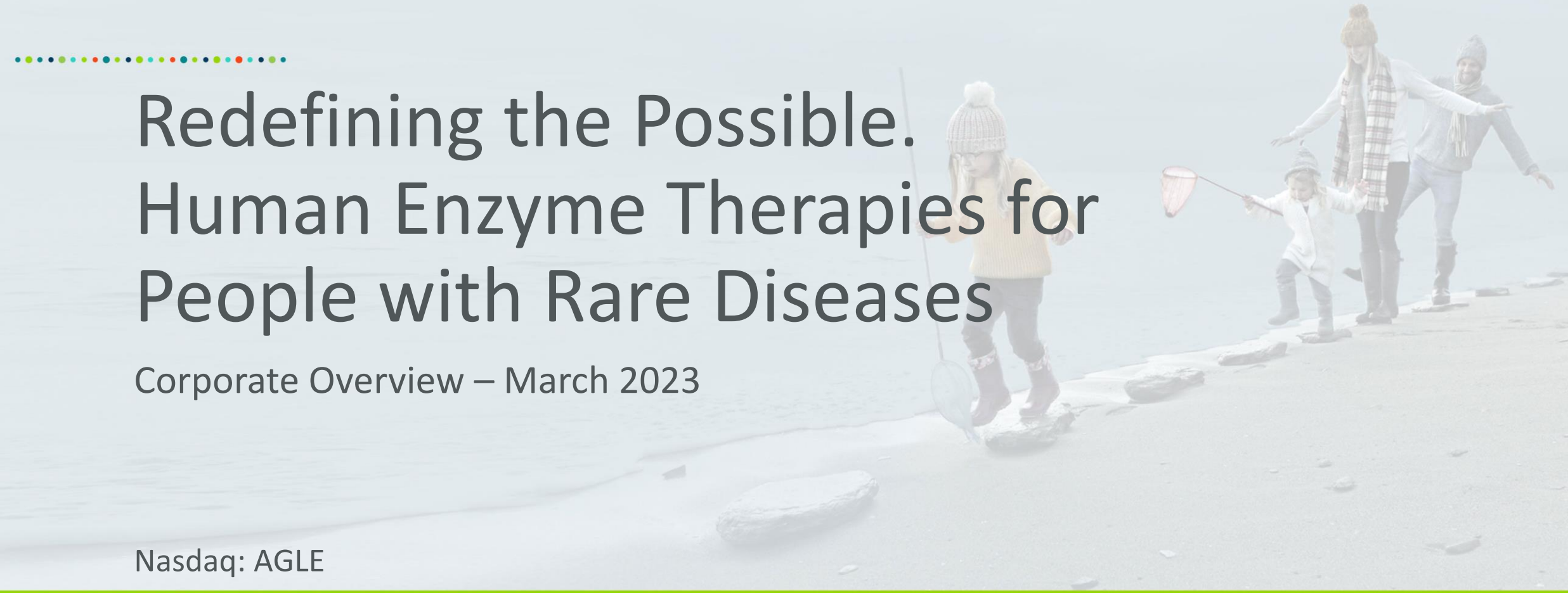
Redefining the Possible. Human Enzyme Therapies for People with Rare Diseases

Corporate Overview – March 2023



Nasdaq: AGLE

Forward Looking Statements

This presentation and the accompanying oral presentation contain “forward-looking” statements that are based on our management’s beliefs and assumptions and on information currently available to management. Forward-looking statements include all statements other than statements of historical fact contained in this presentation, including information concerning our current and future financial performance, business plans and objectives, current and future clinical and preclinical development activities, timing and success of our ongoing and planned clinical trials and related data, the timing of announcements, updates, results of our clinical trials and related data, our ability to obtain and maintain regulatory approval, the potential therapeutic benefits, safety profile and economic value of our product candidates, potential growth opportunities, financing plans, use and adequacy of financing plans, the length of time that we believe our existing cash resources will fund operations, competitive position, industry environment and potential market opportunities.

Forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors including, but not limited to, those related to the success, cost and timing of our product candidate development activities and ongoing and planned clinical trials; our plans to develop and commercialize targeted therapeutics, including our lead product candidates pegzilarginase and pegtarviliase and our other product candidates; the design, progress of patient enrollment and dosing in our clinical trials; the ability of our product candidates to achieve applicable endpoints in clinical trials; the safety profile of our product candidates in clinical trials; the potential for data from our current and future clinical trials to support a marketing application, as well as the timing of these events, including data for our Phase 1/2 trial of pegtarviliase in Classical Homocystinuria, the MAA for pegzilarginase in Europe, and potential resubmission of a BLA for pegzilarginase in the U.S.; the potential for preclinical studies to be predictive of current or future clinical trials; our ability to obtain funding for our operations, development and commercialization of our product candidates; the expected impact of macroeconomic conditions, including inflation and rising interest rates, on our operations and clinical development activities; the timing of and our ability to obtain and maintain regulatory approvals; our ability to obtain regulatory approval for, and commercialize, pegzilarginase, and recognize milestone and royalty payments under our licensing and supply agreement with Immedica; the potential for expedited development and review of pegtarviliase and pegzilarginase as a result of their regulatory designations; the number of possible treatment candidates in potential addressable markets of our product candidates; the rate and degree of market acceptance and clinical utility of our product candidates; the size and growth potential of the markets for our product candidates, and our ability to serve those markets; our commercialization, marketing and manufacturing capabilities and strategy; future agreements with third parties in connection with the potential commercialization of our product candidates; our expectations regarding our ability to obtain and maintain intellectual property protection; our dependence on third party manufacturers; our ability to develop our own commercial manufacturing facility; the success of competing therapies that are or may become available; our ability to attract and retain key scientific or management personnel; and our estimates regarding expenses, future revenue, capital requirements, the length of time that we believe our existing cash resources will fund operations, and needs for additional financing.

Moreover, we operate in a very competitive and rapidly changing environment, and new risks may emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed herein may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Further information on these and other factors that could affect these forward-looking statements is contained in our most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and other reports filed by the SEC. You should not rely upon forward-looking statements as predictions of future events. Although our management believes that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances described in the forward-looking statements will be achieved or occur. We undertake no obligation to publicly update any forward-looking statements, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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Our vision is to redefine the possible, pioneer bold science with human enzymes and deliver groundbreaking medicines that transform lives.

We are on a mission to change lives by bringing innovative therapies to underserved rare disease communities.

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Redefining the Possible with Human Enzyme Therapies

Patient-Focused Approach

By working closely with the patient community, we believe we can:

- Understand the patient and HCP perspective and experience
- Design clinical trials with the patient perspective in mind
- Help make patients' and families' voices heard
- Discover gaps in education and resources and help to fill them

Strong Scientific Foundation

With engineered human enzymes, we believe we can:

- Impact underlying key metabolites that drive clinical manifestations
- Address unmet medical needs with rationally-designed characteristics (e.g., half-life, specificity)
- Develop therapies for a range of rare metabolic diseases

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Aeglea's Human Enzyme Therapies for Rare Metabolic Diseases

Program	Research	Phase 1/2	Phase 3	Regulatory Review	Addressable Market	Geographic Rights
Pegtarviliase Homocystinuria					~25,000 Patients[1]	Worldwide rights
Pegzilarginase Arginase 1 Deficiency				MAA Validated by EMA[4]	>2,500 Patients[2]	Retain rights outside of Europe and Middle East[3] Immedica pharma
Preclinical Programs Including Cystinuria						Worldwide rights

[1] ~25,000 represents estimated treatment candidates in 38 addressable markets of Classical Homocystinuria based on results of U.S. ICD-10 claims analysis extrapolated to global markets; all figures rounded. Estimates also based on internal assumptions and data from Sellos-Moura et al 2020 [2] Catsburg C et al 2022 ; Diez-Fernandez et al. Mutations and common variants in the human arginase 1 (ARG1) gene: impact on patients, diagnostics and protein structure considerations. Hum Mutat. 2018 Aug;39(8):1029-10502 [3] Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and several countries in the Middle East (European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain and Oman) [4] Market Authorisation Application (MAA) validated by the European Medicines Agency (EMA) and currently under review; Company in dialogue with the U.S. Food and Drug Administration following Refusal to File Letter

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Highlights and Upcoming Milestones

Pegtarviliase in Homocystinuria:

- Fast Track Designation received from FDA
- Currently dosing in cohort 3 at 1.35 mg/kg once weekly in Phase 1/2 clinical trial

Pegzilarginase in Arginase 1 Deficiency:

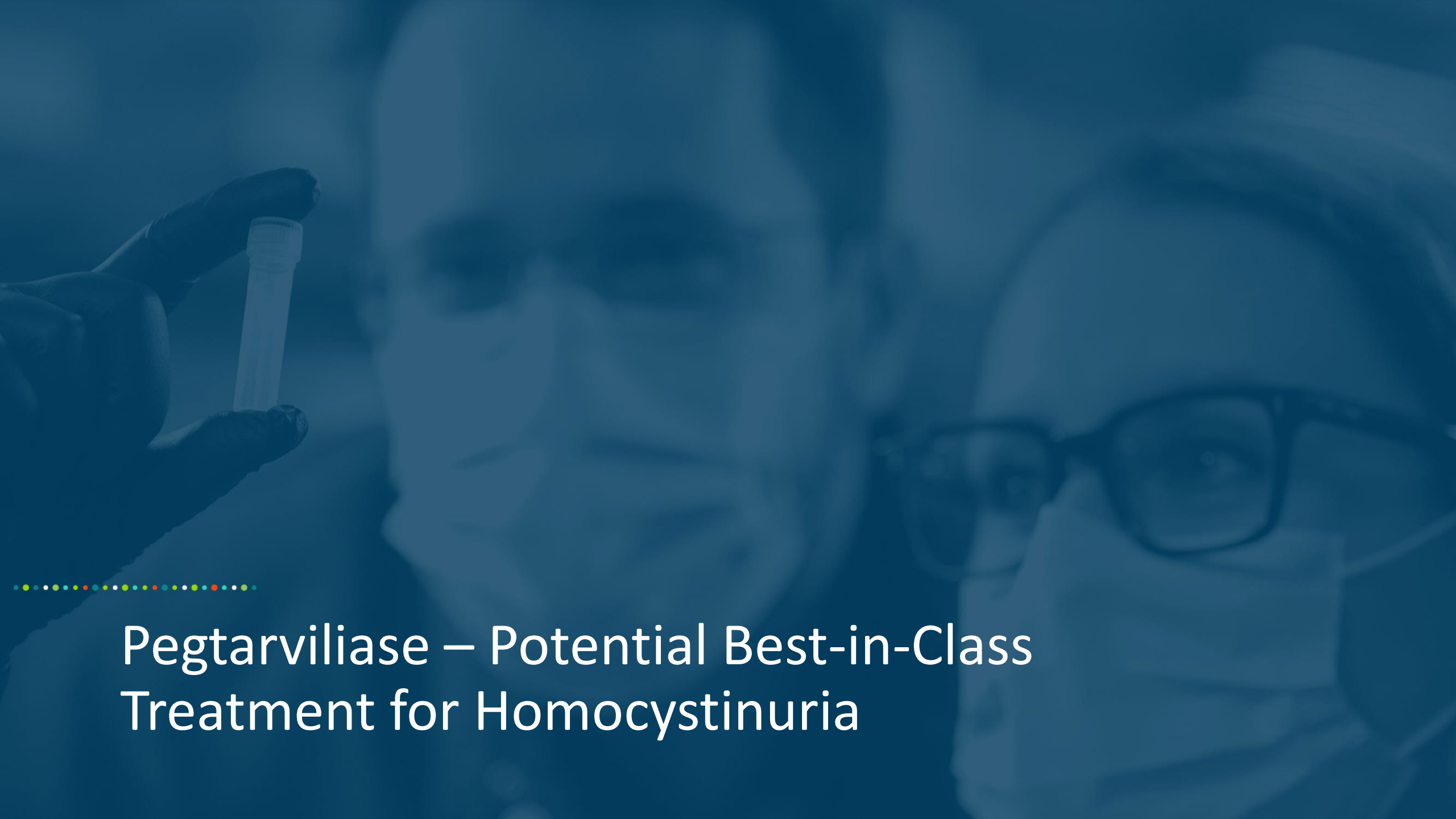
- MAA under review with EMA, potential decision on approval in late 2023
- Continuing to engage with FDA to identify potential path to BLA resubmission

Corporate:

- Jeff Goldberg appointed CEO in November 2022 – highly experienced executive with strong operational and rare disease background
- $57.3 million in cash and available funds[1] as of December 31, 2022; projected runway into fourth quarter of 2023

[1] Includes cash, cash equivalents, marketable securities, and restricted cash

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Pegtarviliase – Potential Best-in-Class Treatment for Homocystinuria

Classical Homocystinuria: A Rare Metabolic Disorder With Serious and Potentially Deadly Complications

Classical Homocystinuria (HCU)

Also known as cystathionine beta synthase (CBS) deficiency, Classical Homocystinuria is a serious and progressive metabolic disorder characterized by elevated levels of the amino acid homocysteine.

- There are no approved disease-modifying treatments for HCU, i.e., addressing high levels of homocysteine[1]
- Toxic levels of homocysteine can lead to sudden catastrophic events, including death
- Manifestations, which are often irreversible, can occur in early childhood and worsen over time

Serious Disease Complications

Eyes
Lens dislocation, glaucoma, severe near-sightedness

Nervous System
Intellectual and developmental delays, behavioral abnormalities, seizures

Vascular
Life-threatening thrombotic events, heart attack, stroke

Skeletal
Long bone (Marfanoid) features, skeletal deformities, osteoporosis

[1]Betaine, approved by the FDA in 1996, can lower homocysteine levels in the blood through remethylation to methionine but does not metabolize homocysteine and clear it from the body

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Patients with Classical HCU Live With Both Disease and Treatment Burden

- Compliance with severe dietary restrictions and amino acid supplementation is extremely challenging and represents a lifelong burden
- Vitamin B6 is largely ineffective at lowering tHcy to guidance levels for the majority of patients
- Betaine can be associated with both safety and tolerability issues such as hypermethioninemia, nausea, gastrointestinal distress, and body odor



One patient's daily protein supplement, which is only one portion of his treatment regimen

> *"For patients with Classical Homocystinuria, [the biggest challenge] would be compliance with diet."*
>
> - U.S. Key Opinion Leader

> *"To get the family to cope with a very difficult life, and to have them compliant for life … is a very big challenge."*
>
> - EU Key Opinion Leader

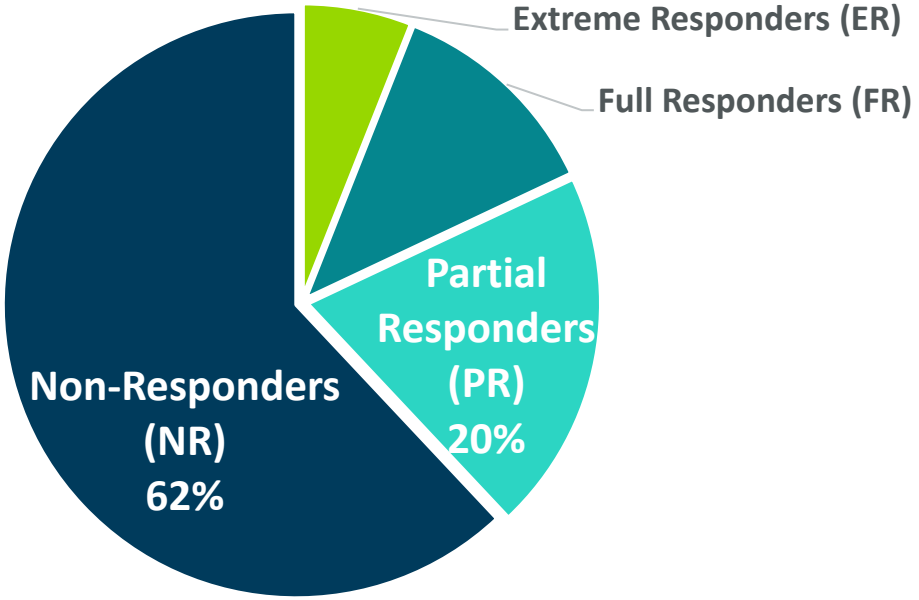
With Persistently High Total Homocysteine Levels, Patients Remain at Risk for Serious and Life-Threatening Complications

tHcy = total homocysteine

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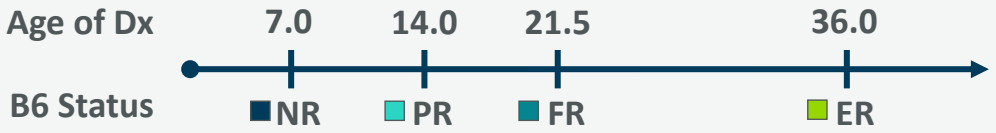
Classical HCU: A Sizeable Patient Population at Serious Risk of Severe Complications

Classical HCU by B6 Responsiveness[2]



- Over 80% of patients are unable to achieve total homocysteine levels <50 µM with B6 alone, the definition of B6 responsiveness
- This translates into an estimated **~25,000** treatment candidates in global addressable markets,[1] approximately **8,500** of whom are in the U.S., EU4, and UK

Average Age of Diagnosis…[2]



Although Non-Responders and Partial Responders are generally diagnosed earlier in life, that diagnosis typically occurs several years following presentation of initial symptoms

…And Often Occurs After Severe Complications[2,3]

At time of diagnosis:

79% Non-Responders and Partial Responders have experienced a **lens dislocation**

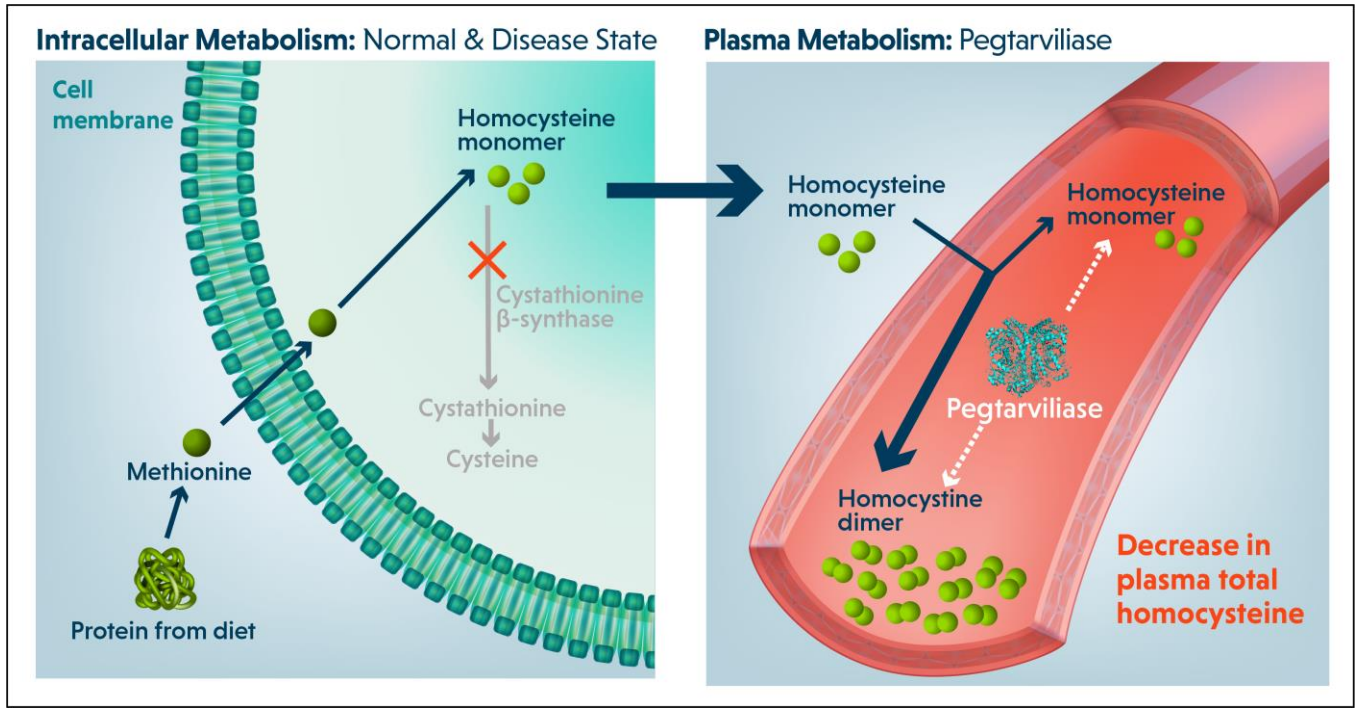
29% Non-Responders and Partial Responders have experienced a **thromboembolic event**

[1] Data on file. Adapted from Sellos-Moura et al 2020. [2] Kozich, Sokolova, Morris, et al. 2021. [3] Mudd, Skovby et al. 1985.

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Pegtarviliase: An Innovative Enzyme Approach to Lowering Homocysteine

Depiction of Normal and Therapeutic Metabolism



Pegtarviliase Mechanism

Engineered Cystathionine γ-Lyase (CGL) enzyme mutated to change its native substrate specificity from cystathionine to both homocysteine and its dimer

- Concentration gradient drives homocysteine out of tissues and into plasma
- Equilibrium in plasma favors dimer over monomer
- Flux enables further metabolism of both monomer and dimer

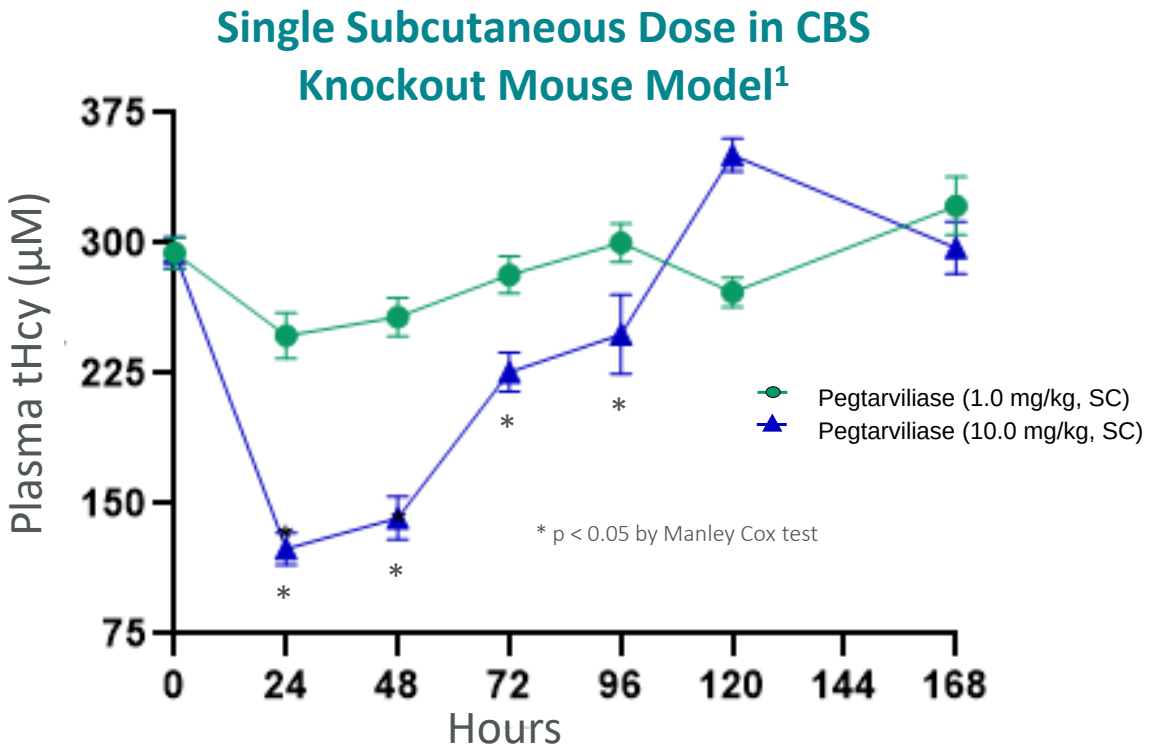
Therapeutic Rationale

- Elevated levels of plasma total homocysteine increase risk for disease manifestations[1]
- Reduction of plasma total homocysteine has been correlated with reduced risk of developing disease manifestations[2]
- Generally accepted aim of treatment is to lower the plasma total homocysteine concentration below certain thresholds to reduce risk of disease-related events

[1]Mudd, Skovby et al. 1985, Al-Dewik, Ali et al. 2019; [2]Mudd, Skovby et al. 1985, Wilcken and Wilcken 1997, Yap and Naughten 1998

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Pegtarviliase Treatment Resulted in Dose-Dependent Response and Statistically Significant Lowering of Homocysteine in Mouse Model



Experimental Design:

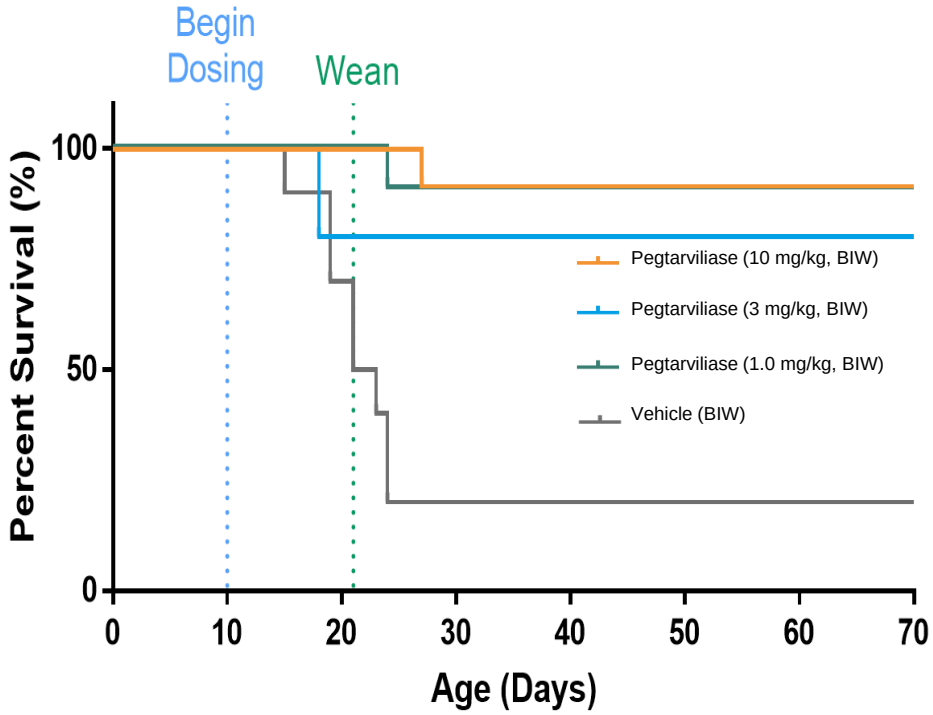
- 10-day old CBS knockout mice were dosed with pegtarviliase twice per week for 5 weeks to ensure they were able to grow to sufficient size for future blood sampling
- Prior to a single subcutaneous dose of pegtarviliase, there was a two-week wash out
- To ensure accurate tHcy assessment, an inhibitor of pegtarviliase was used in sample collection to block further in vitro metabolism of tHcy[2]

[1] Daige C. et al. Poster presented at ASHG 2020 Virtual Meeting. [2] Thornloe K. et al. Poster presented at ACMG 2022 Meeting; tHcy = total homocysteine; SC = subcutaneous

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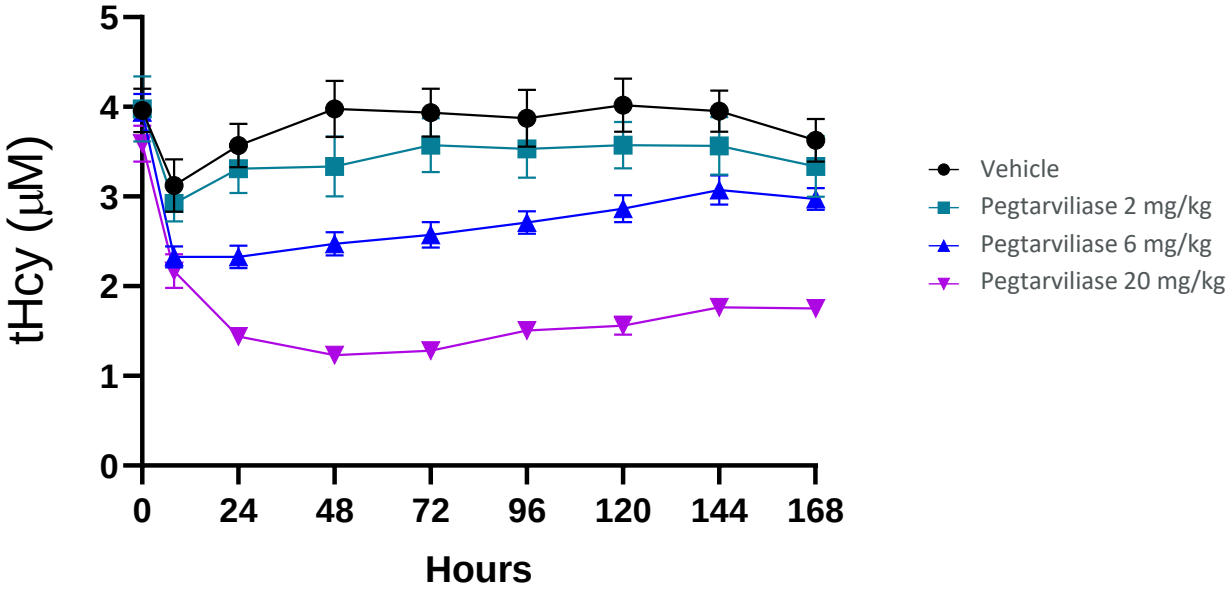
Preclinical Data Support Once-Weekly Dosing of Pegtarviliase

Significant Survival Benefit in Knockout Mouse[1,2]



- Significant survival benefit with pegtarviliase at 1 mg/kg twice per week (BIW)
- Twice-weekly dosing in mice typically translates to once-weekly dosing in humans

Pharmacological Effect on Homocysteine Levels in Normal Animals



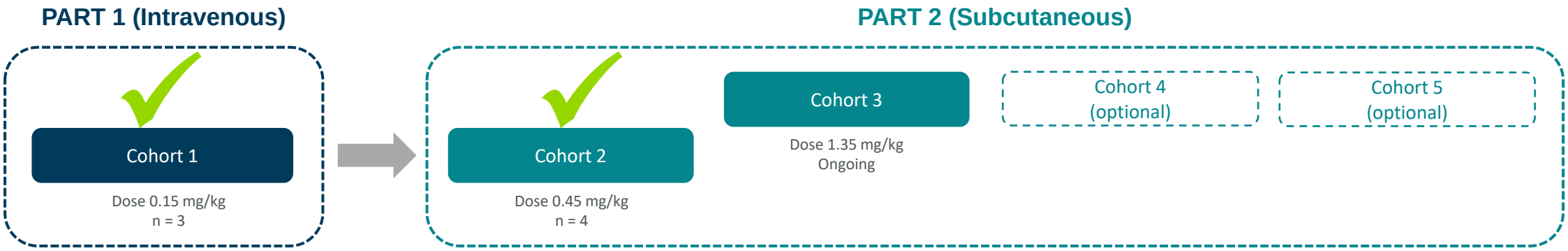
- Substantial decreases in homocysteine after single subcutaneous dose in toxicology studies with cynos (above) and rats (data not shown)

[1] Daige C. et al. Poster presented at ASHG 2020 Virtual Meeting. [2] Mice were maintained on betaine until weaning; tHcy = total homocysteine

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Phase 1/2 Clinical Trial to Generate Proof-of-Concept and Path to Pivotal Trial



Endpoints & Design

- Safety and tolerability
- Pharmacokinetics
- Reduction in plasma homocysteine levels
- 4 once weekly doses

Key Inclusion Criteria

- Classical HCU diagnosis
- Plasma homocysteine ≥50 µM with documented history of plasma homocysteine ≥80 µM
- ≥12 years of age (≥18 years of age in U.S. and certain Australian sites)

Continuing to Dose Patients in Cohort 3

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Advancing a Potential Best-in-Class Therapy for Classical HCU Patients

Preparing for Rapid Transition to Phase 3 Pivotal Trial

- Data from cohorts 1 through 3 may be sufficient for discussions with FDA on pivotal trial design
- Manufacturing at commercial scale
- Stable, high-concentration liquid formulation
- Engagement with the patient and HCP communities to educate and increase awareness
- Orphan Disease, Fast Track and Rare Pediatric Disease designations for Homocystinuria

Addressing an Unmet Need While Focusing on Patient Convenience

- Efficacy: cohort 1 showed reduction in total homocysteine levels in all patients
- Safety: Adverse events have been mild to moderate in data gathered to date
  - Toxicology data indicates a large dosing window
- Potential for convenience of a single once-weekly injection at home

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Pegzilarginase for Arginase 1 Deficiency

Arginase 1 Deficiency (ARG1-D) Disease Overview

ARG1-D is a serious, progressive disease with early mortality and high unmet medical need. It is caused by a mutation in the arginase 1 enzyme, resulting in persistently high levels of arginine.

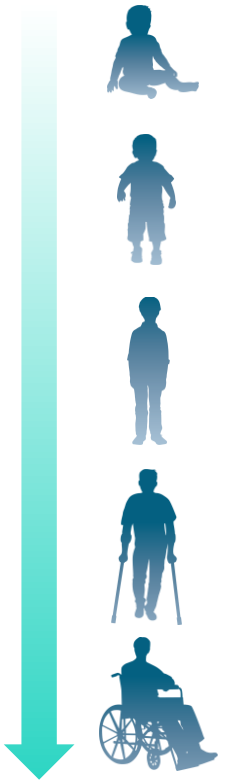
Current Standard of Care

- Focused on lowering plasma arginine levels and controlling hyperammonemia with:
  - Severe dietary protein restriction
  - Amino acid supplementation
  - Ammonia scavengers
- Ineffective at controlling plasma arginine levels

Significant Unmet Need

- High arginine levels
- Severe and progressive disease with early mortality
- Easily diagnosed but often missed due to lack of awareness
- No approved therapies to address high arginine levels

The Progressive Impact of Persistently High Plasma Arginine[1-4]



Infancy[2-4,7,8]

- Initial 6-12 months may be uneventful
- May present with seizures, episodes of hyperammonemia: irritability, feeding difficulties, poor appetite, nausea/vomiting, decreased alertness

Toddlerhood (2-4 years)[2,3,7-9]

- Spasticity in lower limbs (toe walking)
- Seizures, avoidance of protein is common and intellectual disability

Childhood (5-10 years)[2,3,5,6,9]

- Progressive spasticity and growth impairment
- Declining neuromotor and intellectual capabilities
  - Increasing dependence on walking aids
  - Loss of mobility
  - Decrease/loss of vocabulary/language

Adolescence (11-17 years)[2,3,5,10]

- Potential loss of ambulation and bowel/bladder control
- Severe intellectual disability

Adulthood (18+ years)[2,3,11,12]

- Continued decline with increasing disability that may result in early mortality

[1] Diez-Fernandez C, et al. Hum Mutat. 2018;39:1029-1050. [2] Carvalho DR, et al. Pediatr Neurol. 2012;46:369-374. [3] Crombez EA, Cederbaum SD. Mol Genet Metab. 2005;84:243-251. [4] De Deyn PP, et al. Hyperargininemia: a treatable inborn error of metabolism. In: Guanidino Compounds in Biology and Medicine. London, UK: John Libbey Company Ltd.; 1997:53-69. [5] Prasad A, et al. J Child Neurol. 1997;12:301-309. [6] Amayreh W, et al. Dev Med Child Neurol. 2014;56:1021-1024. [7] Scaglia F, Lee B. Am J Med Genet C Semin Med Genet. 2006;142C:113-120. [8] Sin YY, et al. J Mol Med (Berl). 2015;93:1287-1296. [9] Cai X, et al. Medicine (Baltimore). 2018;97:e9880. [10] Schlune A, et al. J. Amino Acids. 2015;47:1751-1762. [11] Sun A, et al. Arginase deficiency. In: Adam MP, et al, eds. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2020. [12] Diaz GA, et al. Poster presented at: 13th European Paediatric Neurology Society (EPNS) Congress; September 17-21, 2019; Athens, Greece. Poster P06-34.

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Pegzilarginase Program Overview

Pegzilarginase is a novel recombinant human enzyme engineered to lower arginine levels

Commercial Opportunity

- >2,500 patients in global addressable markets[1]
- High unmet medical need
- No approved therapies to address high arginine levels

Regulatory Designations

- U.S. Rare Pediatric Disease (PRV eligible)
- Breakthrough Therapy
- U.S. Orphan Drug
- EU Orphan Drug

MAA Under Review with EMA, Potential Decision on Approval in Late 2023

First Clinical Program Ever Conducted in ARG1-D

PEACE Phase 3 Clinical Trial

- First placebo-controlled trial ever conducted in ARG1-D
  - Pegzilarginase reduced arginine levels by 76.7%, normalized arginine levels in 90.5% of patients
  - Positive trend in mobility measure
  - Well-tolerated
- 31 patients enrolled in long-term extension study

Phase 1/2 and Open-Label Extension Trials

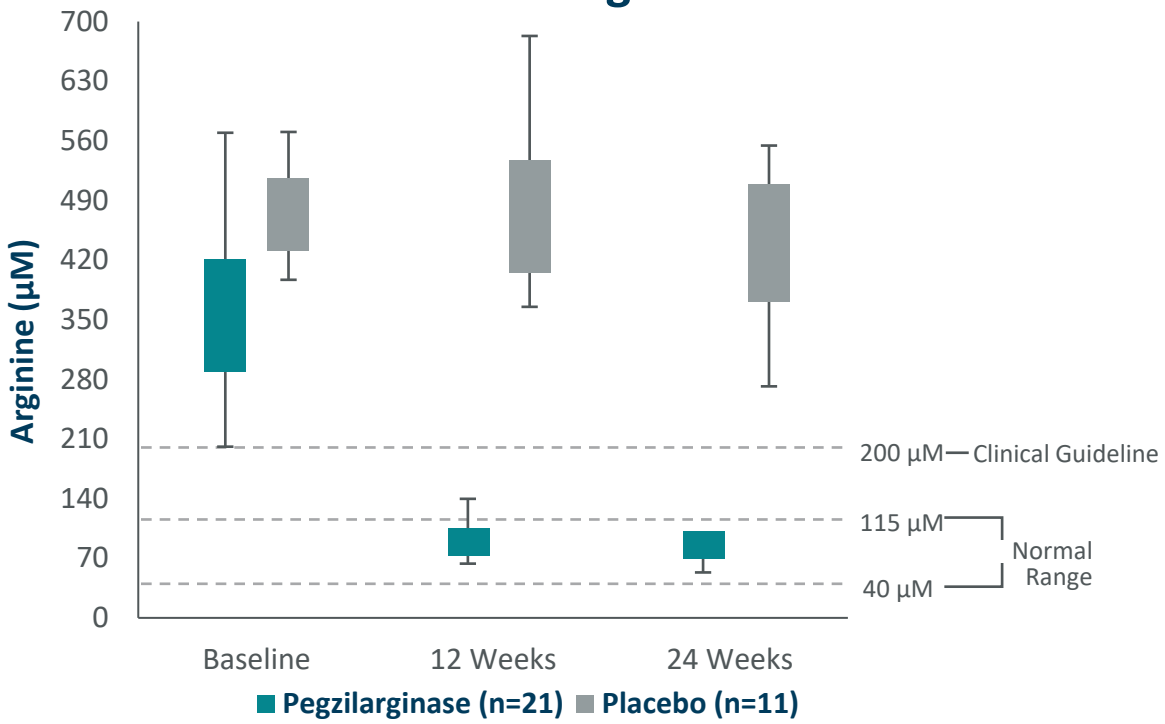
- 13 patients remain on therapy, duration from 2-4 years
- Arginine lowering was rapid and durable
- Improvements in functional measures sustained over time

[1] Catsburg C et al 2022

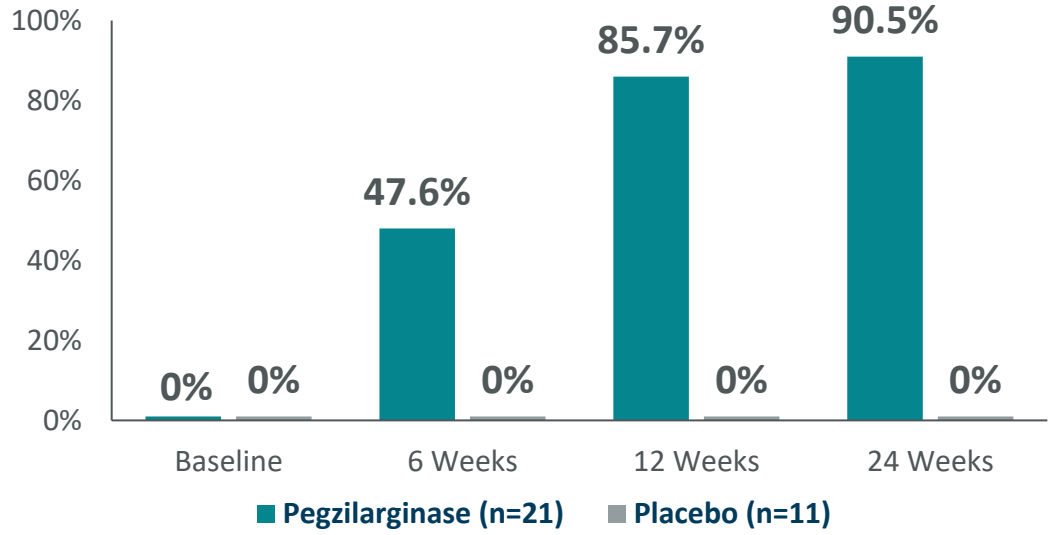
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PEACE Phase 3 Trial: Marked and Sustained Reduction in Plasma Arginine

Primary Endpoint: Reduction in Plasma Arginine*



Proportion of Patients Reaching Normal Arginine Levels (p<0.0001†)



Primary Endpoint Met – 24 Week Analysis

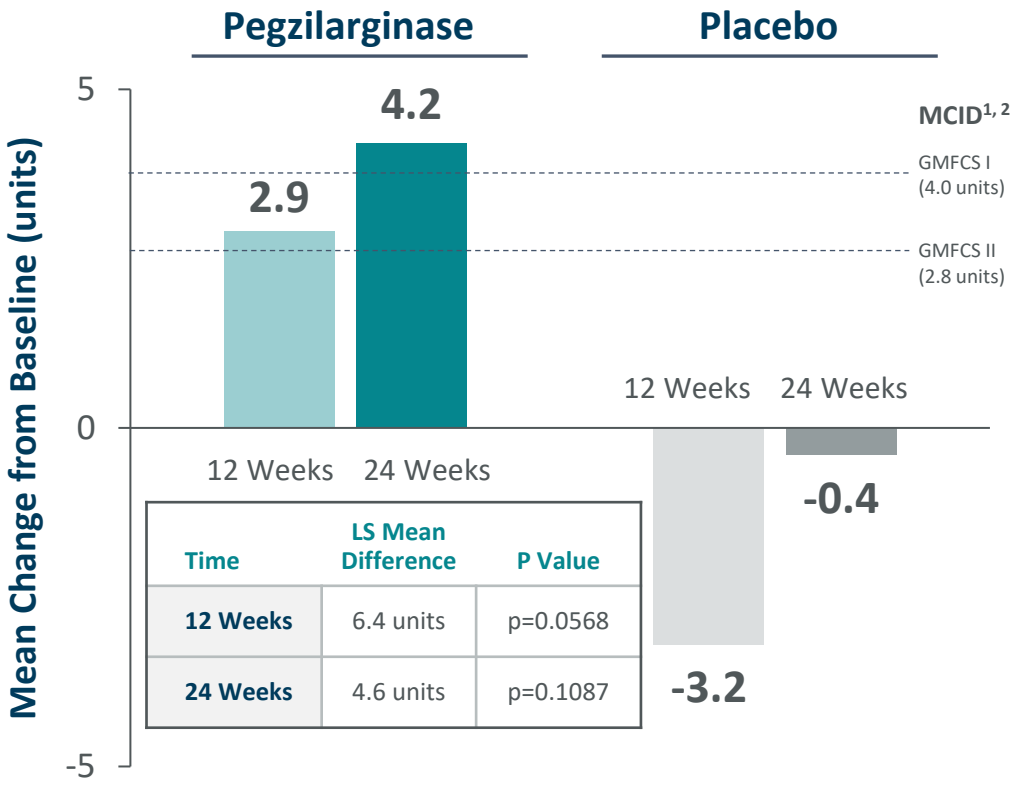
- **76.7% reduction from baseline in mean plasma arginine with pegzilarginase treatment compared to placebo (p<0.0001)‡**

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Enns G, et al. Poster presented at SIMD 2022 Annual Meeting; *Based on arithmetic mean of values from visit and preceding 3 visits, boxes represent middle 50% with error bars depicting 95% confidence interval; ‡ Statistical analysis based on geometric mean; †Nominal p value, based on arithmetic mean of values from visit and preceding 3 visits

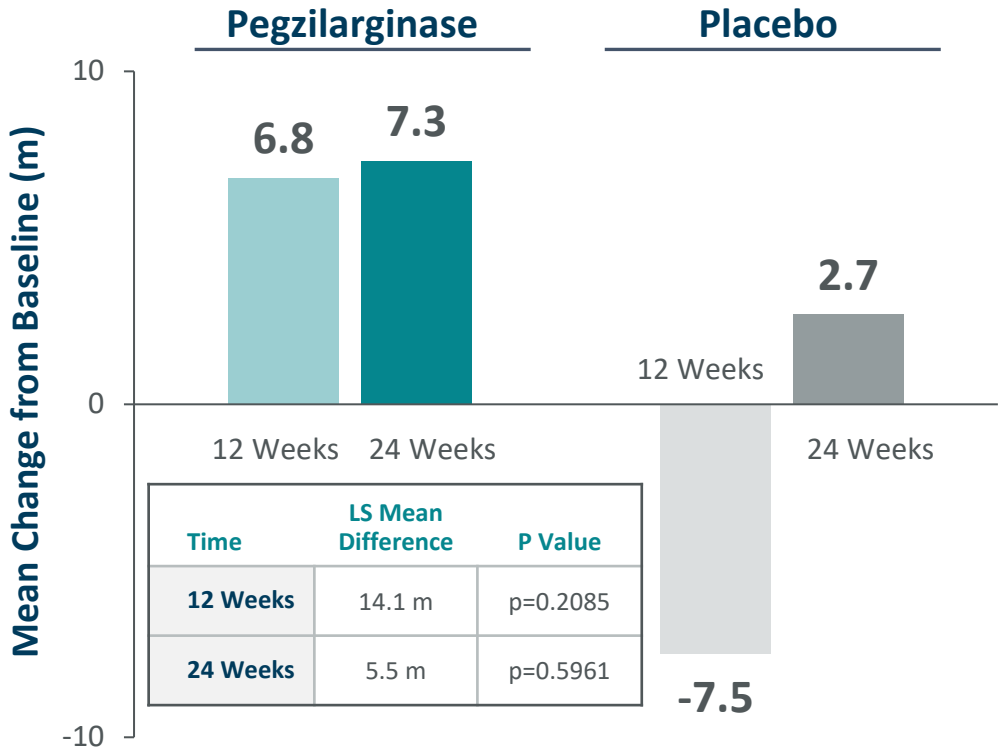
PEACE Phase 3 Trial: Mobility Assessed by GMFM-E and 2MWT

Mean Change from Baseline in GMFM-E



Time	LS Mean Difference	P Value
12 Weeks	6.4 units	p=0.0568
24 Weeks	4.6 units	p=0.1087

Mean Change from Baseline in 2MWT



Time	LS Mean Difference	P Value
12 Weeks	14.1 m	p=0.2085
24 Weeks	5.5 m	p=0.5961

Positive Trend in GMFM-E in Placebo-Controlled Study Suggests Potential Improvement in Mobility

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Enns G, et al. Poster presented at SIMD 2022 Annual Meeting; [1] MCID is minimal clinically important difference defined in Cerebral Palsy population. [2]Oeffinger D et al 2008; GMFM-E = Gross Motor Function Measure Part E; 2MWT = 2-minute walk test; GMFCS = Gross Motor Function Classification System ; LS = least squares

PEACE Phase 3 Patient-Level Outcomes: Impact of Pegzilarginase Across Efficacy Endpoints

GMFCS Level I-III Patients



Met criteria for clinical improvement or normalized pArg

Met criteria for clinical worsening or pArg >200 µmol/L

Did not meet criteria for improvement or worsening

Data not available

- In a patient-level analysis clinically important differences between treatment arms were evident for both arginine normalization and clinical responses
  - 16 of 17 pegzilarginase treated patients normalized arginine levels compared to no patients receiving placebo
  - Clinical response criteria for ≥1 assessment were met by 11 of 17 patients receiving pegzilarginase compared with 4 of 9 patients receiving placebo
  - 8 of 17 pegzilarginase treated patients met clinical response criteria on ≥2 outcomes
  - With placebo, no patient met clinical response criteria on ≥2 clinical assessments

Individual Outcomes for Evaluable Patients Show Impact Across Arginine Levels and Mobility, Providing Further Evidence of Efficacy

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Enns G, et al. Poster presented at SIMD 2022 Annual Meeting; Patient-level outcomes analysis conducted on GMFCS Level I-III patients (pegzilarginase, n=17, placebo, n=9)

PEACE Phase 3: Pegzilarginase Safety Profile

Adverse Events, n (%)	Pegzilarginase (n=21)	Placebo (n=11)
Any treatment-emergent AE	18 (85.7)	11 (100.0)
AEs leading to discontinuation	0	0
AEs of special interest		
Hypersensitivity reaction	2 (9.5)	0
Hyperammonemic episodes	3 (14.3)	4 (36.4)
Serious AEs*	4 (19.0)	4 (36.4)
AEs with incidence ≥15%		
Vomiting	6 (28.6)	3 (27.2)
Cough	4 (19.0)	1 (9.1)
Pyrexia	4 (19.0)	0
Ammonia increased	3 (14.3)	2 (18.2)
Hyperammonemia	2 (9.5)	3 (27.3)
Nausea	1 (4.8)	4 (36.4)
Abdominal pain	1 (4.8)	3 (27.3)
Decreased appetite	0	2 (18.2)

- No discontinuations due to treatment-emergent adverse events
- Most treatment-emergent adverse events were mild or moderate in severity
- Hypersensitivity reactions were mild/moderate, infrequent and managed with routine medical care
- Serious adverse events included hyperammonemia and vomiting (1 patient)

Pegzilarginase was Well-Tolerated with No Discontinuations in Pivotal Study Due to Adverse Events

Enns G, et al. Poster presented at SIMD 2022 Annual Meeting; AE = Adverse Event; *Serious AEs were hyperammonemia/hyperammonemia-related events and vomiting

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Regulatory and Program Status

Regulatory Status

MAA Under Review by EMA

- MAA filing accepted in August 2022
- Potential decision on approval in late 2023
- Manufacturing in place to support commercialization in Europe and Middle East

Continuing to engage with FDA to identify potential path towards BLA resubmission

- Refusal to File (RTF) Received for BLA

Next Steps

Ongoing Discussions with Potential ROW Partners

- Latin America remains a significant commercial opportunity
- EU authorization, if granted, can be used to enable access in many other countries

Clinical Trial Transition Underway

- New open-label trial to provide continued access for study patients in one streamlined, cost-effective study

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Summary

Highlights and Upcoming Milestones

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- Fast Track Designation received from FDA
- Currently dosing in cohort 3 at 1.35 mg/kg once weekly in Phase 1/2 clinical trial

Pegzilarginase in Arginase 1 Deficiency:

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- $57.3 million in cash and available funds[1] as of December 31, 2022; projected runway into fourth quarter of 2023

[1] Includes cash, cash equivalents, marketable securities, and restricted cash

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Financial Summary

Cash and available funds as of December 31, 2022: $57.3[1] million (no debt)

As of February 21, 2023, 94.3 million[2] common shares and pre-funded warrants outstanding

$ Millions	Year Ended 12/31/22	Year Ended 12/31/21
Revenue	$2.3	$18.7
R&D Expense	$58.6	$57.1
G&A Expense	$28.5	$27.3
Net Loss	$83.8	$65.8

Expected funding runway: into fourth quarter of 2023

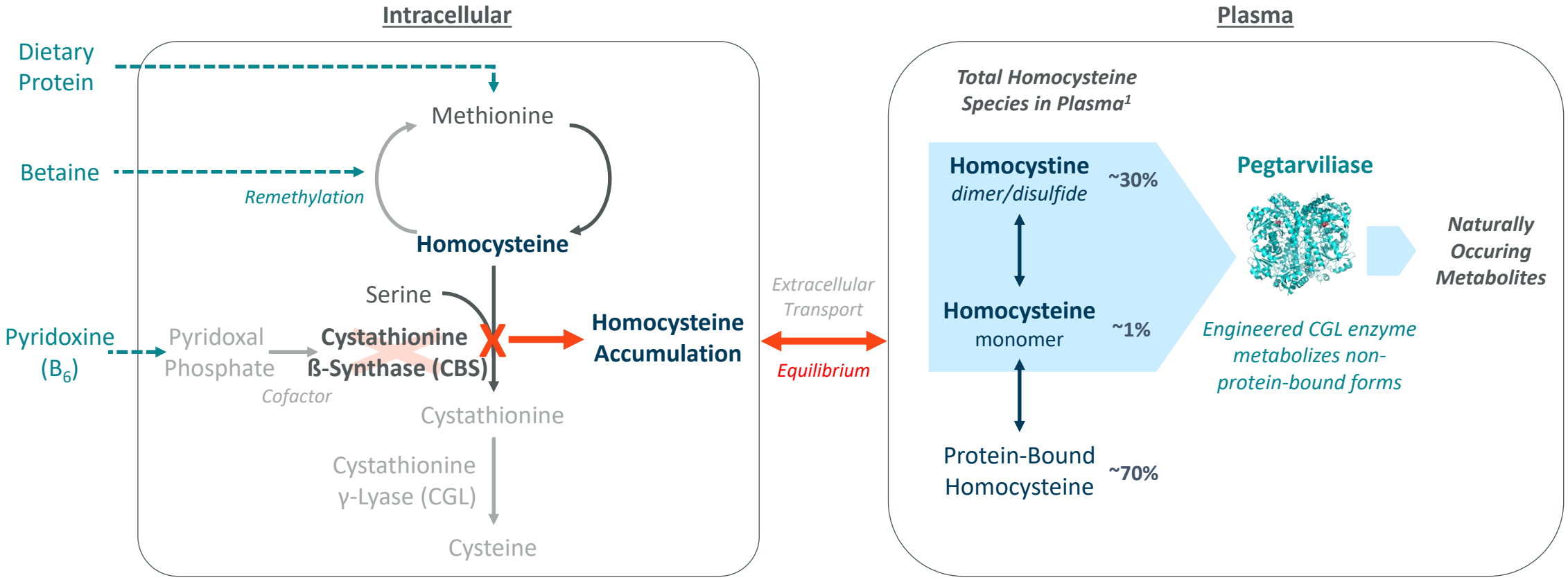
[1] Includes cash, cash equivalents, marketable securities and restricted cash. [2]Includes 65.4 million common shares outstanding and 28.9 million pre-funded warrants.

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Homocysteine Metabolism & Pegtarviliase Mechanism of Action



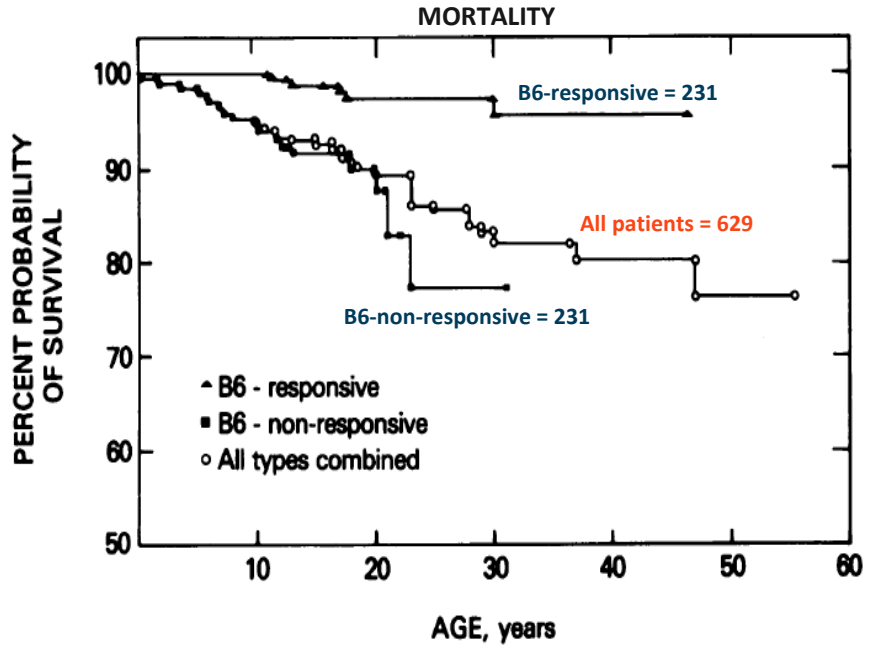
Pegtarviliase: Engineered human enzyme metabolizes multiple forms of free homocysteine to naturally occurring metabolites

1. Morris et al J Inherit Metab Dis 2017

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Increased Mortality and High Risk of Severe Complications

Natural History Study of 629 Untreated Classical Homocystinuria Patients



	B6-non-responsive	B6-responsive
Elevated levels of homocysteine	⊕ ⊕ ⊕	⊕

NATURAL HISTORY

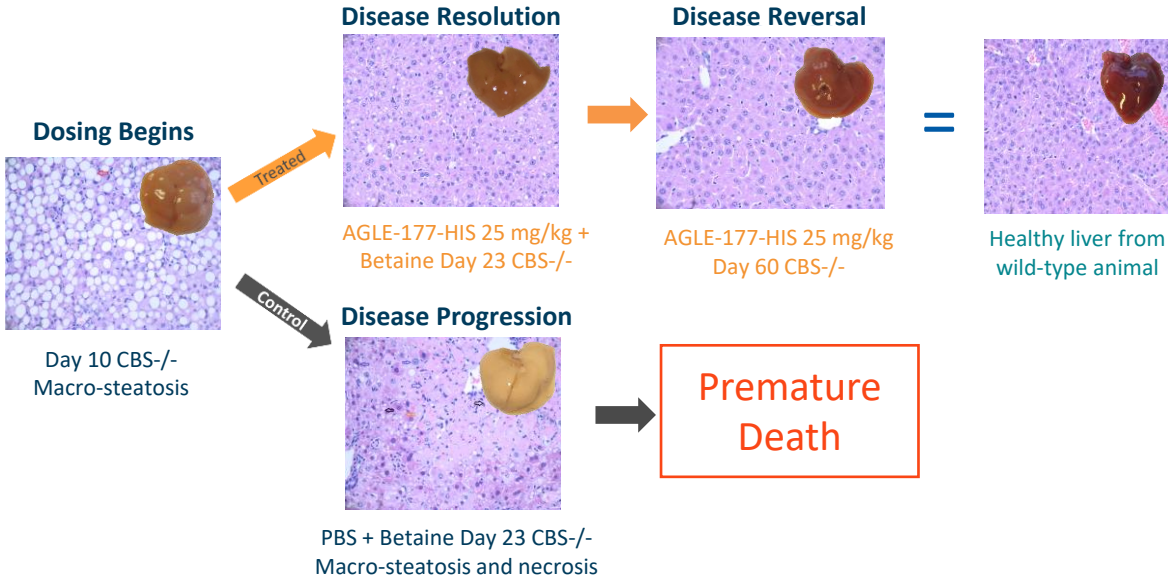
Mortality by age 30	23%	4%
Most common cause of death	Thromboembolism	
Lens dislocation in 50%	Age 6	Age 10
Median IQ	56	78
Chance of thrombosis by age 15	27%	12%

Mudd et al, 1985. Kluijtmans et al, Am. J. Hum. Genet. 65,59-67, 1999

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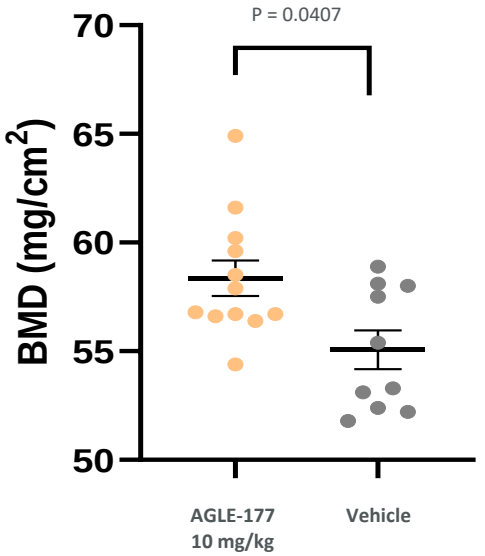
Pegtarviliase Treatment Improved Pathologies and Corrected Disease Manifestations in a Mouse Model of Homocystinuria

Reversal of Severe Liver Abnormalities in CBS Knockout Mouse Model[1]



Reductions in total plasma homocysteine led to improvements in disease-related abnormalities

Beneficial Impact on Osteoporosis[2]



Increased bone mineral density (BMD) in preclinical model of Homocystinuria with multiple doses

[1] Daige C. et al. Poster presented at ASHG 2018; [2] Daige C. et al. Poster presented at ASHG 2020 Virtual Meeting, CBS -/- mice were dosed SC BIW with AGLE-177 starting at D10 through Day 169 were evaluated for bone mineral density (BMD) by dual-energy X-ray absorptiometry; AGLE-177-HIS = AGLE-177/pegtarviliase modified to include a polyhistidine tag; CBS -/- = CBS knockout mouse model

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PEACE Baseline Demographics

Demographic Characteristic	Pegzilarginase n=21	Placebo n=11	Overall N=32
Age at Enrollment, y			
Mean (SD)	9.6 (6.16)	12.9 (6.77)	10.7 (6.47)
Range	2-28	5-29	2-29
Age Category, n (%)			
2y to less than 6y	5 (23.8)	1 (9.1)	6 (18.8)
6y to less than 12y	8 (38.1)	4 (36.4)	12 (37.5)
12y to less than 18y	7 (33.3)	4 (36.3)	11 (34.4)
18y or older	1 (4.8)	2 (18.2)	3 (9.4)
Sex, n (%)			
Male	12 (57.1)	7 (63.6)	19 (59.4)
Female	9 (42.9)	4 (36.4)	13 (40.6)
Region, n (%)			
U.S.	8 (38.1)	6 (54.5)	14 (43.8)
Ex-U.S.	13 (61.9)	5 (45.5)	18 (56.3)

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PEACE Baseline Clinical Characteristics

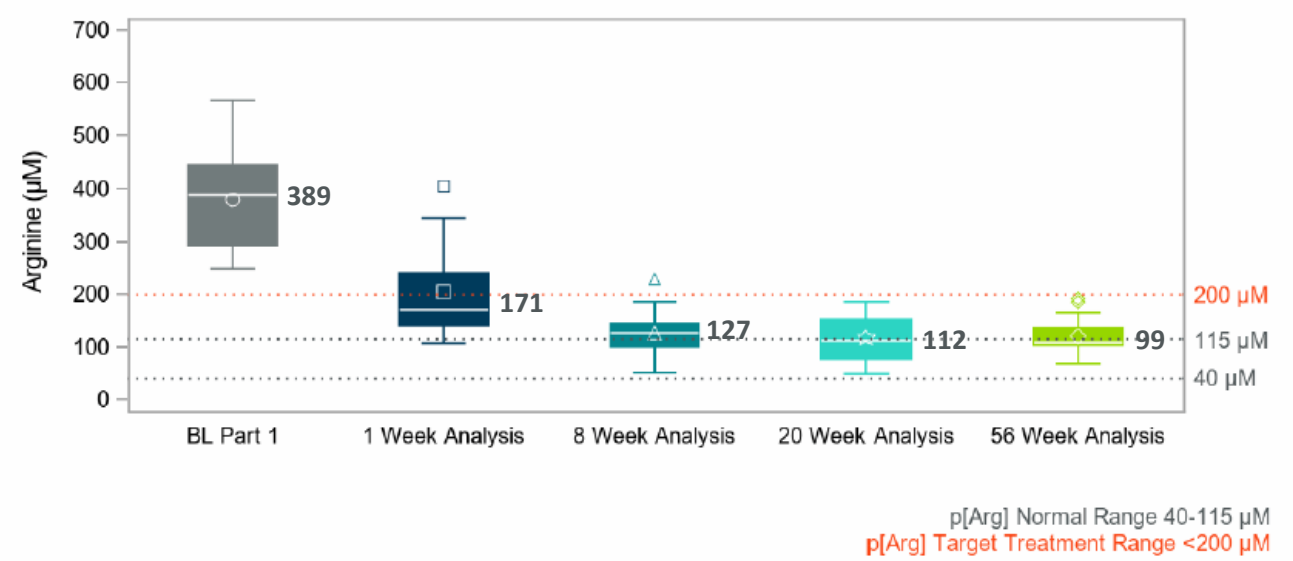
Clinical Characteristic	Pegzilarginase n=21	Placebo n=11	Overall N=32
Plasma Arginine, µM/L			
Mean* (SD)	365.4 (93.7)	471.7 (79.9)	402.0 (101.8)
Median (range)	368.2 (202-572)	483.7 (294-573)	398.2 (202-573)
GMFCS level, n (%)			
1	9 (42.9)	5 (45.5)	14 (43.8)
≥2	12 (57.1)	6 (54.5)	18 (56.2)
GMFM-E			
Mean (SD)	48.3 (19.9)	46.5 (24.6)	47.7 (21.5)
Median (range)	53 (5-71)	56 (0-72)	54 (0-72)
2MWT			
Mean (SD)	109 (55.7)	99.9 (49.0)	105.8 (52.8)
Median (range)	122 (2-202)	102 (0-171)	118 (0-202)

*Based on arithmetic mean

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Pegzilarginase Significantly and Sustainably Reduces Plasma Arginine Levels in Phase 1/2 & OLE

Plasma Arginine in Response to Pegzilarginase in Phase 1/2 & OLE Studies



Baseline:

- Baseline plasma arginine on standard disease management was markedly elevated

20 Week Analysis[1]:

- Median plasma arginine was 112µM
- Median plasma arginine reduction was 277µM

56 Week Analysis[2]:

- Median plasma arginine was 99µM
- 10/13 patients achieved plasma arginine within the normal range (40-115µM)
- **13/13 patients achieved plasma arginine within the target range (<200µM)**

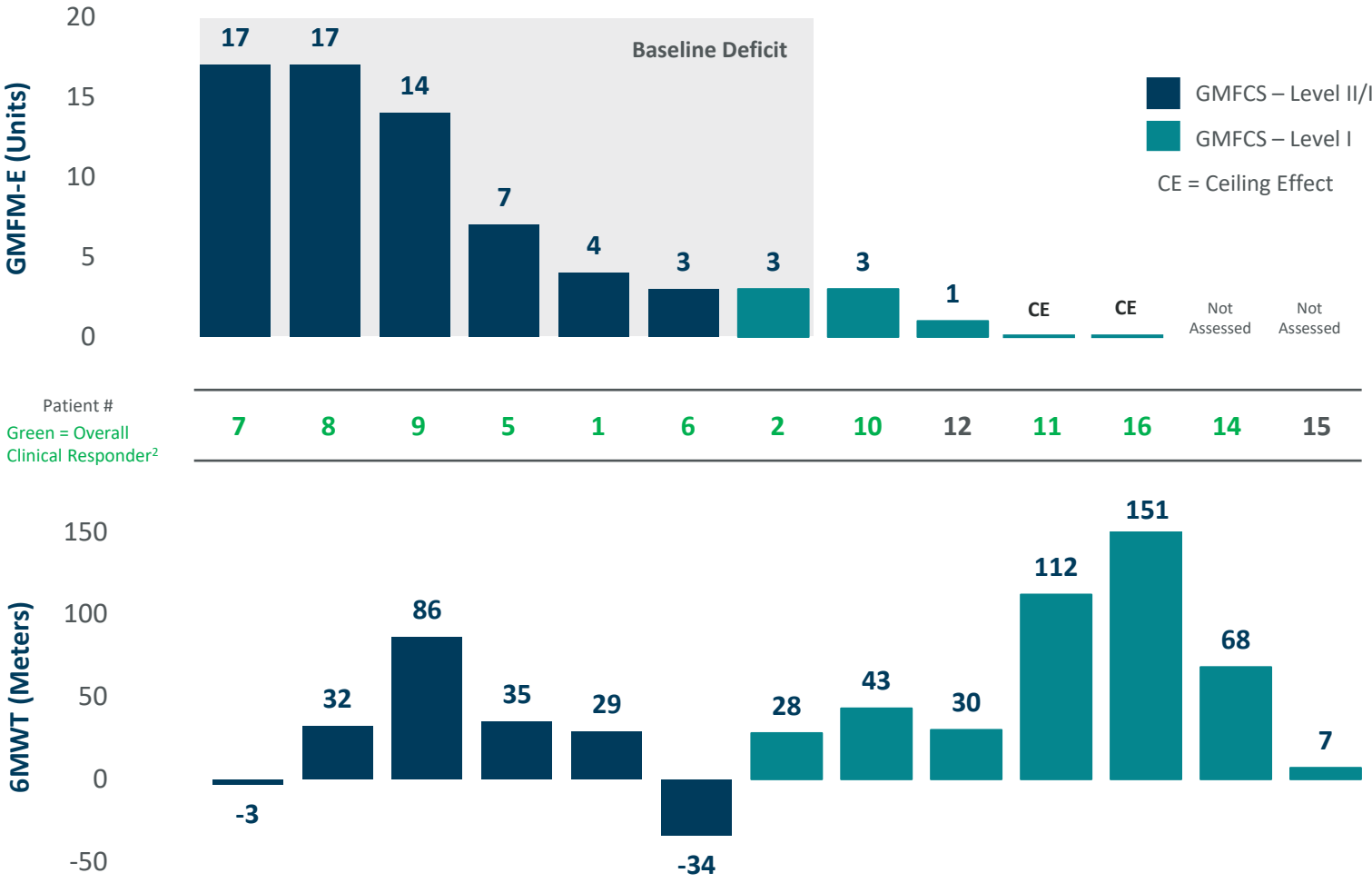
OLE – Open-label extension

[1] Diaz, GA, et al, J Inherit Metab Dis. 2021;44:847-856; [2] Diaz, GA et al, Presented at 2020 European Academy of Neurology Annual Meeting

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Mobility Assessments Capture Potential Clinical Benefit of Pegzilarginase in Phase 1/2 Trial & OLE

Change from Baseline at 56 Week Analysis[1]



Continuous Analysis
Mean Change from Baseline

Endpoint		Analysis	
		20 weeks	56 weeks
GMFM-E	Overall	5 units	6 units
	Baseline Deficit	8 units	9 units
6MWT	Overall	32 m	45 m

Categorical Responder Analysis[2]

20 Week Analysis:
11/14 (79%)

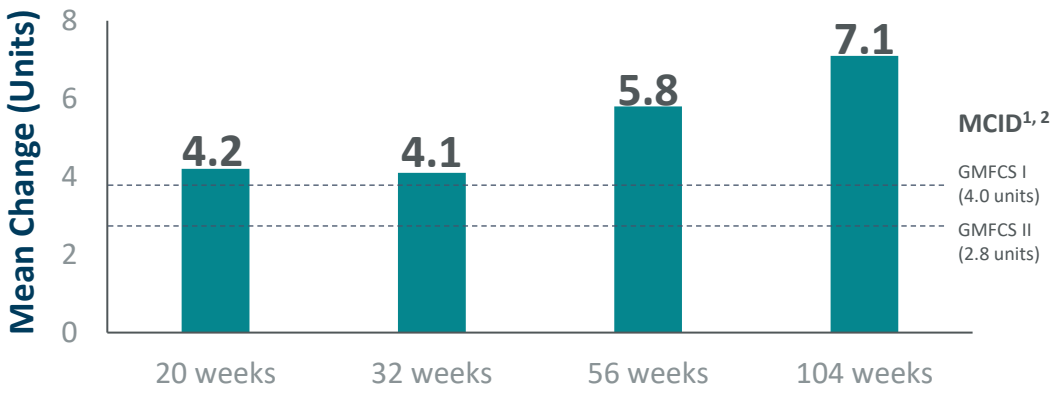
56 Week Analysis:
11/13 (85%)

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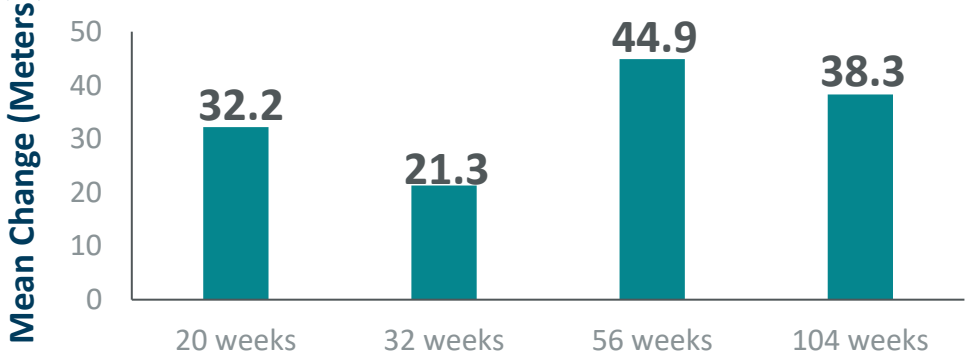
[1]Adapted from Diaz, GA et al, Presented at 2020 European Academy of Neurology Annual Meeting; [2]Clinical Responder defined by achievement of a clinically meaningful response in one or more of three mobility assessments; GMFCS = Gross Motor Function Classification System; OLE = open-label extension; GMFM-E = Gross Motor Function Part E; 6MWT = 6-minute walk test

Improvements in Mobility Measures Sustained Over Time in Phase 1/2 and OLE

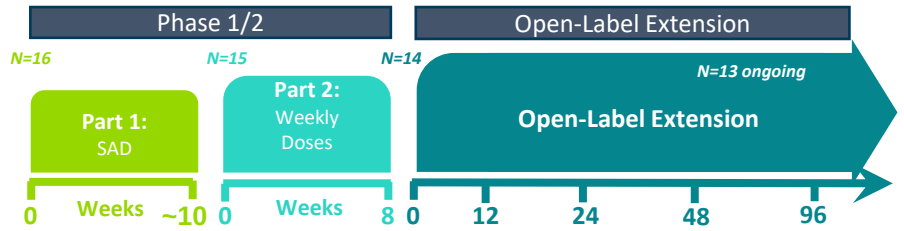
Mean Change from Baseline in GMFM-E



Mean Change from Baseline in 6MWT



Endpoint	Change from Baseline for Phase 1/2 & OLE Studies[3]			
	20-week analysis (N=13)	32-week analysis (N=13)	56-week analysis (N=13)	104-week analysis (N=9)[4]
GMFM-E	4.2 units	4.1 units	5.8 units	7.1 units
6MWT	32.2 m	21.3 m	44.9 m	38.3 m



[1] MCID is minimal clinically important difference defined in Cerebral Palsy population. [2]Oeffinger D et al 2008; [3] Analysis weeks are calculated by adding the 8 weeks from Part 2 of the Phase 1/2 study to the weeks of treatment in the open-label extension (OLE) study (e.g., 8 weeks of Part 2 + 12 weeks of OLE is the 20-week analysis), baseline values were taken at Part 1 of the study; [4] 13 patients remain in the OLE study, 9 of 13 patients had 96-week mobility assessments conducted; GMFM-E = Gross Motor Function Measure Part E; 6MWT = 6-minute walk test; GMFCS = Gross Motor Function Classification System; SAD = single ascending dose

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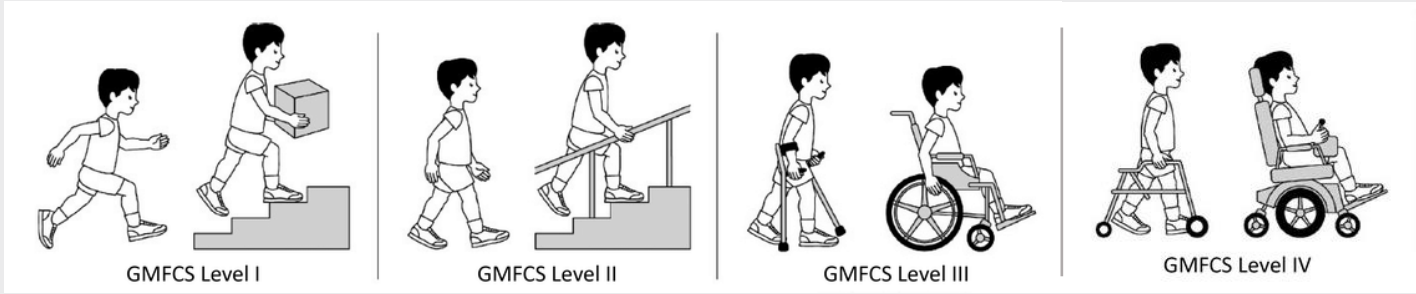
Measuring the Functional Impact of Spasticity in ARG1-D

Classification of Mobility:

Gross Motor Function Classification System (GMFCS)

Overall description of current motor function based on:

- Movements such as sitting, walking
- Use of mobility devices



Level V not pictured: adapted seating and assistance with transfers, and utilize wheeled power mobility independently or manual mobility with assistance in most settings

Measures of Change in Mobility:

Gross Motor Function Measure (GMFM) Part E

Assesses **unaided mobility** without bracing or assistive devices

- 24 tasks involving walking forward/backward, running, jumping and ascending/descending stairs with a score range of 0-72





Timed Walk Tests

Evaluates **aided mobility** with any needed bracing or assistive devices over a defined period of time

- 2 mins (2MWT)
- 6 mins (6MWT)



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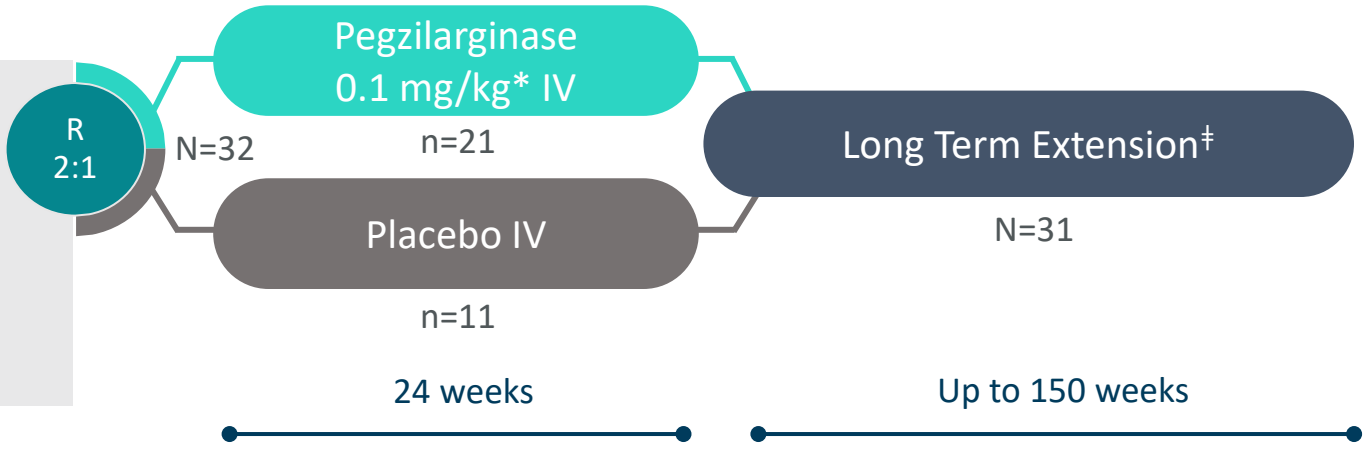
GMFCS graphic adapted with permission from The Royal Children's Hospital Melbourne, Australia

PEACE Phase 3 Study Design

Double-blind portion of trial complete – topline data announced December 2021

Patients with ARG1-D

- ≥2 years old
- Plasma arginine >250 µM (mean)
- Baseline deficit in clinical response assessments



Key Endpoints	Analysis
Primary: • **Plasma arginine reduction**	• Reduction of plasma arginine compared to placebo
Secondary: • **GMFM-E (walking, running & jumping)** • **2-Minute Walk Test (distance walked in 2 min)**	• Continuous analysis • Improvement compared to placebo

*Dosing is weekly and, if needed, dose is modified based on plasma arginine levels with maintenance of blinding.
‡The first 8 weeks of the open-label extension will be blinded. All study participants remain on current disease management for the duration of the trial. Dose adjustments in the double-blind treatment period can be made to optimize plasma arginine control for levels outside the range of 50-150µM. If needed, weekly doses can be increased to 0.15 and 0.2 mg/kg or reduced to 0.05mg/kg; ARG1-D = Arginase 1 Deficiency; IV = intravenous; R = randomized.

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Patient-Level Outcomes: Mobility in Select Patients

Pegzilarginase-Treated Patients Achieving Clinical Response on ≥2 Mobility Outcomes and No Worsening at Week 24

Patient (Age)	GMFM-E (Score Range, 0-72 units)	2MWT*	GMFM-D (Score Range, 0-39 units)
1 (6 years old)	• **Improved** by 7 • Total score: 69	• Improved by 34m to 152m • **Achieved normal** age/sex-matched mean	• **Improved** by 2 • Total score: 35
2 (6 years old)	• **Improved** by 18 • Total score: 45	• Improved by 46m to 96m • Achieved 56% of normal age/sex-matched mean	• **Improved** by 4 • Total score: 32
3 (12 years old)	• **Improved** by 6 • **Achieved maximum score**	• Improved by 43m to 167m • Achieved 82% of normal age/sex-matched mean	• **Improved** by 5 points • **Achieved maximum score**
6 (14 years old)	• **Improved** by 9 • Total score: 62	• No worsening	• **Improved** by 8 • Total score: 37
16 (2 years old)	• **Improved** by 11 • Total score: 52	• Improved distance by 44m* to 150m • **Exceeded normal** age/sex-matched mean	• **Improved** by 8 • Total score: 32
17 (3 years old)	• **Improved** by 21 • Total score: 62	• Improved distance by 95m to 164m • **Exceeded normal** age/sex-matched mean	• No worsening

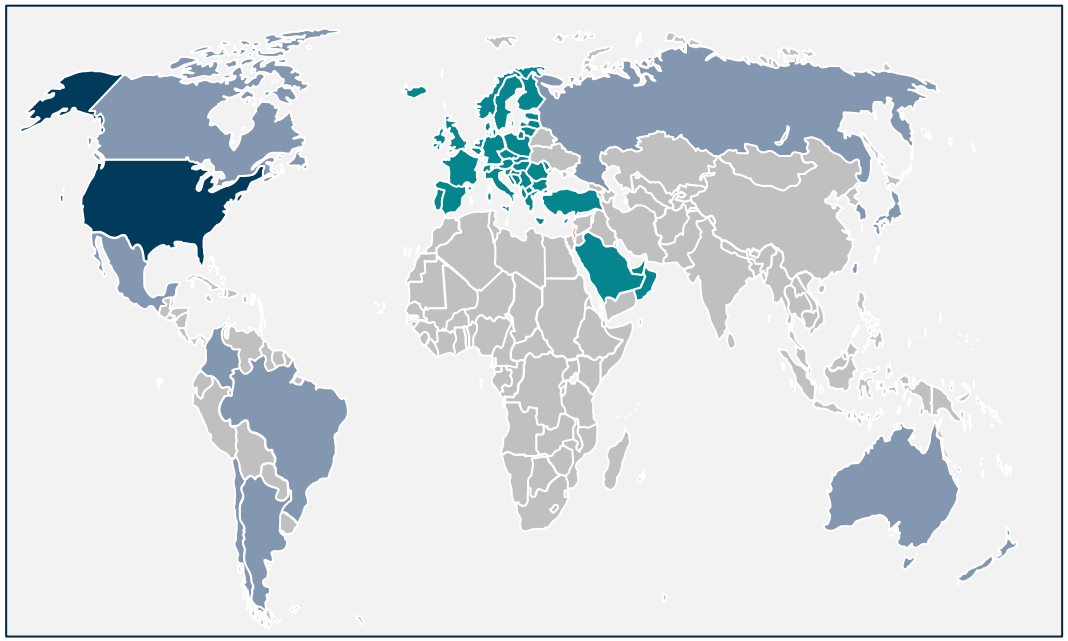
Normalization of Mobility in Progressive Disease Supports the Potential Impact of Pegzilarginase Treatment

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Ages are at the time of enrollment; Normalization defined at ±15% of age/sex-matched mean distance per the NIH toolbox; * Reflects change from Week 12, distance at baseline not assessed owing to age

Attractive Commercial Opportunity and a Targeted Launch Plan

Prevalence of >2,500 Patients[1] with Significant Unmet Need



United States
>250 patients

Western Europe and Middle East[2]
>900 patients

Rest of World
>1,350 patients (including 700 in LatAm, 400 in Asia Pacific)

A Focused Effort to Ensure a Successful Launch

Patient Identification

Accelerating the diagnosis and identification of patients through ongoing HCP engagement

Disease Education and Awareness

Driving HCP dialogue about the devastating and progressive nature of ARG1-D

Access and Reimbursement

Ensuring payer understanding of the significant clinical and economic burden of ARG1-D

Organizational Readiness

Establishing an internal mindset and infrastructure to meet the needs of the global ARG1-D patient community

[1] Catsburg C et al 2022 [2] Licensing and supply agreement signed with Immedica Pharma AB in March 2021; countries in agreement include European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain and Oman.

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