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

Biology
- Pathophysiology characterized

Modality/Technology
- Versatile technology

Disease
- Disease with high unmet medical needs

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

2010’s
- Exploratory research on gene therapy

2020
- Acquisition of Audentes

2021
- Astellas Gene Therapies as Gene Therapy Center of Excellence

2022
- New manufacturing facility in Sanford, North Carolina1

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
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

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

Approaches include:

**DNA 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.

**RNA Level**
- **Transcription Regulation**: Aims to eliminate or repair the mRNA transcripts copied from the mutated gene, can also activate expression of silenced genes.

**Diagram Notes**:
- DNA: Deoxyribonucleic acid, mRNA: Messenger RNA, RNA: Ribonucleic acid.

Astellas Proprietary Information
# Gene Therapy Development is Rapidly Progressing but We Are Learning as We Go

## Genes have long been considered as medicines

There has been a steady increase in the number of clinical trials and multiple approvals of AAV gene therapy.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972</td>
<td>First time gene therapy proposed as treatment for genetic disorders.</td>
</tr>
<tr>
<td>1979</td>
<td>First human test demonstrated safety of retroviral vector for gene therapy.</td>
</tr>
<tr>
<td>1989</td>
<td>First patient successfully treated with gene therapy for defective ADA gene.</td>
</tr>
<tr>
<td>1990</td>
<td>First human rAAV use.</td>
</tr>
<tr>
<td>1999</td>
<td>First patient (Jesse Gelsinger) developed fatal response to gene therapy.</td>
</tr>
<tr>
<td>2003</td>
<td>China approved the world's first commercial gene therapy.</td>
</tr>
<tr>
<td>2012</td>
<td>First EMA approval AAV1-LPL, Glybera.</td>
</tr>
<tr>
<td>2017</td>
<td>FDA approval of the first CAR-T cell therapy for leukemia.</td>
</tr>
<tr>
<td>2017</td>
<td>FDA approval of AAV2-RPE65, Luxturna.</td>
</tr>
<tr>
<td>2019</td>
<td>First patient treated with an Astellas gene therapy.</td>
</tr>
<tr>
<td>2019</td>
<td>FDA approval of AAV9-SMN1 for SMA, Zolgensma.</td>
</tr>
</tbody>
</table>


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\(^1\)


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.
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**
- AT132\* for XLMTM
- AT845 for Pompe disease
- AT753 for Duchenne muscular dystrophy
- AT702 for Duchenne muscular dystrophy
- AT751 for Duchenne muscular dystrophy
- AT466 for Myotonic dystrophy
- MDL-201
- MDL-202

**CNS disorders**
- AT808 for Friedreich’s Ataxia
- HUB for Huntington’s disease
- DAD for Angelman syndrome
- GTFX for Fragile X syndrome

**Ocular programs**
- A1015 for Primary open angle glaucoma
- TFB for Dry age-related macular degeneration, Stargardt macular dystrophy
- GTSG for Stargardt macular dystrophy

**Other**
- ADR for Hepatitis D virus infection

*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


\(^1\) NORD (National Organization for Rare Disorders) (2022). at https://rarediseases.org/rare-diseases/angelman-syndrome/

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)

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

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

**Heart POC mouse study showed reversal of phenotype\(^4\)**

Astellas Proprietary Information

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

Uniquely positioned for leadership in gene therapy

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
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...

- Discovery research
- Validation
- Process development
- Manufacturing
- Clinical trial operation
- Commercialization
- Regulatory
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.
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.
PRODUCTIVITY, SCALE AND YIELD – CRITICAL FOR SUCCESS IN THE FIELD

Audentes / AGT Progress in productivity and yield:\n
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.

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.
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.

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

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

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

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 Therapeutics¹

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.

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

<table>
<thead>
<tr>
<th>Capabilities</th>
<th>Portfolio assets</th>
<th>Partnerships</th>
</tr>
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<tbody>
<tr>
<td>• Novel improved AAV capsids</td>
<td>Novel AAV based projects targeting serious diseases with a strong link between biology/modality and disease</td>
<td>Partnerships with synergistic capabilities to maximizing global development value of project assets</td>
</tr>
<tr>
<td>• Technologies to manage pre-existing immunity and the possible need for redosing</td>
<td>• Neuromuscular Diseases</td>
<td>• Manufacturing</td>
</tr>
<tr>
<td>• Technologies to further improve efficiency and quality of manufacturing of viral vectors</td>
<td>• Central Nervous System</td>
<td>• Global reach, including Japan and Asia</td>
</tr>
<tr>
<td>• Technologies for efficient delivery and expression in target organs</td>
<td>• Ophthalmology</td>
<td></td>
</tr>
<tr>
<td>• Non-viral gene delivery technologies</td>
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</table>
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
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.

GLOBAL REACH

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

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

*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
UPDATE ON AT132 FOR THE TREATMENT OF XLMTM
XLMTM – A DEVASTATING DISEASE WITH NO EFFECTIVE TREATMENT OPTIONS

Half of XLMTM patients do not survive past 18 months

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

XLMTM affects approximately 1 in 40,000 to 50,000 newborn males.

Motor milestones are substantially delayed or not achieved.

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

> 70% require feeding tubes.

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.

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

**ASPIRO** trial currently on clinical hold

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

#### 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

<table>
<thead>
<tr>
<th>Neuromuscular</th>
<th>Respiratory</th>
<th>Muscle biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP INTEND</td>
<td>Ventilator support</td>
<td>Protein expression</td>
</tr>
<tr>
<td>Motor milestones</td>
<td>Maximal inspiratory pressure</td>
<td>Histology / pathology</td>
</tr>
</tbody>
</table>

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

Reduction in ventilator dependence including ventilator independence in several participants\(^1\)

<table>
<thead>
<tr>
<th>Dose (vg/kg)</th>
<th>Baseline</th>
<th>Week 48</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 x 10^{14} (n=6)</td>
<td>20.5 ± 2.0</td>
<td>1.3 ± 2.0</td>
<td>−19.2</td>
</tr>
<tr>
<td>3.5 x 10^{14} (n=17)</td>
<td>23.6 ± 1.2</td>
<td>7.7 ± 1.5</td>
<td>−16.1</td>
</tr>
<tr>
<td>Control (n=15)</td>
<td>20.2 ± 1.3</td>
<td>21.5 ± 1.4</td>
<td>−0.3</td>
</tr>
</tbody>
</table>

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

Age range for normal development:
- Sits unsupported, 5.9–9.2 months
- Walks unsupported, 12.0–17.6 months

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

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

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

AAV: Adeno-associated virus; KOL: Key opinion leader; SAE: Serious adverse event.
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.

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.

Insufficient hepatocellular myotubularin expression may impair bile acid transport.

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.
Liver histopathology in deceased participants

H&E
Masson Trichrome
BSEP

Abnormal bile staining within hepatocytes and bile duct canaliculi observed
Extensive fibrosis observed
BSEP not present

Commonly observed pathology among participants1

- 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.
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
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.

IOPD is rapidly progressive and characterized by cardiomegaly, hepatomegaly, weakness and hypotonia.

LOPD is characterized by slowly progressive myopathy involving skeletal muscle.

Our initial target for treatment:

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

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

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

ERT is known to be immunogenic and can elicit antibodies that further impact effectiveness.

Long-term studies of LOPD patients on ERT show an initial positive effect followed by stabilization and then decline in functional measures.

Pompe clinician experts and patients highlight that a significant unmet need remains given disease progression despite ERT.

ERT: Enzyme replacement therapy; LOPD: Late-onset Pompe disease.
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\(^1\), avoiding the need for repeated infusions.

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


Figure 1a. Astellas proprietary image.

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

**Biweekly ERT**
Optional controlled ERT withdrawal with additional safety monitoring from ≥16 weeks after AT845 administration

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.

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

<table>
<thead>
<tr>
<th>SAFETY PROFILE</th>
<th>Cohort 1 (3 × 10^{13} vg/kg)</th>
<th>Cohort 2 (6 × 10^{13} vg/kg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>P 2002</td>
<td>P 2001</td>
</tr>
<tr>
<td>Follow-up time, weeks</td>
<td>37.1</td>
<td>27.3</td>
</tr>
<tr>
<td>All TEAE</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>1</td>
<td></td>
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<tr>
<td>Headache</td>
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<tr>
<td>Ageusia</td>
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<tr>
<td>ALT increased</td>
<td>1</td>
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<tr>
<td>AST increased</td>
<td>1</td>
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<tr>
<td>Decreased appetite</td>
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<td>Constipation</td>
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<tr>
<td>Abdominal distension</td>
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<td>Irritability</td>
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<td>Palpitations</td>
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<tr>
<td>Night sweats</td>
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<tr>
<td>Cold sweat</td>
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<tr>
<td>Dyspnea</td>
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<td>COVID-19</td>
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<td>Upper respiratory tract congestion</td>
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<tr>
<td>Malaise</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
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<td></td>
</tr>
</tbody>
</table>

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.
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

Individual participant data:
- P 2002 (3 x 10^{13} vg/kg)
- P 2001 (3 x 10^{13} vg/kg)
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.
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.

**POTENTIALLY TRANSFORMATIVE EFFICACY AND PATIENT NEED DRIVES OUR COMMITMENT TO GENE THERAPY**
ON THE FOREFRONT OF HEALTHCARE CHANGE