# PBGM01 Study in Infantile GM1 Gangliosidosis

## Interim Clinical Results from Cohorts 1-4 and Program Update of Imagine-1 Clinical Study

August 7, 2023

PassageBio

Life-transforming therapies

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# Welcome & Agenda

**Will Chou, M.D.**
Chief Executive Officer,
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**Mark Forman, M.D., Ph.D.**
Chief Medical Officer,
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**Samiah Al-Zaidy, M.D.**
Vice President, Clinical Development
Passage Bio

## Welcome

*Will Chou, M.D.*

## Executive Summary

*Mark Forman, M.D., Ph.D.*

## Imagine-1 Interim Clinical Results and Program Update

*Samiah Al-Zaidy, M.D.*

## Closing Remarks

*Will Chou, M.D.*

## Q&A

# Executive Summary

Mark Forman, M.D., Ph.D.

# PBGM01 is a Potentially Transformative Therapy for GM1 Gangliosidosis, a Rare, Underserved Disorder

## GM1 GANGLIOSIDOSIS

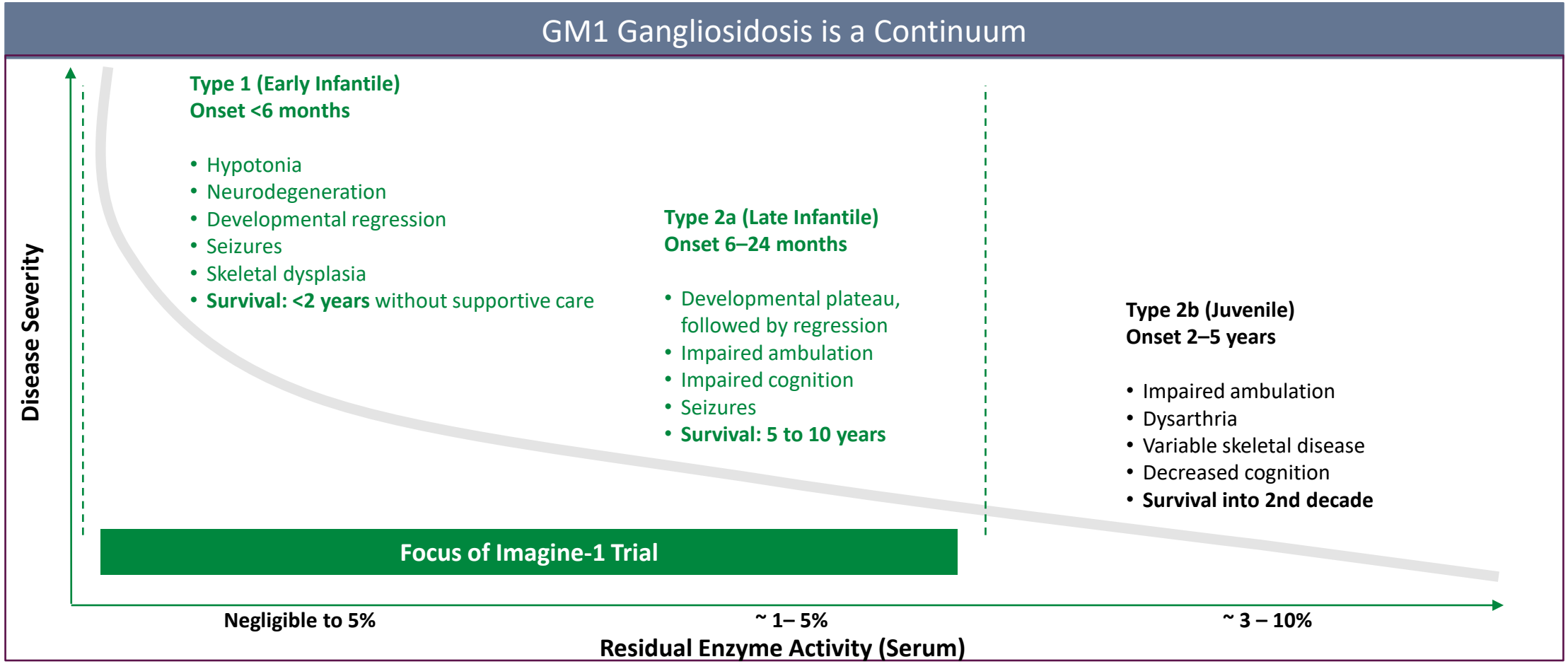
- Inherited lysosomal storage disease that leads to progressive damage to both the CNS and peripheral tissues
- Caused by loss-of-function mutations in the *GLB1* gene
- No approved disease-modifying therapies

## OUR APPROACH – PBGM01

- Next-generation, proprietary AAVhu68 capsid
- Delivers functional *GLB1* transgene encoding β-Gal enzyme to the brain and peripheral tissues through ICM delivery

# GM1 Gangliosidosis Disease Continuum

## Disease severity inversely related to residual β-Gal enzyme activity






Brunetti-Pierri N., Scaglia F. *Mol Genet Metab.* 2008;94(4):391-396. Jarnes JR, et al. *Mol Genet Metab*. 2017;121(2):170-179. Lang FM, et al. *Mol Genet Metab.* 2020;129(3):228-235. Regier DS, Tifft CJ. Rothermel CE. *GLB1*-related disorders. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews® [Internet].

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# Key Objectives for Imagine-1 Study

- Establish Safety Profile of PBGM01
- Determine Optimal Dose for Therapeutic Effect
- Understand PBGM01 Benefit Across Infantile GM1 Patient Populations

# Promising Interim Data from First 8 Treated Patients

- Favorable safety profile and well-tolerated
- Initial evidence of improved survival in study participants
- Dose-dependent increase in CSF β-Gal activity, with increase sustained up to 12-months post-dose
- Dose-dependent decrease in β-Gal substrate (GM1 ganglioside) in CSF, with Dose 2 able to achieve healthy control levels

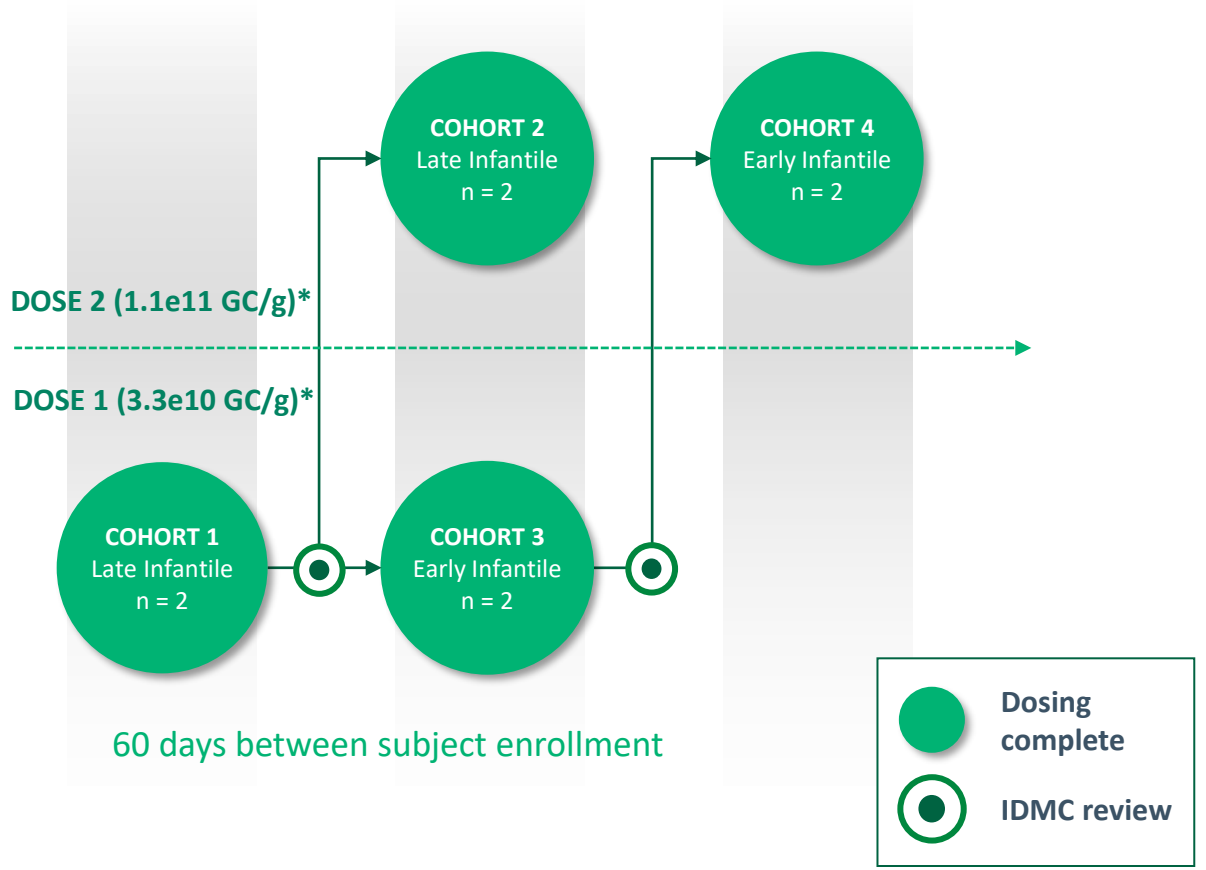
# Imagine-1 Interim Clinical Results

Samiah Al-Zaidy, M.D.

# Imagine-1: Global Phase 1/2 Trial with PBGM01

## Completed dosing of initial four cohorts evaluating two doses in early and late infantile GM1

| | |
|---|---|
| **Trial Design** | Phase 1/2, multi-center, open-label, dose escalation and confirmatory study |
| **Route of Administration** | Intra-cisterna magna (ICM) |
| **Vector** | AAVhu68 |
| **Immunosuppression** | Low dose steroids for 4 weeks then taper |
| **Duration** | Two years, with rollover into long-term follow-up study |
| **Primary Endpoints** | • Safety and tolerability<br>• Efficacy (confirmatory cohort) |
| **Biomarkers** | • β-Gal activity (CSF & serum)<br>• GM1 gangliosides (CSF)<br>• Other exploratory biomarkers |




10 * Genome copies per gram of estimated brain weight

# Imagine-1 Baseline Patient Characteristics

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 |
|---|---|---|---|---|---|---|---|---|
| **Diagnosis** | Late Onset | Late Onset | Early Onset | Late Onset | Early Onset | Late Onset | Early onset | Early onset |
| **Dose level received** | Dose 1 | Dose 1 | Dose 1 | Dose 2 | Dose 1 | Dose 2 | Dose 2 | Dose 2 |
| **Cohort** | 1 | 1 | 3 | 2 | 3 | 2 | 4 | 4 |
| **Gender** | Male | Male | Female | Female | Male | Male | Female | Male |
| **Onset of symptoms (months)** | 14 | 12 | 5 | 13 | birth | 12 | 4 | birth |
| **Chronological age at baseline (months)** | 14 | 31 | 15 | 18 | 6 | 17 | 7 | 6 |
| **DBS β-Gal activity (nmol/ml/hr)[(1)]** | 0.0 | 0.2 | 0.0 | 0.0 | 0.1 | 0.0 | 0.4 | 0 |
| **Genotype** | c.601C>T, c.601C>T | c.601C>T, c.1733AA>G | c.694dupC, c.694dupC | c.1370G>A, c.168C>G | c.1577dup, c.1577dup | c.1733A>G, c.802G>C | c.765G>C, c.841C>T | c.176G>A, c.176G>A |



DBS, dry blood spot.

[1]Lower limit of normal: <5.0 nmol/mL/h..

# Imagine-1 Study: Cohorts 1-4 Safety & Tolerability

## PBGM01 was well tolerated and had a favorable safety profile at interim analysis*

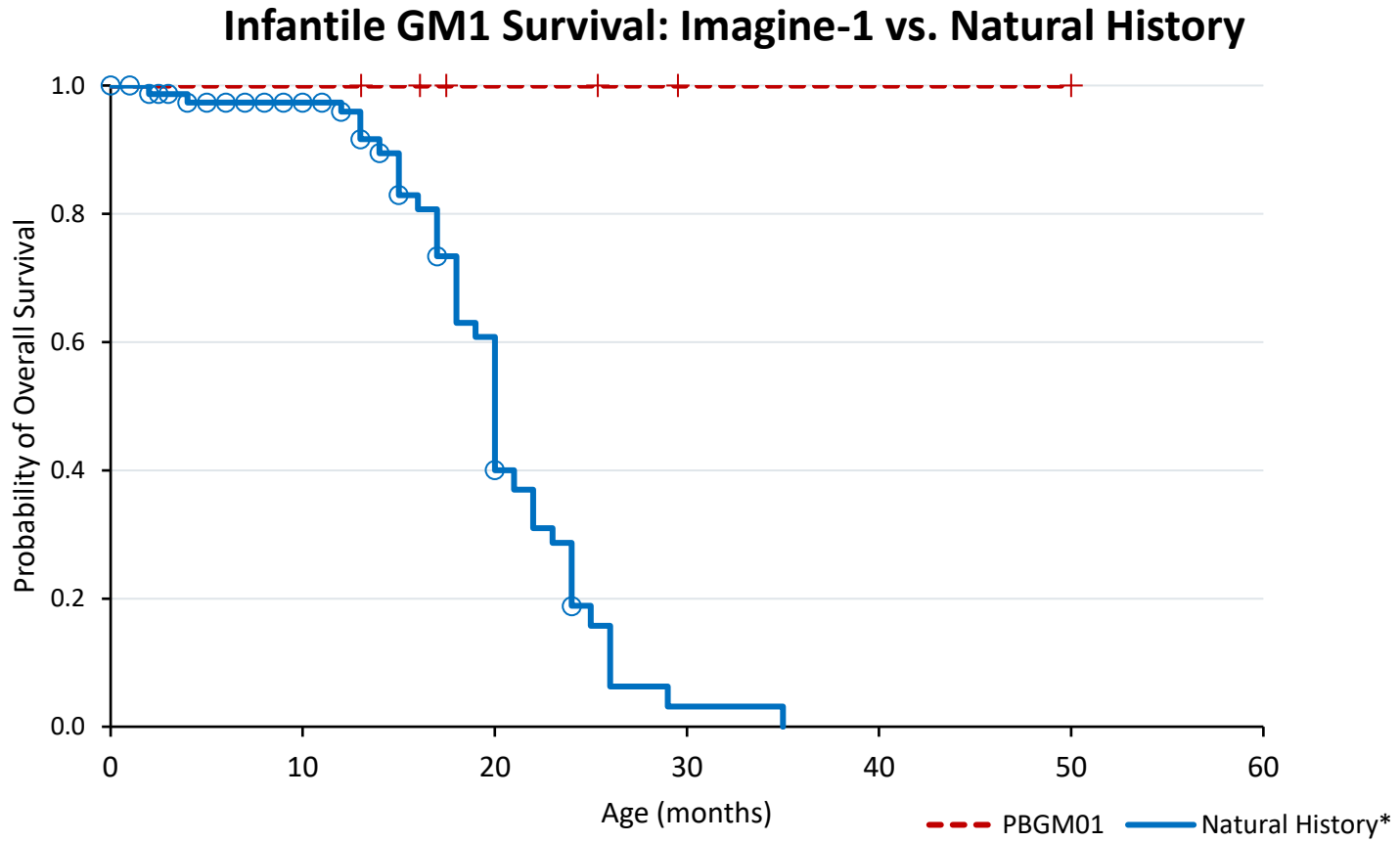
- No treatment-related serious adverse events (SAEs)
- All treatment-related adverse events (AEs) were mild-to-moderate in severity
- No clinically significant changes in liver function requiring intervention
- No evidence of DRG toxicity, as measured by nerve conduction studies
- No complications related to ICM administration
- Favorable immunological profile with no clinically significant immune responses[1]



*Patient follow-up ranges from 8 to 28 months post-dosing as of a data cutoff of June 26, 2023

[1] No patients required adjustment to immunosuppression regimen.

# Initial Evidence of Improved Survival Among Study Participants vs. Natural History




| Number of subjects at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Natural History* | 154 | 139 | 82 | 4 | 0 | 0 | 0 |
| Imagine-1 | 6 | 6 | 3 | 1 | 1 | 1 | 0 |

## Key Points

**Infantile GM1 Natural History:**

- Mean survival: 18.9 months
- No survival beyond 35 months

**Imagine-1:**

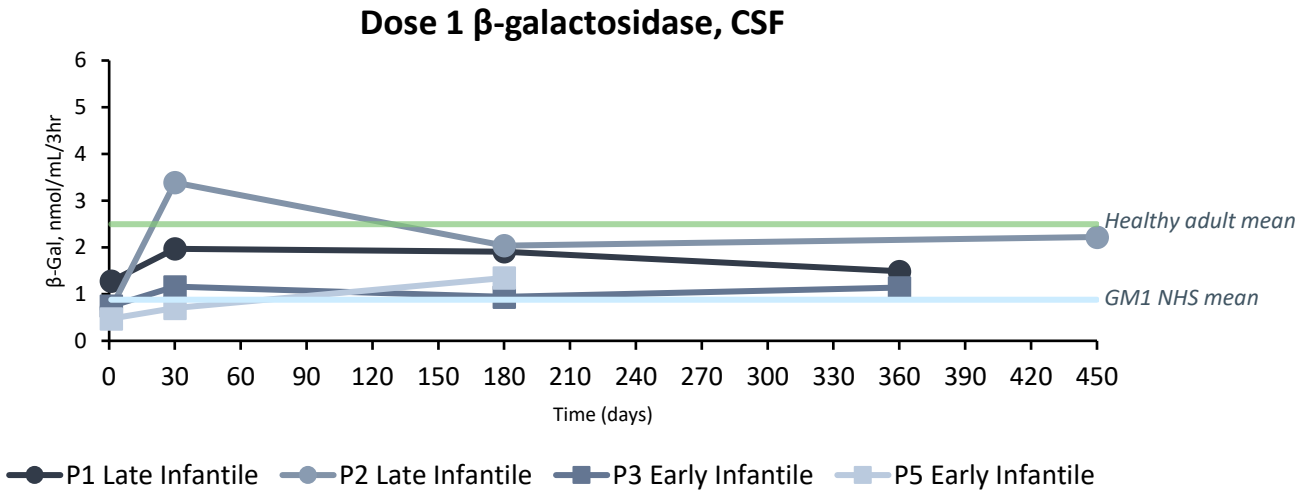
- 100% survival in subjects > 20 months of age (n=3) that received PBGM01

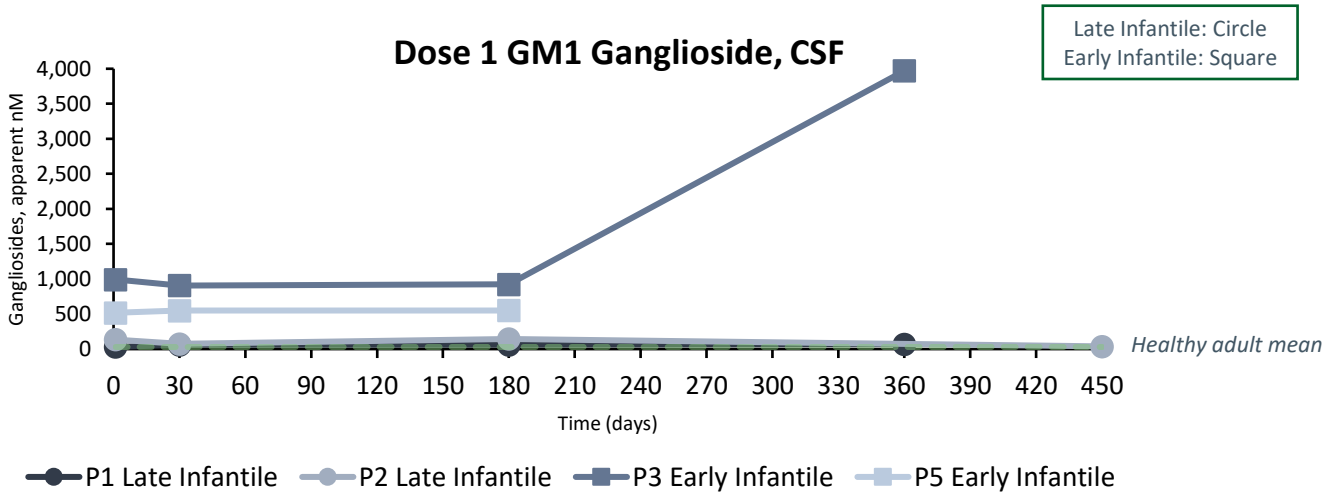


* From Lang FM, et al. *Mol Genet Metab*. 2020;129(3):228-235. Lang et al meta-analysis defined GM1 Type I as disease onset ≤12 months of age (n=154)

# Dose 1 Exhibited Modest Effects on Key CSF Biomarkers






## Key Points – Dose 1

**β-Gal**

- Dose 1 PBGM01 resulted in modest (1.5 to 4.8x) increase in CSF β-Gal activity relative to baseline at day 30
- No patients maintained a normal adult level of β-Gal activity

**Gangliosides**

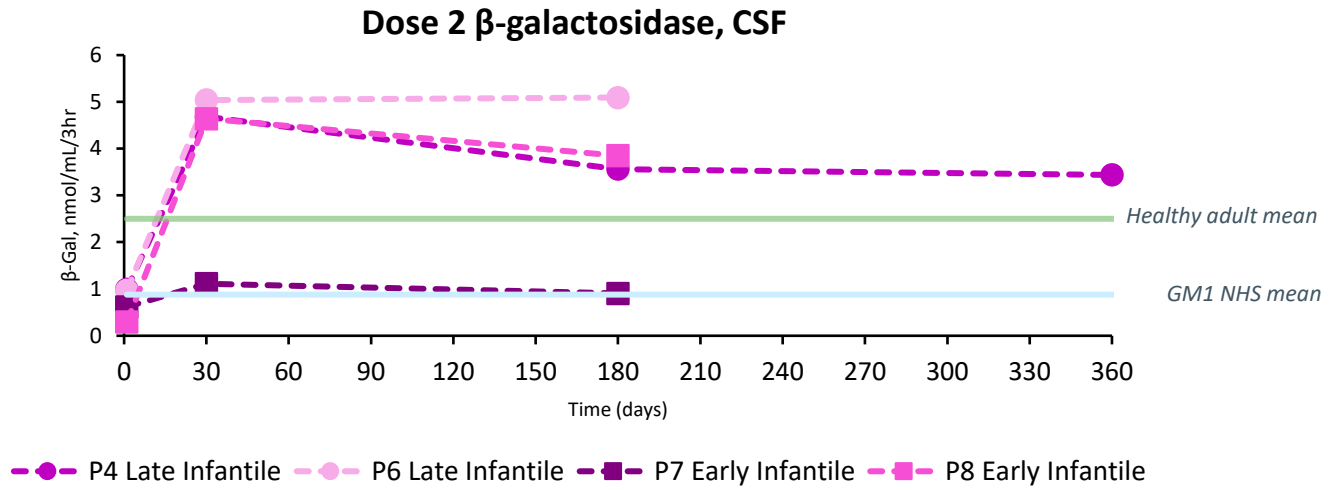
- Dose 1 PBGM01 did not result in reduction of GM1 gangliosides
- Patient 3 (modest increase in β-Gal activity): increased GM1 ganglioside levels were associated with clinical worsening

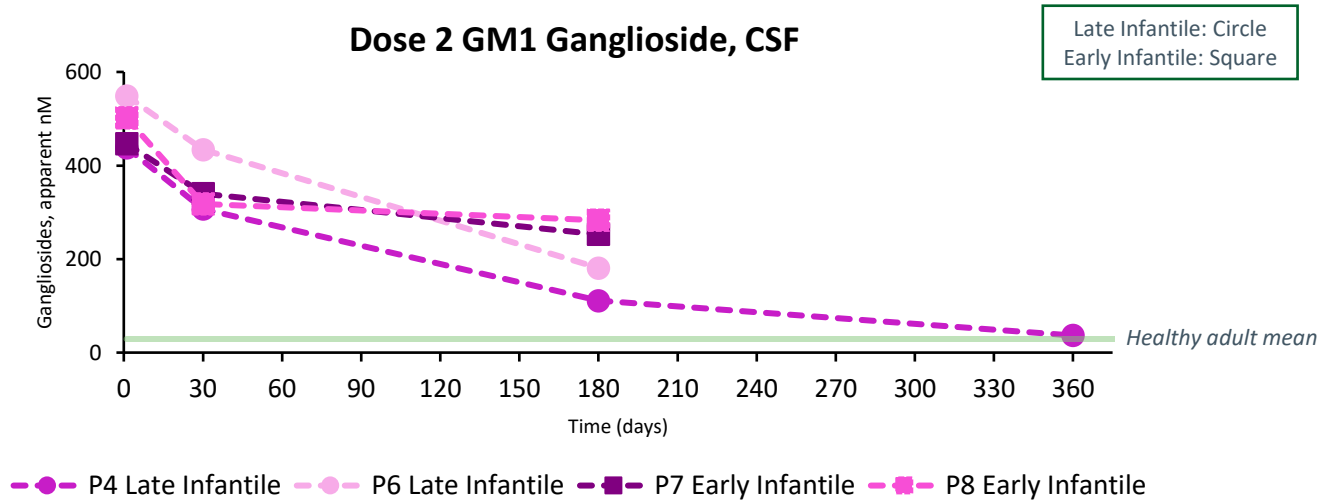


CSF= Cerebrospinal Fluid

# Dose 2 Resulted in Robust Increases in CSF β-Gal Activity and Decreases in GM1 Gangliosides

Imagine-1




## Key Points – Dose 2

**β-Gal**

- In 3 of 4 children, Dose 2 PBGM01 resulted in CSF β-Gal **exceeding average levels seen in healthy adults** and GM1 Natural History Study (NHS)*
  - 4.7x to 16.1x increase in CSF β-Gal activity vs. baseline at day 30 (n=3)
- Increased CSF β-Gal activity **can be sustained for up to 12 months**

**Gangliosides**

- GM1 gangliosides achieved **normal adult levels** at 1-year post-dose
  - Gangliosides continue to decline over time in all patients

*GM1 gangliosides hypothesized to mediate CNS manifestations of disease[1]*



1. Lang FM et al., Mol Genet Metab.2020;129:228-235; CSF= Cerebrospinal Fluid

*Based on preliminary data from University of Pennsylvania's ODC Natural History Study (NHS) (NCT04041102); value range (0.3-1.81 nmol/mL/3hr)

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# Summary

## SAFETY & CLINICAL DATA

PBGM01 continues to have a favorable safety profile in both early and late infantile GM1

- No serious AEs related to study treatment
- No evidence of DRG toxicity
- No complications related to ICM injection

PBGM01 shows initial evidence of improved survival vs. historical controls

## BIOMARKER DATA

PBGM01 can achieve healthy control levels of missing enzyme and deleterious substrate

- In 3 of 4 patients, Dose 2 resulted in CSF β-Gal activity that exceeded average levels seen in healthy adults and GM1 Natural History Study*
- Reduction in GM1 gangliosides following Dose 2 has ability to achieve normal adult levels

PBGM01 has demonstrated durability up to 12 months after treatment

Dose-dependent pharmacodynamic effects

AEs=adverse events; ICM=intra-cisterna magna

*Based on preliminary data from University of Pennsylvania's ODC Natural History Study (NHS) (NCT04041102).

# Program Update

Samiah Al-Zaidy, M.D.

# Advancing Program to Evaluate Higher Dose (Dose 3)

## Potential for an incremental benefit with dose escalation

### Preclinical Rationale for Dose Escalation

- Expectation of further increase in β-Gal activity and improved lysosomal function
- Dose 3 (2.2 x $10^{11}$ GC/g) maintains safety window to maximum dose tested in NHP toxicology study

| ***GLB1 -/-* Mice** | **Minimum Effective Dose Study[1]** | | | |
|---|---|---|---|---|
| ICV Dose (GC): | **4.4 x $10^9$** | **1.3 x $10^{10}$** | **4.4 x $10^{10}$** | **1.3 x $10^{11}$** |
| **Elevated β-Gal activity – Brain** (Fold increase vs normal control*) | 0.6 | 0.8 | 2.6 | 3.8 |
| **Elevated β-Gal activity – CSF** (Fold increase vs normal control*) | 1.4 | 1.4 | 4.1 | 6.8 |
| **Improved lysosomal function – Brain** Reduced LAMP1 staining | X | ✓ | ✓✓ | ✓✓✓ |
| **GC/g Brain Mass Equivalent** | **1.1 x $10^{10}$ (MED)** | **3.3 x $10^{10}$** | **1.1 x $10^{11}$** | **3.3 x $10^{11}$** |
| **Imagine-1 Dose** | | **Dose 1** | **Dose 2** | **Dose 3** |

### Clinical Rationale for Dose Escalation

- Absence of dose-limiting toxicities in both Early and Late Infantile GM1
- Dose-dependent increase in CSF β-Gal
- Dose-dependent decrease in CSF GM1 gangliosides
- Achievement of normal adult levels required 1 year

### Drug Product Supply

- Additional cohorts can leverage existing product inventory

*Normal control = age-matched, vehicle-treated *GLB1* +/- littermate

[1] Assays evaluated at 150 and/or 300 days post-dose

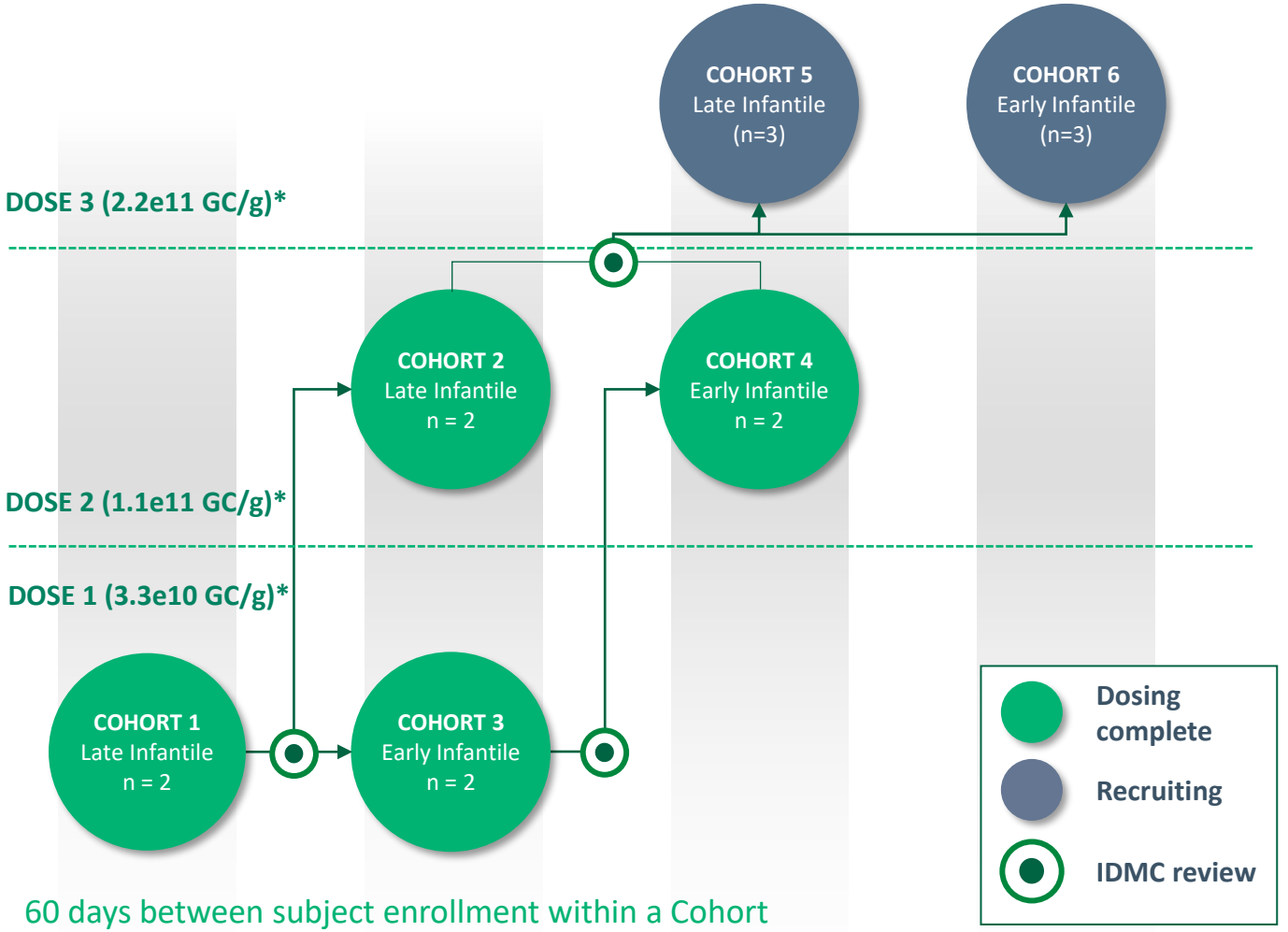
*Abbreviations:* β-Gal, beta-galactosidase; CSF, cerebrospinal fluid; d, day; GC, genome copies; GLB, galactosidase beta-1 gene; ICV, intra-cerebroventricular; MED, minimum effective dose; NHP, non-human primate; NT, not tested

# PBGM01 – Amended Protocol

## Addition of 2 cohorts to explore dose 2x higher than Dose 2

### Cohorts 5 & 6 (Dose 3) Status Update

- Concurrent dosing of Early and Late Infantile GM1
- Updated Inclusion/Exclusion Criteria to enroll children with earlier stage of disease
  - *Early Infantile:*
    - Decreased age at enrollment from 4-24 months to 1-12 months
  - *Late Infantile:*
    - Decreased upper age limit at enrollment from 36 months to 24 months
    - Added requirement of minimum function of sitting without support
- Amended protocol approved in multiple countries including United States, Canada, Brazil and Turkey
- **Treated first patient at Dose 3 in July, with multiple additional patients being evaluated for study eligibility**




60 days between subject enrollment within a Cohort

# Closing Remarks

Will Chou, M.D.

# Imagine-1 Progressing Well Against Key Study Objectives

## Establish Safety Profile of PBGM01

- ✓ Favorable safety and immunological profile at Dose 1 & 2
  - No SAEs related to study treatment
  - No evidence of DRG toxicity
  - No complications related to ICM injection

## Determine Optimal Dose for Therapeutic Effect

- ✓ Dose 2 able to achieve healthy control levels of CSF β-Gal activity and GM1 gangliosides
- ✓ Biomarker changes were durable for up to 12 months
- ✓ Dose-dependent preclinical effect translated into clinic

***Dose 3 has potential to further improve biomarker response and therapeutic effect***

## Understand PBGM01 Benefit Across Infantile GM1 Patient Populations

- ✓ PBGM01 shows initial evidence of improved survival vs. historical controls

***Recent study modifications target patients earlier in disease progression, thereby maximizing the potential for clinical benefit***

# PBGM01 Program Anticipated Next Steps

## Complete enrollment of Cohorts 5 and 6

- Treated first patient at Dose 3 in July
- Plan to share initial safety and biomarker data from Dose 3 by mid-2024

## Determine optimal dose for confirmatory study

- Analyze data from Cohorts 1-6 to establish safety/tolerability profile and therapeutic potential of each dose

## Continue engagement with regulatory authorities

- Continued interactions with regulatory authorities as data set matures to align on design of confirmatory study and pathway to Biologics License Application

# Q&A

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