Reimagining The Potential Of Human Enzyme Therapeutics

Corporate Overview – March 2022

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 and our planned BLA submission for our lead product candidate pegzilarginase, our ability to obtain and maintain regulatory approval, the potential therapeutic benefits, safety profile and economic value of pegzilarginase and our other product candidates, potential growth opportunities, financing plans, use and adequacy of financing plans, 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 candidate pegzilarginase and our product candidates for the treatment of homocystinuria and cystinuria; 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; 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 impact of the COVID-19 pandemic on our operations and clinical development activities, including on the timing of enrollment of our clinical trials; 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 from our licensing and supply agreement with Immedica; the potential for expedited development and review of pegzilarginase as a result of its Breakthrough Therapy designation; the 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; our ability to identify additional product candidates with significant commercial potential consistent with our commercial objectives; and our estimates regarding expenses, future revenue, capital requirements 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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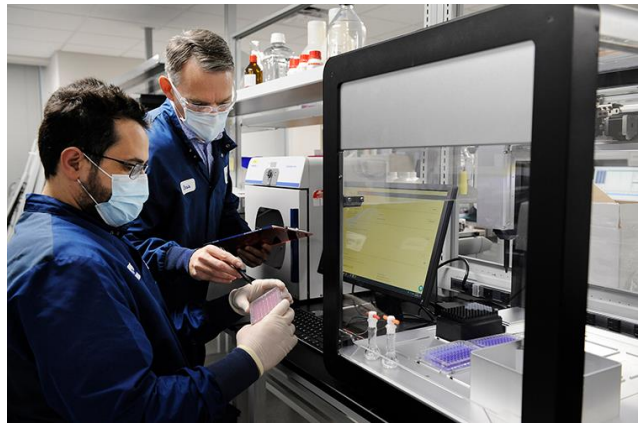
Addressing Metabolic Imbalances to Improve the Lives of Patients

Aeglea BioTherapeutics

At Aeglea, we believe that every patient deserves a chance at a better life. We are committed to helping people with rare and devastating metabolic diseases who have limited treatment options. Having a rare disease does not mean that you are in the fight alone.











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Recent Accomplishments and 2022 Outlook

Key Highlights

Pegzilarginase (Arginase 1 Deficiency)

- Met with FDA in late February 2022
- Announced positive topline Phase 3 data
  - Reduced arginine by 80%; normalized plasma arginine levels in 90.5% of patients; trend in mobility measure
- Progressed key launch objectives including:
  - Patient identification and profiling of population and prescriber base; payer engagement; advancing patient services and distribution activities

AGLE-177 (Homocystinuria)

- Dosing patients in cohort 2 (0.45 mg/kg SC) of Phase 1/2 study
  - Cohort 1 (0.15 mg/kg IV): Well-tolerated with no safety concerns, reductions in total homocysteine in all patients
- Advanced manufacturing, formulation work to enable Phase 3 trial
- Completed long-term toxicology studies

Looking Ahead

Pegzilarginase

- Submit U.S. BLA (2Q 2022), EU MAA (2022)
- Continue preparations for strong, rapid launch in U.S., Europe and Middle East
- Presentation of PEACE data at SIMD; publication of long-term data

AGLE-177

- Clinical data from Phase 1/2 trial (2H 2022)
- Plan to open U.S. sites (submitted IND in February 2022)

AGLE-325 (Cystinuria)

- IND-enabling studies for optimized molecule

SC = subcutaneous; IV = intravenous

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Aeglea's Human Enzyme Platform for Rare Metabolic Diseases

Program	Research	Phase 1/2	Phase 3	Approved	Addressable Market	Geographic Rights
Pegzilarginase Arginase 1 Deficiency					>2,500 Patients[2]	Retain rights outside of Europe and Middle East[1] partnership Immedica pharma
AGLE-177 Homocystinuria					>30,000 Patients[3]	Worldwide rights
AGLE-325 Cystinuria					>10,000 Patients[4]	Worldwide rights
Undisclosed Rare Diseases						Worldwide rights

[1] Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and certain 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) [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] >30,000 represents estimated prevalence of Classical Homocystinuria in 38 addressable markets based on results of U.S. ICD-10 claims analysis extrapolated to global markets; all figures rounded. Sellos-Moura et al 2020 [4] Castro Pereira DJ et al 2015; Leslie and Nazzal Renal Calculi (Cystinuria, Cystine Stones) (2018) Reference; Rozanski et al, Mil Med (2005); Soucie et al, JM Kidney Int (1994); Claes & Jackson, Pediatr Nephrol (2012) 27, 2031; Chillarón, J. et al. Nat. Rev. Nephrol. 2010, 6, 7, 424-34; Biyani, C.S and Cartledge, J.J. EAU-EBU Update Series, 2006, 4, 175-183; Mattoo, A. and Goldfarb D.S. 2008 Sem. Nephrol, 28, 2, 181-191

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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.

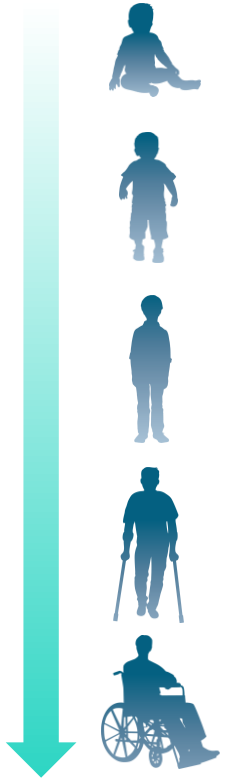
Current Standard of Care

- 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]
  - >1,150 patients in territories with regulatory and launch plans underway
- 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

Planned BLA Filing in 2Q 2022

First Clinical Program Ever Conducted in ARG1-D

Phase 1/2 and Open-Label Extension Trials

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

PEACE Phase 3 Clinical Trial

- First placebo-controlled trial ever conducted in ARG1-D
- Topline announced December 2021
  - Pegzilarginase reduced arginine levels by 80%, normalized arginine levels in 90.5% of patients
  - Positive trend in mobility measure
  - Well-tolerated
- 31 patients enrolled in long-term extension study

[1] Catsburg C et al 2022

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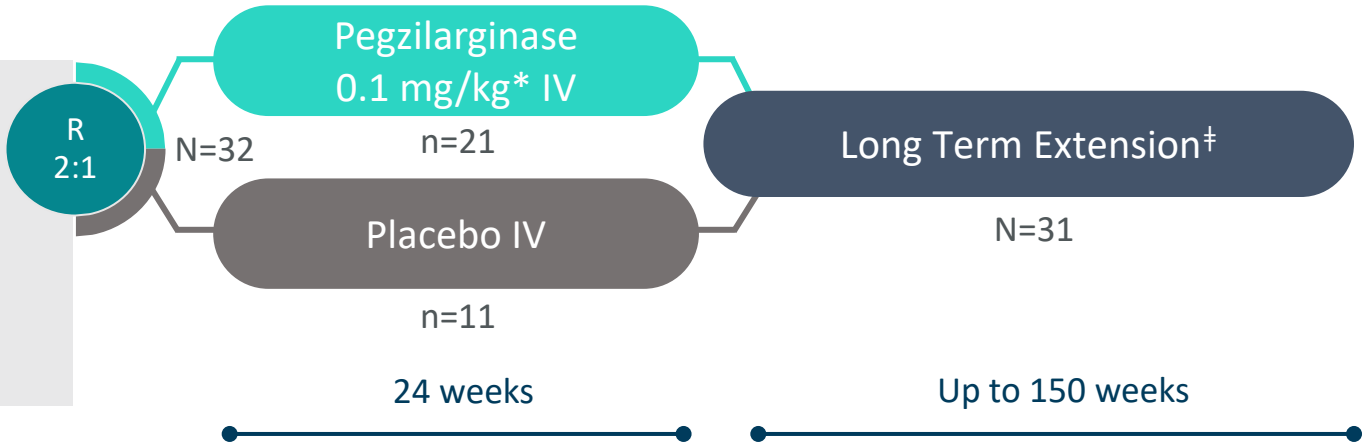
PEACE Phase 3 Study Design

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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Pegzilarginase Safety Profile – Results from PEACE

Patients With:	Pegzilarginase n (%)	Placebo n (%)
Any TEAE *	18 (85.7)	11 (100.0)
TEAE Leading to Discontinuation	0	0
SAE ‡	4 (19.0)	4 (36.4)
Hypersensitivity Reaction ◊	2 (9.5)	0
Hyperammonemia ◊	3 (14.3)	4 (36.4)

- No discontinuations due to TEAEs
- Most TEAEs were mild or moderate in severity
- Common TEAEs occurring in >15% of patients in treatment and placebo arms included vomiting, ammonia increased, cough, hyperammonemia, nausea, abdominal pain, pyrexia, decreased appetite
  - With exception of vomiting, cough, and pyrexia, each event occurred at lower rate compared to placebo
- Hypersensitivity reactions were mild/moderate, infrequent (<10% of patients) and managed with routine medical care
- SAEs included hyperammonemia and vomiting (1 patient)

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

* TEAE: Treatment-Emergent Adverse Event; ‡ SAE: Serious Adverse Event; ◊ Adverse Event of Interest

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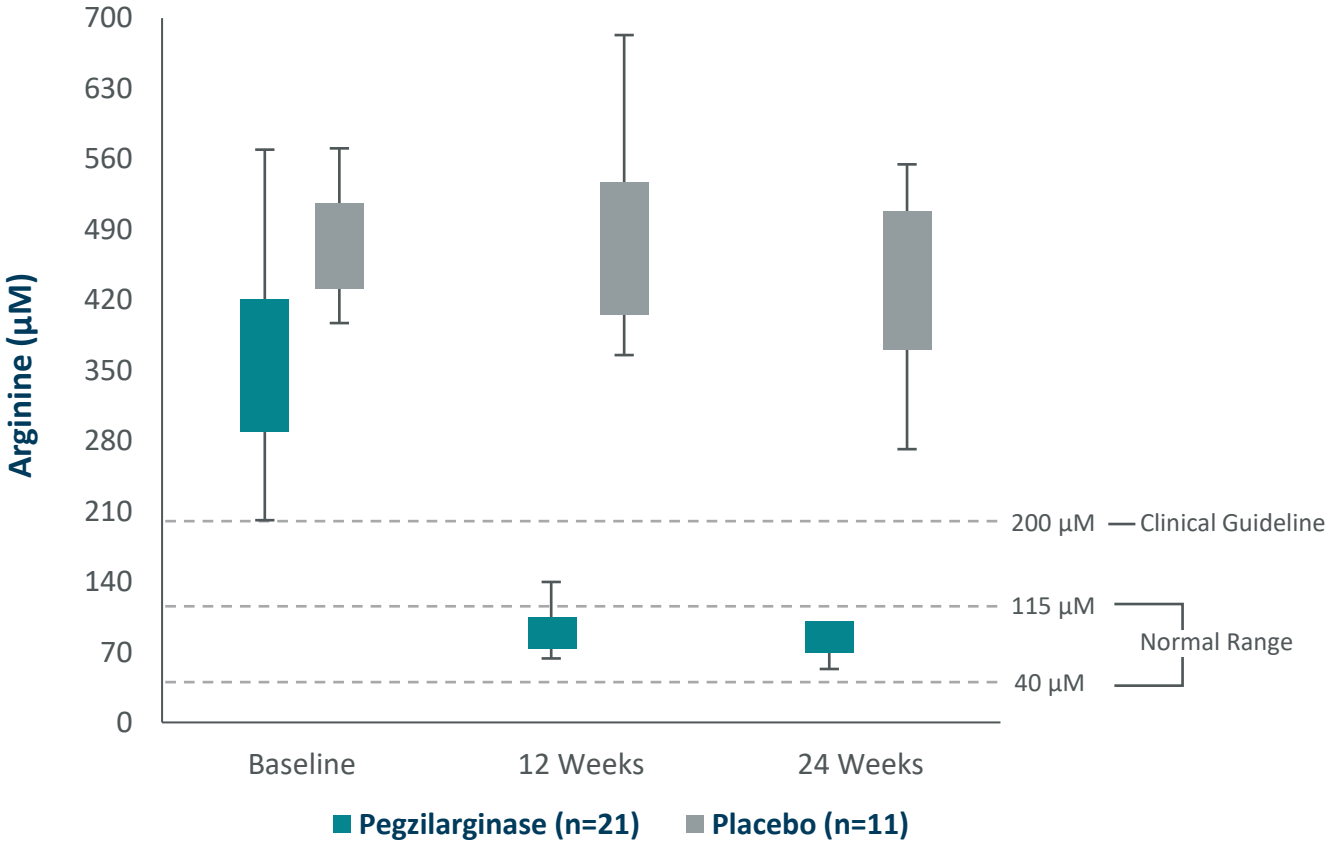
Primary Endpoint Met – Marked and Sustained Reduction in Plasma Arginine

Reduction in Plasma Arginine*



- Highly elevated plasma arginine despite standard of care
- Mean plasma arginine*
  - Pegzilarginase
    - Baseline: 365.4 µM
    - 24-week: 105.5 µM
  - Placebo
    - Baseline: 471.7 µM
    - 24-week: 448.8 µM

Primary Endpoint – 24-Week Analysis

- **80% reduction in mean plasma arginine with pegzilarginase (p<0.0001)‡**

*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`

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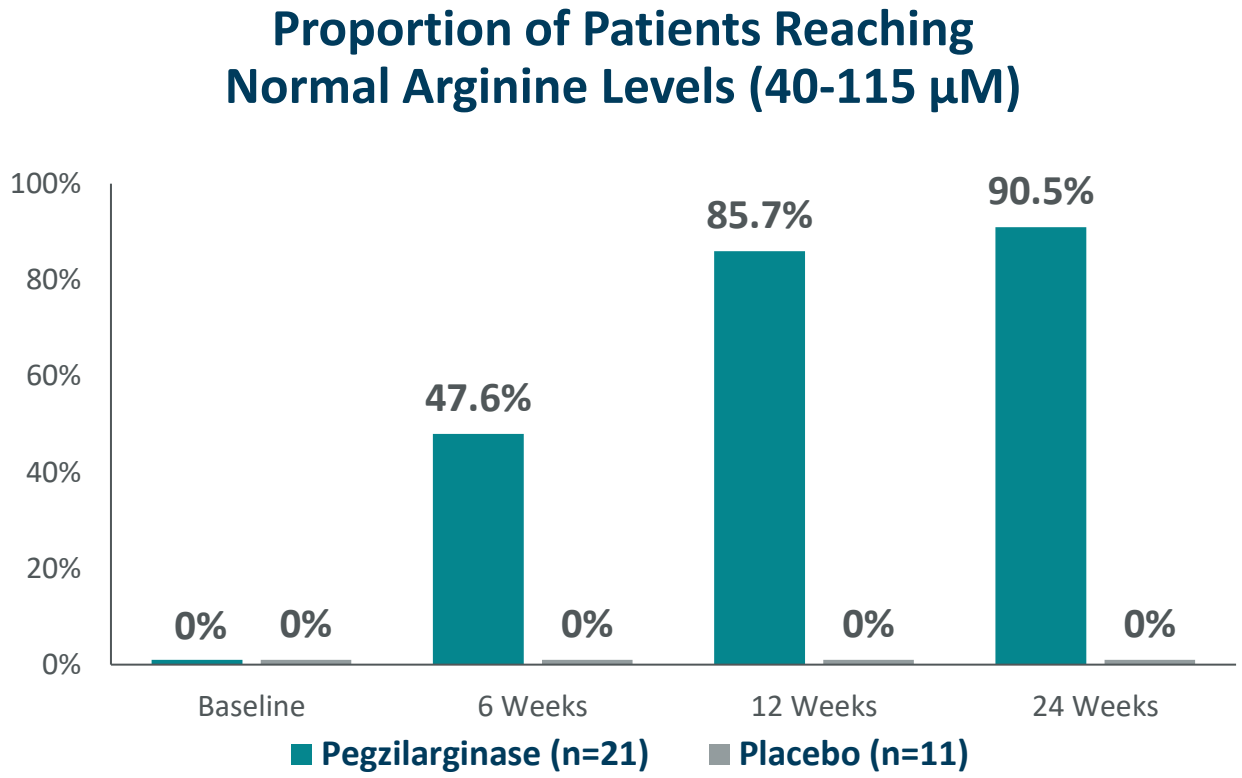
Normalization of Plasma Arginine Levels in ARG1-D Patients



- 90.5% of pegzilarginase treated patients achieved normal plasma arginine levels ($p<0.0001$)*
- No meaningful change in plasma arginine levels in placebo arm
- Treatment with pegzilarginase surpassed current clinical guideline goals of reducing arginine levels below 200 µM

Potential Transformative Therapy for a Patient Population with Previously Unachievable Control of Arginine to Normal Levels

* Nominal p value, based on arithmetic mean of values from visit and preceding 3 visits

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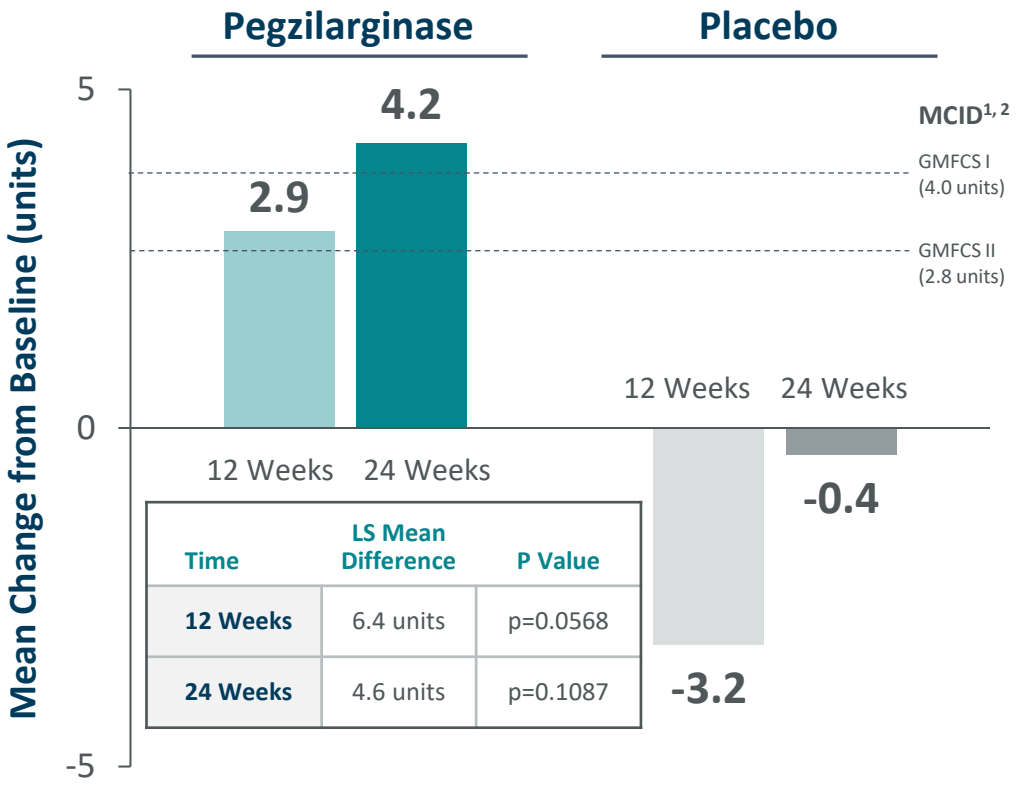
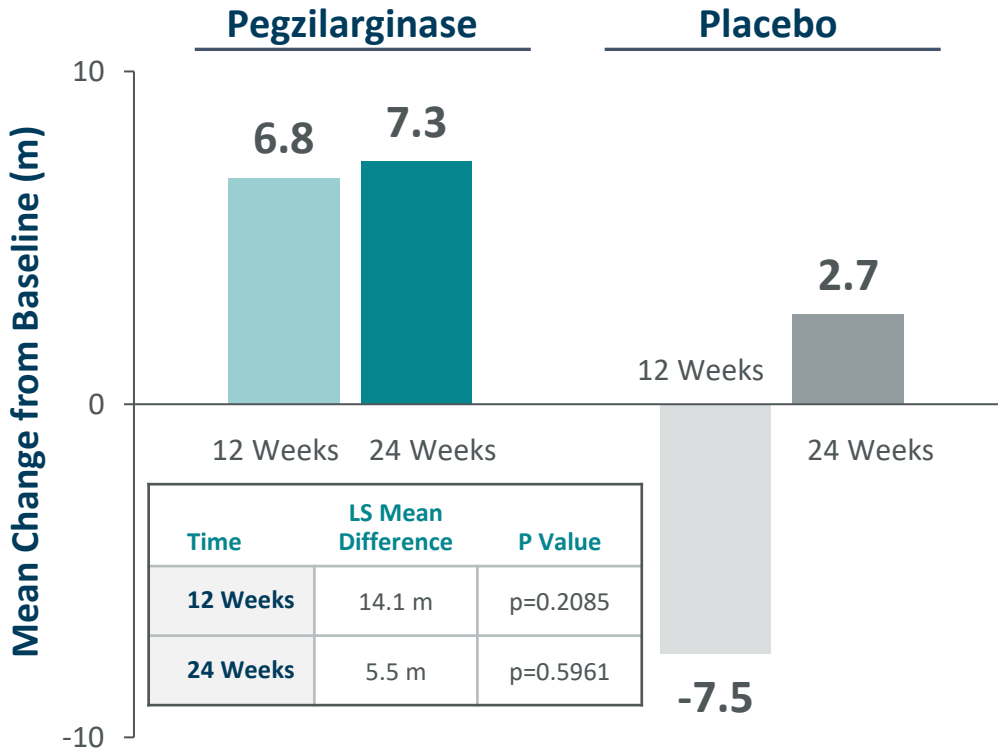
PEACE Mobility Assessed by GMFM-E and 2MWT

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 Improvements in Mobility

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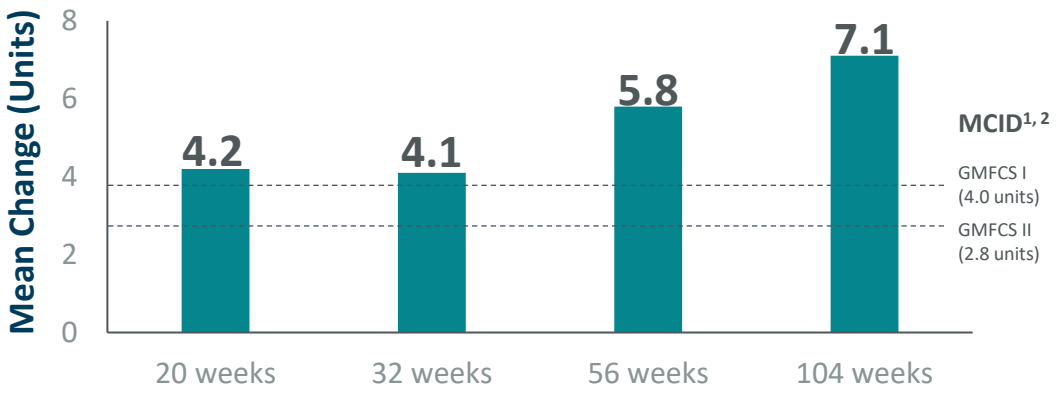
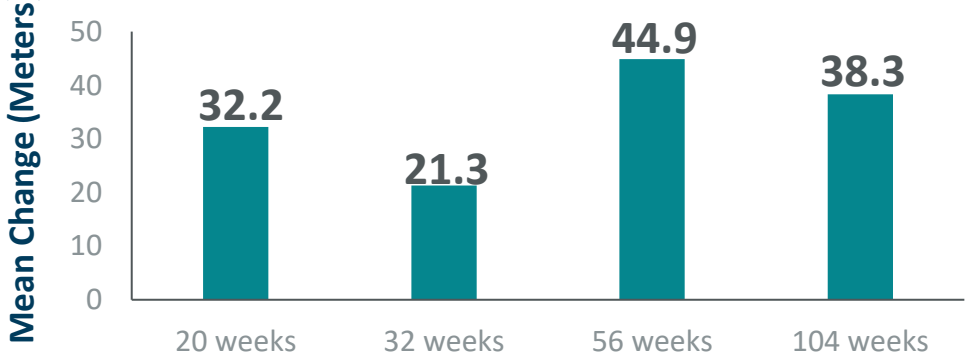
[1] MCID is minimal clinically important difference defined in Cerebral Palsy population. [2]Oeffinger D et al 2008; GMFM-E = Gross Motor Function Measure Part E; 2MWT = 2-minute walk test; GMFCS = Gross Motor Function Classification System ; LS = least squares

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

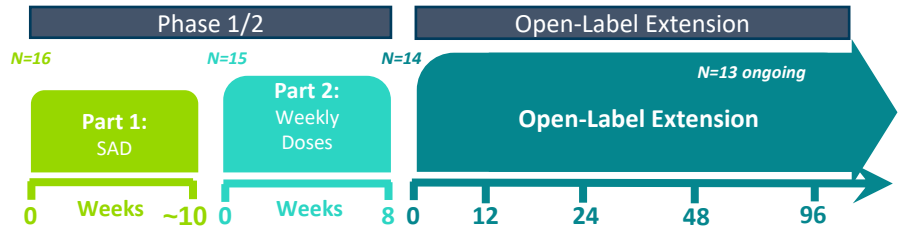
Mean Change from Baseline in GMFM-E



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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Confidence in Path to Regulatory Submission and Approvability

Clinically Meaningful Results

- Normalized arginine levels which was previously unachievable in this patient population
- GMFM-E trend highly suggestive of mobility benefit with improvement over time
  - Mean changes in both trials greater than MCID of 4 units and 2.8 units for GMFCS Levels I and II respectively[1]
- Strength and consistency of data support favorable benefit/risk profile

Timeline to Potential U.S. Approval and Launch

- Held meeting with FDA in late February 2022
- Planned BLA submission in second quarter of 2022
  - Plan to request priority review
  - PDUFA date typically ~8 months from submission with priority review
- Preparing for strong, rapid launch

Robust Regulatory Package

- **Strong Clinical Data**
- **Established Manufacturing**
- **Multiple Regulatory Designations**

[1] Oeffinger D et al 2008; MCID = minimal clinically important difference; GMFCS = Gross Motor Function Classification System

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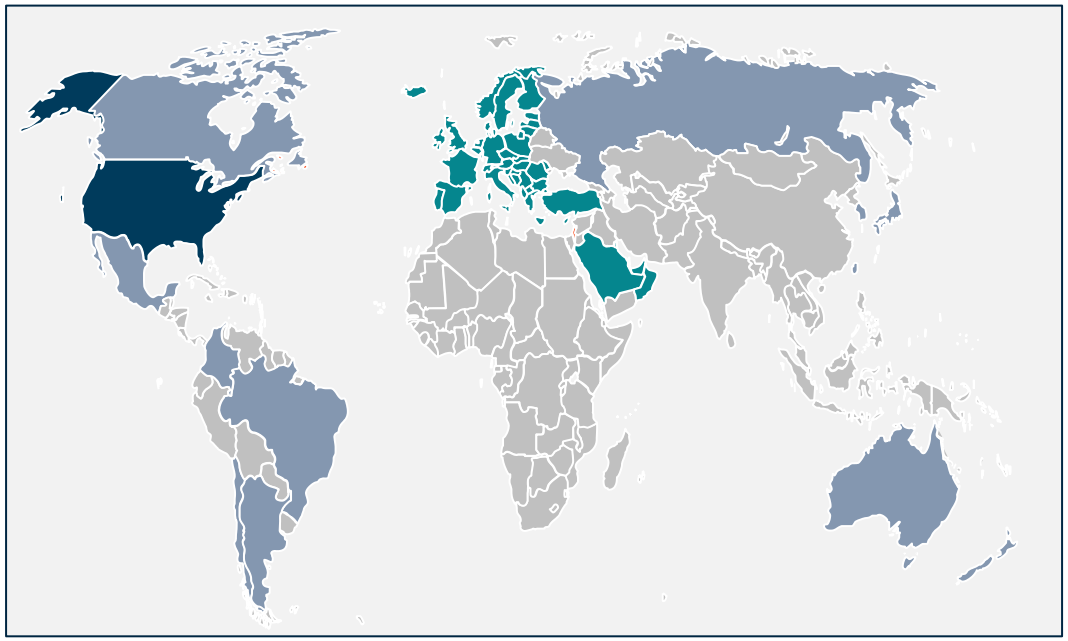
Attractive Commercial Opportunity and a Targeted Launch Plan

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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Engaging with HCP and Patient Communities to Accelerate Diagnosis, Broaden Awareness, and Deepen Understanding of ARG1-D

Patient Identification



- Continued patient identification momentum across key markets
  - Gaining valuable insights into disease management and patient characteristics
  - Progress is outpacing relevant benchmarks
- Driving increased awareness of ARG1-D to facilitate accurate diagnosis
  - THINK ARGININE™: a disease awareness initiative with diagnostic testing for eligible patients
  - Focus on key specialties with highest likelihood of potential un- or misdiagnosed patients

Disease Education and Awareness



- Ongoing scientific discourse to broaden awareness and deepen ARG1-D understanding and advocacy among HCP community
- High concentration of identified patients in relatively few metabolic institutions with very knowledgeable specialists
- Thoughtful engagement with the patient community to strengthen understanding of patient journey and unmet needs

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Laying the Groundwork to Transition Smoothly to Commercial Operations

Access and Reimbursement



- High-touch patient services model is being developed based on our deep understanding of the needs of the ARG1-D patient community
- Thoughtful, targeted approach to payer engagement focused on payers most likely to have ARG1-D covered lives

Organizational Readiness



- Core commercial and medical team in place with deep ultra-rare launch experience
- Commercial formulation on stability and distribution strategy in place
- Tight coordination with Immedica, our commercial partner in certain countries in Europe and the Middle East
- Commercial infrastructure built with pegzilarginase and earlier-stage pipeline programs in mind

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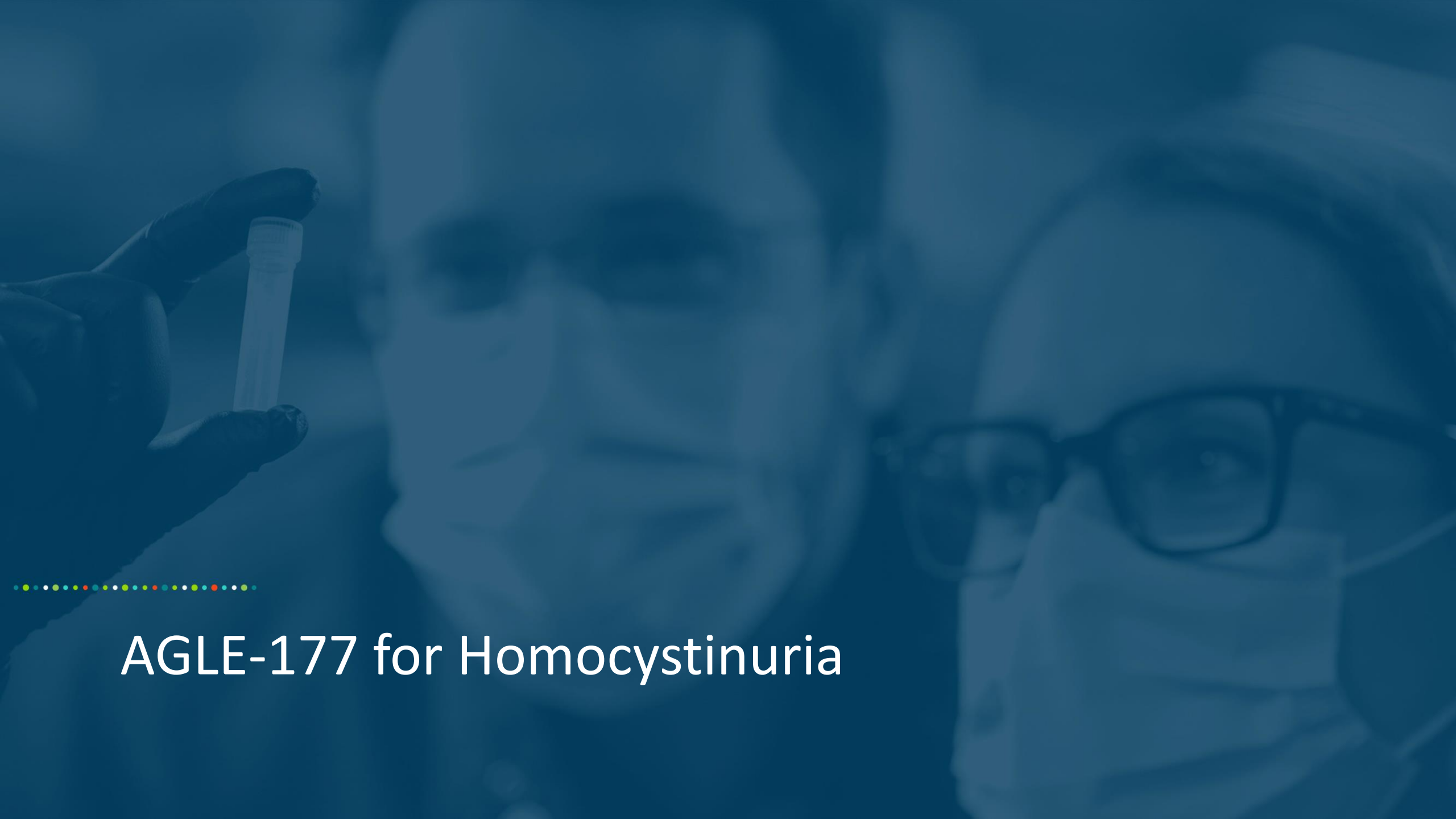

AGLE-177 for Homocystinuria

Homocystinuria Disease Overview

Homocystinuria (HCU):

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

Addressable Market:

>30,000 HCU patients[1]

Includes ~15,000 – 18,000
with B6-non-responsive disease[2,3]

Significant U.S. & EU4 + UK opportunity with ~6,000-6,600 B6-non-responsive patients[4]

Current disease management is inadequate with an inability to control homocysteine levels:

- Limited effectiveness
- Non-compliance
- Poor tolerability of amino acid supplementation and Betaine

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] >30,000 represents estimated prevalence of Classical Homocystinuria (including B6-responsive and B6-non-responsive) in 38 addressable markets. [2] Mudd et al 1985. [3] Kožich et al, 2020.
[4] ~6,000-6,600 represents estimated prevalence of B6-non-responsive Homocystinuria in the U.S (~3,300) and the EU4 plus UK (~3,300)

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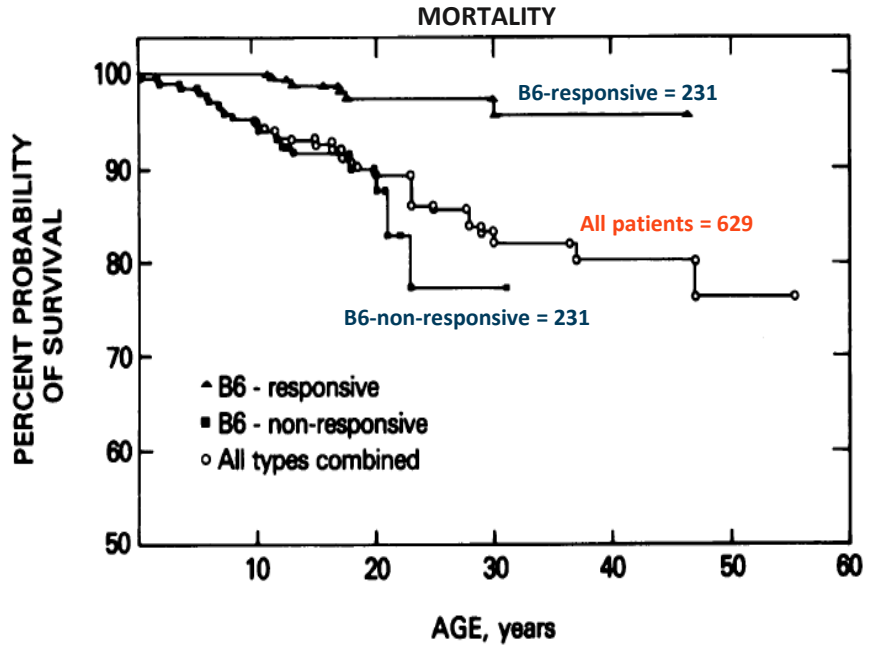
Increased Mortality and High Risk of Severe Complications

Natural History Study of 629 Untreated Classical Homocystinuria Patients



NATURAL HISTORY

	B6-non-responsive	B6-responsive
Elevated levels of homocysteine	⊕ ⊕ ⊕	⊕
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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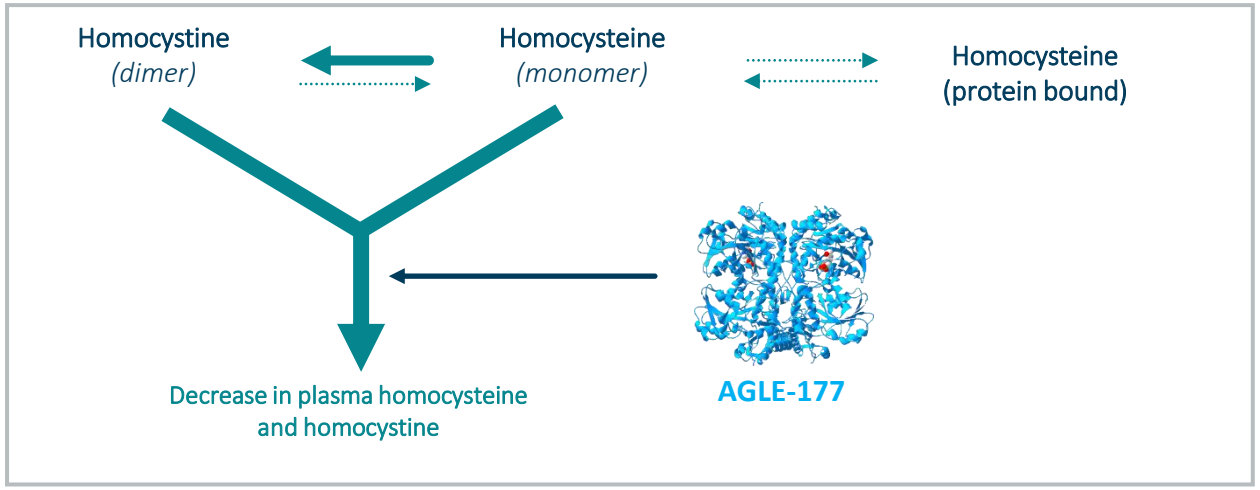
AGLE-177 for Homocystinuria Overview

Intracellular Metabolism – Normal & Disease State



Plasma Metabolism – AGLE-177



AGLE-177 Mechanism

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

Efficiently degrading both monomer and dimer creates steep concentration gradient aimed at driving intracellular homocysteine out of tissue

Therapeutic Rationale

- Elevated levels of plasma homocysteine increase risk for disease manifestations[1]
- Reduction of plasma homocysteine has been correlated with reduced risk of developing disease manifestations[2]
- Generally accepted aim of treatment is to lower the plasma homocysteine concentration to a safe level while maintaining normal nutrition
- Current treatments rarely sustain reductions in homocysteine

[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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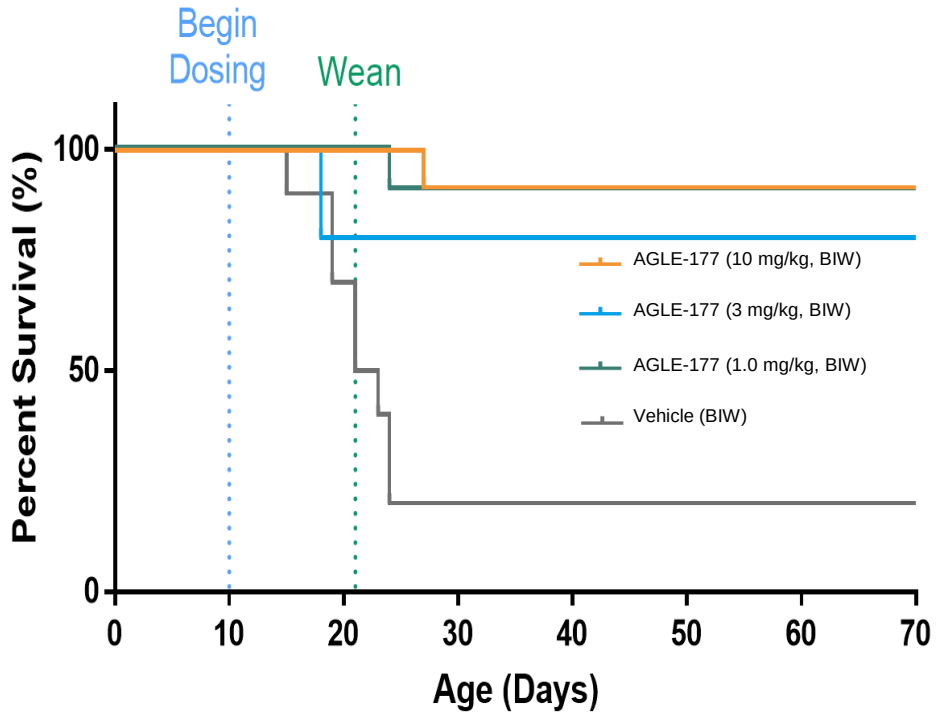
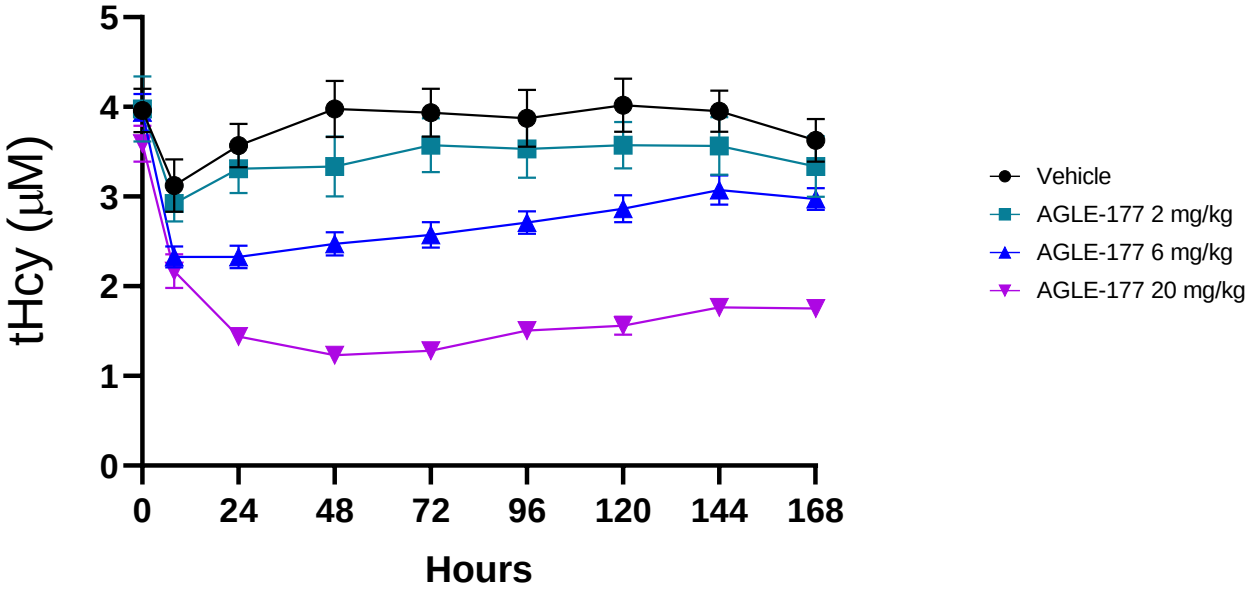
Preclinical Data Support Potential Advantages of AGLE-177

Marked survival benefit with total weekly dose as low as 2 mg/kg



- Twice weekly subcutaneous doses AGLE-177 in CBS -/- mouse model[1,3]
- Significant survival benefit with AGLE-177 at substantially lower total weekly dose of 2 mg/kg compared to a total weekly dose of 22.5 mg/kg reported for a competitor enzyme[2]

Demonstrated pharmacological effect on homocysteine level in normal animals in toxicology studies



- Substantial decreases in homocysteine after single subcutaneous dose in toxicology studies
- Pharmacological effect in normal animals dosed with AGLE-177 differentiated from reported data for a competitor enzyme[2]

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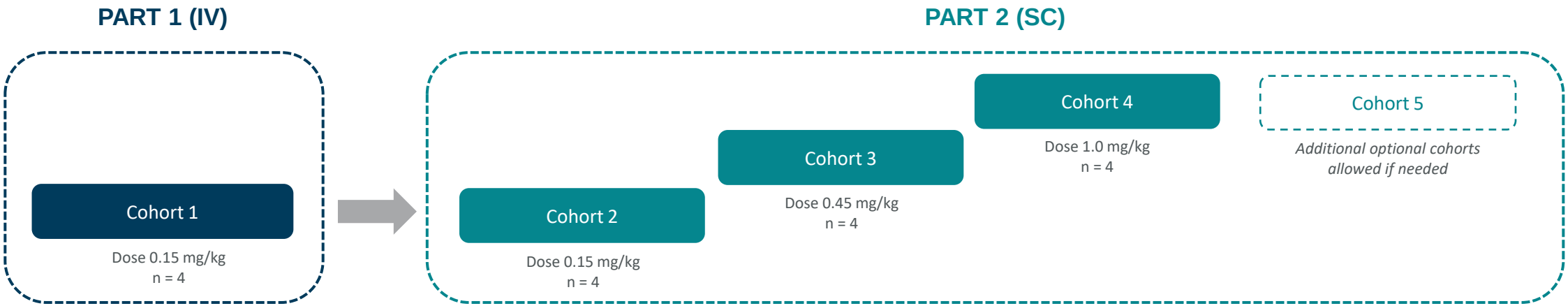
[1] Daige C. et al. Poster presented at ASHG 2020 Virtual Meeting. [2] Majtan T. et al., Life Sci. 2018; May 1;200:15-25. [3] Mice were maintained on betaine until weaning; tHcy = total homocysteine

Phase 1/2 Clinical Trial Design



Endpoints

- Safety and tolerability
- PK
- Reduction in plasma total homocysteine levels

Key Inclusion Criteria

- Classical Homocystinuria diagnosis
- Plasma homocysteine >80 µM
- ≥12 years of age

Enrollment & Dosing

- Anticipate enrolling 16-20 patients
- Weekly dosing for 4 weeks
- Sites in UK and Australia

IV = intravenous; SC = subcutaneous;

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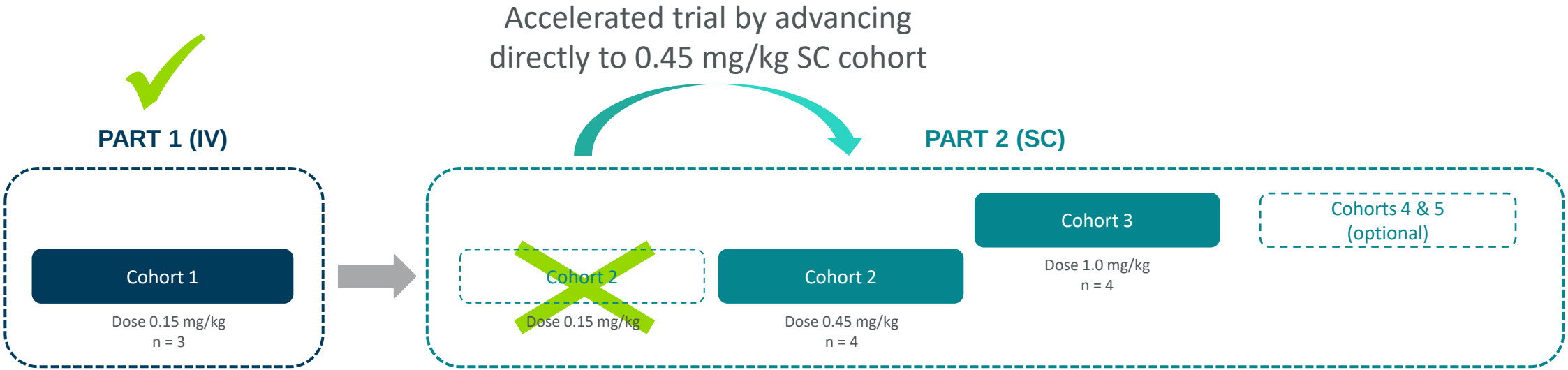
Phase 1/2 Clinical Trial – Study Acceleration

Completed Cohort 1 Dosing: Encouraging total homocysteine reduction in all patients; Safety and tolerability support advancement to higher subcutaneous dose



Submitted IND to the FDA in February 2022 and Plan to Open U.S. Trial Sites; Clinical Data Expected in 2H 2022

IV = intravenous; SC = subcutaneous;

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AGLE-177: a Potentially Differentiated Treatment for Homocystinuria

AGLE-177 Key Attributes

- ✓ Metabolizes both homocysteine (monomer) and homocystine (dimer)
- ✓ Showed total homocysteine reduction, no safety concerns in cohort 1 of Phase 1/2 trial
- ✓ Demonstrated significant survival benefit in CBS -/- mice at low total weekly doses
- ✓ Reduces homocysteine levels in CBS -/- mice with single and twice weekly dosing
- ✓ Demonstrated potency to reduce homocysteine from normal levels in normal rats and cynos

CMC

- Scaled up and optimized manufacturing process to commercial scale
- Registration manufacturing campaign in process
- Product characterization and analytical methods in place
- Stable, high concentration liquid formulation with real-time and stressed conditions stability data

Chronic Toxicology Studies

- Pharmacological effects and no significant findings in chronic toxicology studies
  - Well-tolerated at NOAEL of 6.67 mg/kg human equivalent dose in cynos[1] and juvenile rats[2] through 6-months of once weekly dosing
  - AGLE-177 related events were limited to dosing site reactions that resolved across species with recovery

Regulatory Designations

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

Phase 1/2 Clinical Data Expected in 2H 2022 and Well-Positioned to Advance into Potential Pivotal Study

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[1] Dosed subcutaneously; [2] Dosed intravenously; NOAEL = no observed adverse effect level



Human Enzyme Engineering Platform

Cystinuria Overview

Cystinuria:

Cystinuria is a metabolic disorder characterized by high levels of amino acid cystine in the urine, leading to the formation of stones in the kidney, ureter and bladder. Persistent stones can result in serious damage to the kidneys, causing an increased risk of hypertension and chronic kidney failure.

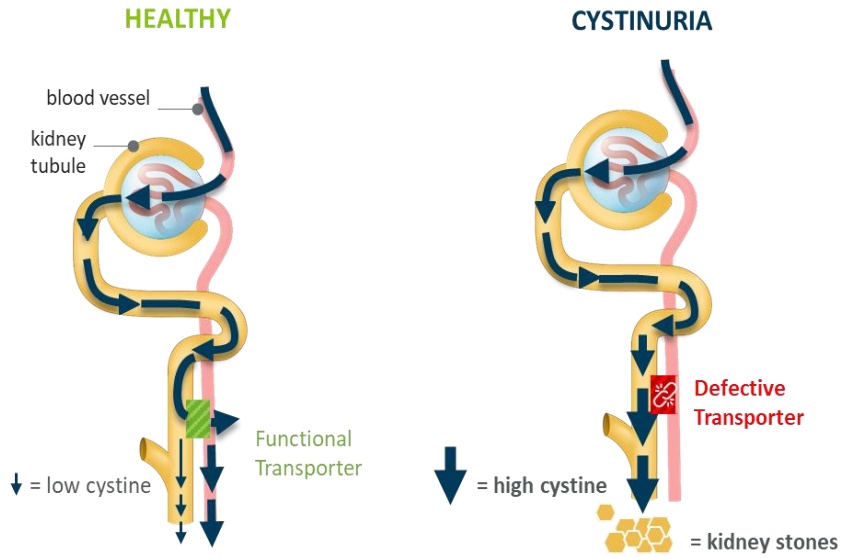
Addressable Market:

Estimated prevalence rate 1:15,000

Based on literature

>10,000

Patients in addressable markets



Low cystine in urine	High cystine in urine → cystine precipitates → stone formation
Healthy	Severe pain, surgical interventions, kidney failure

Biyani and Cartledge EAU-EBU Update Series 4 (2006) 175-183, Leslie and Nazzal Renal Calculi (Cystinuria, Cystine Stones) (2018)

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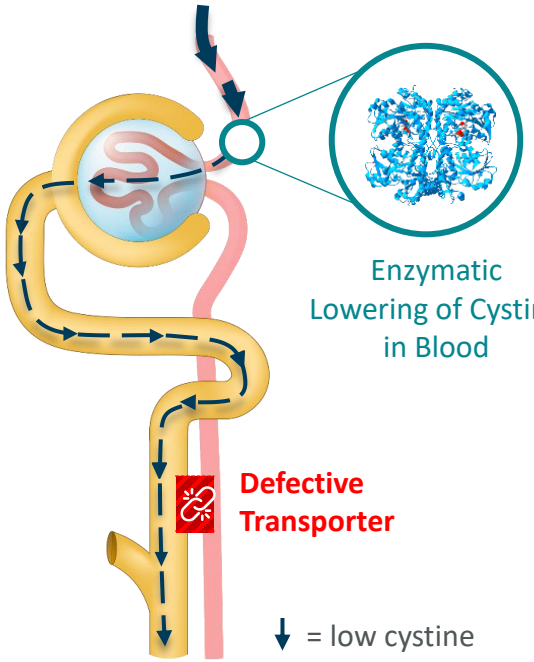
AGLE-325 Preclinical Advancement

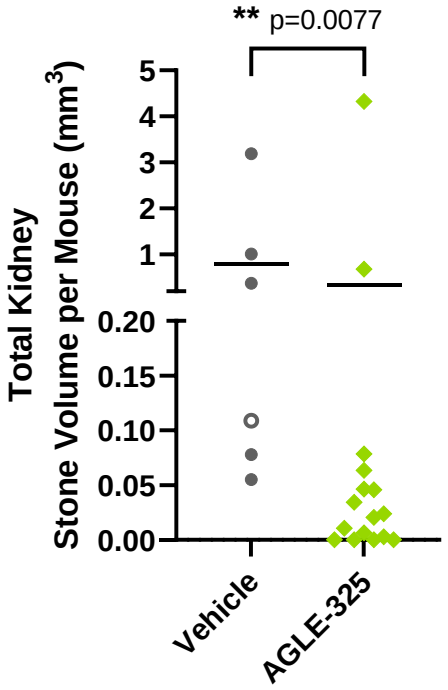
INNOVATIVE ENZYME APPROACH



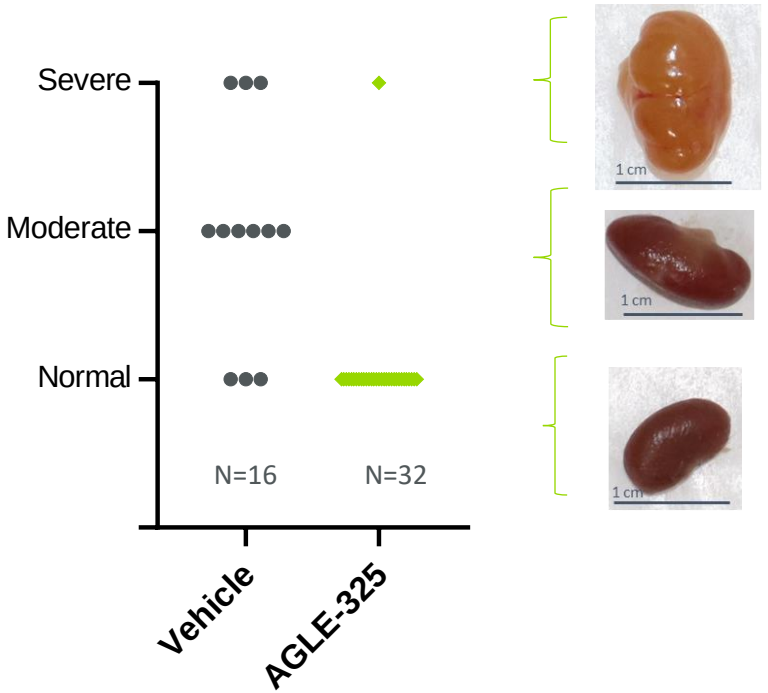
Enzymatic reduction of plasma cystine should lower urine cystine and reduce cystine stone formation

New candidate advanced through lead optimization with preclinical efficacy and PK/PD profile which support attractive clinical dosing schedule

µCT Kidney Stone Volume[1]



Kidney Pathology[1]



Plans to Advance AGLE-325 Through IND-Enabling Studies in 2022 and Potential Subsequent Initiation of First-in-Human Study

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[1] Experiments performed using a clinically relevant dose range; PK = pharmacokinetics; PD = pharmacodynamics

Leveraging Aeglea's Next Generation Human Enzyme Platform

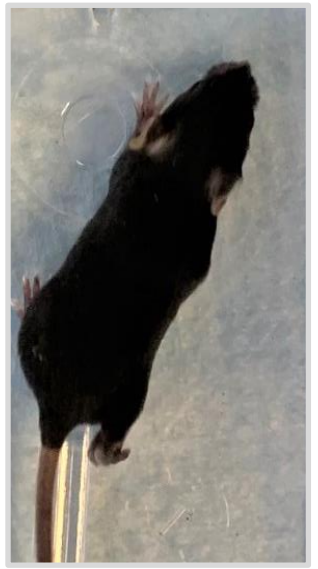
Therapeutic Approach	**Pegylated enhanced human enzyme** • Enzymatic control of high levels of a metabolite considered important in disease pathogenesis
Unmet Medical Need	• Very high - no effective therapy • Early mortality and serious complications with continued disease progression
Patient Population (Addressable Markets)	• **>5,000** patients
Diagnosis	• Plasma metabolite levels and mutation analysis

PROOF OF CONCEPT

Vehicle Control



Therapeutic Enzyme



- High activity human pegylated investigational enzyme
- Degrades key accumulating metabolite
- Results in restorative phenotypic improvements in genetically engineered mouse model

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Summary

Recent Accomplishments and 2022 Outlook

Key Highlights

Pegzilarginase (Arginase 1 Deficiency)

- Met with FDA in late February 2022
- Announced positive topline Phase 3 data
  - Reduced arginine by 80%; normalized plasma arginine levels in 90.5% of patients; trend in mobility measure
- Progressed key launch objectives including:
  - Patient identification and profiling of population and prescriber base; payer engagement; advancing patient services and distribution activities

AGLE-177 (Homocystinuria)

- Dosing patients in cohort 2 (0.45 mg/kg SC) of Phase 1/2 study
  - Cohort 1 (0.15 mg/kg IV): Well-tolerated with no safety concerns, reductions in total homocysteine in all patients
- Advanced manufacturing, formulation work to enable Phase 3 trial
- Completed long-term toxicology studies

Looking Ahead

Pegzilarginase

- Submit U.S. BLA (2Q 2022), EU MAA (2022)
- Continue preparations for strong, rapid launch in U.S., Europe and Middle East
- Presentation of PEACE data at SIMD; publication of long-term data

AGLE-177

- Clinical data from Phase 1/2 trial (2H 2022)
- Plan to open U.S. sites (submitted IND in February 2022)

AGLE-325 (Cystinuria)

- IND-enabling studies for optimized molecule

SC = subcutaneous; IV = intravenous

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Financial Summary

Cash, cash equivalents and marketable securities as of December 31, 2021: $95.0 million[1] (no debt)

As of December 31, 2021, 65.9 million[2] common shares and pre-funded warrants outstanding

$ Millions	Year Ended 12/31/21	Year Ended 12/31/20
Revenue	$18.7*	-
R&D Expense	$57.1	$59.6
G&A Expense	$27.3	$21.8
Net Loss	$65.8	$80.9

Expected funding runway: into first quarter of 2023

[1]Includes $1.8mm of restricted. [2]Includes 49.3 million common shares outstanding and 16.6 million pre-funded warrants. *Includes $12.0 million of license revenue and $6.7 million of development fee revenue.

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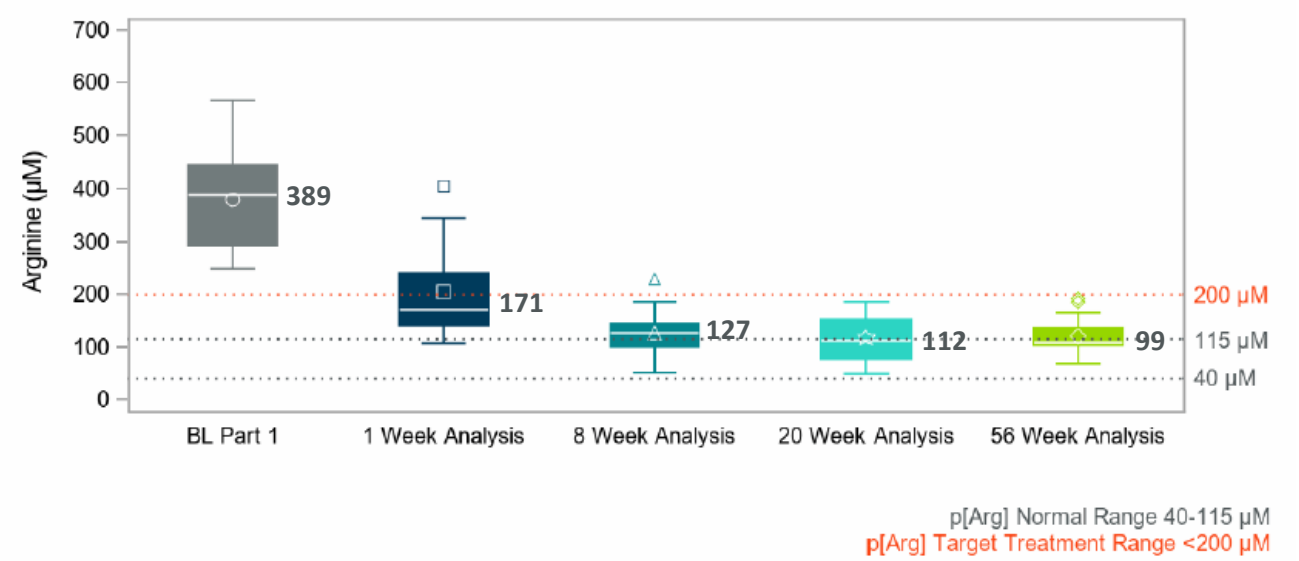
Pegzilarginase Significantly and Sustainably Reduces Plasma Arginine Levels in Phase 1/2 & OLE

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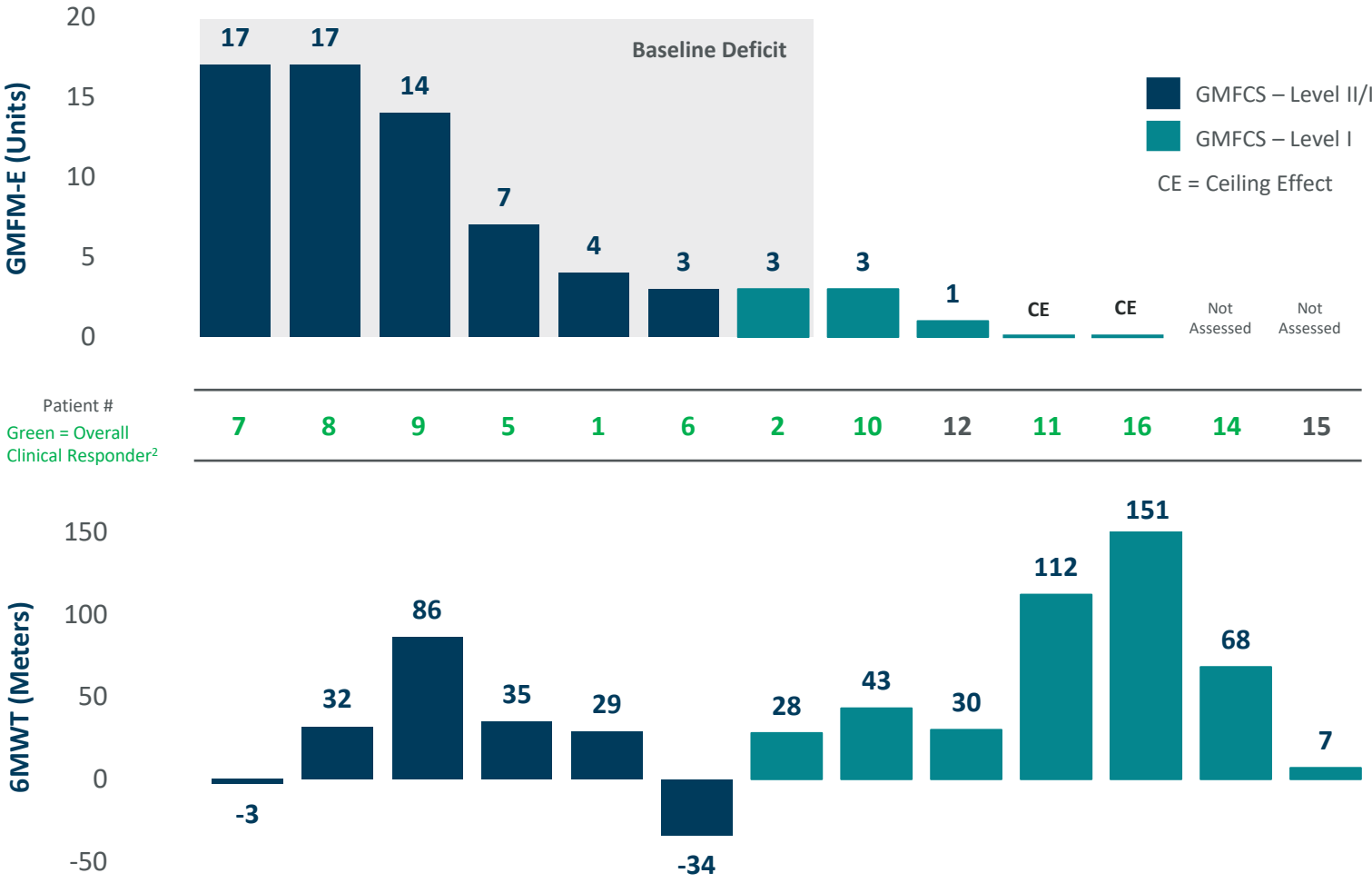
Mobility Assessments Capture Potential Clinical Benefit of Pegzilarginase in Phase 1/2 Trial & OLE

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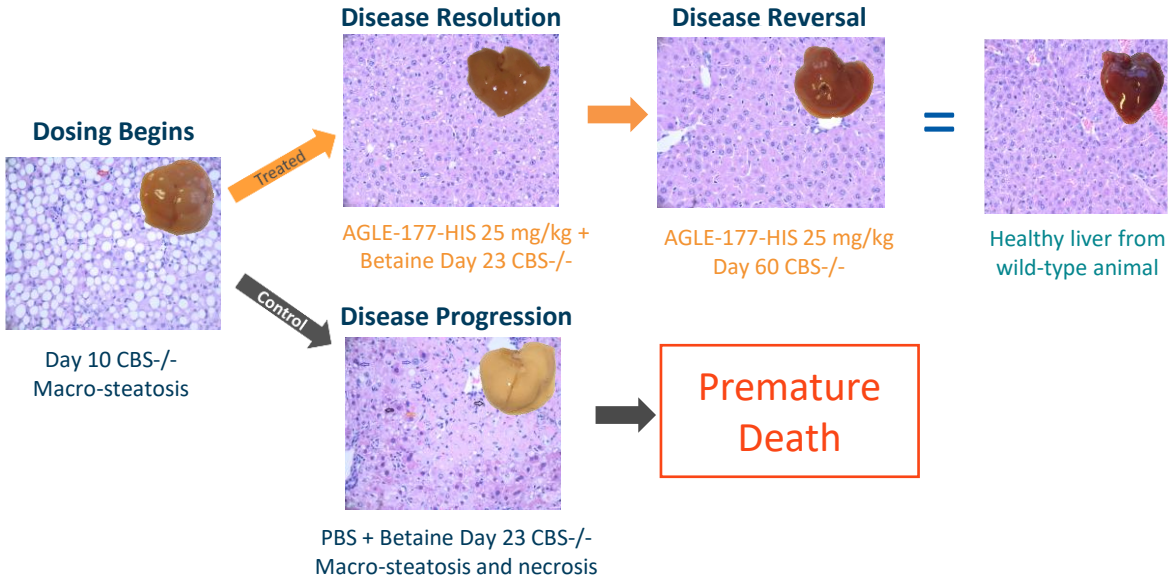
[1]Adapted from Diaz, GA et al, Presented at 2020 European Academy of Neurology Annual Meeting; [2]Clinical Responder defined by achievement of a clinically meaningful response in one or more of three mobility assessments; GMFCS = Gross Motor Function Classification System; OLE = open-label extension;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

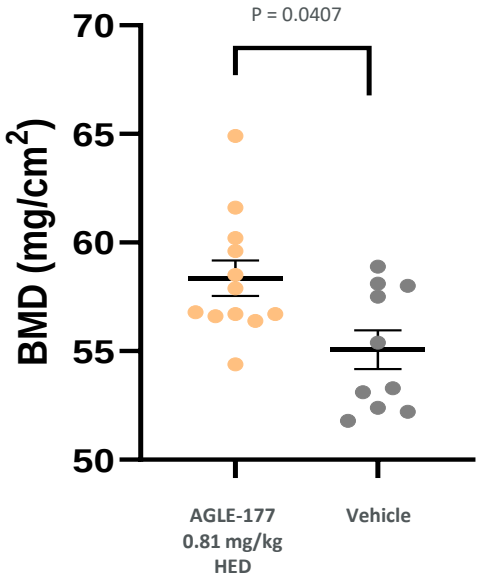
AGLE-177 Improves Pathologies and Correction of Disease Manifestations in a Preclinical Model of Homocystinuria

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



Reductions in total plasma homocysteine leads to improvements in disease related abnormalities

Effects on the Long-term Pathologies of Osteoporosis[2,3]



Increased BMD in preclinical model of Homocystinuria with multiple doses of AGLE-177

[1] Daige C. et al. Poster presented at ASHG 2018 Annual Meeting [2] Daige C. et al. Poster presented at ASHG 2020 Annual Meeting [3] CBS -/- mice were dosed subcutaneously twice weekly with AGLE-177-HIS starting at D10 through Day 169 were evaluated for bone mineral density (BMD) by dual-energy X-ray absorptiometry; HED = human equivalent dose

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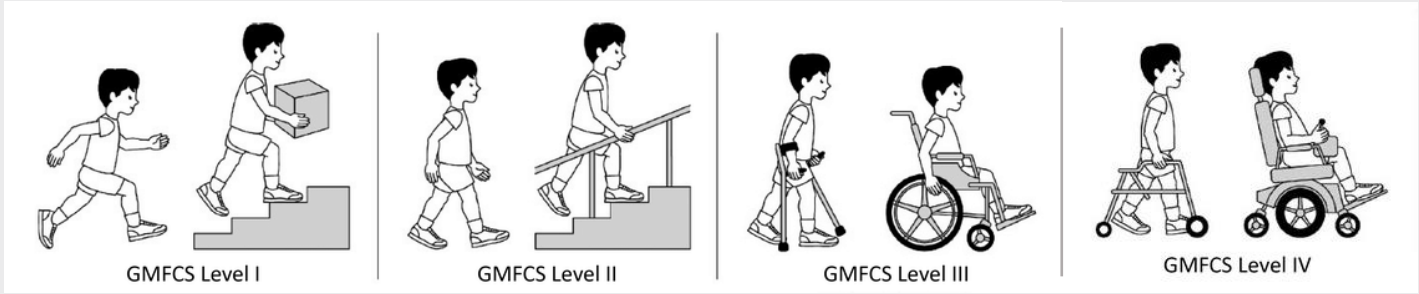
Measuring the Functional Impact of Spasticity in ARG1-D

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