Reimagining The Potential Of Human Enzyme Therapeutics

Corporate Overview – December 2021

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 Quarterly Report on Form 10-Q 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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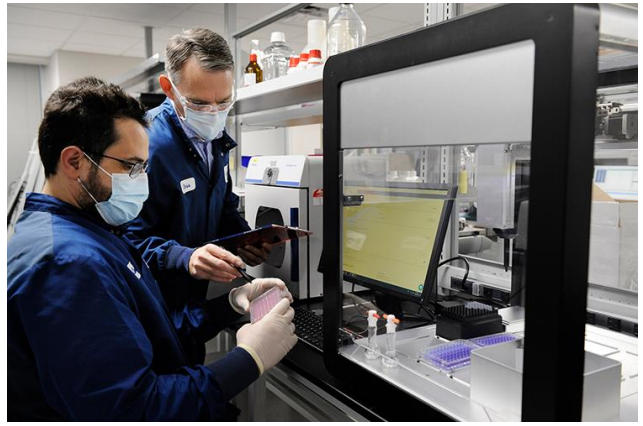
Delivering Metabolic Harmony

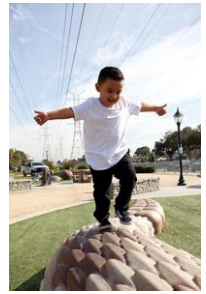
Aeglea BioTherapeutics

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 because having a rare disease doesn't mean that you are in the fight alone.











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Looking Beyond the Conventional with Next Generation Human Enzyme Therapeutics

Expertise and focus in rare genetic disease

Efficient and agile development process

Tailored, innovative market approach

Discovery

- Specialized expertise in human enzyme engineering
- Distinctive disease selection approach
- Validated metabolite targets
- Translatable disease models
- Reduced toxicology risk

Development and regulatory

- Established manufacturing approach
- Faster, smaller clinical trials
- Innovative trial design to meet needs of patient communities
- Favorable regulatory access

Commercial

- Patient-centric mindset to ensure access to impactful therapies
- Attractive reimbursement potential
- Substantial barriers to entry
- Highly efficient and targeted approach

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Aeglea's Human Enzyme Platform for Rare Metabolic Diseases

Program	Indication	Research	Phase 1/2	Phase 3	Approved	Addressable Market
Pegzilarginase[1] Immedica pharma	Arginase 1 Deficiency					>2,500 Patients[2]
AGLE-177	Homocystinuria					>30,000 Patients[3]
Research Programs	Cystinuria					>10,000 Patients[4]
	Undisclosed Rare Diseases					

[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] ARG1-D case reports ; 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

Pegzilarginase Program Overview

Arginase 1 Deficiency (ARG1-D)

ARG1-D is a serious, progressive disease with early mortality and high unmet medical need due to an autosomal recessive disorder of arginine metabolism.

Addressable Market:

>2,500 patients

Genetic prevalence estimates

>500 patients in US and EU4 + UK

Continued patient identification momentum across key markets

Status:

- Phase 3 topline data announced in December 2021
- Ongoing extension studies
- BLA filing planned in 1H 2022

Regulatory Designations:

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

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 (tiptoe 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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ARG1-D Patient Needs Not Adequately Addressed by Standard of Care



Current standard of care:

- Severe dietary protein restriction
- Amino acid supplementation
- Ammonia scavengers



Current disease management is inadequate:

- Limited effectiveness
- Challenging to maintain
- Doesn't address non-dietary sources of arginine

Key Areas of Unmet Medical Need in ARG1-D

1. **Diagnosis:** Delays in diagnosis and misdiagnoses are common due to lack of disease awareness
2. **Arginine Management:** Patients are rarely, if ever, able to reach targeted arginine levels
3. **Disease Progression:** Ineffective and burdensome treatment options result in disease progression and poor outcomes

No Treatments or Approved Therapies that Effectively Reduce Arginine Levels

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First Potential Therapy to Normalize Plasma Arginine Levels in ARG1-D

Substantial Reduction in Plasma Arginine	**Phase 3 Primary Endpoint Met** • 80% reduction in plasma arginine at 24-week analysis ($p<0.0001$)‡ **Additional Evidence of Arginine Control** • 90.5% of patients achieved normal plasma arginine levels ($p<0.0001$)*
Impact on Mobility	**Positive Trend In Mobility Assessment** • GMFM-E mean score improved by 4.2 units with pegzilarginase and worsened by 0.4 units with placebo • Least squares mean difference of 4.6 units ($p=0.1087$)
Favorable Safety Profile	**Well-Tolerated** • Safety data consistent with results from previous clinical trials • No treatment discontinuations due to adverse events

Lowering Plasma Arginine Accompanied by Improvement in Mobility

Pivotal Data Supports Planned BLA Submission in First Half of 2022

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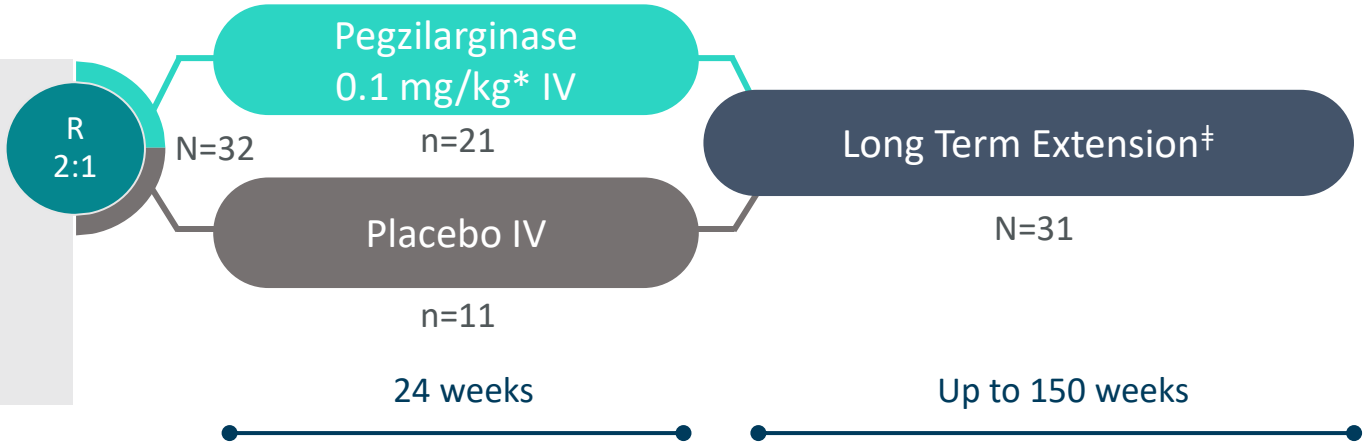
GMFM-E = Gross Motor Function Measure Part E which is comprised of 24 individual tasks of walking, running and jumping, each scored from 0 to 3 for a total possible score of 72; ARG1-D = Arginase 1 Deficiency; ‡geometric mean; *nominal p value

PEACE Phase 3 Study Design

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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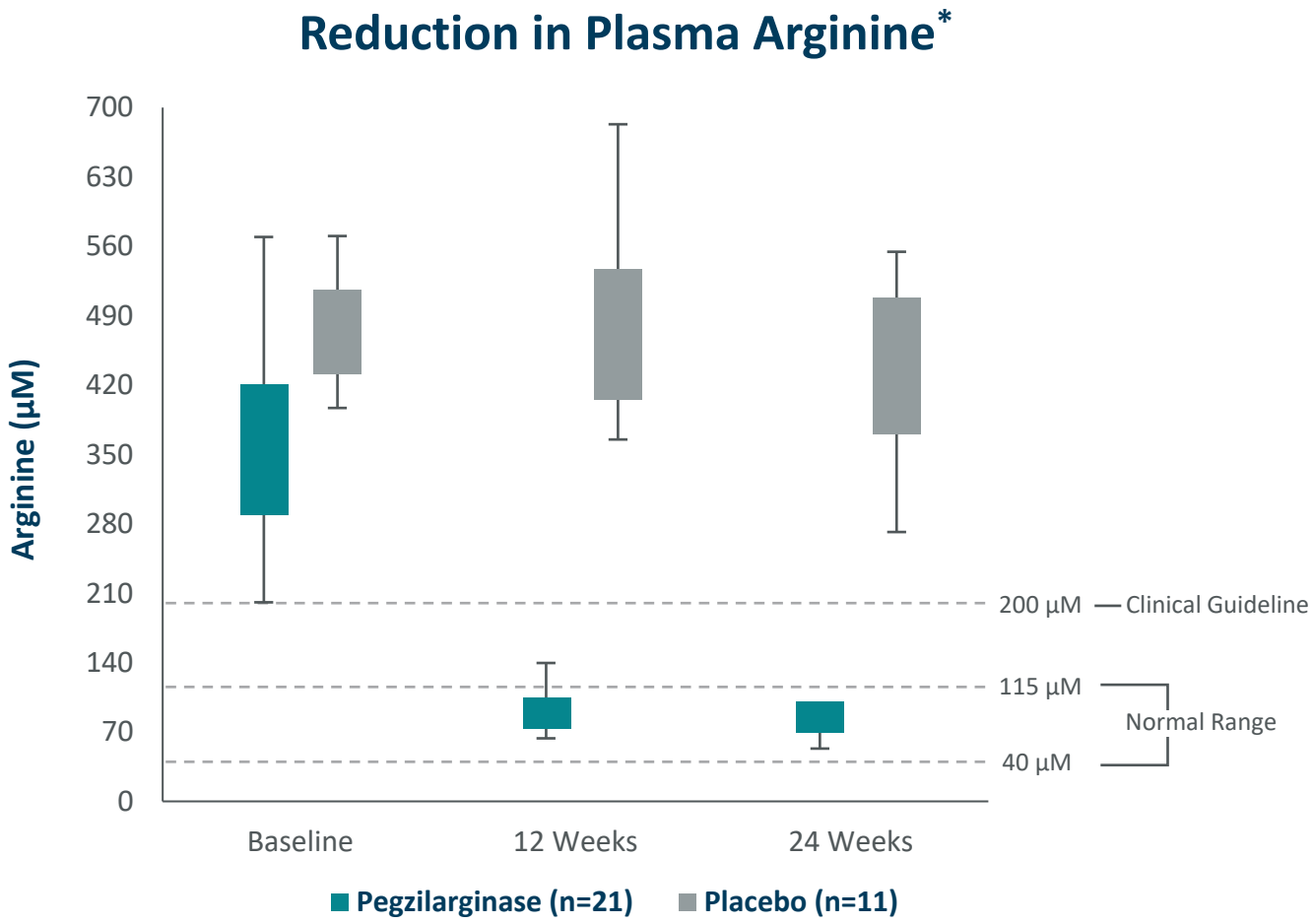
Primary Endpoint Met – Marked and Sustained Reduction in Plasma Arginine



- 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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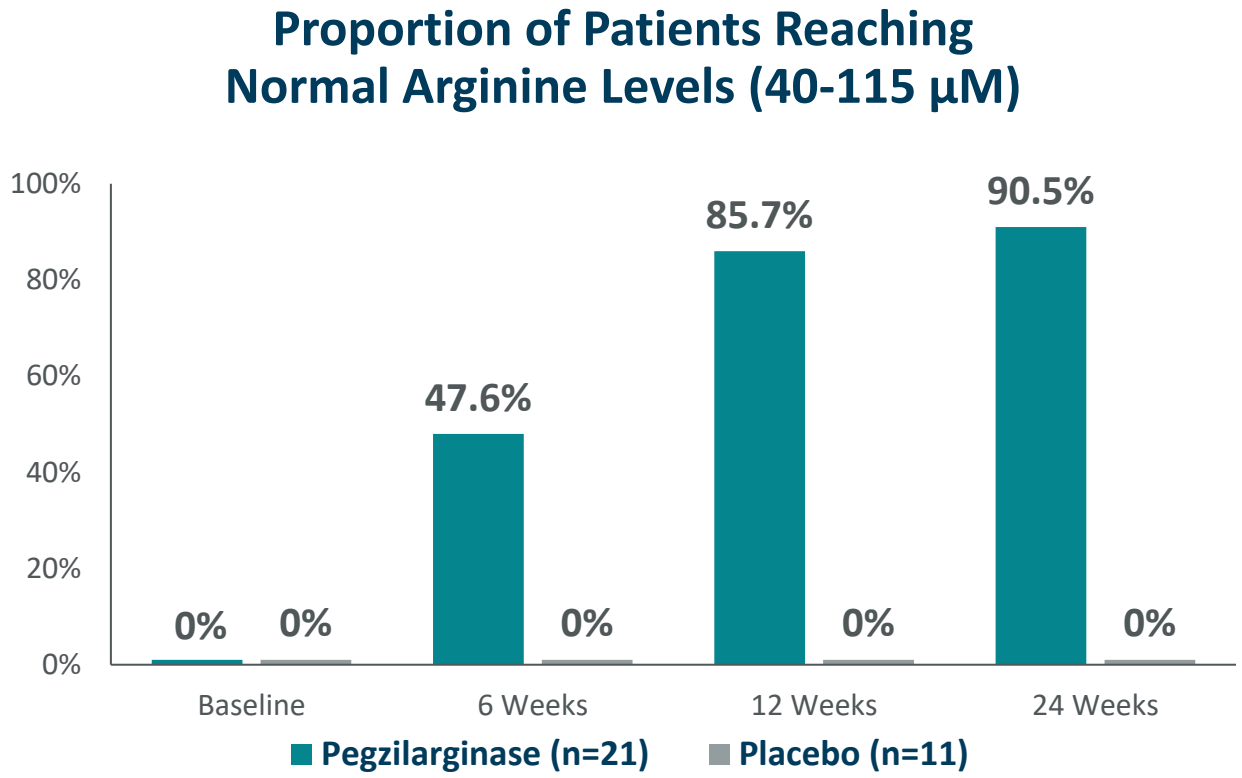
Normalization of Plasma Arginine Levels in ARG1-D Patients



- 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 Key Mobility Measurements

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, each scored from 0 to 3 with a total score range of 0-72





2-Minute Walk Test

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



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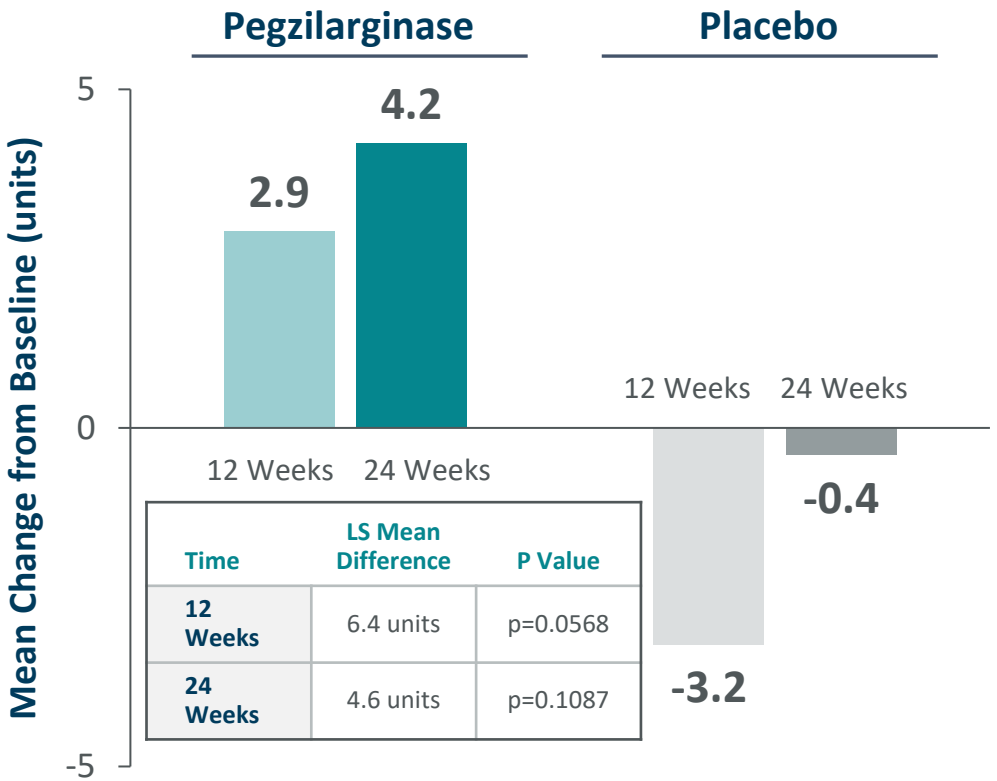
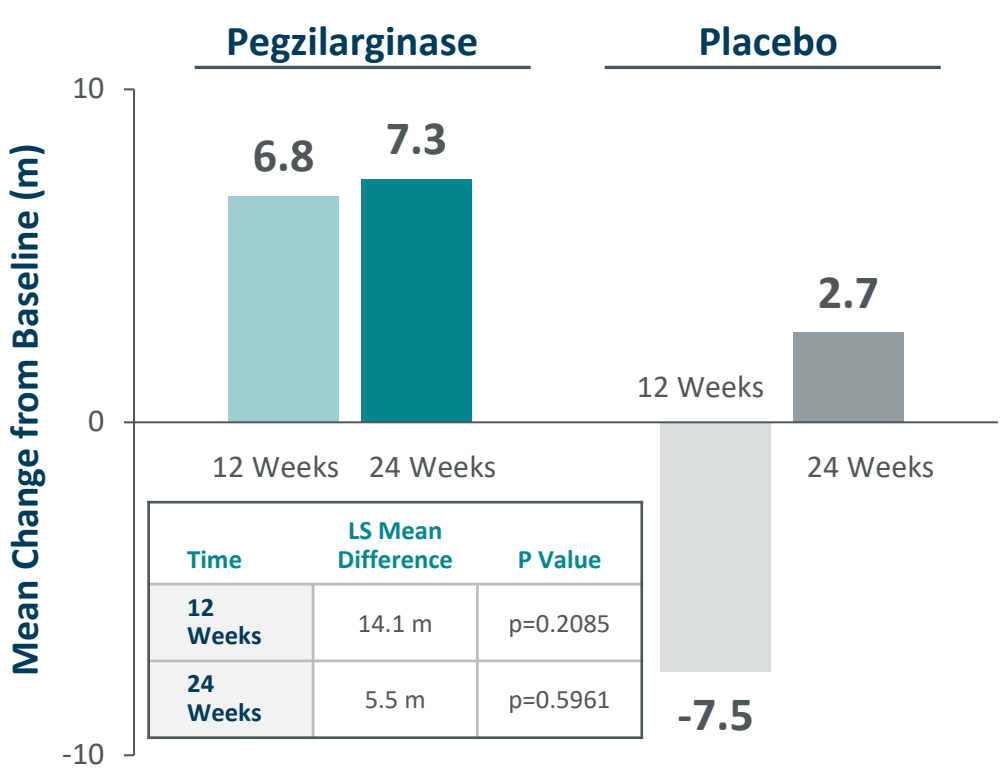
PEACE Mobility Assessed by GMFM-E and 2MWT

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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Pegzilarginase Safety Profile

PEACE Topline Safety Summary

Patients With:	Pegzilarginase n (%)	Placebo n (%)
Any TEAE *	18 (85.7)	11 (100.0)
Drug-related TEAE	5 (23.8)	1 (9.1)
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)

Safety Summary from Ph 1/2 & OLE

- Approximately 1,850[1] doses administered
  - Approximately 500[1] intravenous doses
- Most treatment-related adverse events were mild
- The frequency of treatment-related adverse events decreased over time
- Hypersensitivity and hyperammonemia were the most common treatment-related serious adverse events; expected and manageable

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
[1] Dose data as of June 11, 2021

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Robust Data Package Generated For Pegzilarginase Program

Clinical Data

- PEACE demonstrated normalization of elevated plasma arginine levels accompanied by a positive trend in mobility assessment
- Favorable long-term data from Phase 1/2 OLE, consistent with PEACE results
- Additional PEACE LTE data available to support filing

Manufacturing

- Robust straightforward biologics manufacturing process
- Well understood regulatory CMC path
- Commercial formulation on stability

Regulatory Designations

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

Substantial Derisking of Path to Successful Commercial Launch

OLE = open label extension; LTE = long-term extension

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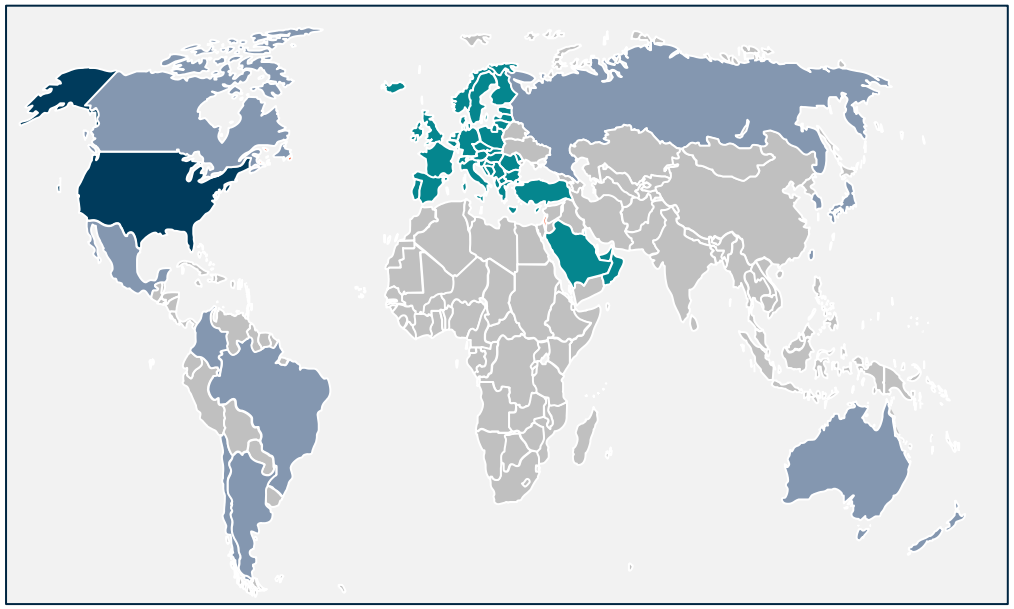
Attractive Commercial Opportunity for Pegzilarginase in ARG1-D

Significant Unmet Need

- Severe and progressive disease with early mortality
- Easily diagnosed but often missed due to lack of awareness
- Standard of care provides poor control of plasma arginine levels
- No approved therapies to address high arginine levels

Estimated Prevalence of >2,500 Patients in Key Global Markets



United States
>250 patients

Western Europe and Middle East[1]
>900 patients

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

[1] 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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Building the Foundation for a Successful Launch and Enduring Commercial Presence



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

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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 no-charge diagnostic testing
  - 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 Europe and the Middle East
- Commercial infrastructure built with pegzilarginase and earlier-stage pipeline programs in mind

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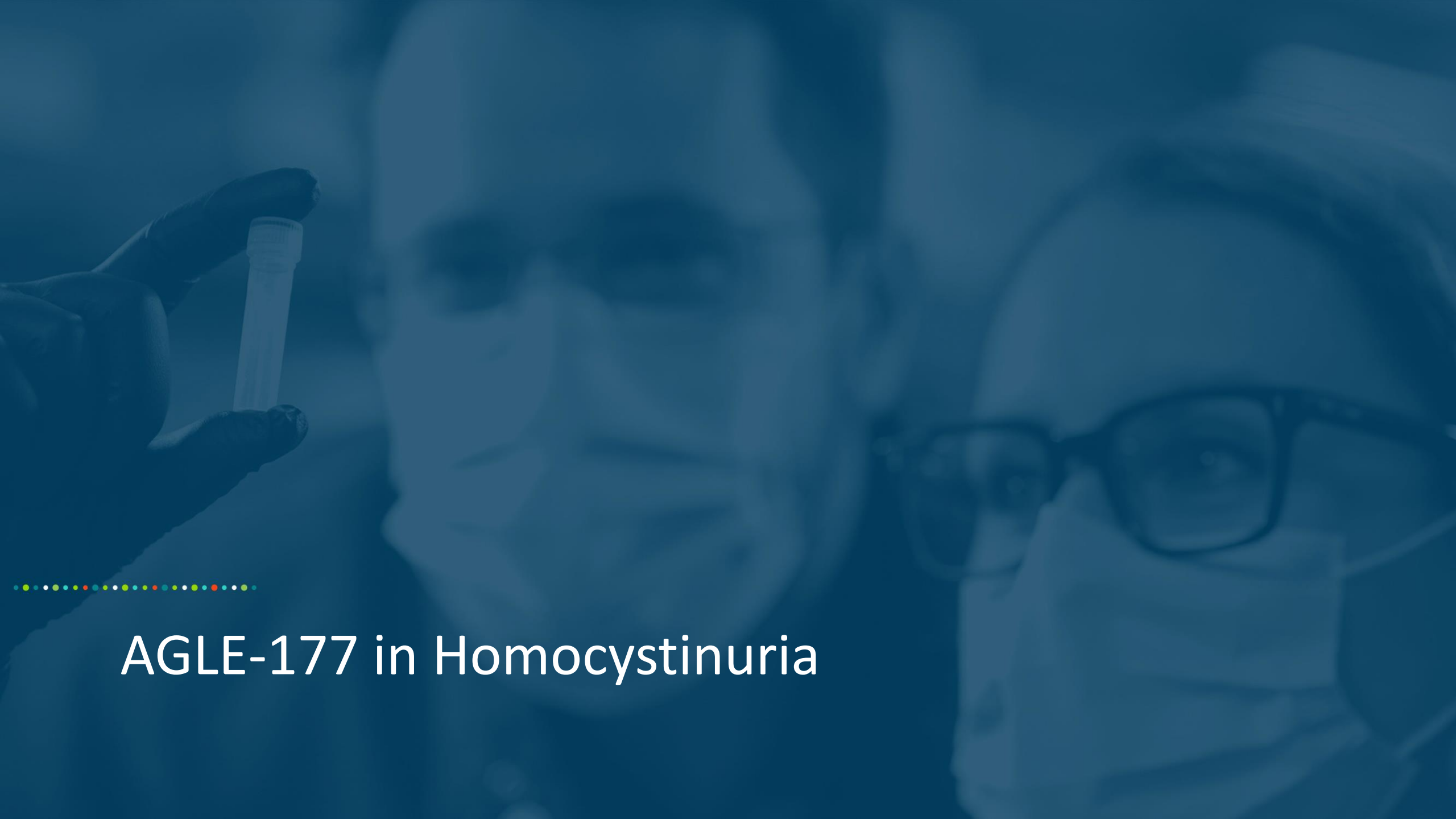

AGLE-177 in Homocystinuria

AGLE-177 Program Overview

Homocystinuria (HCU):

Cystathionine beta synthase (CBS) deficiency, also known as Classical Homocystinuria, is a serious and progressive metabolic disorder characterized by elevated levels 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]

Status:

- Enrollment ongoing in Phase 1/2 clinical trial

Regulatory Designations:

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

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

PRV – Priority Review Voucher
[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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Current Homocystinuria Treatments Have Limited Effectiveness and Create a Significant Burden for Patients



Current standard of care:

- B6 (pyridoxine) for responsive patients
- Low-methionine diet + amino acid supplements
- Betaine



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

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

KEY AREAS:

1. **Therapy-resistant patients** on standard disease management
2. **Patients who are at high risk of non-compliance** which places them at increased risk of severe complications
3. **Patients intolerant of available adjunctive therapies** due to either safety issues or other adverse reactions

Unmet Need: Therapy that addresses both disease and treatment burden

tHcy – Total plasma homocysteine

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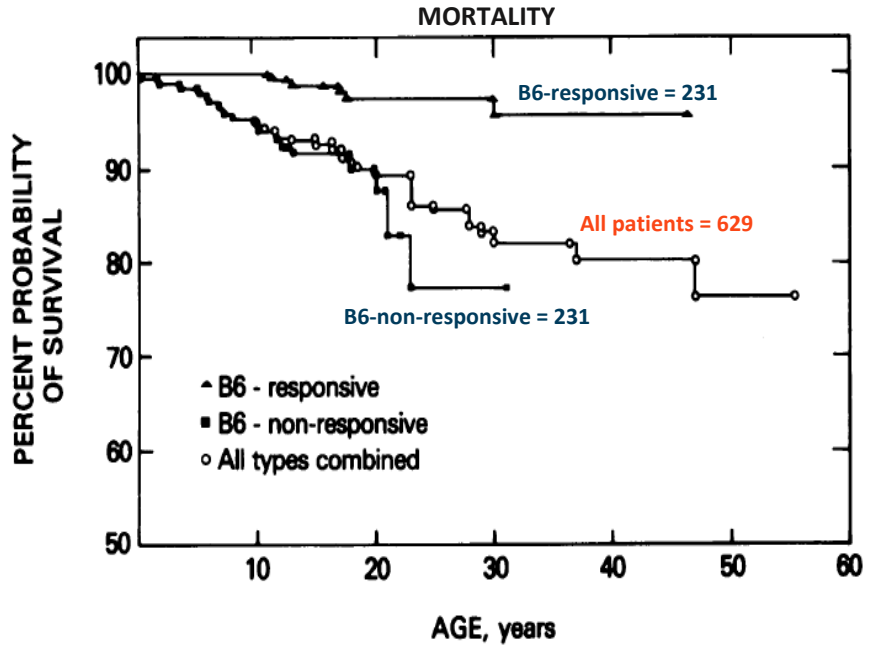
Increased Mortality and Severe Complication Risk in Patients with Homocystinuria

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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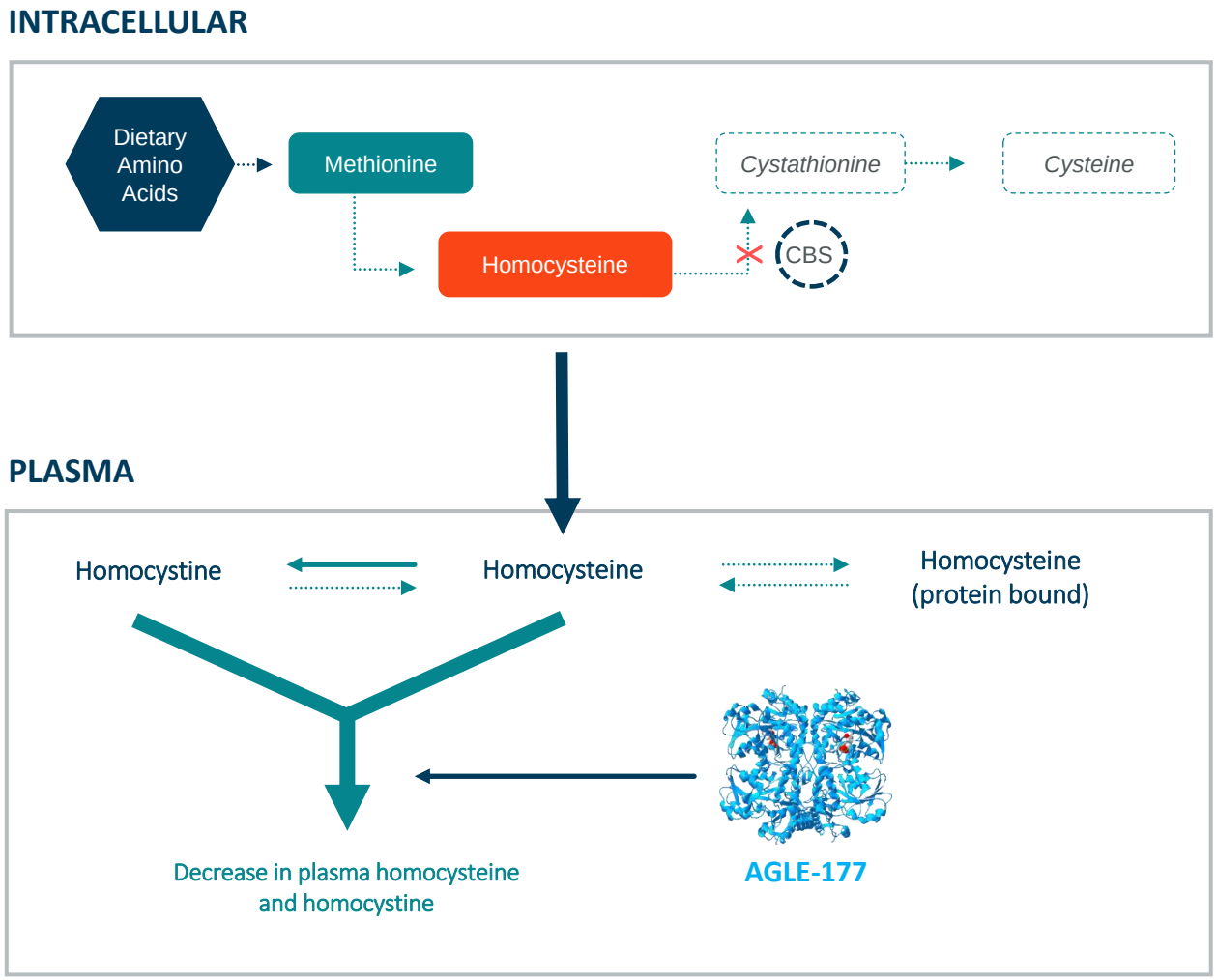
Therapeutic Goal is to Improve Control of Total Plasma Homocysteine



Therapeutic Rationale

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

AGLE-177

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

Advantage

Degrading both homocysteine and homocystine is likely to enable more efficient lowering of plasma homocysteine levels

[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
tHcy – Total plasma homocysteine

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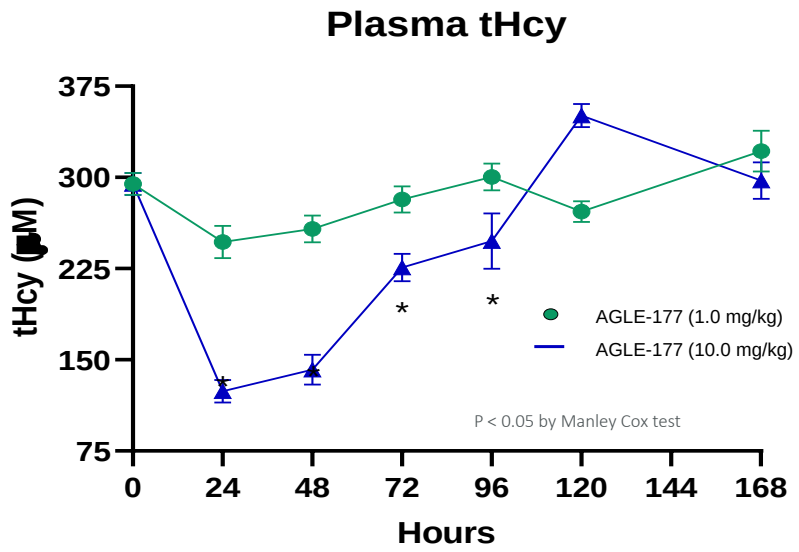
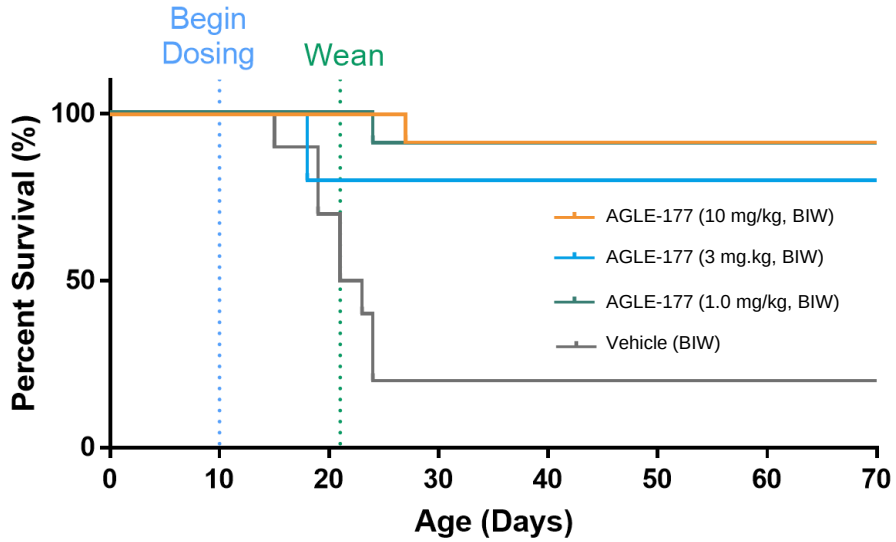
Subcutaneous Dosing Reduces Total Plasma Homocysteine and Improves Survival in Preclinical Model

Single SC Dose in CBS -/- Mouse Model[1,2]



AGLE-177 statistically significant reduction in total plasma homocysteine

In Vivo Efficacy at Multiple SC Dose Levels[1,3]



Improvement in survival following subcutaneous treatment in CBS-/- mouse model

[1] Daige C. et al. Poster presented at ASHG 2020 Virtual Meeting. [2] CBS -/- mice were dosed twice per week (BIW) starting at D10 with 10.0 mg/kg AGLE-177 for 5 weeks to ensure survival. ADA development that impacts the PD response cannot be ruled out at this latter timepoint. Animals underwent a two-week washout of drug followed by a single subcutaneous (SC) injection of AGLE-177 and PD assessed (tHcy) over 1 week. [3] Animals dosed SC BIWx3. tHcy = total Homocysteine

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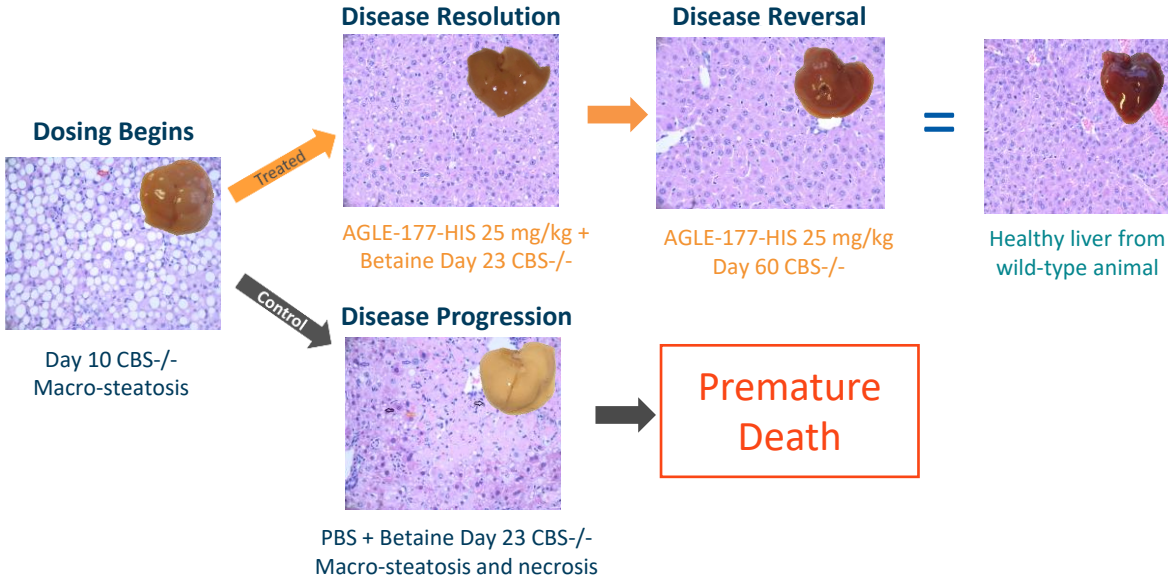
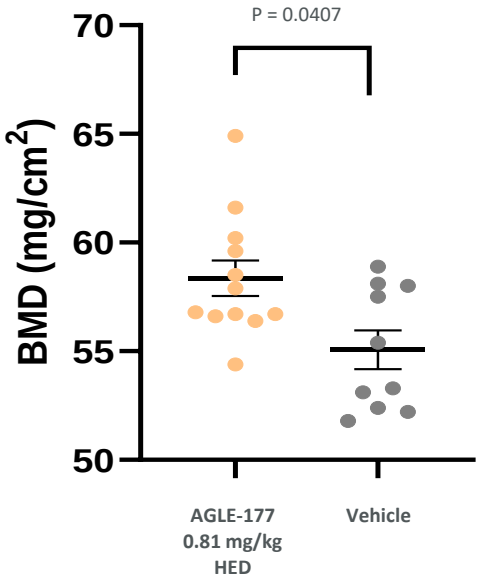
AGLE-177 Improves Pathologies and Correction of Disease Manifestations in a Preclinical Model of Homocystinuria

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



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



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

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 SC BIW with AGLE-177-HIS starting at D10 through Day 169 were evaluated for bone mineral density (BMD) by dual-energy X-ray absorptiometry

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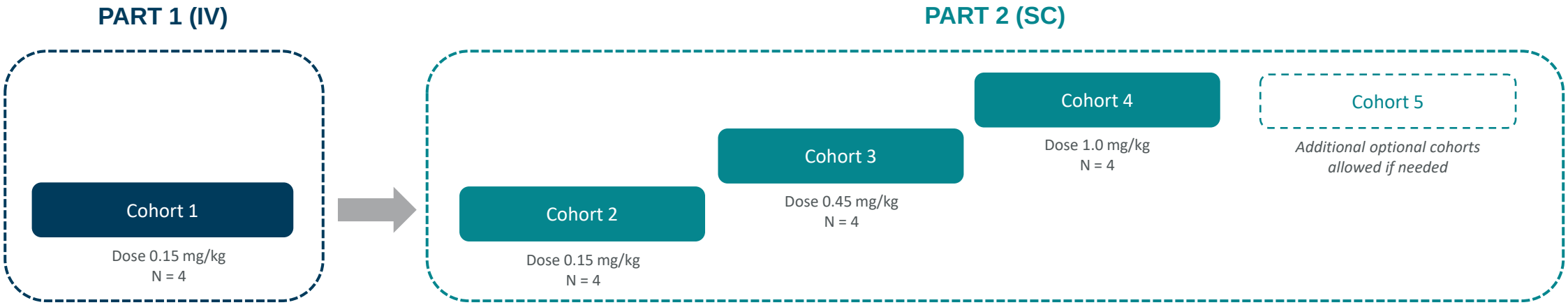
AGLE-177 for Homocystinuria – Enrollment and Dosing Underway



Endpoints

- Safety and tolerability
- PK
- Reduction in plasma total homocysteine (tHcy) levels

Key Inclusion Criteria

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

Enrollment & Dosing

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

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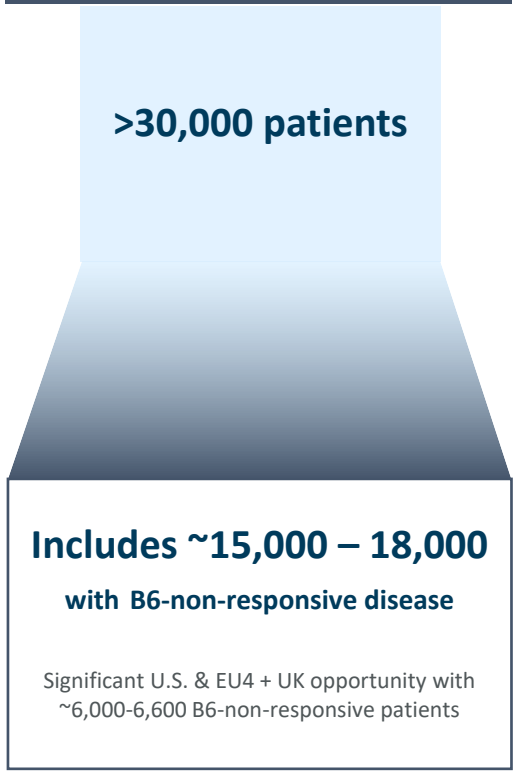
AGLE-177 Program – Key Highlights

ADDRESSABLE MARKET



REGULATORY DESIGNATIONS

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

Limited effectiveness of SOC

Limited effectiveness of lowering homocysteine, non-compliance and poor tolerability of low methionine diet and Betaine

AEGLEA'S APPROACH

- AGLE-177 is an engineered human enzyme designed to address the needs of this patient population which we anticipate will lower the harmful plasma homocysteine levels

Currently enrolling

Phase 1/2 clinical trial

PRV – Priority Review Voucher

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Human Enzyme 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.

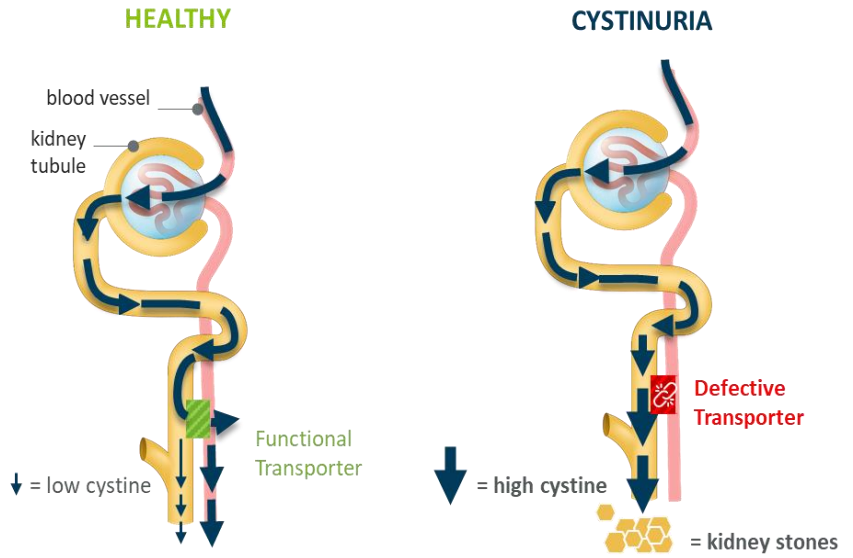
Addressable Market:

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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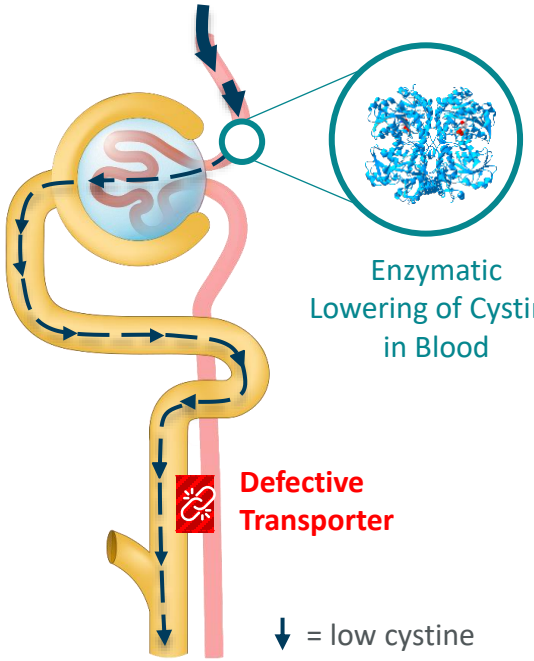
Novel Therapeutic Approach for Cystinuria – Enzymatic Reduction of Cystine in Blood

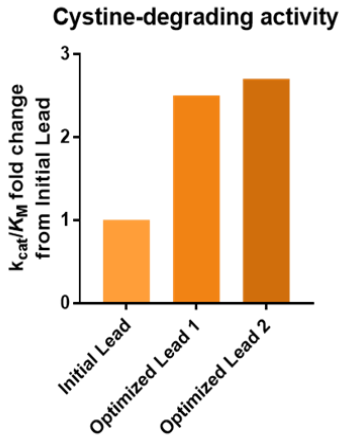
INNOVATIVE ENZYME APPROACH



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

Protein Engineering

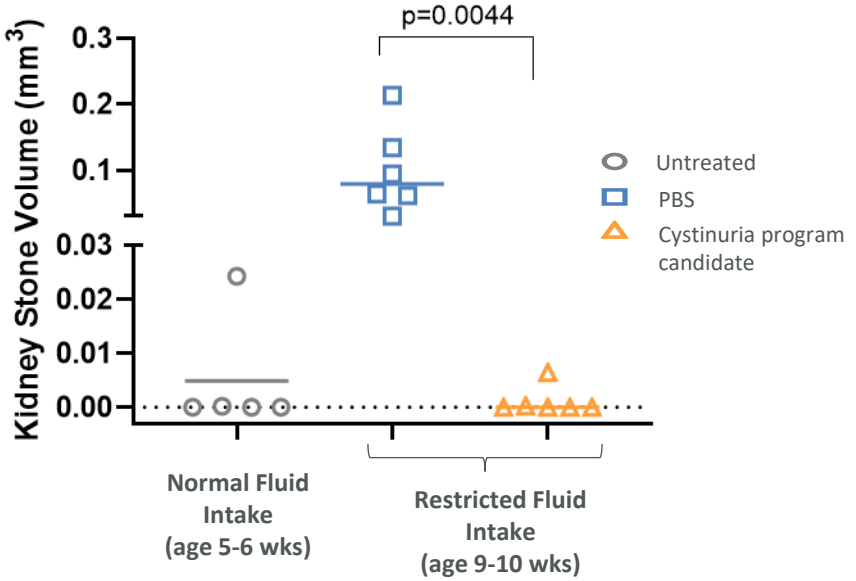
Creating Novel Cystine Degrading Activity[1]



- Increase catalytic activity
- Increase serum stability
- Improve manufacturability

Proof of Concept in Preclinical Cystinuria Model

Prevention of Kidney Stone Formation in Cystinuria Model (Slc3a1 -/- mice)[2]



[1]Cramer SL et al, 2017 Nature Medicine 23:120-7; [2]Agnello, et al American Society of Nephrology #TH-P0815

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Leveraging Aeglea's Next Generation Human Enzyme Platform

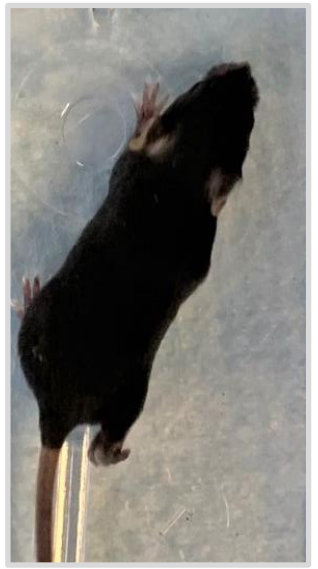
Therapeutic Approach	**Pegylated enhanced human enzyme** • Enzymatic control of high levels of a metabolite considered important in disease pathogenesis
Unmet Medical Need	• Very high - no effective therapy • Early mortality and serious complications with continued disease progression
Patient Population (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

Strong Momentum with Near-Term Catalysts

PROGRAM HIGHLIGHTS

Pegzilarginase: ARG1-D

- PEACE Phase 3 data supports BLA filing in 1H 2022
  - 80% reduction in plasma arginine at 24-week analysis ($p<0.0001$) ‡
  - 90.5% of patients achieved normal plasma arginine levels ($p<0.0001$)*
- Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and several Middle East countries
- Long-term data from Phase 1/2 & OLE
- Breakthrough Therapy Designation (BTD)
- PRV eligible: Rare Pediatric Disease Designation (RPD)
- Subcutaneous dosing; all eligible patients in OLE

AGLE-177: Homocystinuria

- First patient dosed in Phase 1/2 trial
- U.S. and EU Orphan Designations
- PRV eligible: Rare Pediatric Disease Designation (RPD)
- Preclinical proof of concept: Plasma homocysteine levels reduction improves disease-related abnormalities
- Novel engineered human enzyme designed to degrade both homocysteine and homocystine

Cystinuria Program

- Innovative human enzyme-based solution for disease management
- Proof of concept: Lowering of plasma cystine lowers urine cystine levels and reduces kidney stone formation in a preclinical disease model

2021 MILESTONES

Pegzilarginase: ARG1-D

- Enrollment complete ✓
- Ex-U.S. license and supply agreement with Immedica ✓
- Topline pivotal Phase 3 data: December ✓

AGLE-177: Homocystinuria

- Patient enrollment and dosing underway ✓

‡geometric mean; *nominal p value

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Financial Summary

Cash, cash equivalents and marketable securities as of September 30, 2021: $114.3 million[1] (no debt)

As of September 30, 2021, 65.9 million[2] common shares and pre-funded warrants outstanding

$ Millions	Three Months Ended 9/30/21	Nine Months Ended 9/30/21
Revenue	$1.4	$15.1*
R&D Expense	$14.9	$40.3
G&A Expense	$6.8	$20.0
Net Loss	$20.3	$45.4

Expected funding runway: into 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 $3.1 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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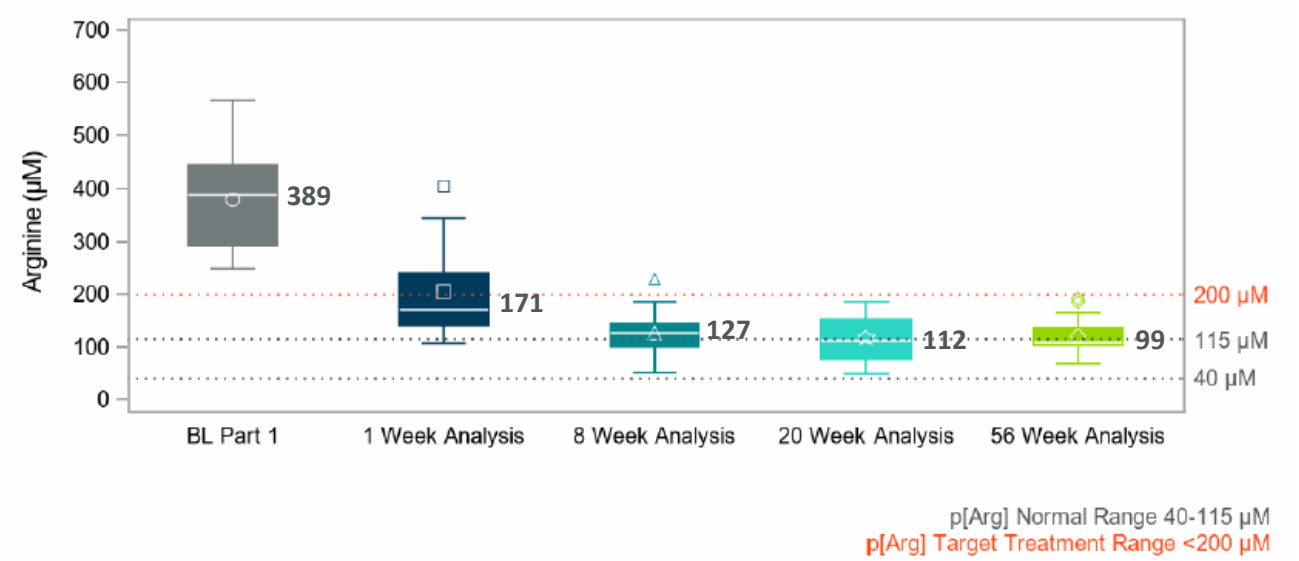
Pegzilarginase Significantly and Sustainably Reduces Plasma Arginine Levels in Phase 1/2 & OLE

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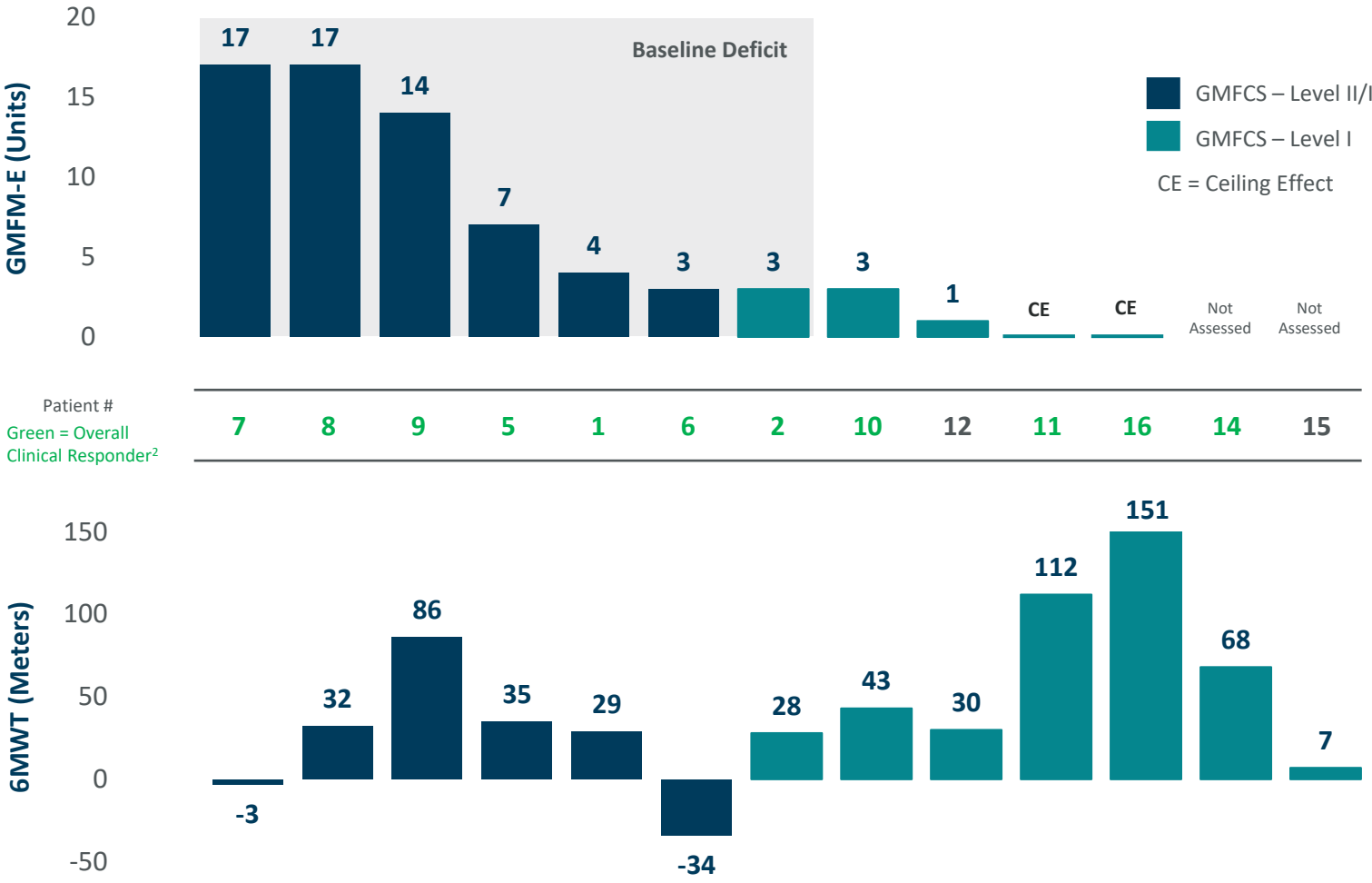
Mobility Assessments Capture Potential Clinical Benefit of Pegzilarginase in Phase 1/2 Trial & OLE

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