INITIATIVES FOR GENE THERAPY

R&D Meeting - March 9, 2022

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION

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.

AGENDA

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

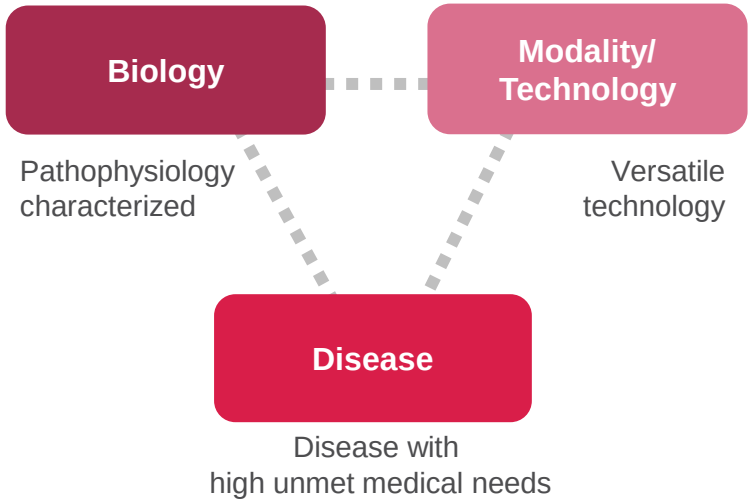
INTRODUCTION

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

WHY WE WORK ON GENE THERAPY

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

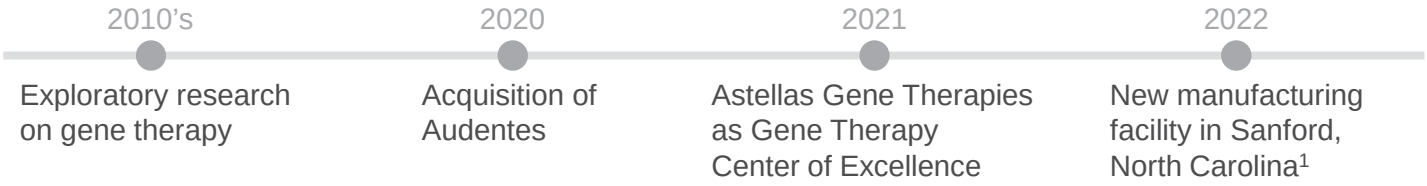
FOCUS AREA APPROACH



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 by mid-2022

OVERVIEW OF TODAY'S PRESENTATIONS

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

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GT-RTO: Gene Therapy Research & Technical Operations

BUILDING LEADERSHIP IN GENE THERAPY

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

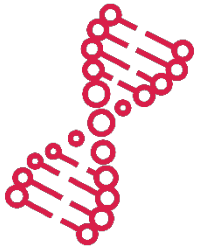
At Astellas, our goal is to boldly push the boundaries of what is possible to **discover, develop and deliver** breakthrough, first-of-their-kind gene therapies with **life-changing value for patients across many disease areas**

WHAT IS A GENETIC DISEASE?

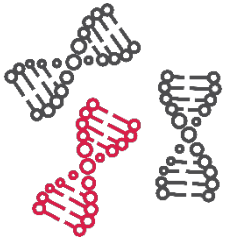
Genetic diseases are often **rare and complex to treat** with **limited** or no **therapeutic options** and **significantly reduce quality of life and life expectancy**[1]

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

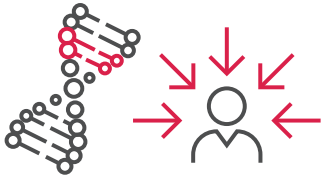
Genetic disorders can be caused by[3]:



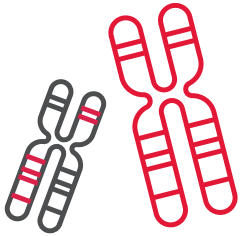
A **mutation in one gene** (monogenic disorder)



Multiple genes (multifactorial inheritance disorder)



A combination of gene mutations and environmental factors



Damage to chromosomes that carry genes

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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.

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

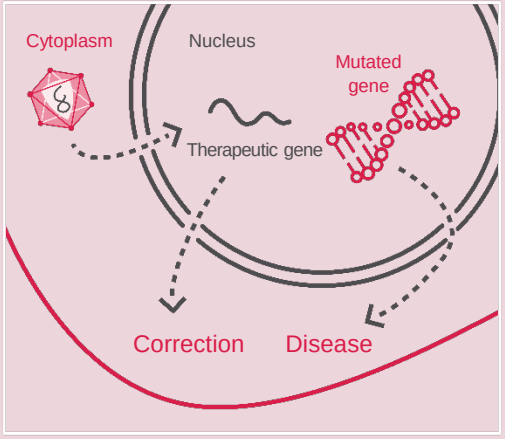
Approaches include[1]:

DNA Level

RNA Level

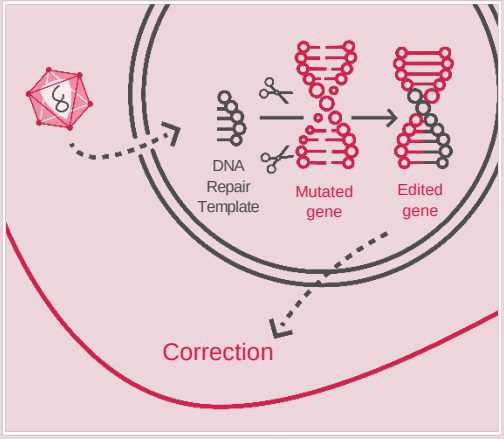
Gene Transfer or Replacement

Aims to replace the defective gene or introduce a new gene, frequently using viral delivery vectors



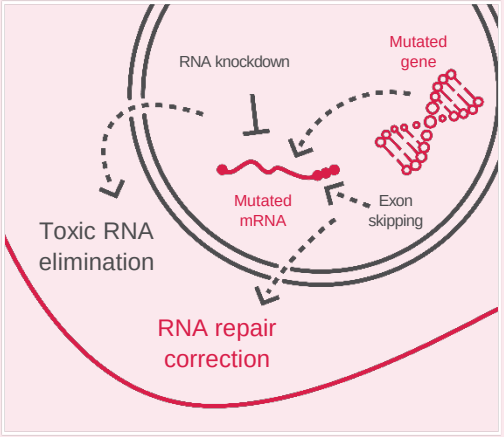
Gene Editing

Aims to repair mutations directly in the DNA using 'molecular scissors', frequently using viral delivery vectors



Transcription Regulation

Aims to eliminate or repair the mRNA transcripts copied from the mutated gene, can also activate expression of silenced genes

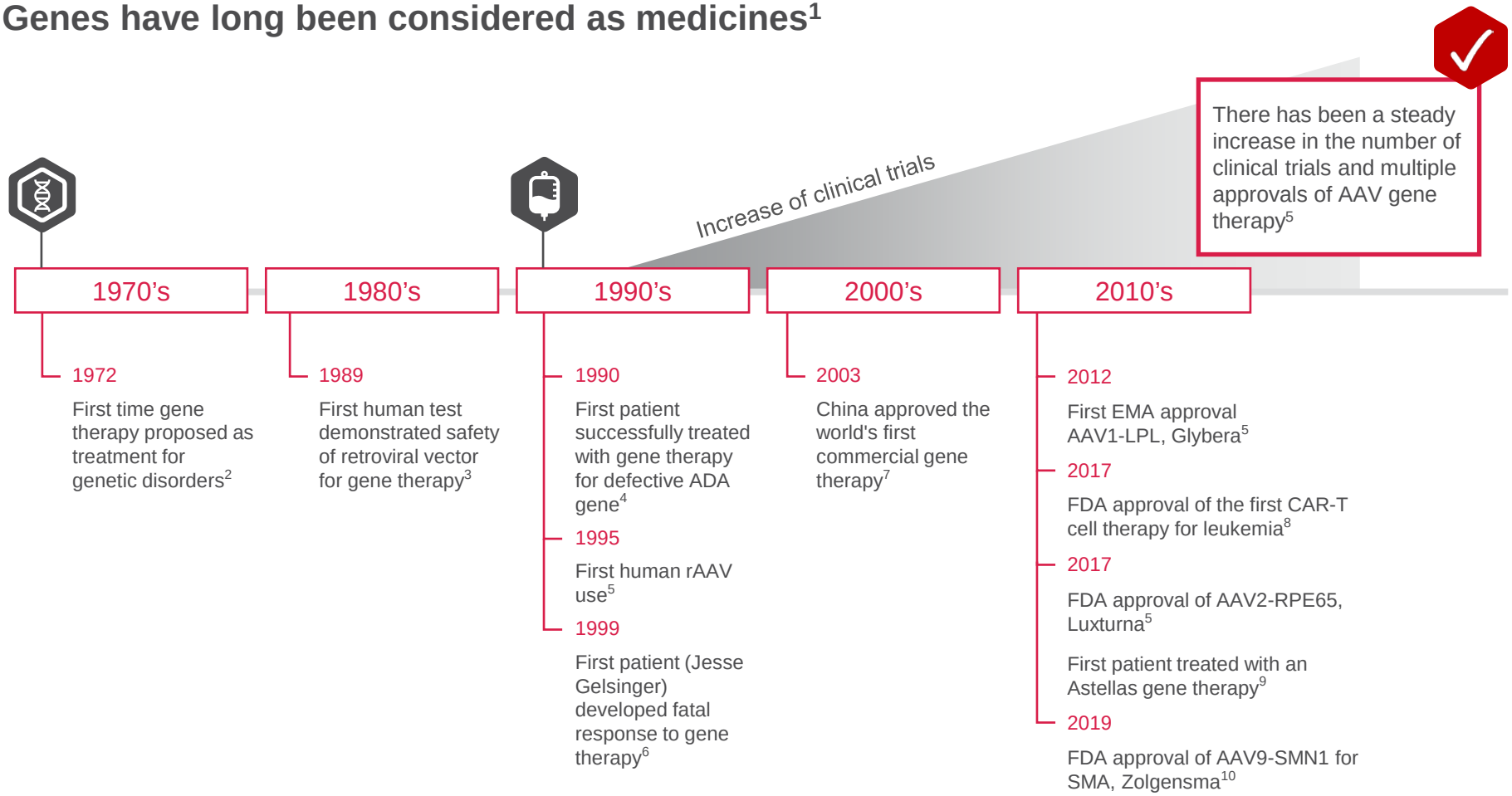


DNA: Deoxyribonucleic acid, mRNA: Messenger RNA, RNA: Ribonucleic acid.

1. Wang, D. & Gao, G. *Discovery Medicine* 18, 151-156 (2014).

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

Genes have long been considered as medicines[1]



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; 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; accessed July 2020.

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

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[1]

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

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).

TWO PRIMARY STRATEGIES OF GENE THERAPY ADMINISTRATION

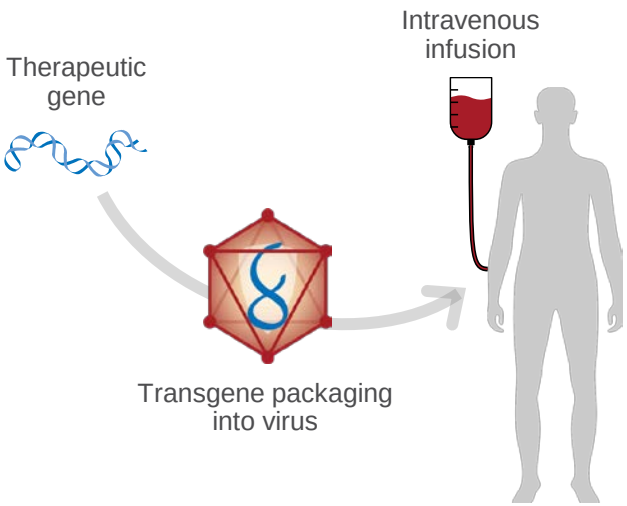
Two primary strategies: *in vivo* vs. *ex vivo* delivery

In vivo

Vector delivered directly to patient via single intravenous infusion

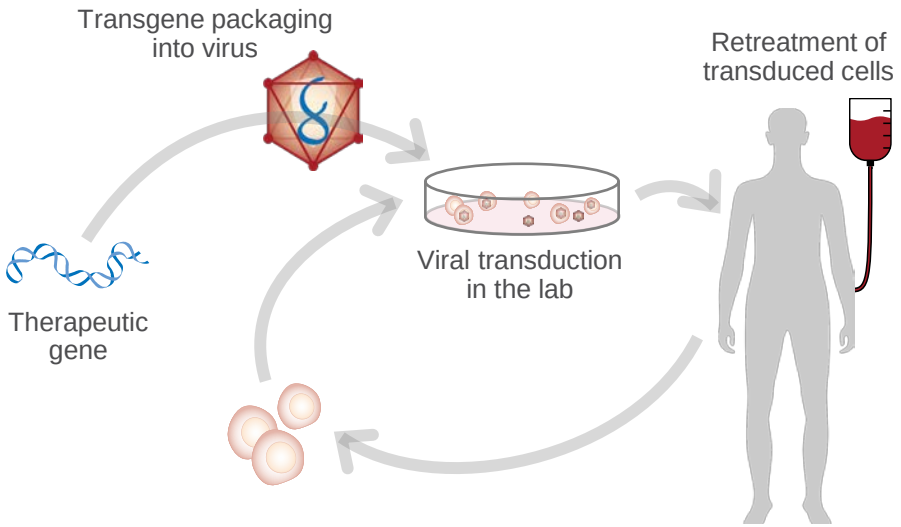
Transduction of a long-lived cell type in which integration is not necessarily required

Often accomplished with AAV vectors



Ex vivo

Patient's cells taken out of body
↓
Transduced by vector in culture
↓
Gene-modified cells delivered back to patient



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).

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 delivered 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.

SPOTLIGHT ON DAD FOR ANGELMAN SYNDROME (AS)

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[1]

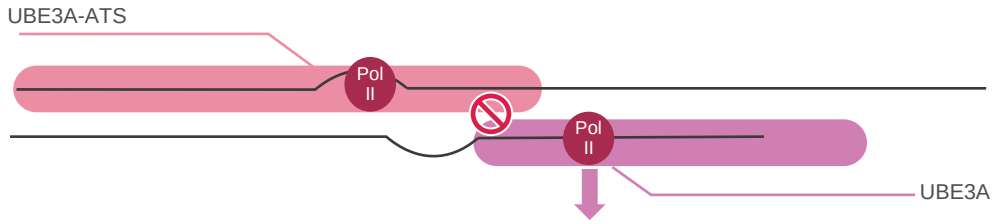
Prevalence is estimated to be ~60,000 – 100,000 (EU, US, Japan)[1]

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[2]

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).

SPOTLIGHT ON AT808 FOR FRIEDREICH'S ATAXIA (FA)

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)[1]

The most common form of inherited ataxia has an estimated prevalence of ~15,000 – 20,000 worldwide[2]

Characterized by unsteady posture, frequent falling, and progressive difficulty in walking due to impaired ability to coordinate voluntary movements[2]

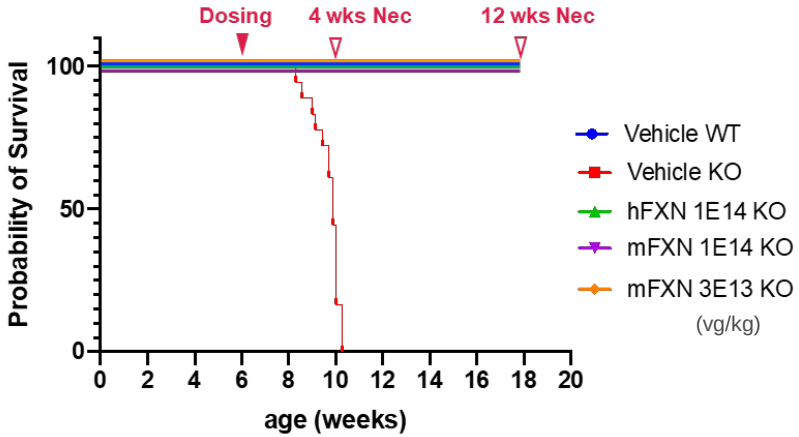
No approved disease-modifying treatments

Common cause of death is due to the FA-associated cardiomyopathy[3]

INVESTIGATIONAL AT808 – AAV gene therapy to express FXN in affected tissues

AT808: AAV8-hPGK-hFXNco
(1576 bp)

Heart POC mouse study showed reversal of phenotype[4]



- 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.

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

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

astellas + AUDENTES An Astellas Company =

Global footprint

Substantial resources e.g. talent, capabilities to grow portfolio etc.

Development, regulatory and commercialization capabilities

Agility

Top skills and talent, deep heritage in gene therapy

Unique capabilities in gene therapy manufacturing scale

Uniquely positioned for leadership in gene therapy

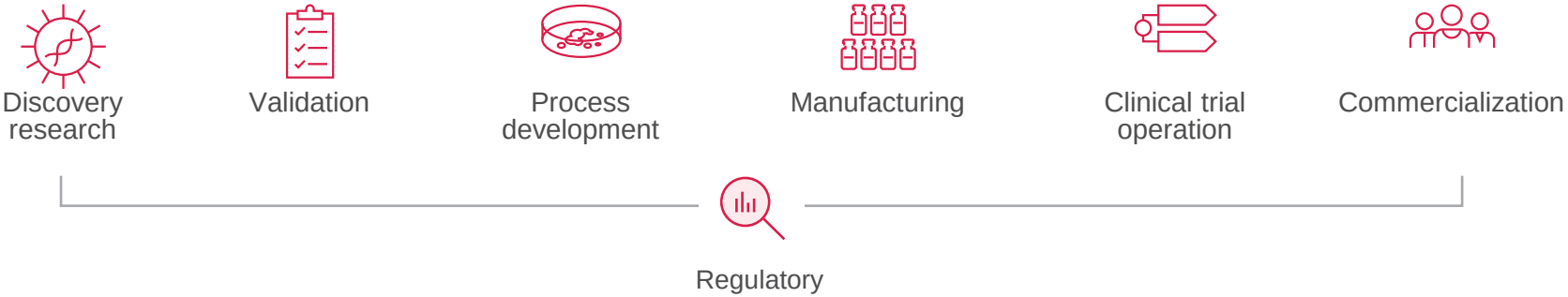
astellas

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

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

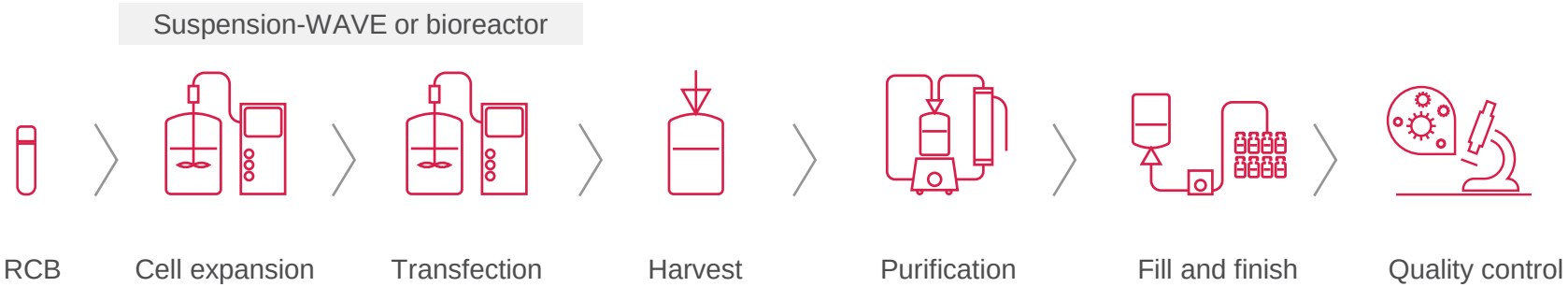
One of the broadest early pipelines in the industry, capacity to produce high-quality gene therapy products to meet anticipated demand, and an aligned commercial team already working to optimize our in-market potential

Capabilities across the value chain…



AAV MANUFACTURING – UNDERSTANDING A COMPLEX INDUSTRY CHALLENGE

Sample AAV manufacturing workflow:



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

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

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**

Tsukuba, Ibaraki

Early research, process & analytical development

South San Francisco, California

Preclinical research, manufacturing from research to commercial

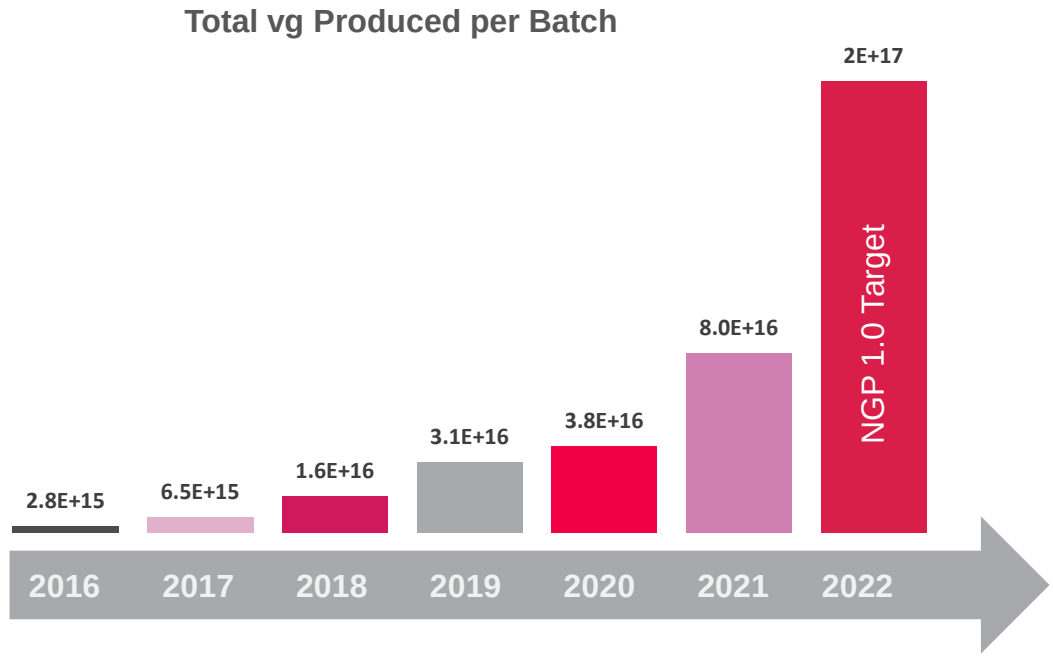
Sanford, North Carolina

Manufacturing from clinical to commercial

AAV: Adeno-associated virus.

PRODUCTIVITY, SCALE AND YIELD – CRITICAL FOR SUCCESS IN THE FIELD

Audentes / AGT Progress in productivity and yield[1]:



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.

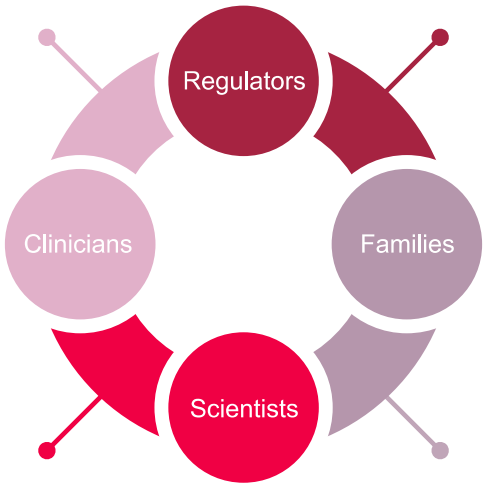
STAYING AHEAD: COLLABORATION AND PARTNERSHIP FOR SUCCESS IN GENE THERAPY

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.

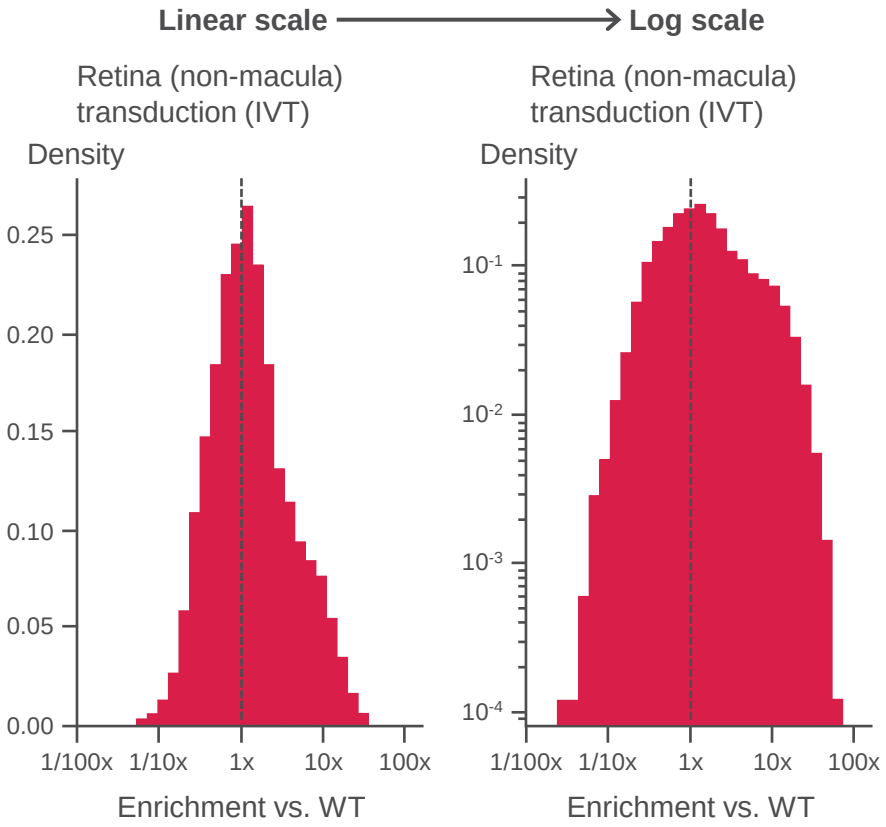
WORKING TO OPTIMIZE CURRENT AAV TECHNOLOGY AND INVESTING IN NOVEL CAPSIDS

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[1]

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**

Library-wide distribution



Capsids with altered and improved transduction in the non-macular retina: Results pooled from non-macula retinal samples[2]

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

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

Capabilities

- Novel improved AAV capsids
- Technologies to manage pre-existing immunity and the possible need for redosing
- Technologies to further improve efficiency and quality of manufacturing of viral vectors
- Technologies for efficient delivery and expression in target organs
- Non-viral gene delivery technologies

Portfolio assets

Novel AAV based projects targeting serious diseases with a strong link between biology/modality and disease

- Neuromuscular Diseases
- Central Nervous System
- Ophthalmology

Partnerships

Partnerships with synergistic capabilities to maximizing global development value of project assets

- Manufacturing
- Global reach, including Japan and Asia

AAV: Adeno-associated virus

ASTELLAS IS FIRMLY POSITIONED TO DELIVER TRANSFORMATIVE THERAPIES FOR GENETIC DISEASES

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

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

Full value chain capabilities, globally consistent standards and processes

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

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

ASTELLAS GENE THERAPIES AT-A-GLANCE

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

GLOBAL REACH

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.

UPDATE ON CLINICAL PROGRAMS IN GENE THERAPY

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

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

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In the clinic

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

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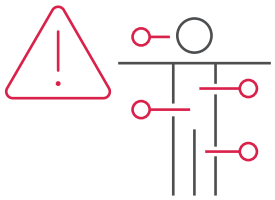
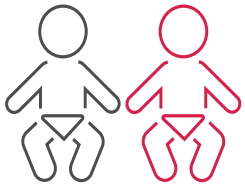
UPDATE ON AT132 FOR THE TREAMENT OF XLMTM

XLMTM – A DEVASTATING DISEASE WITH NO EFFECTIVE TREATMENT OPTIONS

Half of XLMTM patients do not survive past 18 months[1]

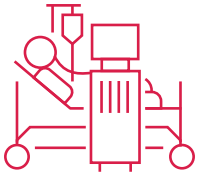


XLMTM is a life-threatening neuromuscular disease characterized by extreme muscle weakness and respiratory failure[1]



XLMTM affects approximately 1 in 40,000 to 50,000 newborn males[2]

Motor milestones are substantially delayed or not achieved[3,5]



90% require respiratory support at birth, continuing to demonstrate chronic, life-long ventilator dependence up to 24 hours per day[1,2]

> 70% require feeding tubes[3,4]

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).

AT132 DELIVERS REPLACEMENT GENETIC MATERIAL FOR THE HUMAN MTM1 GENE

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

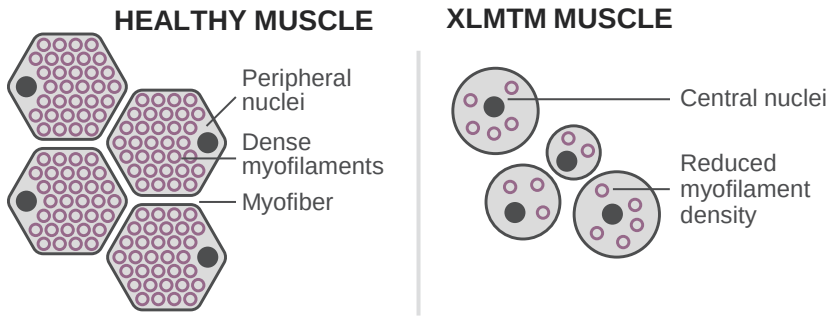


Figure 1a. Astellas proprietary image.

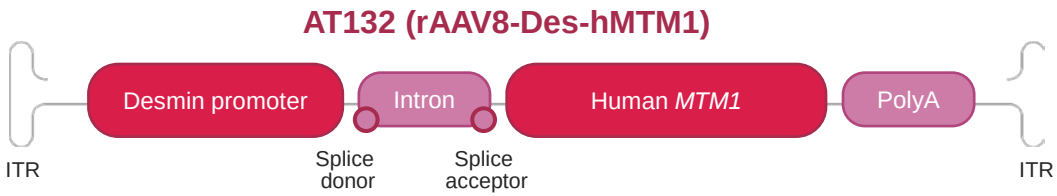


Figure 1b. Adapted from Astellas InVivo Gene Editing Summit Presentation November 2021.

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

ASPIRO*: STUDY ENDPOINTS AND ASSESSMENTS[1]

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^{14} vg/kg cohort: n=6 dosed
- 3.5 x 10^{14} vg/kg cohort: n=17 dosed
- Control[2]: 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.

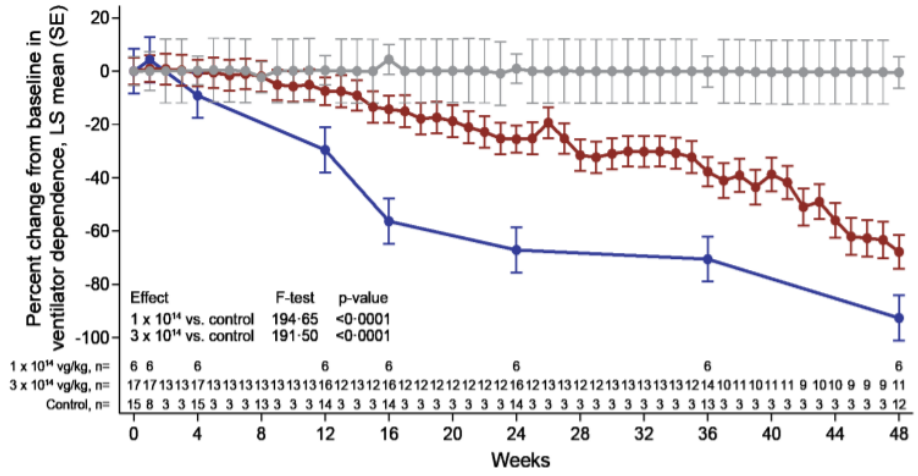
*ASPIRO trial currently on clinical hold

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.

AT132 HAS DEMONSTRATED SIGNIFICANT IMPROVEMENTS IN RESPIRATORY FUNCTION AT 48 WEEKS

Reduction in ventilator dependence including ventilator independence in several participants[1]



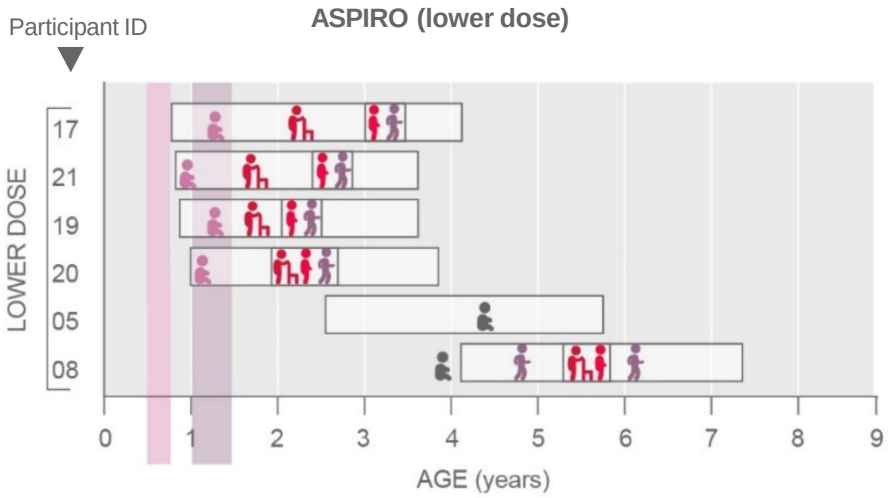
Daily hours of ventilator dependence (LSM ± SE)

Dose (vg/kg)	Baseline	Week 48	Change
1.3 x 10^{14} (n=6)	20.5 ± 2.0	1.3 ± 2.0	–19.2
3.5 x 10^{14} (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

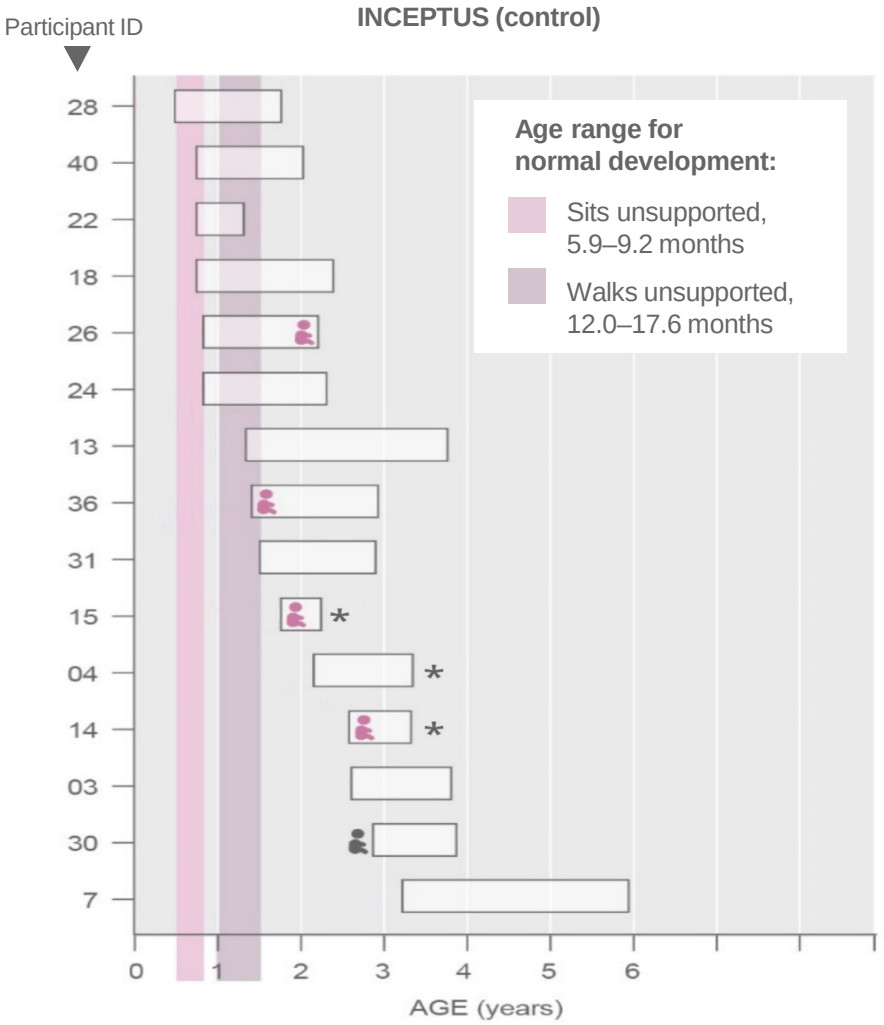
LSM: Least square mean; SE: Standard error; vg: vector genome.

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

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



At follow-up durations shown on the charts



Able to sit unassisted at baseline

Sits without support for >30 seconds

Rising self to stand

Stands alone

Walks unsupported

* Deceased during study

White boxes start at age at dosing or age of enrollment in INCEPTUS (Controls). The length of the box indicates the patient's time on study. Icons indicate age at motor milestone achievement. Interim data as of January 29, 2021

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

ASPIRO IS CURRENTLY ON CLINICAL HOLD PENDING FURTHER INVESTIGATIONS

Four ASPIRO participants have died following serious hepatic adverse events

2020

In 2020, there were three fatal SAEs among participants receiving AT132 higher dose[1]

No findings suggest that an immune response has caused these fatal SAEs or caused severe liver dysfunction, though investigations are ongoing

Clinical hold

Clinical hold lifted

Study protocol modified to lower dose, upper age limit set, risk mitigation measures put in place

2021

On resumption in 2021, one further study participant who received a lower dose of AT132 died[2,3]

Severe liver abnormalities following dosing, similar to 2020 fatalities

Clinical hold

Second clinical hold

Investigations and collaboration with FDA, KOLs and other stakeholders ongoing

Investigations and collaboration with FDA and other external stakeholders ongoing

All four participants…

…had evidence of cholestasis pre-dating AT132 dosing

…met trial eligibility criteria

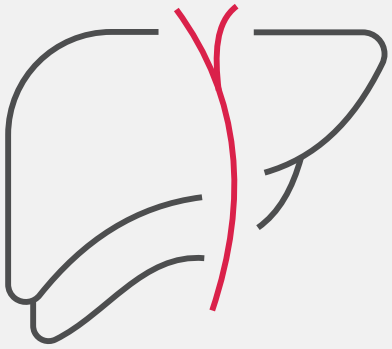
…showed acute increases in liver function parameters weeks after dosing

This clinical picture has not been observed with other systemically administered AAV gene therapies[4]

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.

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



Cholestasis is a condition in which the flow of bile from the liver is reduced or blocked, potentially leading to fibrosis and liver failure[1]

Given the **ultra rare nature of the disease** and profound neuromuscular impairment, there has **been limited recognition of the role of myotubularin outside of the skeletal muscle**

It is increasingly understood that **XLMTM patients have a cholestatic vulnerability** featuring recurrent elevated serum bile acids and transaminitis ± hyperbilirubinemia[1]

Insufficient hepatocellular myotubularin expression may **impair bile acid transport**[2,3]

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

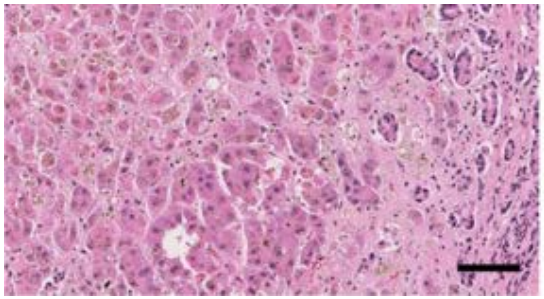
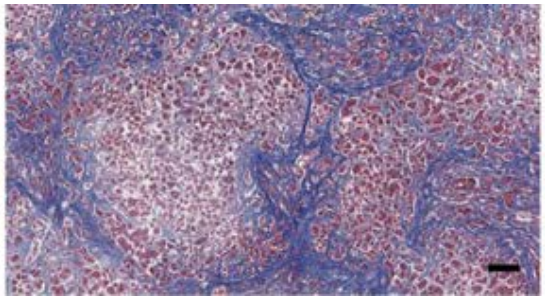
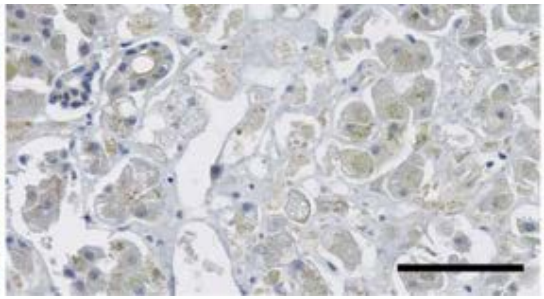
XLMTM: X-linked myotubular myopathy.

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.

LIVER HISTOPATHOLOGY CONSISTENT ACROSS DECEASED SUBJECTS AND WITHOUT INFLAMMATORY INFILTRATES

Liver histopathology in deceased participants

Participant 6

H&E	Masson Trichrome	BSEP
		
Abnormal bile staining within hepatocytes and bile duct canaliculi observed	Extensive fibrosis observed	BSEP not present

Scale bars indicate 100 µm

Commonly observed pathology among participants[1]

- 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: Hemaltoxylin 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.

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

In vivo and *in vitro* experiments to understand the mechanism of cholestasis in XLMTM and how this may be exacerbated by AAV

Product enrichment – reduction of empty capsids to enable a lower total capsid dose

Modification of participant eligibility criteria to reduce risk of hepatic toxicities

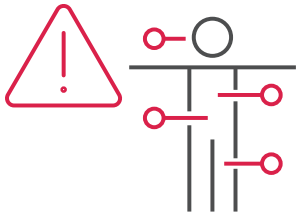
Engagement with external experts and the patient advocacy community

Discussions with Regulatory Authorities to address clinical hold

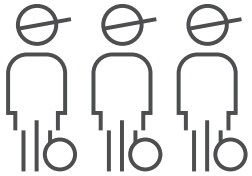
AAV: Adeno-associated virus; BLA: Biologics license applications; XLMTM: X-linked myotubular myopathy.


INTRODUCING AT845
FOR POMPE DISEASE

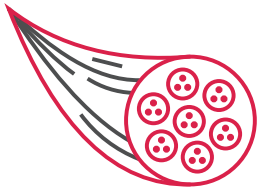
AN INTRODUCTION TO POMPE DISEASE



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[1]



IOPD is rapidly progressive and characterized by cardiomegaly, hepatomegaly, weakness and hypotonia[2]

Our initial target for treatment:

LOPD is characterized by slowly progressive myopathy involving skeletal muscle

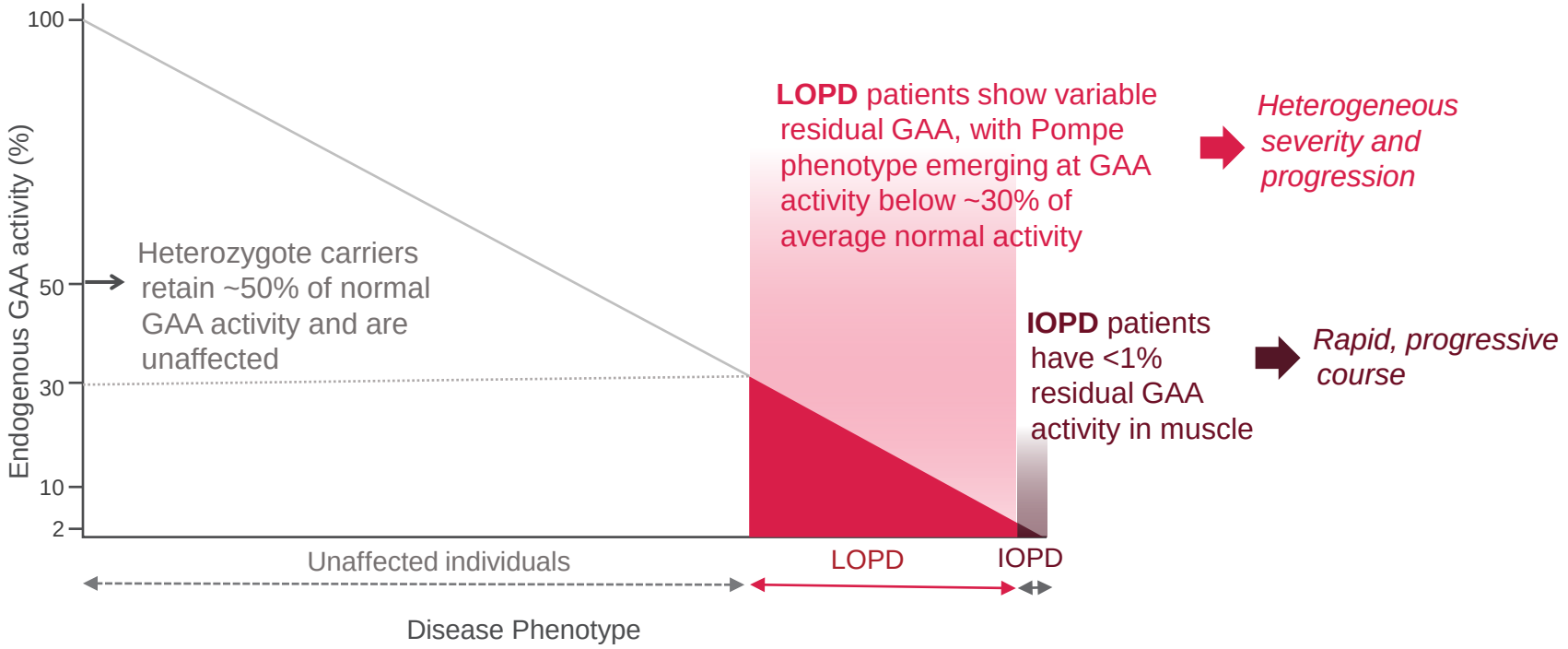
GAA: Acid alpha-glucosidase; IOPD. Infantile-onset Pompe disease; LOPD: Late-onset Pompe disease.

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).

REDUCED GAA ACTIVITY IS A HALLMARK OF SYMPTOMATIC POMPE DISEASE

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

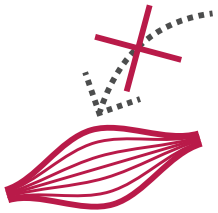


GAA: Acid alpha-glucosidase, IOPD. Infantile-onset Pompe disease; LOPD: Late-onset Pompe disease.

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).

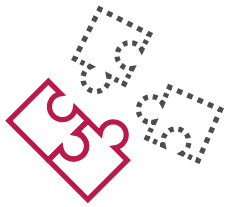
LIMITATIONS OF CURRENT STANDARD-OF-CARE: ENZYME REPLACEMENT THERAPY (ERT)

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**[1,2]

ERT is known to be immunogenic and can elicit antibodies that further impact effectiveness[3]



Pompe clinician experts and patients highlight that **a significant unmet need remains** given disease progression despite ERT[4,5]

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).

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 lysomosal 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[1], avoiding the need for repeated infusions

Systemic gene replacement therapy with muscle-specific promoter

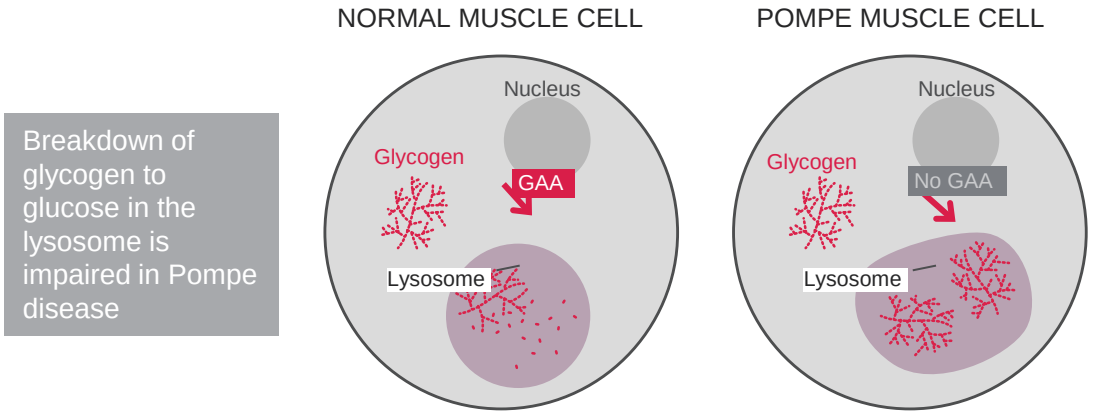


Figure 1a. Astellas proprietary image.

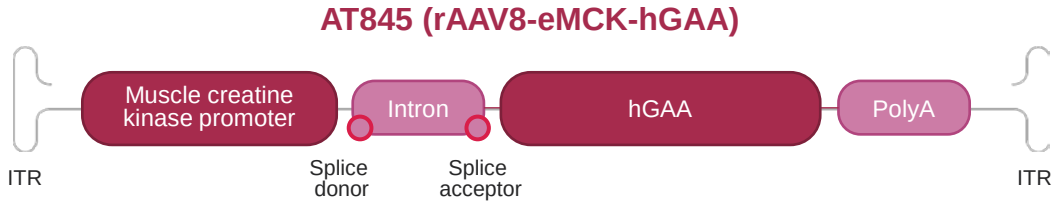


Figure 1b. Adapted from Astellas InVivo Gene Editing Summit Presentation November 2021.

AAV: Adeno-associated virus; GAA: Acid alpha-glucosidase; hGAA: Human acid alphaglucosidase; ITR: Inverted terminal repeat; MCK: Muscle creatine kinase; PolyA: Polyadenylation signal.

1. Eggers, M. et al. *EMBO Molecular Medicine* 14, (2021).

FORTIS: STUDY ENDPOINTS AND ASSESSMENTS

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

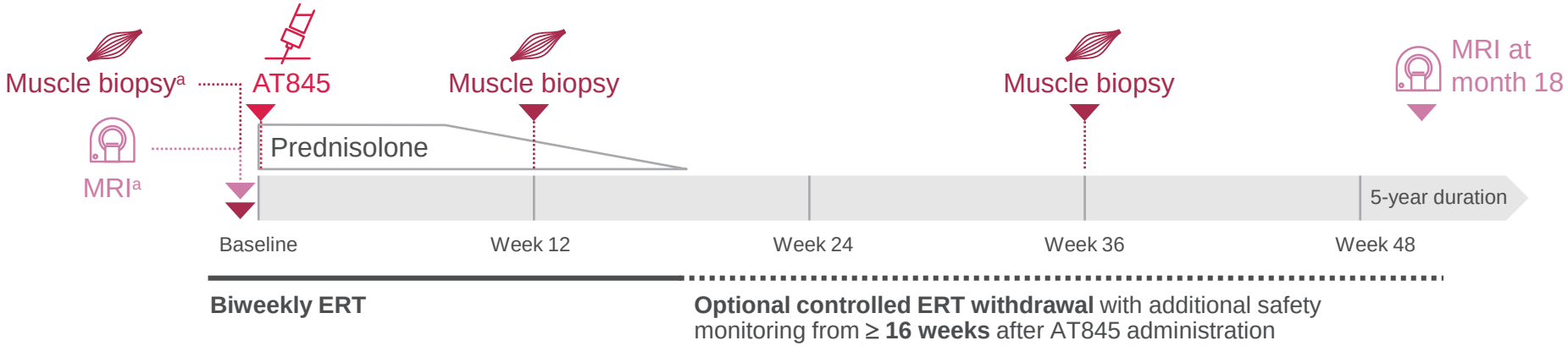
Change from baseline in GAA protein expression and enzyme activity in muscle (week 12)

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



a. 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.

INITIAL SAFETY DATA OF AT845 IN ADULTS WITH LOPD

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 (3×10^{13} vg/kg)		Cohort 2 (6×10^{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 Ageusia		1	1 1
ALT increased AST increased		1 1	
Decreased appetite			1
Constipation Abdominal distension			1 1
Irritability			1
Palpitations			1
Night sweats Cold sweat			1 1
Dyspnea			1
COVID-19			1
Upper respiratory tract congestion			1
Malaise Fatigue			1 1

Information based on a data cut on 14 December 2021

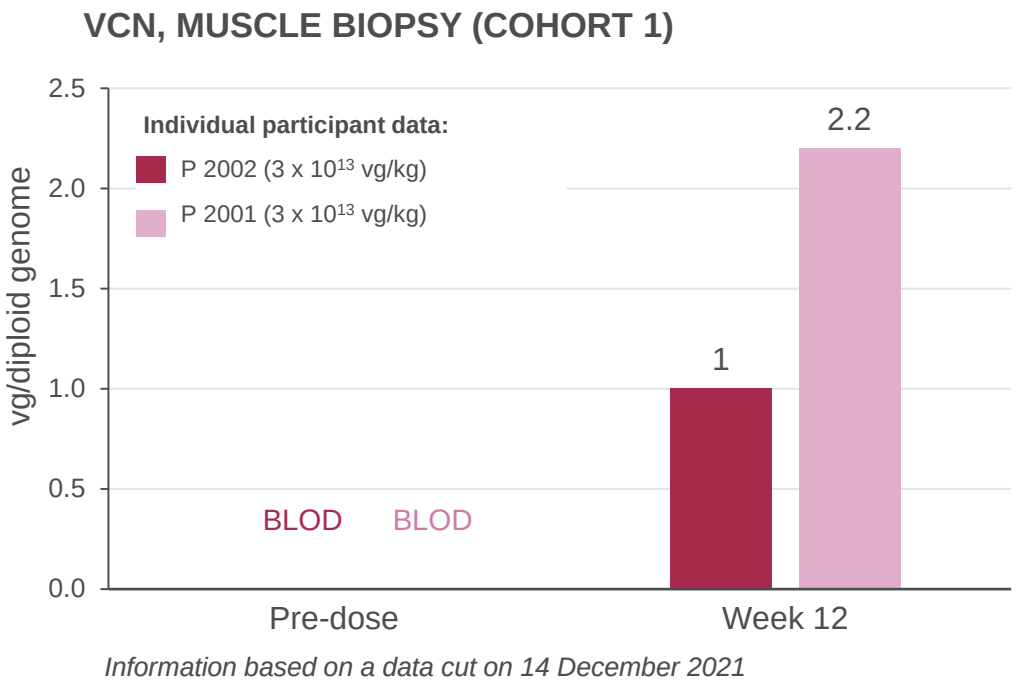
AAV: Adeno-associated virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TEAE: Treatment emergent adverse event; vg: vector genome.

FORTIS_PP_2002.rtf – Patient profile listing, page 28

FORTIS_PP_2001.rtf – Patient profile listing, page 31

TRANSDUCTION OF AT845 VECTOR GENOME IN MUSCLE CELLS

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



Information based on a data cut on 14 December 2021

VCN, muscle (first two participants only)

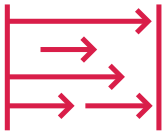
BLOD: Below limit of detection, VCN: Vector copy number; vg: vector genome.

FORTIS_PP_2002.rtf – Patient profile listing, page 28
FORTIS_PP_2001.rtf – Patient profile listing, page 31

NEXT STEPS FOR AT845

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

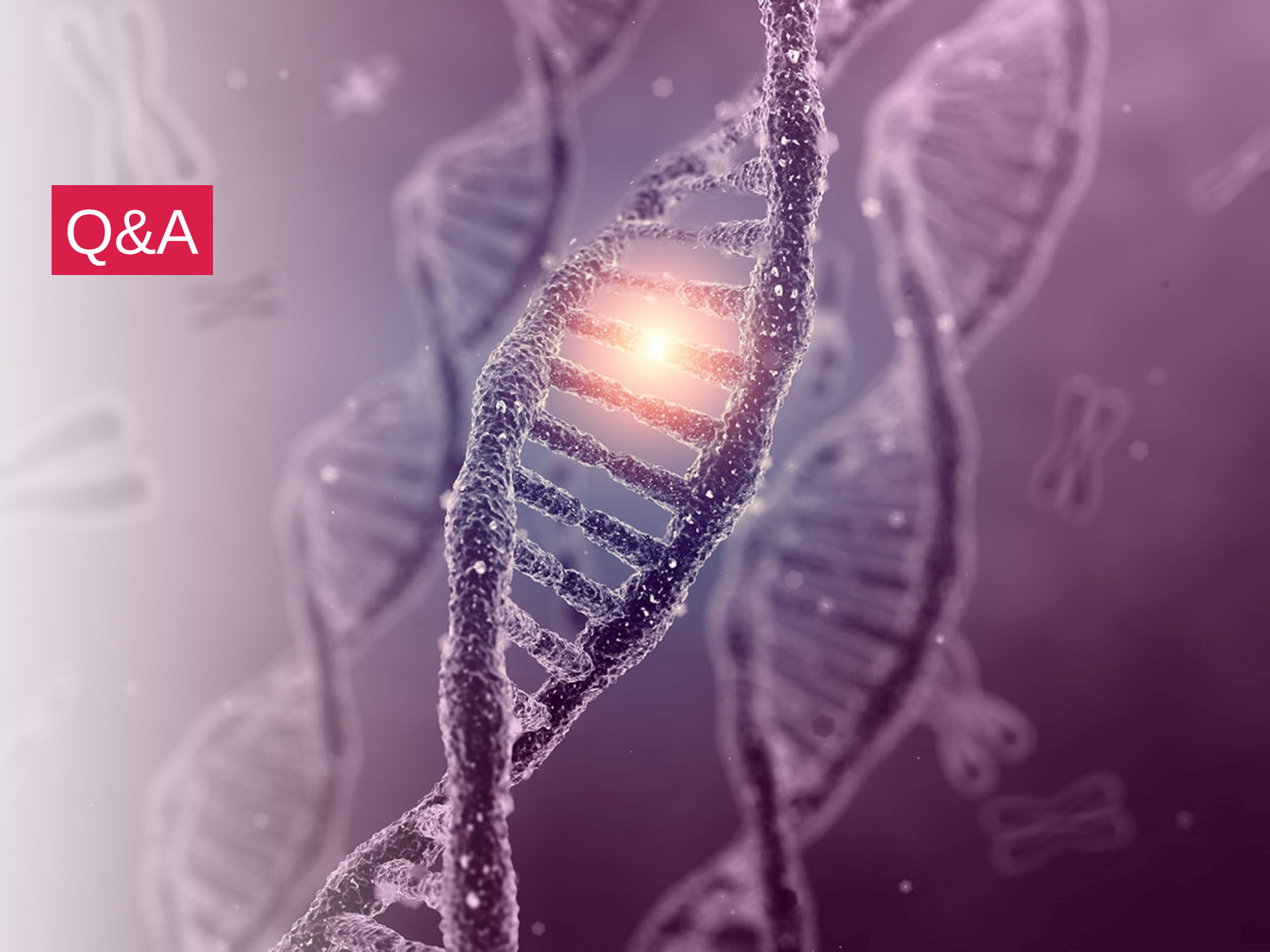
POTENTIALLY TRANSFORMATIVE EFFICACY AND PATIENT NEED DRIVES OUR COMMITMENT TO GENE THERAPY

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

Q&A



ON THE FOREFRONT OF HEALTHCARE CHANGE

astellas