Reimagining The Potential Of Human Enzyme Therapeutics

Corporate Overview – November 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 and results of our clinical trials and related data, our ability to obtain and maintain regulatory approval, the potential therapeutic benefits and economic value of our lead product candidate 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 other 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 agreement with Immedica; the potential for expeditated development and review of pegzilarginase as of a result of its Breakthrough Therapy designation; the potential addressable markets of the 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 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.

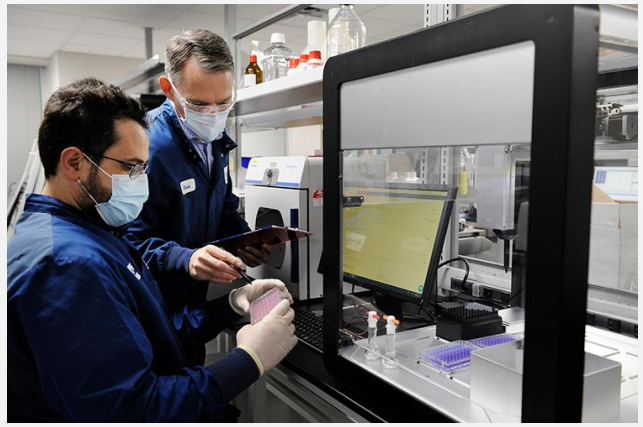
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Addressing Metabolic Imbalances to Improve the Lives of Patients

Delivering Metabolic Harmony

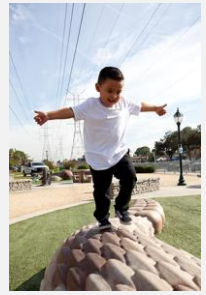
Aeglea BioTherapeutics

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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Rethinking the Potential of Human Enzyme Therapeutics

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

>65% of U.S. genetic prevalent population identified

Status:

- Enrollment completed in Phase 3 pivotal trial
- Topline data expected in December

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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Arginase 1 Deficiency Patient Needs Not Adequately Addressed



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:

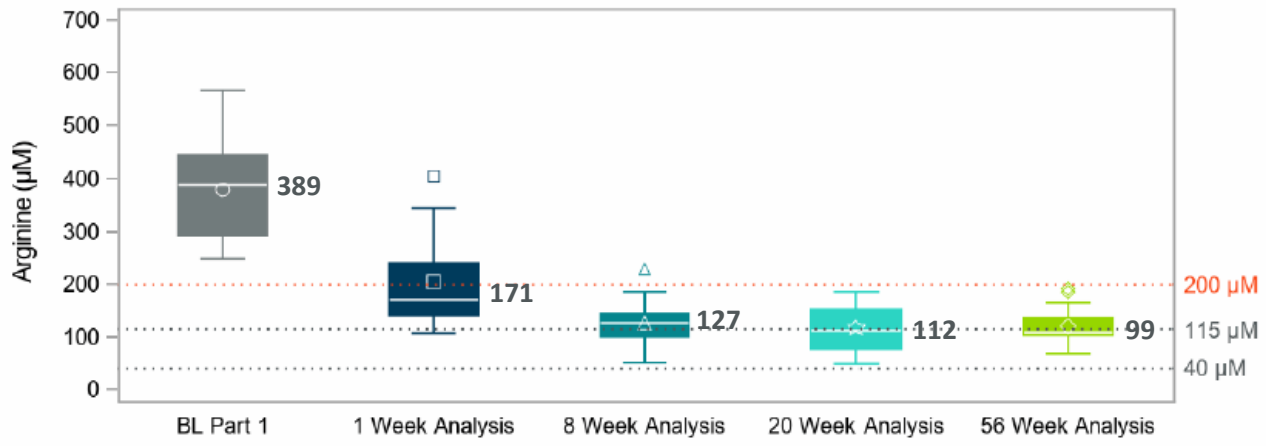
1. **Patients not reaching target arginine levels** with their current disease management strategy
2. **Ineffective treatment options** result in disease progression and poor outcomes
3. **Delayed and un/misdiagnosed patients** due to lack of disease awareness

No treatments or approved therapies that effectively reduce arginine levels

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Pegzilarginase Significantly and Sustainably Reduces Plasma Arginine Levels

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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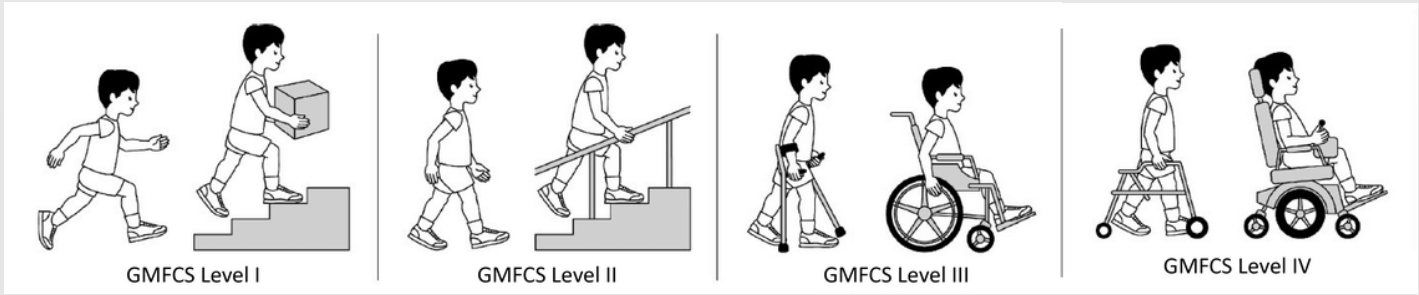
Measuring the Functional Impact of Spasticity in ARG1-D

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)

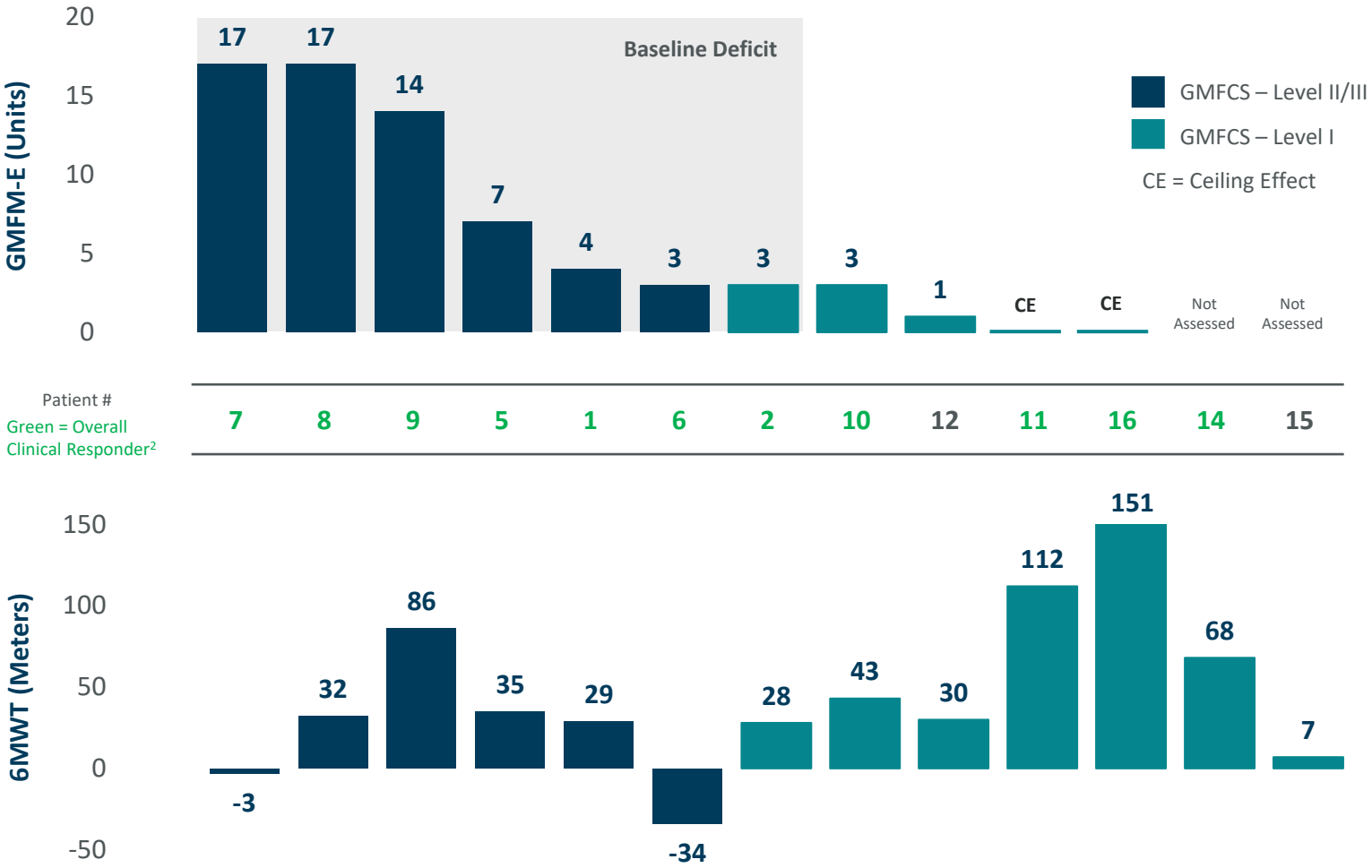


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GMFCS graphic adapted with permission from The Royal Children's Hospital Melbourne, Australia

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

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

Safety Summary

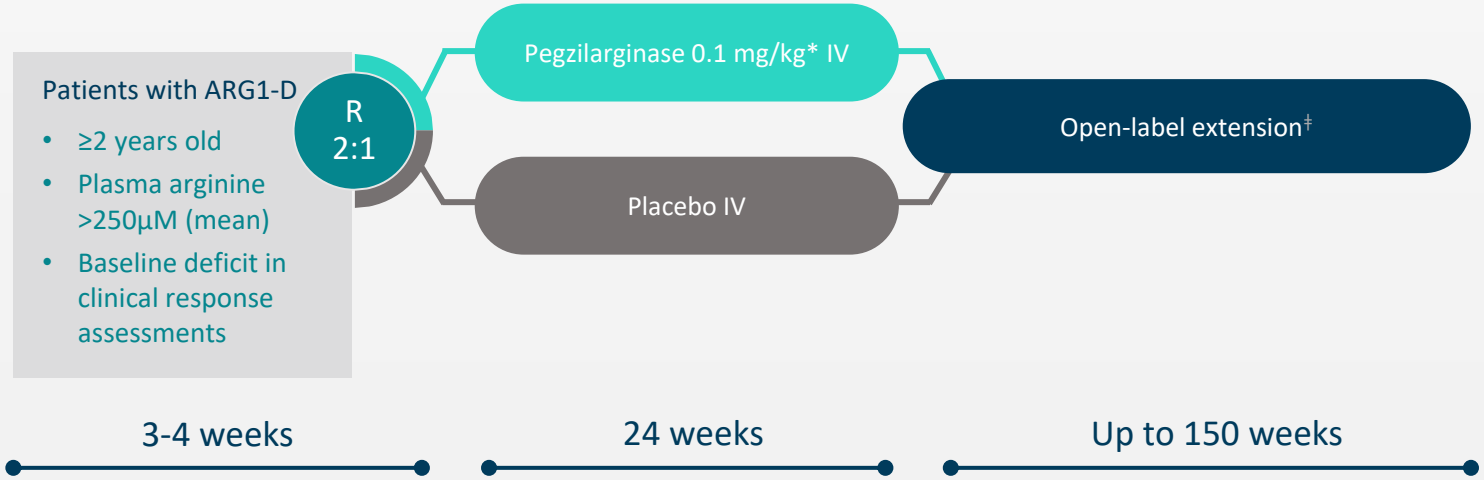
Phase 1/2 Trial and Open Label Extension Study of Pegzilarginase in Arginase 1 Deficiency

- Clinical data shows pegzilarginase has a favorable safety profile
- 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

[1]Dose data as of June 11, 2021

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PEACE Trial Design – Single Global Pivotal Phase 3 Trial to Support Registration



Topline data December

Key Endpoints	Analysis	Rationale
Primary: • **Plasma arginine reduction**	• Reduction of plasma arginine compared to baseline vs placebo	• Based on key role of elevated arginine levels in the development and progression of clinically important disease manifestations
Secondary: • **GMFM-E (Walking, running & jumping)** • **Timed Walk Test (2MWT)**	• Continuous analysis • Improvement compared to baseline vs placebo	• Previous trial results support utility of GMFM-E in capturing baseline disease burden and clinical impact of treatment • Timed walk test provides complementary insights on mobility improvements and is especially useful for GMFCS level 1 patients • Simplifies analysis and reduces complexity of statistically controlling for multiple comparisons

*Dosing is weekly and, if needed, 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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PEACE Patient Population Similar to Phase 1/2 But With Greater Mobility Impairments

- PEACE baseline characteristics generally in line with Phase 1/2 patient population
- Key differences include:
  - Increased number of patients categorized by GMFCS as Level 2 or greater
  - Increased number of patients with mobility deficit for the GMFM-E assessment

Baseline Characteristic	Phase 3	Phase 1/2
Median pArg	407 µM	389 µM
Mean Age ± SD (range)	11 ± 6.5 (2-29)	15 ± 8.5 (5-31)
GMFCS		
Level 1	44%	54%
Level 2+	56%	46%
Mobility Deficits		
GMFM-E	84%	56%
Timed Walk Test	84%	86%

pArg = plasma arginine

More PEACE participants have measurable mobility impairments at baseline compared to Phase 1/2 patient population

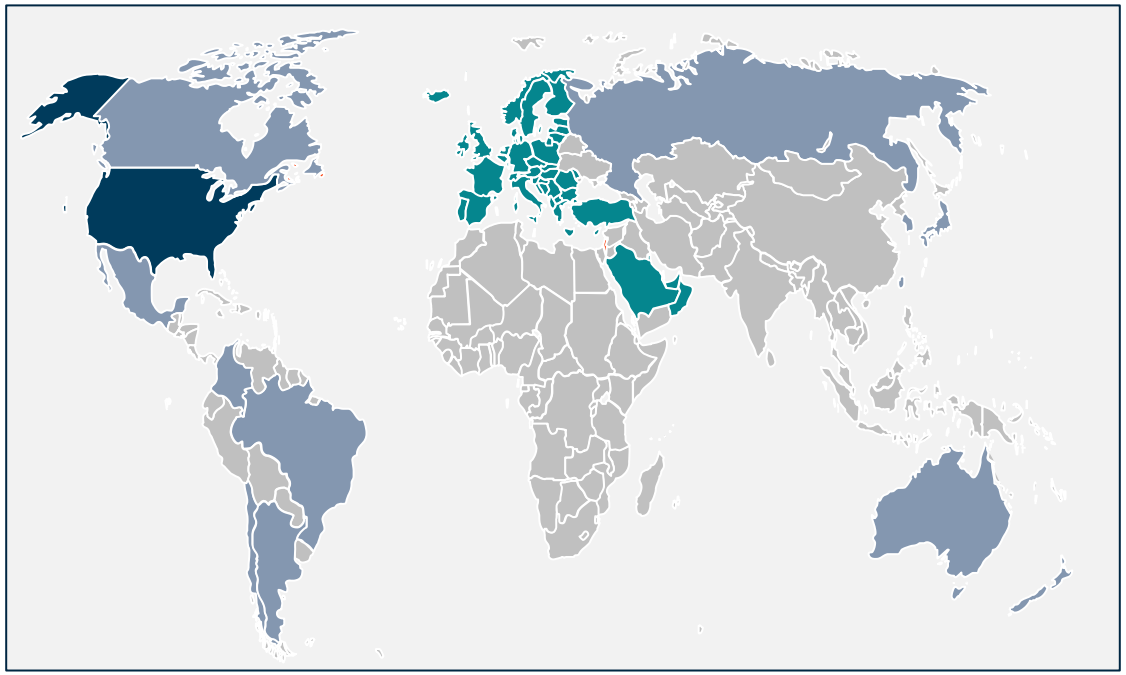
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Attractive Commercial Opportunity for Pegzilarginase in ARG1-D

Significant Unmet Need

- Severe and progressive disease with early mortality
- Easily diagnosed with simple lab test or genetic testing
- No approved therapies to address underlying driver of disease
- Inadequate management options in severe protein-restricted diet, amino acid supplementation, and ammonia scavengers
  - Suboptimal control of plasma arginine levels
  - Poor patient compliance due to challenges with administration

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 PLC in March 2021; agreement covers countries in the European Economic Area and certain countries in the Middle East, 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



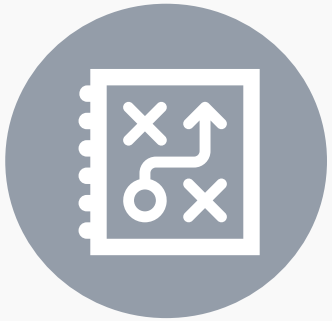
Driving HCP dialogue about the devastating and progressive nature of ARG1-D

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 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
  - Results outpacing relevant benchmarks
  - >65% of the estimated U.S. genetic prevalence identified

Disease Education and Awareness



- Driving increased recognition and understanding of ARG1-D
  - THINK ARGININE™: a disease awareness initiative with no-charge diagnostic testing
  - Engagement with key institutions responsible for significant proportion of patients
- Ongoing scientific discourse to broaden awareness and deepen ARG1-D understanding and advocacy among HCP community
- 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



- Preliminary planning around patient services based on our deep understanding of the needs of the ARG1-D patient community
- Payer profiling to understand likely coverage policies at launch
- Initial payer dialogue providing key insight into disease understanding, educational opportunities, and management approaches

Organizational Readiness



- Core commercial team in place with deep ultra-rare launch experience
- Commercial formulation on stability and distribution strategy in place
- High-touch patient services approach in development
- Commercial infrastructure built with pegzilarginase and earlier-stage pipeline programs in mind

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Pegzilarginase Program - Key Highlights and Next Steps

Phase 1/2 & OLE data demonstrates clinical impact

- Sustained control of plasma arginine
- 85% (11/13) of patients at the 56 week analysis were clinical responders
- Well tolerated and the rates of treatment-related adverse events decreased over time

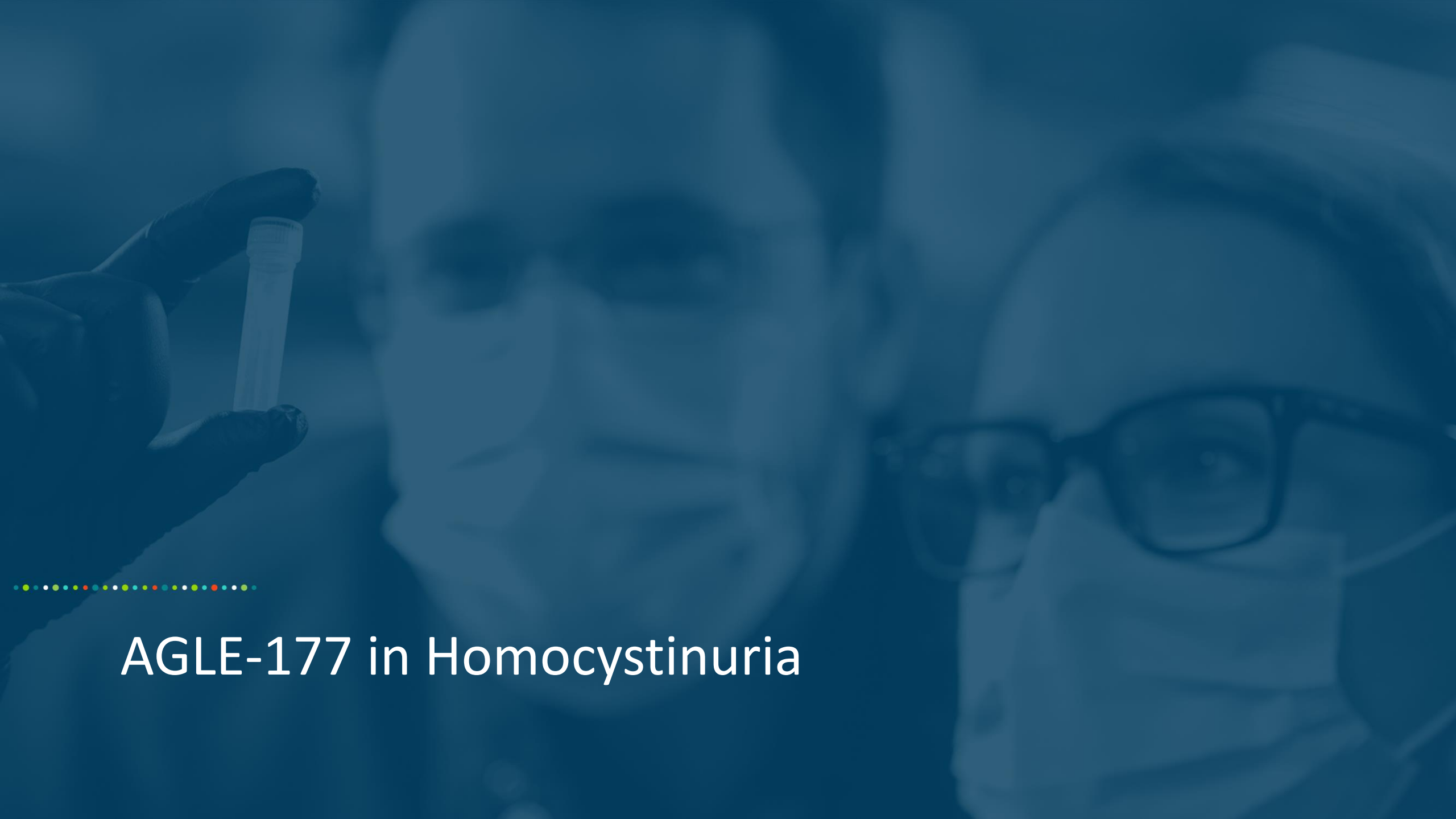
PEACE: A single, global pivotal trial designed with input from FDA and EMA

- Primary endpoint: arginine reduction; secondary endpoints: clinical outcomes, safety and PK
- 32 patients, randomized 2:1 (pegzilarginase: placebo)
- 24 weeks dosing period
- Baseline characteristics generally align with Phase 1/2 patient population but with greater mobility impairments
- Topline results expected in December 2021

Opportunity

- Significant unmet medical need; no effective treatments currently available
- Estimated >2,500 patients worldwide with patient identification outpacing relevant benchmarks
- U.S. launch planning and efforts underway; building enduring commercial infrastructure
- Significant ex-U.S. opportunity: considerable progress in EU/Middle East with Immedica licensing agreement, retained rights in rest of world

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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

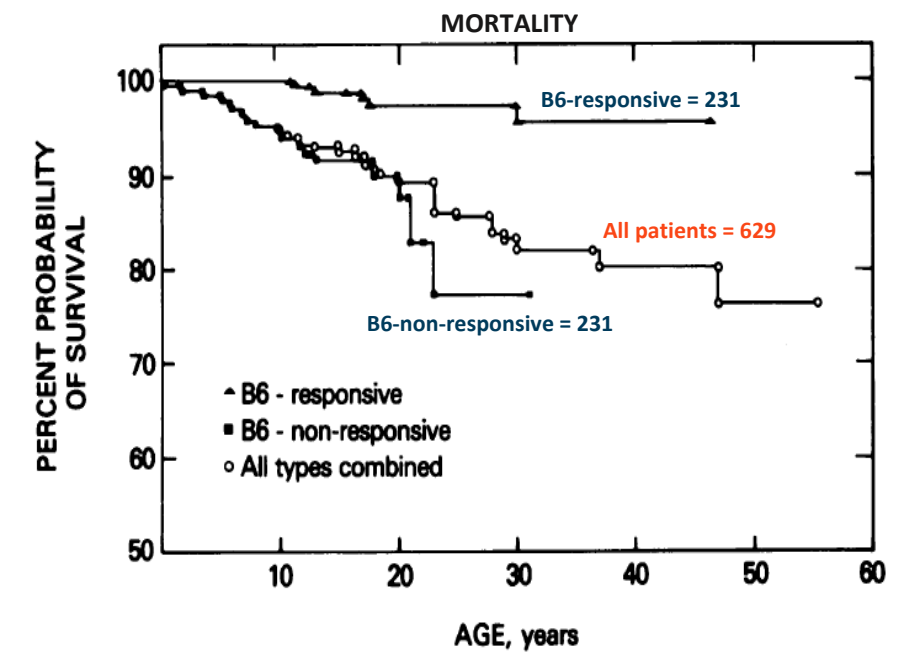
tHcy – Total plasma homocysteine

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Increased Mortality and Severe Complication Risk in Patients with Homocystinuria

Natural History Study of 629 Untreated Classical Homocystinuria Patients



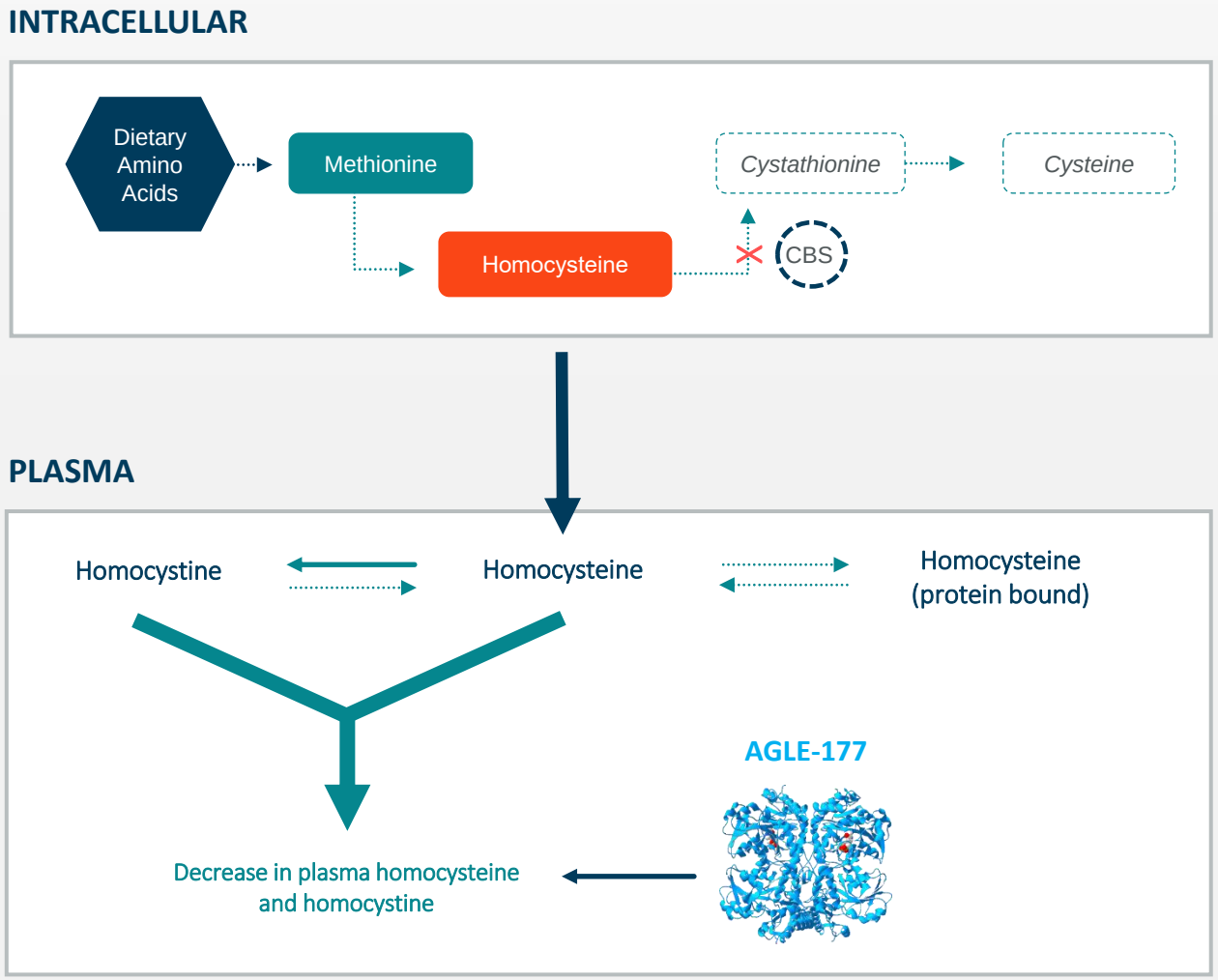
	B6-non-responsive	B6-responsive
Elevated levels of homocysteine	⊕ ⊕ ⊕	⊕
NATURAL HISTORY		
Mortality by age 30	23%	4%
Most common cause of death	Thromboembolism	
Lens dislocation in 50%	Age 6	Age 10
Median IQ	56	78
Chance of thrombosis by age 15	27%	12%

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

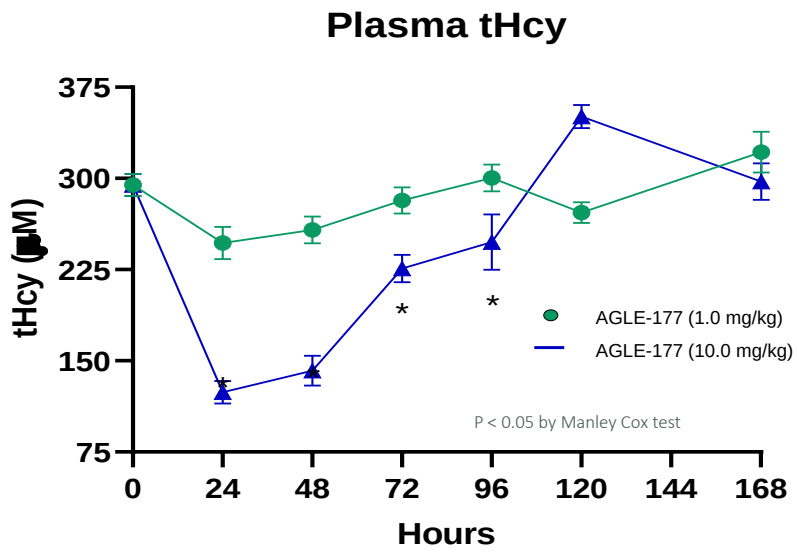
Degrading both homocysteine and homocystine is likely to enable more efficient lowering of plasma homocysteine levels

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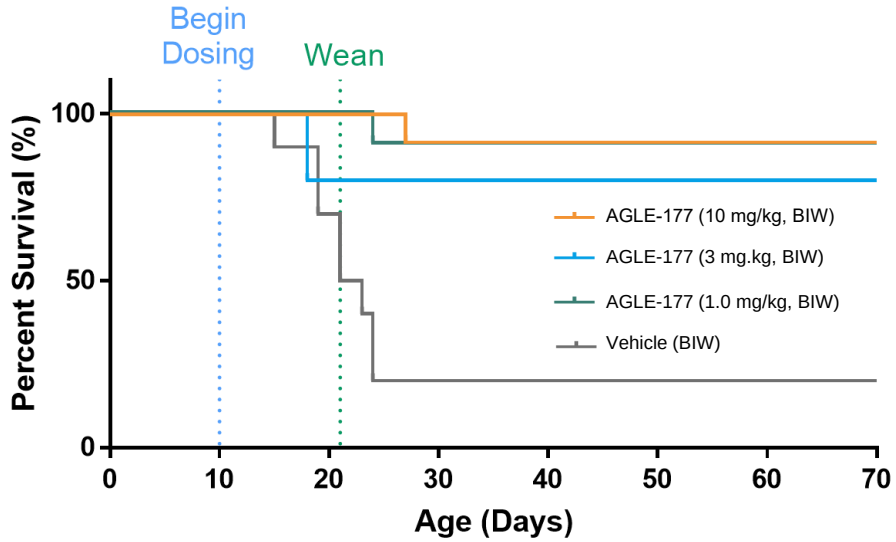
Subcutaneous Dosing Reduces Total Plasma Homocysteine and Improves Survival in Preclinical Model

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]



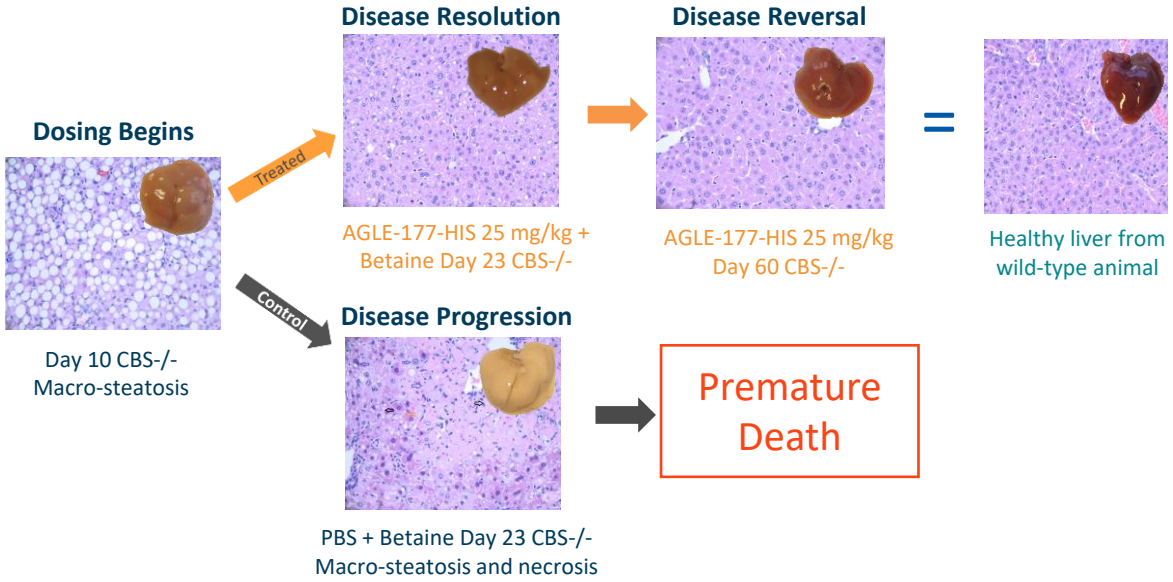
Improvement in survival following subcutaneous treatment in CBS-/- mouse model

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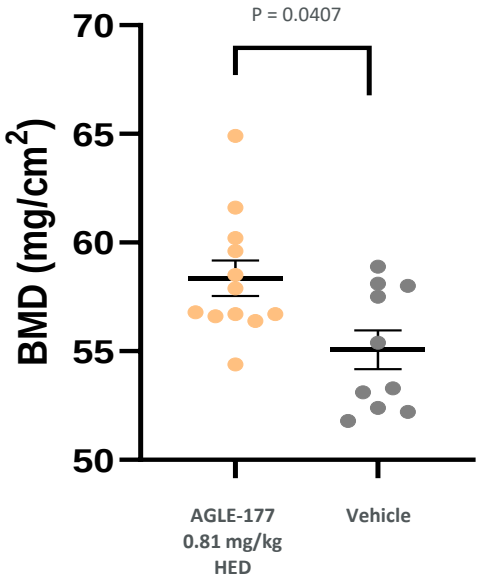
AGLE-177 Improves Pathologies and Correction of Disease Manifestations in a Preclinical Model of Homocystinuria

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



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

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

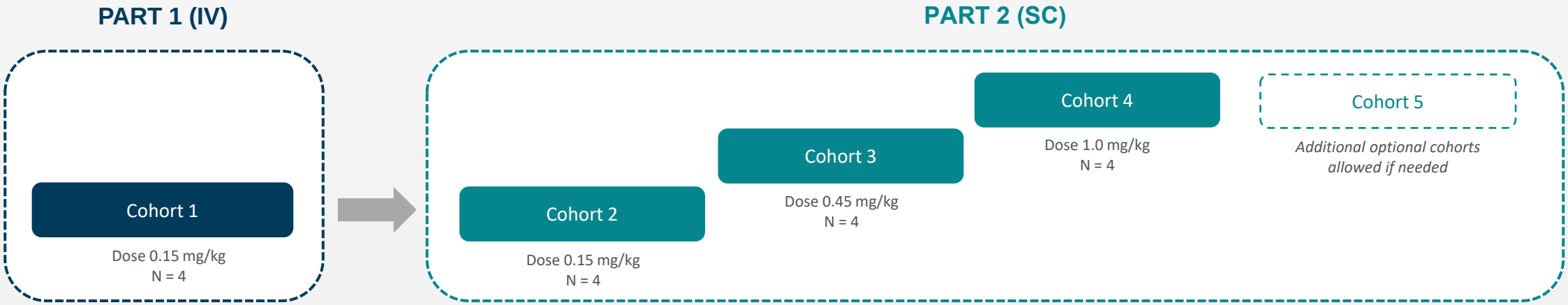


Increased BMD in preclinical model of Homocystinuria with multiple doses of AGLE-177

[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 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

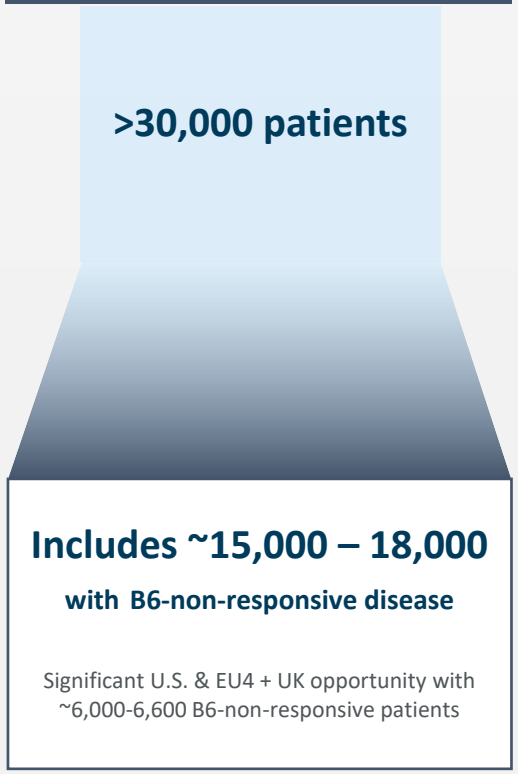
Enrollment & Dosing

- 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.

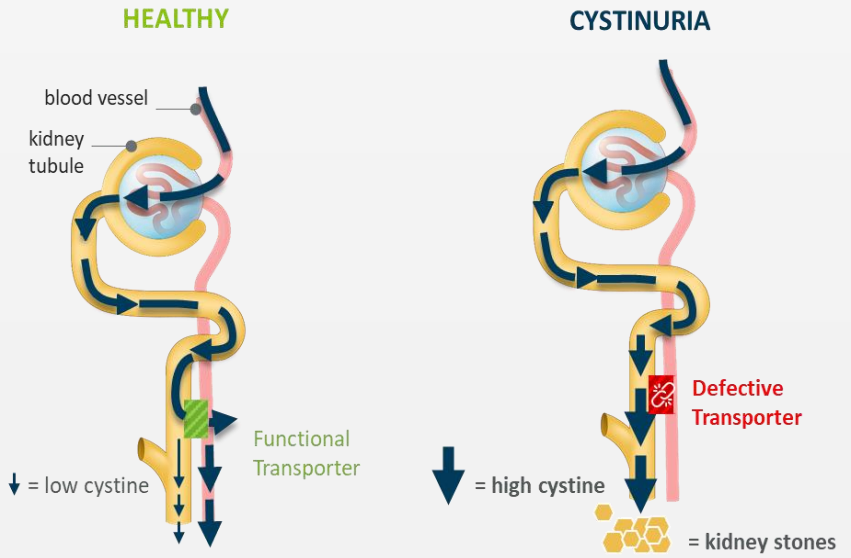
Addressable Market:

Estimated prevalence rate 1:15,000

Based on literature

>10,000

Patients in addressable markets



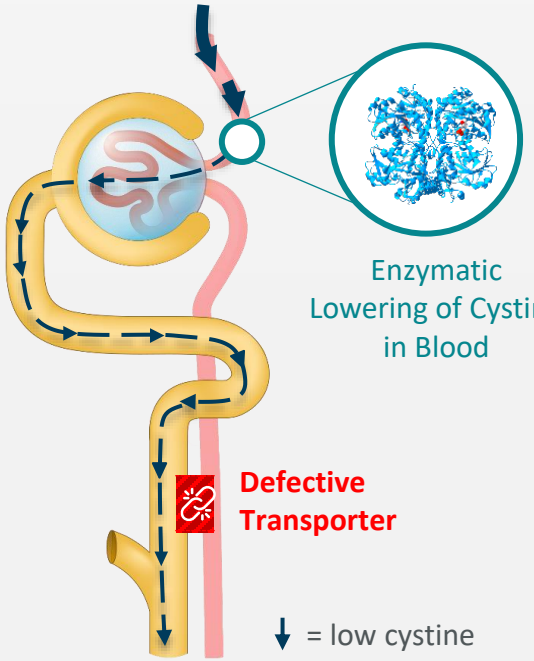
Low cystine in urine	High cystine in urine → cystine precipitates → stone formation
Healthy	Severe pain, surgical interventions, kidney failure

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

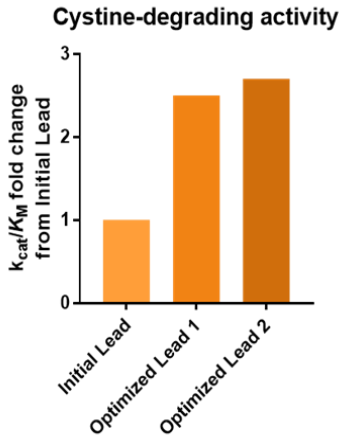
INNOVATIVE ENZYME APPROACH



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

Protein Engineering

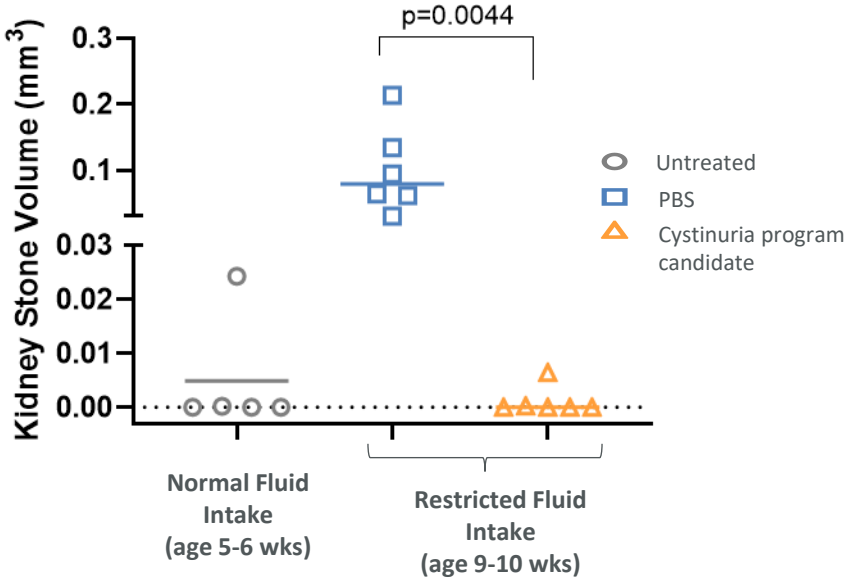
Creating Novel Cystine Degrading Activity[1]



- 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

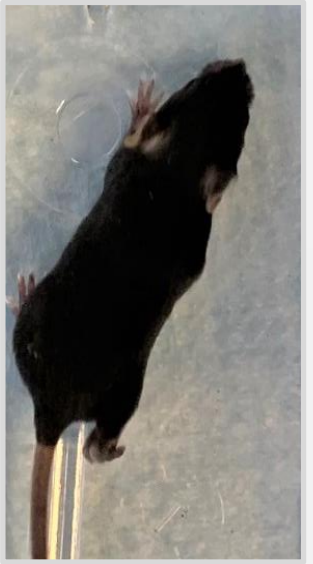
Therapeutic Approach	**Pegylated enhanced human enzyme** • Enzymatic control of high levels of a metabolite considered important in disease pathogenesis
Unmet Medical Need	• Very high - no effective therapy • Early mortality and serious complications with continued disease progression
Patient Population (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 enrollment complete
- Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and several Middle East countries
- Phase 1/2 & OLE efficacy data at 56 week analysis:
  - Statistically significant arginine reduction vs baseline ($p<0.001$)
  - Durable high clinical responder rate, 85%
- 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 ✔

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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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A Disruptive Platform Producing a New Generation of Human Enzyme Solutions

- Lead assets in three areas of high unmet medical need
- Looking beyond the conventional, redefining the potential of human enzymes to deliver disruptive solutions
- Driven by the urgent needs of the communities we serve
- Pursuing our vision to become the premier human enzyme company
- Changing the lives of patients and their families now and for the future

CLINICAL

Pegzilarginase

Pivotal Phase 3

Arginase 1 Deficiency

AGLE-177

Phase 1/2

Homocystinuria

RESEARCH

Cystinuria Program

Undisclosed Programs

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Phase 1/2 Study of Pegzilarginase Baseline Demographics & Patient Characteristics

Baseline Characteristics (n=16)	
Age*, years (range)	15 (5-31)
Sex, female, n	11 (69%)
Race, white, n	11 (69%)
Height, <10th Centile, n	12 (75%)
Weight, <10th Centile, n	3 (19%)
p[Arg]*, µM (normal range 40-115)	389 (238-566)
NH_3*, µM (upper limit of normal ~32)	38 (9-77)

Mobility Assessments

88% (14 of 16) had at least one mobility deficit at baseline

- 6MWT 13 of 15**
- GMFM-D 8 of 16
- GMFM-E 9 of 16

*Values are median (range) unless stated otherwise.
Arg, arginine; ARG1, arginase 1; BL, baseline; NH_3, ammonia; 6MWT, 6-minute walk test; GMFM-D/E, Gross Motor Function Measure Part D/E; Pt, patient, ** 1 patient non-assessable (wheelchair bound)
[1]Dose data as of September 10, 2020

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Pegzilarginase Demonstrates Durable Clinical Response at 56 Week Analysis in Phase 1/2 Open-Label Extension

Overall Clinical Response Rate:

20 Week Analysis:

11/14 (79%)

56 Week Analysis:

11/13 (85%)

Clinical Responder defined by achievement of a clinically meaningful response* in one or more of three mobility assessments

	Overall Combined Response	6MWT			GMFM-D Max = 39			GMFM-E Max = 72			
	56 Week Analysis	BL	▲	%▲	BL	▲	%MCID	BL	▲	%MCID	BL
Patient 1	Responder	102	29	28%	15	6	4.0x	12	4	2.2x	III
Patient 2	Responder	261	28	11%	30	2	0.8x	63	3	0.8x	I
Patient 5	Responder	174	35	20%	21	7	2.1x	27	7	2.5x	II
Patient 6	Responder	168	(34)	(20%)	25	8	2.4x	34	3	1.1x	II
Patient 7	Responder	272	(3)	(1%)	12	0	0	12	17	9.4x	III
Patient 8	Responder	208	32	15%	23	3	0.9x	22	17	6.1x	II
Patient 9	Responder	160	86	54%	24	6	1.8x	31	14	5.0x	II
Patient 10	Responder	349	43	12%	37	2	0.8x	69	3	0.8x	I
Patient 11	Responder	602	112	19%	39	0	0	72	0	0	I
Patient 12		443	30	7%	37	0	0	70	1	0.3x	I
Patient 14	Responder	354	68	19%	38			69			I
Patient 15		350	7	2%	38			69			I
Patient 16	Responder	473	151	32%	39	0	0	72	0	0	I

Responder (≥1 MCID increase) | Baseline deficit | ≥-1 MCID decrease

No improvement on decline | No baseline deficit | Not assessed

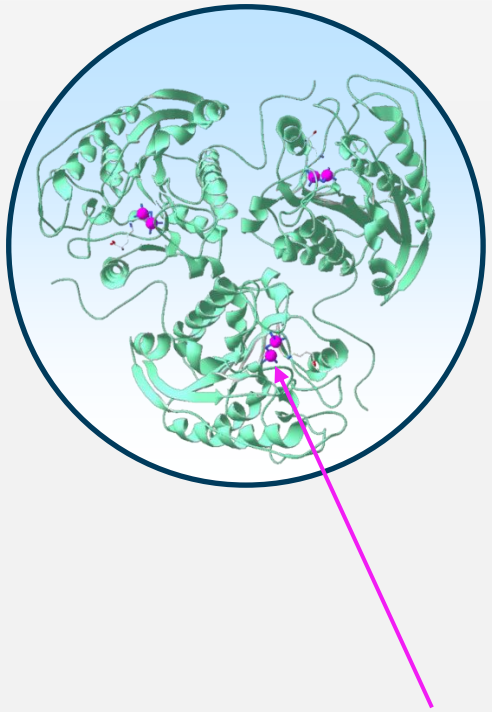
*Clinically meaningful response defined as an improvement in Minimal Clinically Important Difference (MCID) MCID for 6MWT = 9%; MCID for GMFM Part D is 2.4, 3.3, and 1.5 for GMFCS Levels I, II and III, respectively; MCID for GMFM Part E is 4.0, 2.8, and 1.8 for GMFCS Levels I, II and III, respectively. Maximum values for GMFM-D and GMFM-E are 39 and 72, respectively.

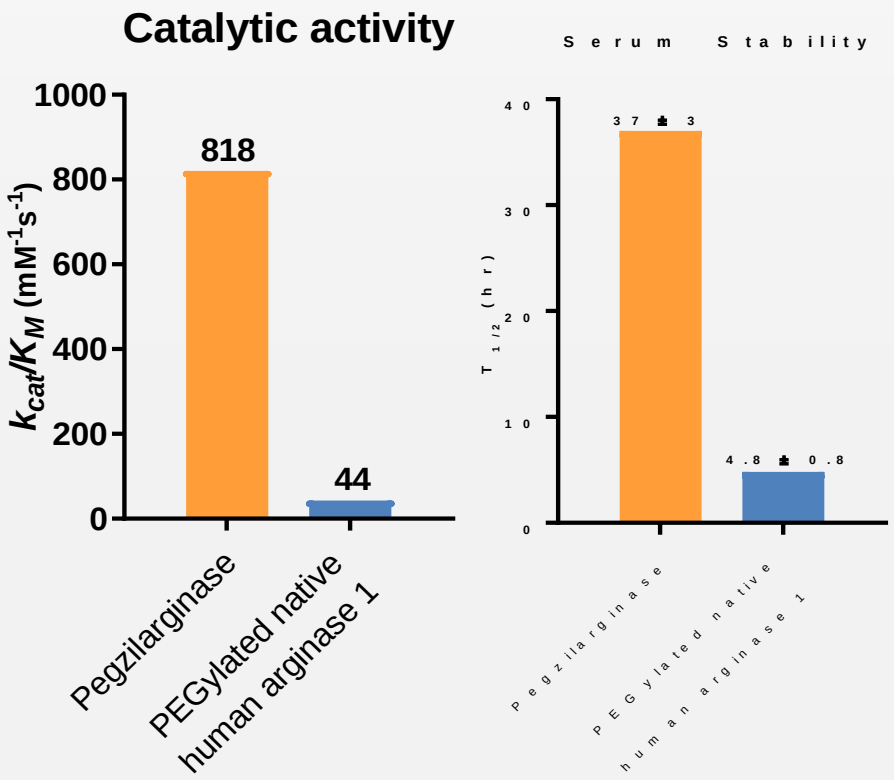
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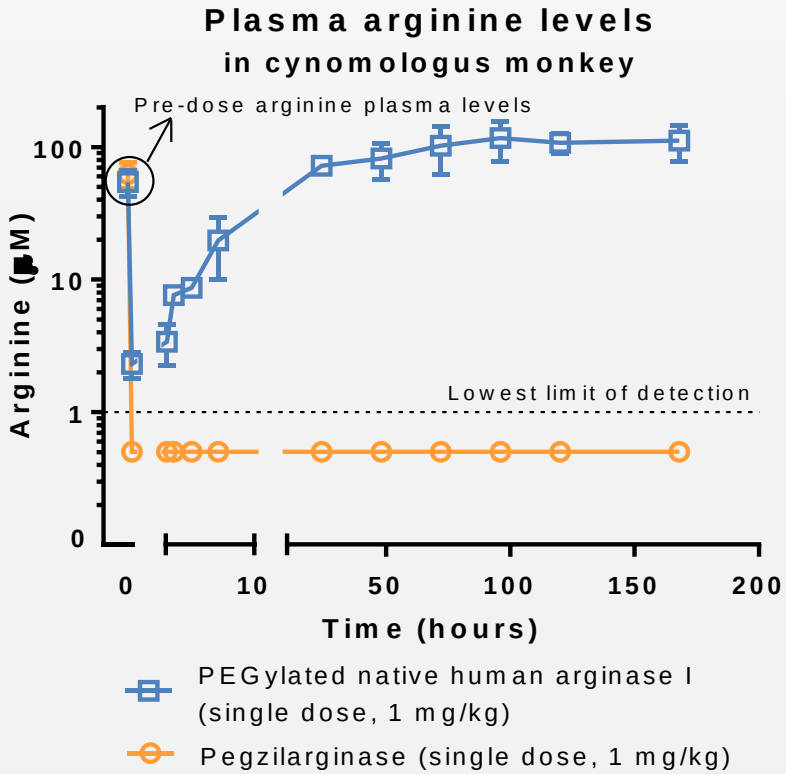
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Designing Enzyme Therapeutics - Pegzilarginase

Pegzilarginase







Substituted Metal Cofactor
(Mn^{2+} replaced with Co^{2+})

Improved Catalytic Activity & Serum Stability

Reduced Circulating Arginine levels

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