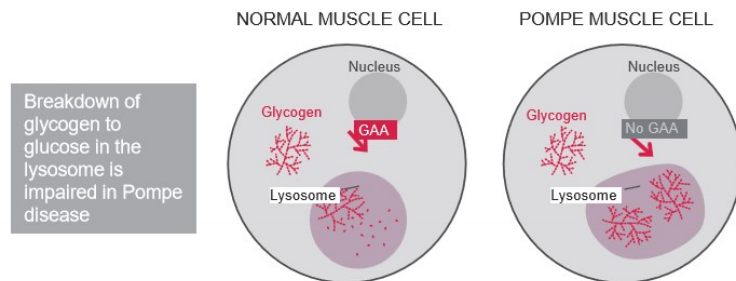


Figure 1a. Astellas proprietary image.

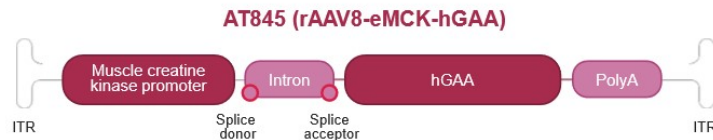


Figure 1b. Adapted from Astellas InVivo Gene Editing Summit Presentation November 2021.



AAV: Adeno-associated virus; GAA: Acid alpha-glucosidase; hGAA: Human acid alpha-glucosidase; ITR: Inverted terminal repeat; MCK: Muscle creatine kinase; PolyA: Polyadenylation signal.  
 1. Eggers, M. et al. *EMBO Molecular Medicine* 14, (2021).

Astellas Proprietary Information

Please move to slide 44. We believe that AT845 has the potential to address the limitations of ERT.

AT845 is a serotype 8 AAV with a full-length human acid alpha-glucosidase gene, or human hGAA gene, that's driven by cardiac and skeletal muscle-specific creatine kinase promoters. By directly targeting GAA expression in the muscle, AT845 is intended to overcome a key limitation of ERT, which is believed to be related to insufficient muscle GAA activity.

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FORTIS: ongoing multicenter, open-label, ascending dose Phase I/II clinical trial to determine safety and tolerability of AT845 in adults with LOPD

### PRIMARY ENDPOINT SAFETY

Frequency of adverse events, serious adverse events and changes from baseline in relevant clinical tests

### PRIMARY ENDPOINT EFFICACY

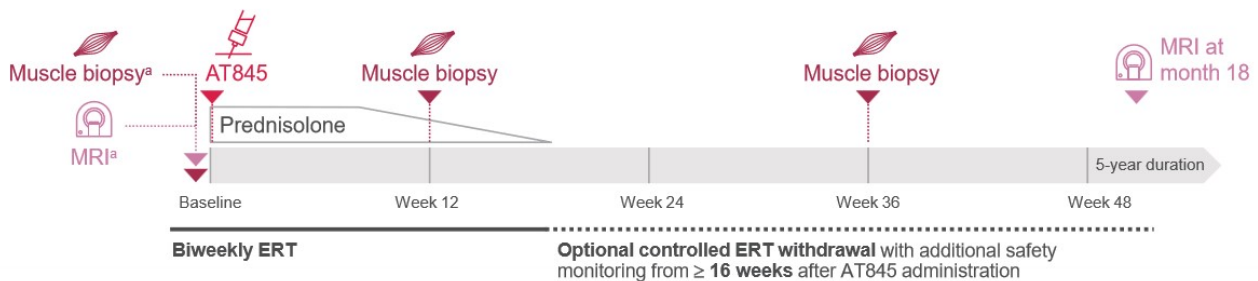
Change from baseline in GAA protein expression and enzyme activity in muscle (week 12)

### SECONDARY ENDPOINTS

Evaluate improvements in respiratory (FVC, MIP, MEP), endurance (6MWT, GSGC), and QoL (R-PAct, EQ-5D-5L, PROMIS)

### ELIGIBILITY CRITERIA

- Aged ≥18 years (ambulatory or nonambulatory)
- Received ERT with rhGAA for the previous ≥2 years



<sup>a</sup> Baseline cardiac and muscle MRIs at Day -21 to -14 before AT845 dosing; muscle biopsy ~1 week before dosing

6MWT: Six-minute walk test; ERT: Enzyme replacement therapy; FVC: Forced vital capacity; GAA: Acid alpha-glucosidase; GSGC: Gait, stairs, gower, chair; MEP: Maximum expiratory pressure; MIP: Maximum inspiratory pressure; PROMIS: Patient-reported outcomes measurement information system; QoL: Quality of life; rhGAA: Recombinant human acid alpha-glucosidase; R-PAct: Rasch-built Pompe-specific Activity.

1. Clinicaltrials.gov (2022). at <https://www.clinicaltrials.gov/ct2/show/NCT04174105>. Clinical Protocol AT845-01.



Please move to slide 45. Last month, we presented initial data from the FORTIS study at the World Symposium meeting.

FORTIS is an ongoing multicenter open-label ascending dose Phase I/II first-in-human clinical trial to determine if AT845 is safe and well tolerated in adults with LOPD. Enrolled participants receive a onetime intravenous infusion of AT845, followed by one year of frequent monitoring of safety, clinical, and biochemical endpoints. The primary endpoints are safety and tolerability, as well as efficacy measures, including change from baseline in muscle GAA protein expression and enzyme activity.

As of the December 3, 2021 data cutoff, four participants have enrolled in FORTIS with two participants dosed at  $3 \times 10^{13}$  vector genome per kilogram in Cohort 1 and two participants dosed at  $6 \times 10^{13}$  vector genome per kilogram in Cohort 2. The reported data includes interim safety and tolerability assessments with 24 weeks of follow-up for the two participants in Cohort 1 and three-week follow-up data for the first participant in Cohort 2.

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No serious adverse events reported following dosing in any participants as of the time of the data cut

- One participant had a rise in transaminases after tapering of prednisolone prophylaxis, which responded well to re-initiation of steroid treatment
- This is consistent with what has been observed with other AAV gene therapies, but not similar to the cholestatic adverse events in the AT132 program

SAFETY PROFILE	Cohort 1 ( $3 \times 10^{13}$ vg/kg)		Cohort 2 ( $6 \times 10^{13}$ vg/kg)
	P 2002	P 2001	P 2003
Follow-up time, weeks	37.1	27.3	13.3
All TEAE	1	3	14
Procedural pain	1		
Headache		1	1
Ageusia			1
ALT increased		1	
AST increased		1	
Decreased appetite			1
Constipation			1
Abdominal distension			1
Irritability			1
Palpitations			1
Night sweats			1
Cold sweat			1
Dyspnea			1
COVID-19			1
Upper respiratory tract congestion			1
Malaise			1
Fatigue			1

Information based on a data cut on 14 December 2021



AAV: Adeno-associated virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TEAE: Treatment emergent adverse event; vg: vector genome.  
 FORTIS\_PP\_2002.rtf – Patient profile listing, page 28  
 FORTIS\_PP\_2001.rtf – Patient profile listing, page 31

Astellas Proprietary Information

Please move to slide 46. Overall, the treatment appears to be well tolerated with no serious events reported at the time of this data cutoff. Of the treatment-emergent adverse events, all but two were mild and were not considered to be related to AT845 but rather, due to COVID-19.

One participant experienced elevated transaminases, Grade 3 elevated ALT with Grade 1 elevated AST, which was considered to be possibly related to AT845 and which developed at the end of the prophylactic steroid paper and resolved with steroid reinitiation. This event is considered to be an immune-mediated event similar to what has been observed with other AAV gene therapies. However, this is not similar to the cholestatic events in the AT132 program, which occurred while on steroids and failed to respond to immunosuppressive therapy.

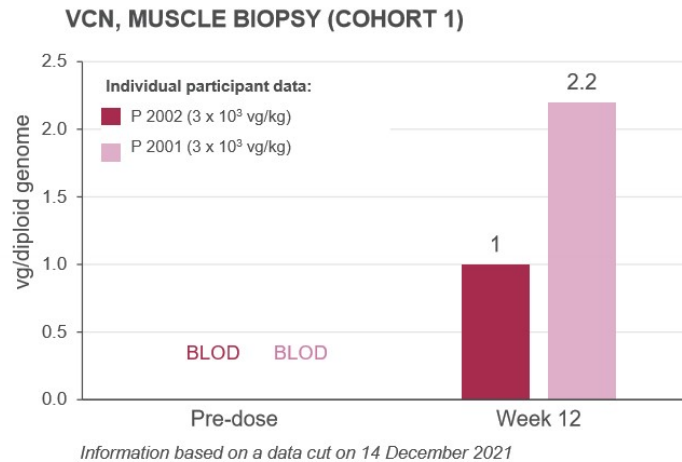
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Both participants in Cohort 1 **showed transduction of the gene of interest in the muscle** by 12 weeks post-infusion of AT845



VCN, muscle (first two participants only)

BLOD: Below limit of detection, VCN: Vector copy number, vg: vector genome.  
 FORTIS\_PP\_2002.rtf – Patient profile listing, page 28  
 FORTIS\_PP\_2001.rtf – Patient profile listing, page 31



Astellas Proprietary Information

Please move to slide 47. At the time of this interim analysis, we do not have the muscle GAA protein or activity data to report. However, we did see evidence that the AT845 vector genome was transducing in other words, getting into the muscle cells. As shown in the figure, the two subjects in Cohort 1 had an average 1 and 2.2 vector genomes per diploid genome. In other words, 1 to 2 vectors per muscle cell. At our next data cut in early FY2022, we plan to reassess safety, and we will have GAA activity for our four participants at 12 weeks and for two participants out to 36 weeks.

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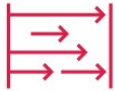




**Safety is paramount** and we are continually assessing the benefit-risk profile of this therapy, in collaboration with our panel of internal and external experts



**This initial safety data is encouraging** as this program continues to enroll participants in the FORTIS study



We expect to assess clinical **Proof of Concept** based on efficacy data from the first two cohorts in early FY2022, prior to advancement into Phase 3



Astellas Proprietary Information

Please move to slide 48. As with any complex gene therapy investigation, safety is paramount.

We are encouraged by the preliminary safety profile of AT845, and we'll continue to monitor participants closely. As I mentioned, we expect to have GAA data in Cohort 1 and Cohort 2 in early FY2022. And this data will enable us to decide whether to expand the 3 or 6 x 10<sup>13</sup> dose cohorts or to go to a higher dose level. While still very early, we believe AT845 has the potential to be a significant step forward in the treatment of adults with LOPD, by directly delivering the gene for GAA into affected muscle cells. We also hope to be able to expand our investigative efforts to a broader Pompe disease population in the future.

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## POTENTIALLY TRANSFORMATIVE EFFICACY AND PATIENT NEED DRIVES OUR COMMITMENT TO GENE THERAPY

49

The pioneering development of gene therapies is **uniquely complex**

As an industry and as part of the gene therapy community, we are **continually learning** about the platforms and diseases we work in

Early insight into the **truly life-changing promise** that can be achieved for patients with so little hope **propels us forward** in our commitment to delivering these therapies – now and in the future



Please move to slide 49. Hopefully, through this presentation, you can see both the tremendous promise as well as the challenges associated with this pioneering field of gene therapy.

In my more than 20 years working in drug development, I've not worked on a therapy that had such remarkable clinical improvements as AT132 in XLMTM and I'm personally amazed and moved by seeing boys on ventilators and unable to sit independently being liberated from mechanical ventilation and walking independently.

Still, we have much to learn and many challenges to overcome. And success will require the efforts of mass research and manufacturing organizations working very closely with our development and regulatory teams to advance what we believe to be one of the most robust gene therapy pipelines in the industry.

In such a rapidly evolving field, we will also need to continue acquiring new capabilities and technologies through collaborations like Dino Therapeutics. And further, we must remain at the cutting edge by learning from other gene therapy companies and ensuring our programs meet what is likely to be a continuously evolving regulatory landscape.

Thank you to everyone for your time and attention today.

**Okamura:** Okamura speaking. Thank you very much for your support. Before going to Q&A, I have one point to add. Earlier, as Bernie Zeiher mentioned, as for AT132, after the second clinical hold, we had a variety of progress.

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The timeline overall is going to be delayed according to our forecast. We will perform several scenario analyses. And we will make a conservative estimation of the presence or the absence of the reduction in the value we can expect as of now, and we are going to perform impairment loss testing within FY2021.

That's all from me.

**Fujii:** So that's all the explanation from our company.

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## Question & Answer

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**Fujii [M]:** Next, we'd like to entertain questions from the audience.

**Moderator [M]:** From the Japanese conferencing system, Mr. Yamaguchi from Citigroup Securities, please.

**Yamaguchi [Q]:** Yamaguchi speaking. Thank you. Thank you for the presentations and explanation. First, about Angelman syndrome, DAD program on page 15. The approach, there is 1, 2, and 3 as potential approaches. You are targeting the combination of all these three. Is that the approach you're considering right now? 1, 2, 3 look different as an approach. Are you going to take one of the three or are you going to use all? I'd like to first hear about your strategy in DAD.

**Yasukawa [M]:** Thank you for your question. Mat is going to explain.

**Pletcher [A]\*:** Yes. Thank you very much for the question. Our approach and our strategy is to explore each of the three mechanisms independently and then use a series of in vitro assays to determine which of these mechanisms work best to achieve our goal. And again, our goal here is the reactivation of the healthy paternal copy of UBE3A. We use in vitro systems to assess the effectiveness of each of these approaches in accomplishing that. Then ultimately, we will select the one that achieves this to the highest degree, most efficiently, and then validate that in an in vivo mouse model and then take one of these approaches forward.

**Yamaguchi [Q]:** The next question is on slide 39. It seems that there are several approaches available. And out of this, you might not know yet, but which one is the most effective approach? That is, to eliminate empty capsid or you are going to change the eligibility of the subjects. Of course, it's yet to be unclear. But what is the most potential approach out of this?

**Yasukawa [M]:** Thank you for the question. Bernie, could you answer this question?

**Zeiber [A]\*:** Yes. Thank you for the question. One of the challenges working in rare disease is that you're dealing with small numbers, one or two patients, and often trying to draw conclusions from them. At this stage, given that we have had several deaths as I described, we are taking all measures. We think product enrichment and reducing the number of empty capsids and reducing the total dose may have some benefit, but we don't think that's sufficient because, in fact, throughout the development of the program, the product has become more enriched, not to the level we're seeking now, but it has become improved. And so, we think that may help some, but it is unlikely to be sufficient. And thus, we believe that we will also need to modify the protocol to identify patients who are less likely to have cholestasis and keep in place or put in place other mitigation measures if they do develop cholestasis.

**Yasukawa [A]:** Yasukawa speaking. Page 39 left three and right two. Those are different in nature. First of all, the left three. Now what we look at, just like Bernie explained a little while ago, first of all, for FDA consultation, we are going to prepare our data. And of course, our first milestone is FDA gets convinced to our explanation. We are going to work for the left three with having the timelines. So far, all of these are considered to be important.

**Yamaguchi [Q]:** Thank you very much. Lastly, just briefly on page 47, vector genome introduction number is shown on page 47. Sorry for a layperson's question. 1 or 2.2 here, considering the efficacy, if there is 1 or 2 transductions, is it going to be fine? In relationship to the efficacy, I couldn't understand scientifically speaking. Please let me know.

**Yasukawa [M]:** Thank you very much. Bernie, could you respond, please?

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**Zeiber [A]\*:** Thank you for the question. And it's a very good question. Unfortunately, we don't know the answer yet. And you can't necessarily tell from animal models because, again, the gene expression may be different there. At this stage, all we can say is we know the gene of interest is getting into the muscle. But very soon in the upcoming data cut, we will see, is there sufficient GAA protein and activity in that muscle cell. And then we can correlate do we need more because our goal is to have at least 50% GAA activity. And that will really be the key hurdle, even much more important than whether the vector is actually getting in the muscle.

**Yamaguchi [M]:** Okay. Understood. Thank you very much. That's all for me.

**Fujii [M]:** Thank you. Next question, please.

**Operator [M]:** Daiwa Securities, Mr. Hashiguchi, please?

**Hashiguchi [Q]:** Hashiguchi speaking. Thank you. First question, AT845. That's what I'd like to ask you about. POC data is going to be available in early FY2022. And I suppose that data is just as it's been expected. And directly after that, near future, you're getting to Phase III. Is this understanding right? The timing of submission, timing of the approval, expected timing of the approval, if you have any ideas with that, would you please explain that?

**Yasukawa [M]:** That's about the development plan. Bernie, could you answer this question?

**Zeiber [A]\*:** Hashiguchi-san, Thank you for the question. We will have POC data in early FY2022. However, it will only be from, well, two or four subjects, depending on which dose or whether both doses hit that level. Our plan is to dose more individuals before we would go into Phase III. And the reason for doing that is to make sure that there isn't a huge amount of variability. We don't want to be in a situation where, let's say, two patients have a sufficient level, let's say they're over 50%, but if you dosed four additional patients, that you find out that two of them are below 50% and some are above 50%. The plan is that once we have that data, we will have an expansion cohort. We will dose more individuals either at one of these two doses, or it may be that we have to go to a higher dose. That's really a key decision point.

And we want to again have a larger number of participants dosed before we would then jump into Phase III. And we will definitely provide updates as we progress. We can, in FY2022, provide information on did we achieve proof of concept? And then are we expanding one or both dose groups or going to a higher dose group because again, we would do that before we move into Phase III.

**Hashiguchi [Q]:** Thank you very much. Another question. For each program, I'd like to know about the overall speed of each program. Today, regarding most of the projects, the future outlook was not demonstrated today. In your CSP2021, when you presented your CSP2021 in gene therapy, during the course of CSP2021, there are seven projects which you'll have a POC stage to identify. Such outlook has not changed since?

In December 2020, AT753 will enter the clinical program in 2021 fiscal year. Is this program making progress as planned? Based on our AT132 program, you may be getting more cautious about the gene therapy programs, and there may be a possibility of a slight delay in some projects. What's the overall situation right now?

**Yasukawa [A]:** Thank you for the question. During the period of CSP2021, the number of POC would depend on the progress of research. And also, technology platform for each project and manufacturing issues are also related as well. When we have an earnings call, what's our outlook as of April 2022 will be explained on that occasion.

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The worst-case scenario for us is that the hepatic toxicity seen in AT132 may not be just myopathy, but it may seem in all diseases, that is going to be a worst-case scenario. If we fall into that scenario, most of the projects must be revisited in that scenario. But as Bernie explained earlier, right now, we don't have such a position right now. Of course, we have to consult with FDA going forward. Overall, because of the events in AT132, we don't have to review our programs as a whole.

As Mat explained, it's not just a transduction of a single gene. There are technical hurdles and barriers for some programs. This is not just about gene therapy, but also applicable to antibody, small molecule, and also cell therapies as well. Of course, we review projects one by one. The number of POCs and the progress of each program will be reported on a separate occasion.

**Hashiguchi [Q]:** Thank you very much. The timing of AT753 entering the clinical stage, is it possible to give us some comments today?

**Yasukawa [A]:** Today, sorry, we'd like to refrain from disclosing information on AT753.

**Hashiguchi [M]:** That's all for me. Thank you very much.

**Fujii [M]:** Thank you. Next question, please.

**Operator [M]:** Nomura Securities, Mr. Kohtani, please?

**Kohtani [Q]\*:** This is Kohtani, Nomura Securities. My first question is on AT845. I'm really encouraged to find that Astellas is continuing the investigation of AT132. I think the results you reported for both the ventilator independence and unassisted walking is clearly clinically significant. And you made it clear that the best report in AT132 is the combined result of cholestasis as a natural disease progression of XLMTM, also compounded by the high dose of AAV, which affects the liver.

My question is just, first of all, can you clarify what you said, the timeline you stated on slide 39? I think you said something about the enrichment of all capsids, but that's not being ready until 2025. I want to confirm that. And my question is how do you remove empty capsids? I assume Astellas is already using density gradient centrifugation to separate out empty/full capsids. How will you improve on this? Can you just spin it for longer or something like that? Or is it going to be a different method that's being used? This is my first question.

**Yasukawa [M]:** Thank you for the question. Empty capsid reduction, technology related questions. Mat, could you answer this question?

**Pletcher [A]\*:** Yes, happy to. As far as, I mean, some of the details of how we go about eliminating and further purifying our product are proprietary, and so we can't get into great detail. But what I could say is we have moved past just gradient density as a method of being able to separate the two. And so certainly, it is about identifying new technologies, new capabilities, as well as just improving the purification process itself.

This is part of the internal investment we discussed before and sort of the continued innovation, both in the field and within our organization as well. There are additional techniques that we've added to the process, additional technologies that are enabling us to continue to push and generate purer and purer material.

Hopefully, that answers your question.

**Kohtani [Q]\*:** Did Bernie say something about that sort of this improved process not being ready until 2025? Or am I mishearing something?

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**Zeiber [A]\*:** This is Bernie. Maybe I'll just clarify. The resuming clinical dosing will be FY2023 and because of, again, the time it takes to develop a new drug product and provide the comparability information to FDA, so resuming clinical work in FY2023 and then not submitting a BLA until beyond the CSP period, which is FY2025. And that's just given the time it would take to now do additional clinical studies. Those were the two time points: 2023 for resuming study; beyond 2025 for the BLA.

**Kohtani [Q]\*:** Second question's regarding AT845 for Pompe disease. The muscle biopsy result on page 47 is very encouraging. I think can I ask where the sample is taken from? I assume it's either the arm or the quadriceps, but I'm asking because the disease progression in Pompe disease results in respiratory failure. It would obviously be best if you could see GAA expression in the diaphragm, which is obviously the main muscle responsible for breathing. What level of variability also in GAA expansion is acceptable when you report the POC results? And will there be also functional data, such as 6MWT or other motor milestones reported at that time?

**Yasukawa [M]:** Thank you for the question. The site of the muscle biopsy and pharmacodynamic data to be captured from now on, so, Bernie, could you respond to that question, please?

**Zeiber [A]\*:** Yes. And to be honest, I'm not 100% sure where we have done the biopsy. I know it is not the diaphragm. You said it's a skeletal muscle. And a key point is just, as you said, are we getting sufficient levels, not just a one muscle but more to diaphragm and other locations?

In terms of what level we need or what degree of variability, I think this is an important question, and that's why we don't want to make a dosing decision just based on two patients because we want to see that we can consistently achieve a level above 50%. And we're not going to make this decision in terms of dose and advancing the Phase III on our own. We work with experts in Pompe disease, in fact, where we can actually look at the totality of the data as was presented at the World Symposium. There was some biomarker data that was very encouraging as well. It showed that treating kinase reduced shortly after dosing and did not go back up to baseline, so information like that as well as some functional data. Although the challenge with functional data is that all of the subjects in the trial are on enzyme replacement therapy, so you're trying to get, say, improvement beyond that. There is an option beginning around week 16 for participants to go off of enzyme replacement therapy. And so some of that information will also be used to give us confidence that again, the GAA activity is sufficient.

We already have individuals who, together with the investigator, the individual has made the decision to go ahead, go off enzyme replacement therapy, so some of that long-term data will also be incredibly helpful as we make the decision about do we have a sufficient dose and what dose we take forward into Phase III?

Again, it will be a variety of different components that we'll be looking at, including some of this functional data, some of which will be how do people do even if they decide to go off enzyme replacement therapy.

**Kohtani [Q]\*:** Has anyone opted for that option of going off of ERT? Are you aware of any of the four patients adopting that option?

**Zeiber [A]\*:** Yes. We have two that have, two of the four, and there's a fourth individual that's kind of coming up to that time point where that decision can be made. And again, I think this will be very helpful data to help guide whether we're again getting sufficient levels, how people do once they go off enzyme replacement therapy.

**Kohtani [Q]\*:** Those two are probably the ones presumably that show GAA expression, high expression levels?

**Zeiber [A]\*:** Well, at this time, we don't have the GAA expression levels yet. We just have the transduction data that I showed you.

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**Kohtani [Q]\*:** Yes. Sorry, the transaction level. The ones as shown on that slide are probably the ones that opted for ERT going off of ERT?

**Zeiber [A]\*:** We had one of the two in the first cohort. And then there's two in a higher dose cohort that have been dosed and one has gone up and we're waiting on another what decision is made.

**Kohtani [Q]\*:** Thanks. Just third question on the enhancement promoter for AT845. I think Audentes originally developed something called AT192, which use AAV, just like AT845 but used what was called a hybrid promoter. I don't think this was really disclosed. And suppose we have strong expression in the heart muscle, obviously, safety signals were identified in primate experiments, and I think you switched to 845, which is an enhancer in combination with MCK promoter.

Looking at the expression level of GAA, I think this combination is pretty promising. My question is this. What does this have any implication? Does this have any implication on AT702 and AT753 for Duchenne? Because I think you could use the same enhancer promoter. It's showing pretty strong expression in muscle. Or do you need to switch to something else because Duchenne's requires more expression probably in the heart muscles?

**Yasukawa [M]:** That's a clinical timeline-related question. Mat, do you think you can answer this question?

**Pletcher [A]\*:** I'm happy to comment on this. No, it's a very good point. And I think this is exactly the kind of cross-learnings that we hope to be able to apply across our entire portfolio; that as we gain both preclinical and now eventually clinical data with our different constructs, that we can then apply those to earlier programs as they come through.

Now to your specific question about the promoter enhancer combinations in the Duchenne's program versus the Pompe, part of our process for how we develop these is to actually try multiple combinations at the very beginning and ultimately, select through the combination of in vivo and in vitro assays, what the best are.

I would say that actually for the majority of our Duchenne programs, we're still in the process of doing that optimization. I can't say as of yet, that whether or not the ultimate selection of enhanced promoter combinations that we would take forward in a clinical candidate for Duchenne is the exact same one as the 845, but certainly, this is the opportunity is that we are gaining actual clinical translational data to inform that selection for other programs. But no, it's too early to give you a direct answer on the question you asked.

**Kohtani [Q]\*:** Thank you. That's it for me for my questions.

**Fujii [M]:** Thank you very much. Next person, please.

**Moderator [M]:** From the Japanese conference system, Schroder Investment Management, Ms. Sato, please.

**Sato [Q]:** Thank you very much for your presentation today. First of all, on BS, how much asset remains subject to impairment loss check? And is this going to be not early impairment loss for the gene therapy as a whole, but contributing to the delay in the AT132 program? That's my first question.

**Okamura [A]:** Thank you for your question. The amount is going to be JPY44.4 billion as of the end of the third quarter for loss impairment. It's going to be AT132 specific impairment loss checking. We are not going to tackle other programs because of AT132. You mentioned a delay, but the timeline overall is so long, but as Bernie Zeiber explained, what kind of patient population this is going to be, we can assume a certain range as of now. Even if it's going to be an impairment loss testing, we haven't finished our discussions with the FDA.

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What is going to be the final protocol? What is going to be the speed of patient enrollment? How many participants do we need? We do have certain assumptions, but they are not definitive. We are considering various scenarios. And what is going to be the variability in the value of all which is going to be evaluated. Did I answer your question?

**Sato [Q]:** Thank you very much. Understood. What remains on the balance are all intangible assets, right.

**Okamura [A]:** AT132 in process R&D for AT132.

**Sato [Q]:** Understood. AT132 delay and also the number of the patients targeted are reduced. That's the reasons for impairment test?

**Okamura [A]:** I'm not saying exactly that the patient population is reduced, but who are going to be the target patients, that's all depending on the discussion with the regulator.

**Sato [Q]:** Thank you. Second question, that is about the improvement for manufacturing. Empty capsid is to be reduced to reduce the side effects. That is not specific to AT132. For all other gene projects, I think it is related. So, you are thinking about the improvement of the production method. But before that technology is established, other technology, other developments are going to proceed. Is it possible to be done? I'm talking about product enrichment.

**Shitaka [A]:** Shitaka speaking. Reduction of the percentage of the empty capsid, meaning that the total dosage is going to be reduced, therefore, this is going to be common to all the projects. That's going to be the point of the improvement for the formulation. And these kinds of improvements tend to be never ending.

We come to this level for AT132, and we are going to try to improve it furthermore. Considering the prospect of this improvement of the enrichment, I believe that pipeline-wise, I think we can still go on as has been planned.

**Sato [Q]:** The volume of the empty capsid, depending on that dose, it's going to be changed. At the time you change the technology, you are going to also modify the investigational product. Is that kind of approach viable?

**Shitaka [A]:** Well, suppose we look at the empty capsid as impurities, the contained level might be 30% or 10%. Well, that is something we can work on with this product enrichment.

**Sato [Q]:** So, you think you can carry out ongoing with considering the empty capsid level?

**Yasukawa [A]:** With that regard, the regulatory field's perspective, Bernie, do you have any additional comment on this point?

**Zeiber [A]\*:** I understand a little bit of the question, and I may ask for some clarification. But from a regulatory perspective and one of the things that we like to see is have a potentially almost commercial-ready type product even when we're starting very early in development. And the reason being, especially in these rare diseases, you want to characterize the efficacy and safety profile with the same drug product in your clinical studies as what you would use on the market. And so that's where a lot of these advancements that we've talked about can be applied, not only to AT132 but to AT845 and then earlier programs, so that we ensure that what we're studying is as close to what we would use commercially as possible.

If we change in the middle and let's say, there's new safety findings or issues arise, it always brings up questions: could it have been anything related to the drug product or any comparability issues? I think that's

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where this learning and the improvements in technology that Mat and his team are making are so critically important to all of our programs.

I don't know, Mat, if you want to comment any further on that.

**Pletcher [A]\*:** Thanks, Bernie. I do. I mean, as we mentioned in the presentation, we are continually looking to improve our process. And this does speak to where the field is right now, that each year, we've seen tremendous gains in both productivity as well as our ability to create more enriched products. And we're not at the end of that innovation pipeline yet. There are still significant gains to be had and we plan to continue to innovate because we see benefits from cost of goods to potential gains in efficacy and safety as well. We're not stopping to push.

But to Bernie's point, certainly, there is a point where you need to move the program forward even while these changes are happening in the background. And it's always the question as we move forward is, do we see the value in changing the process, essentially delaying the program, versus what we're seeing in the clinic. And if there does not seem to be any impact from the manufacturing process or any benefit to be gained, then it's not reasonable to make that change.

But again, I just want to note where the field is, that because of the fact that it is rapidly developing, because our ability to—our technology in the spaces are rapidly developing, this is not uncommon either for a manufacturing process to change in the course of a clinical trial; that, in fact, a number of other companies have already been through this path with regulators and have been able to show us how you do make this switch if and when it is necessary.

And the other thing I mentioned in my presentation was the cross-learning. And I think this is one of the places, especially where we benefit and have benefited from talking to other companies, where we're sharing knowledge and we're sharing their experience on how they were able to traverse this particular issue, how they were able to work with regulators to be able to switch out and to create or to introduce a product into an ongoing clinical trial that decreases empty capsids or changes some aspect of manufacturing process.

So again, I think the question you asked speaks to both the fluidness of this field, but also the fact that there is a pathway established for how we address this. Hopefully, that's helpful.

**Sato [Q]:** Very clear. Thank you very much for the follow-up comments as well. Thank you very much. That's all from me.

**Fujii [M]:** Thank you very much. There may be other questions you want to ask, but time is up. We'd like to close today's meeting here. Thank you very much for joining today.

[END]

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