Reimagining The Potential Of Human Enzyme Therapeutics

Corporate Overview – March 2021



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 ability for patients who participate in the Phase 3 PEACE trial to participate in a long-term extension study, 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; the timing of and our ability to obtain and maintain regulatory approvals; 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 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.

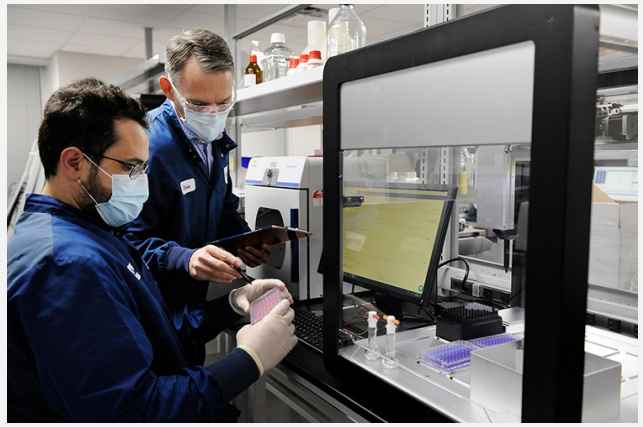
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Addressing Metabolic Imbalances to Improve the Lives of Patients

Delivering Metabolic Harmony

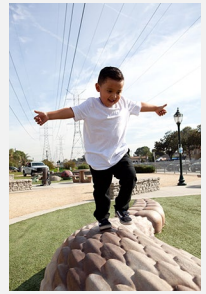
Aeglea BioTherapeutics (Nasdaq: AGLE)

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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Unlocking the Potential of Human Enzymes to Deliver Life-Changing Solutions for People with Rare Metabolic Diseases

PEGZILARGINASE IN ARGINASE 1 DEFICIENCY

Enhanced human arginase that enzymatically lowers arginine levels

PEACE – pivotal Phase 3 trial enrolling

AGLE-177 IN HOMOCYSTINURIA

Novel recombinant human enzyme that enzymatically lowers homocysteine levels

Phase 1/2 trial initiated

ENZYME THERAPEUTICS PLATFORM

Rare metabolic disease monogenic focus

Most advanced program in Cystinuria

Cash, cash equivalents and marketable securities as of December 31, 2020: $148.1[1] million (no debt)

Expected funding runway: into 2023

[1]Includes $1.8mm of restricted cash.

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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

- Distinctive disease selection approach
- Validated metabolite targets
- Translatable disease models
- Reduced toxicology risk

Development and regulatory

- Established manufacturing approach
- Faster, smaller clinical trials
- Favorable regulatory access

Commercial

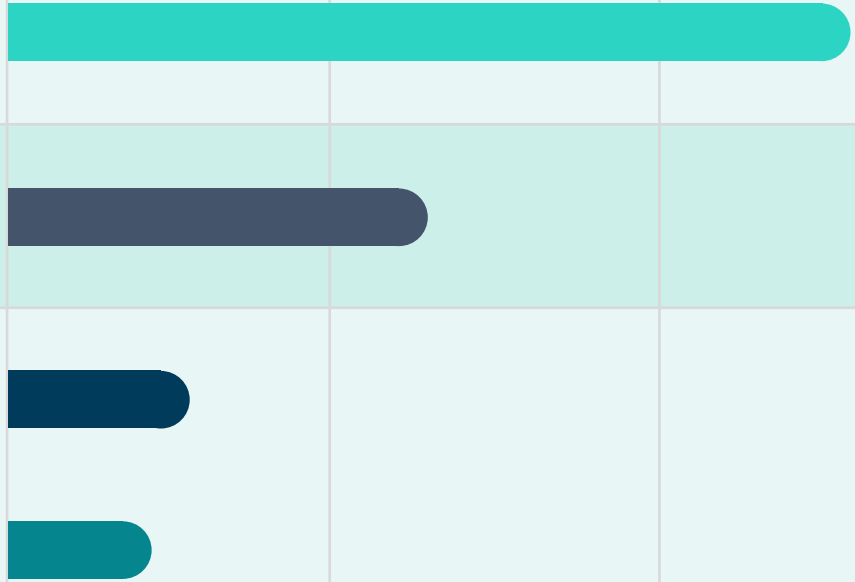
- Attractive reimbursement potential
- Substantial barriers to entry
- Lower costs

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Rethinking the Potential of Human Enzyme Therapeutics

Program	Indication	Research	Phase 1/2	Phase 3	Approved
Pegzilarginase	Arginase 1 Deficiency				
AGLE-177	Homocystinuria				
Research Programs	Cystinuria				
	Undisclosed Rare Diseases				



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Highly Experienced Leadership Team in Drug Discovery & Development



Anthony G. Quinn, MD PhD
Chief Executive Officer



Leslie Sloan, PhD
Chief Operating Officer



Michael C. Hanley, MBA
Chief Commercial Officer



Scott Rowlinson, PhD
Vice President of Research



Eric Bradford, MD MBA
Chief Development Officer

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Pegzilarginase in Arginase 1 Deficiency

Arginase 1 Deficiency Overview

Arginase 1 Deficiency (ARG1-D)

Arginase 1 Deficiency 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

>300 patients identified to date

~65% (~160 patients) of U.S. genetic prevalent population identified

Regulatory Designations:

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

Typical ARG1-D Patient Journey

Birth to 1 Year[2,3,5]

- Diagnosis often not captured at birth due to limitations of newborn screening
- Initial 6-12 months often uneventful
- May present with seizures, episodes of mild hyperammonemia: irritability, feeding difficulties, poor appetite, nausea/vomiting, decreased alertness

2-5 years[1-5]

- Spasticity in lower limbs (tip-toe gait)
- Seizures
- Developmental delay and regression
- Aversion to high-protein foods

5-10 years[1-5]

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

1. Crombez EA and Cederbaum SD. Mol Genet Metab. 2005;84(3):243-251. 2. Sin YY, et al. J Mol Med (Berl). 2015;93(12):1287-1296. 3. Carvalho DR, et al. Pediatr Neurol. 2012;46(6):369-374. 4. Cai X, et al. Medicine (Baltimore). 2018;97(7):e9880. 5. Scaglia F and Lee B. Am J Med Genet C Semin Med Genet. 2006;142c(2):113-120.

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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:

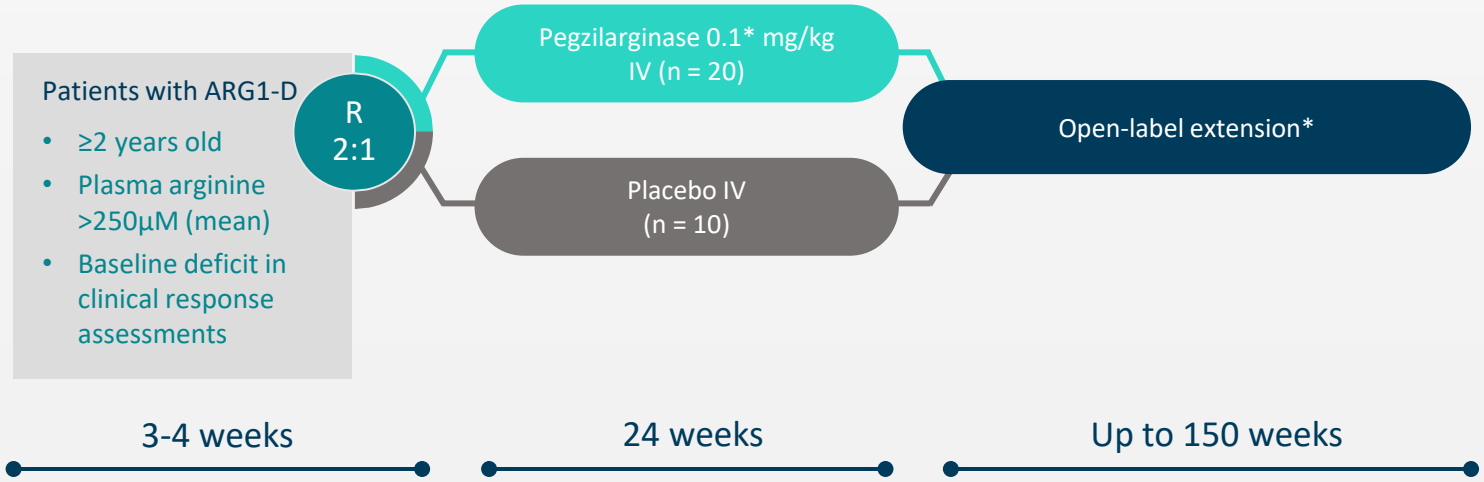
1. **Patients not reaching target arginine levels** with their current disease management strategy
2. **Ineffective treatment options** result in disease progression and poor outcomes
3. **Delayed and un/misdiagnosed patients** due to lack of disease awareness

No effective treatments or approved therapies that treat the underlying cause

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Global Pivotal Phase 3: PEACE Trial Design

Single, Pivotal Phase 3 Trial Based on Input From FDA and EMA to Support Registration



Enrollment Completion:

March 2021

Topline data in 4Q2021

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: • **Timed Walk Test (2MWT)** • **GMFM-E (Walking, running & jumping)**	• 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

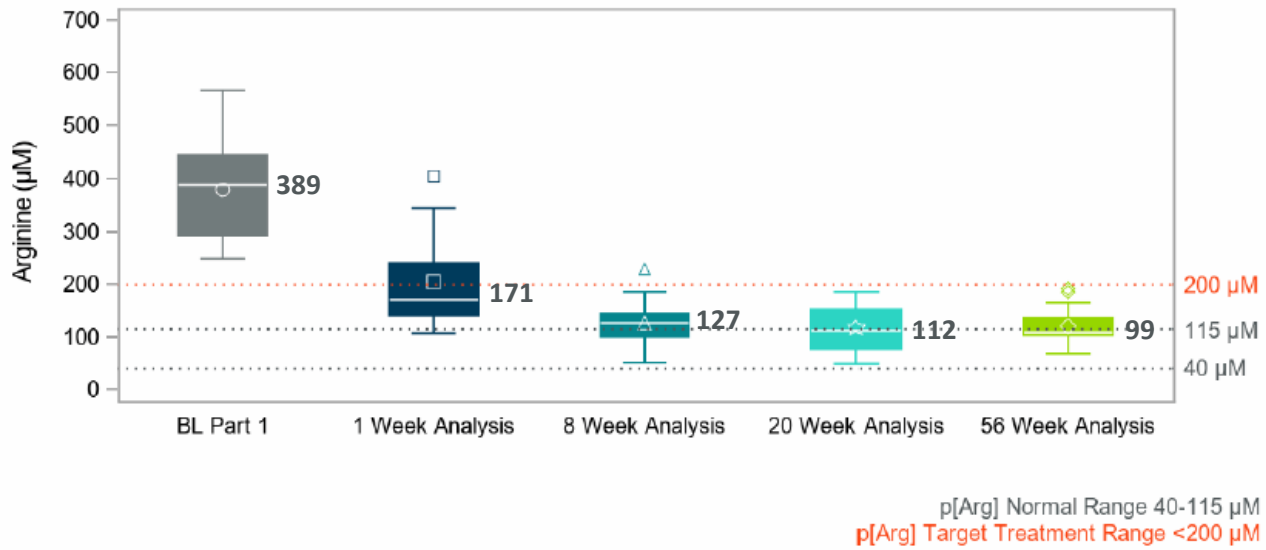
*Dosing is weekly and, if needed, modified based on plasma arginine levels with maintenance of blinding. The first 8 weeks of the open-label extension will be blinded. All study participants remain on current disease management for the duration of the trial. ARG1-D = Arginase 1 Deficiency; IV = intravenous; R = randomized. 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

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Pegzilarginase Significantly and Sustainably Reduces Plasma Arginine Levels

Plasma Arginine in Response to Pegzilarginase



Baseline:

- Baseline plasma arginine on standard disease management was markedly elevated

20 Week Analysis:

- Median plasma arginine was 112µM

56 Week Analysis:

- 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)**

*#'s are medians

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Pegzilarginase Demonstrates Durable Clinical Response

Overall Clinical Response Rate:

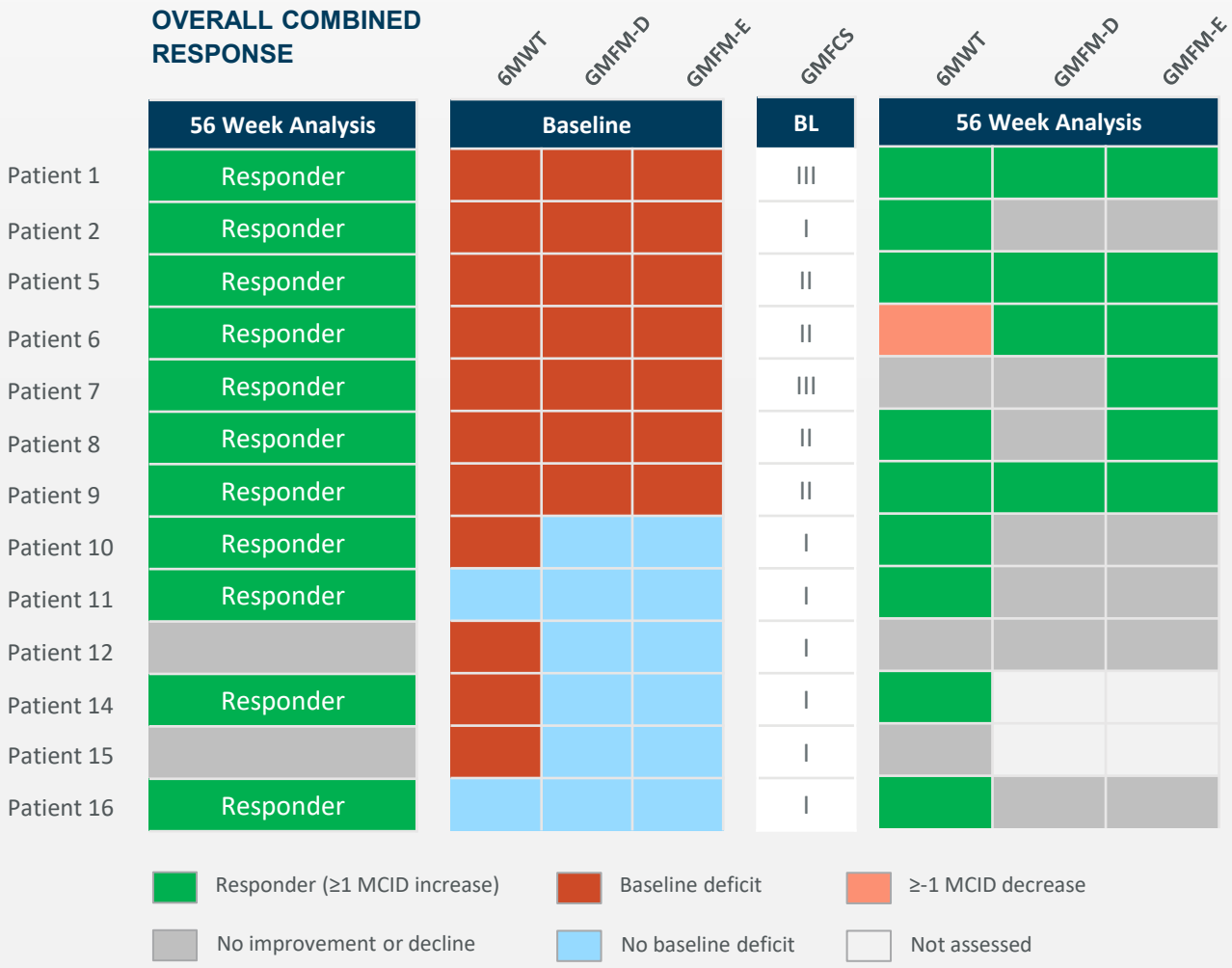
20 Week Analysis:

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



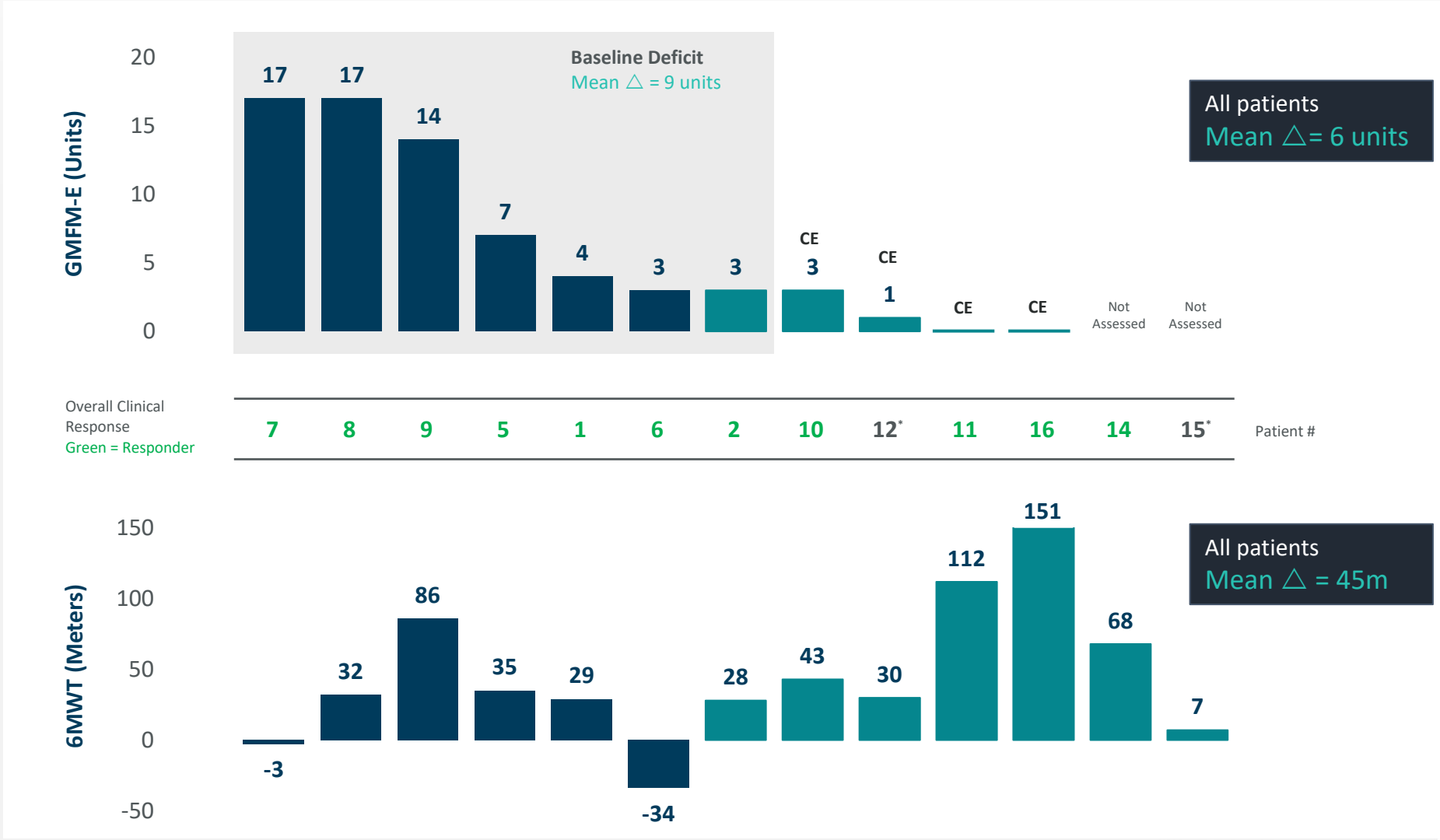
*Clinically meaningful response defined as an improvement in Minimal Clinically Important Difference (MCID) MCID for 6MWT = 9%; MCID for GMFM Part D is 2.4, 3.3, and 1.5 for GMFCS Levels I, II and III, respectively; MCID for GMFM Part E is 4.0, 2.8, and 1.8 for GMFCS Levels I, II and III, respectively.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

Baseline deficits for 6MWT were defined by the 5th percentile for normal pediatrics/adolescents and adults by age and gender. 5th percentile for Normal pediatric/adolescent for 6MWT are from Geiger 2007 J Ped and adult 5th percentile are from Enright 1998 J Resp Crit Care Med

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Key Insights on Effectiveness of Timed Walk and GMFM-E in Capturing Clinical Benefit with Pegzilarginase

Change from Baseline at 56 Week Analysis



GMFCS – Level II/III

GMFCS – Level I

CE = Ceiling Effect

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*Not an overall clinical responder

Safety Summary

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

- Pegzilarginase was shown to have a favorable safety profile
- More than 1,350[1] doses administered in the Phase 1/2 clinical trial (101A) and Phase 2 OLE study (102A)
  - 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 September 10, 2020

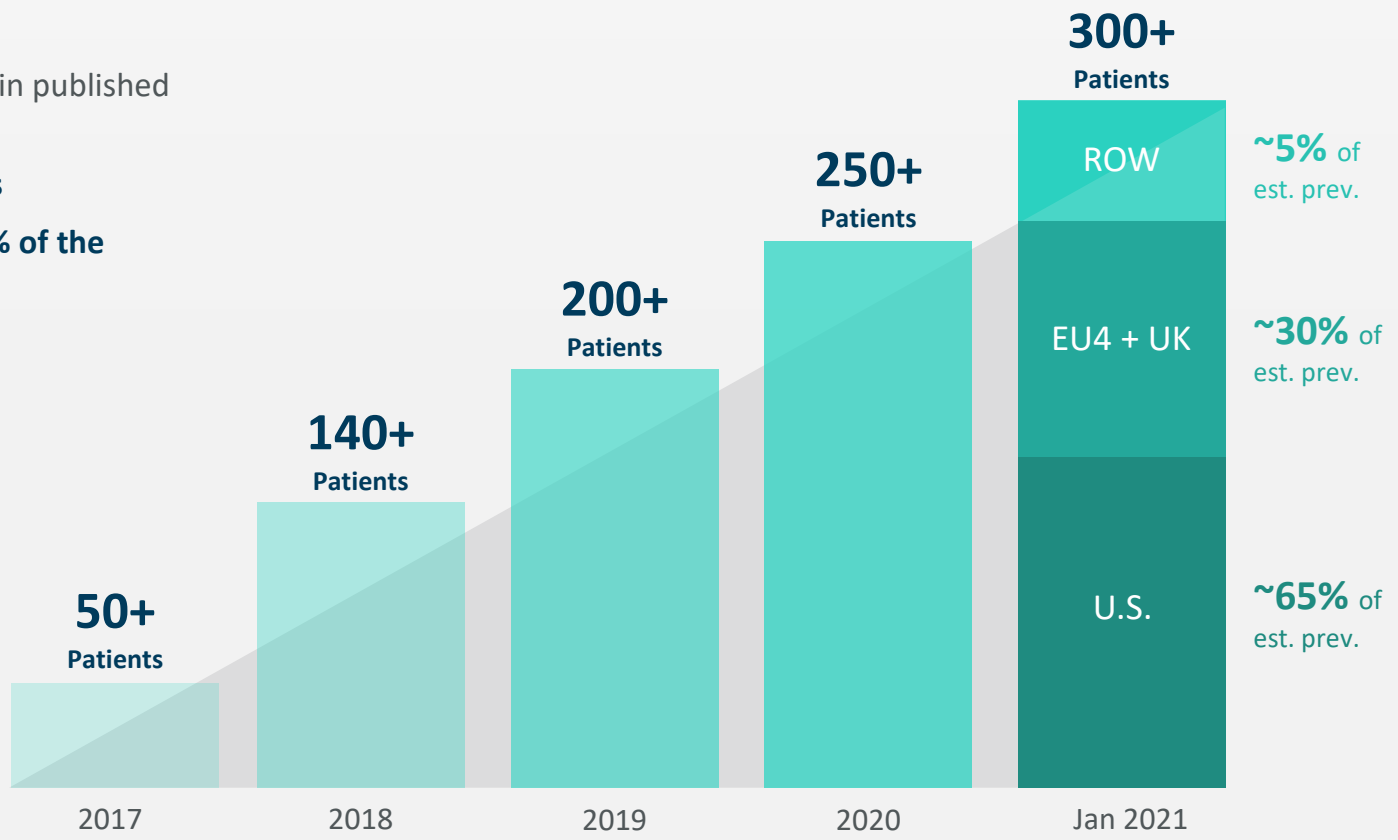
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Arginase 1 Deficiency Market Opportunity

ARG1-D Genetic Prevalence

- Genetic analysis indicates a prevalence of ~2,500 in global addressable markets
- Estimates based on ARG1 genetic mutations identified in published literature and in Aeglea clinical development program
- **>300 patients identified in global addressable markets**
- **~160 patients identified in the U.S. (representing ~65% of the estimated genetic prevalence)**

Addressable Market	ARG1-D Prevalence Estimates
North America	285 (250 in U.S.)
Europe	740 (260 in EU4 + UK)
Latin America	700
Middle East	375
Asia Pacific	405



Source: 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. Notes: Estimates assume 38 target markets only; All figures rounded

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Building a Commercial Organization to Serve the Future

Key Pillars

Patient Identification



Scientific Communications



Access & Reimbursement



Commercial Planning

- Senior commercial leadership team in place with deep ultra-rare launch experience
- Building a focused and agile U.S. commercial organization
  - Field-based medical, patient access and sales teams (~15-20 total FTEs) to educate and serve a highly targeted set of physician specialties
  - Additional key functions including marketing, analytics, patient services, market access and public affairs
  - Ability to leverage commercial infrastructure to benefit earlier-stage pipeline programs
- Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and several Middle East countries
  - Strong partner, highly experienced in bringing important rare disease products to market

Countries included in license and supply agreement – 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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Arginase 1 Deficiency

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
- 30 patients, randomized 2:1 (pegzilarginase: placebo)
- 24 weeks dosing period
- Enrollment completion March 2021; topline results in 4Q2021

Opportunity

- Estimated >2,500 patients worldwide
- >300 patients identified worldwide (~160 patients in U.S.)
- Ex-U.S. license and supply agreement with Immedica to commercialize pegzilarginase in Europe and several Middle East countries
- Worldwide commercial rights on all other regions

Countries included in license and supply agreement – 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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AGLE-177 in Homocystinuria

Homocystinuria 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 patients[1]

~15,000 – 18,000 patients

B6-non-responsive population [2,3]

~6,000-6,600 estimated B6-non-responsive patients in the U.S. & EU4 + UK[4]

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 based on results of U.S. ICD-10 claims analysis extrapolated to global markets; all figures rounded. Sellos-Moura et al 2020. [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

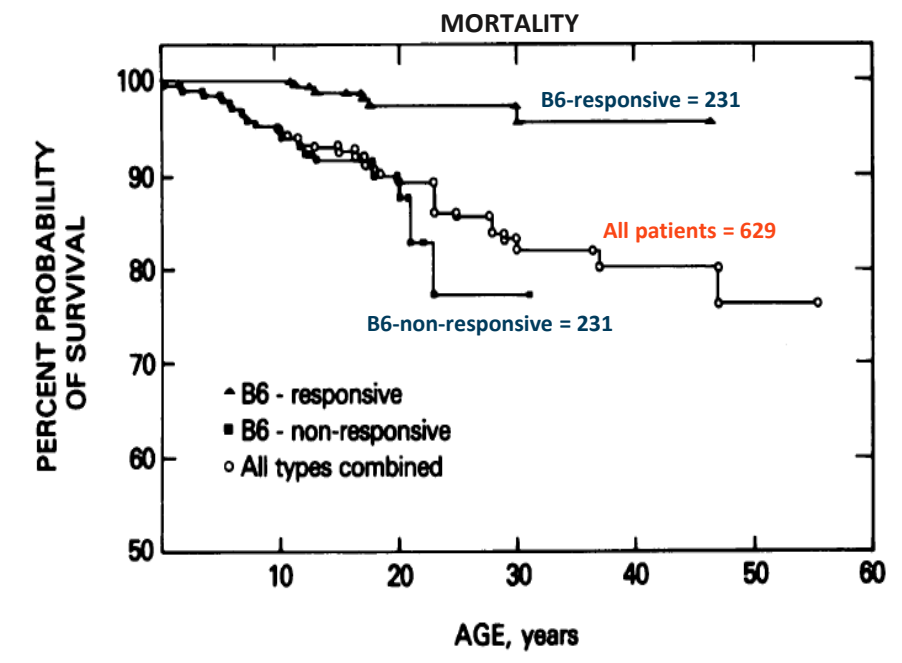
Unmet Need: Therapy that addresses both disease and treatment burden

tHcy – Total plasma homocysteine

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Increased Mortality and Severe Complication Risk in Patients with Homocystinuria

Natural History Study of 629 Untreated CBS Deficient Patients



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

NATURAL HISTORY

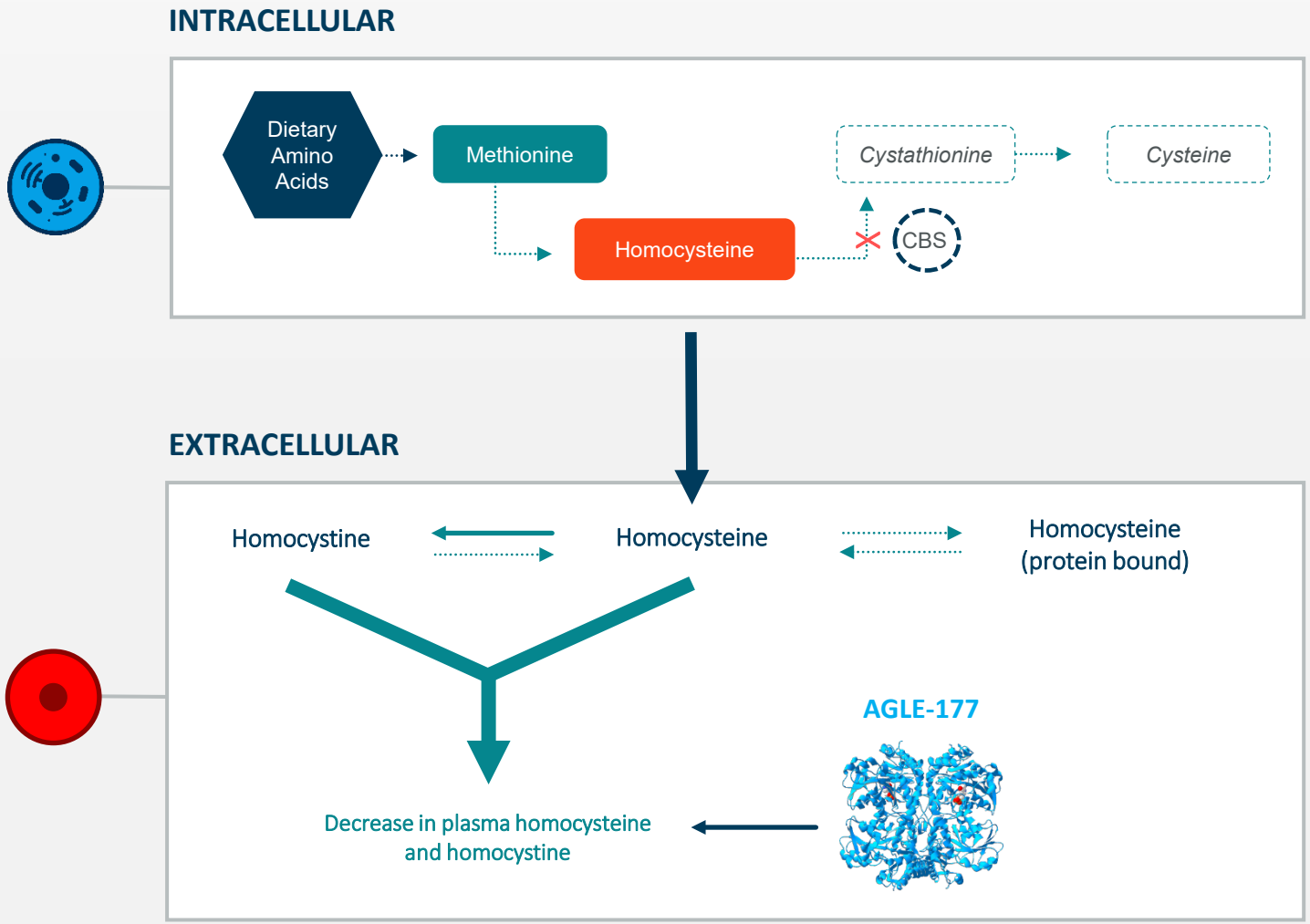
Mortality by age 30	23%	4%
Most common cause of death	Thromboembolism	
Lens dislocation in 50%	Age 6	Age 10
Median IQ	56	78
Chance of thrombosis by age 15	27%	12%

Mudd et al, 1985. Kluijtmans et al, Am. J. Hum. Genet. 65,59-67, 1999, CBS – Cystathionine β-synthase

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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

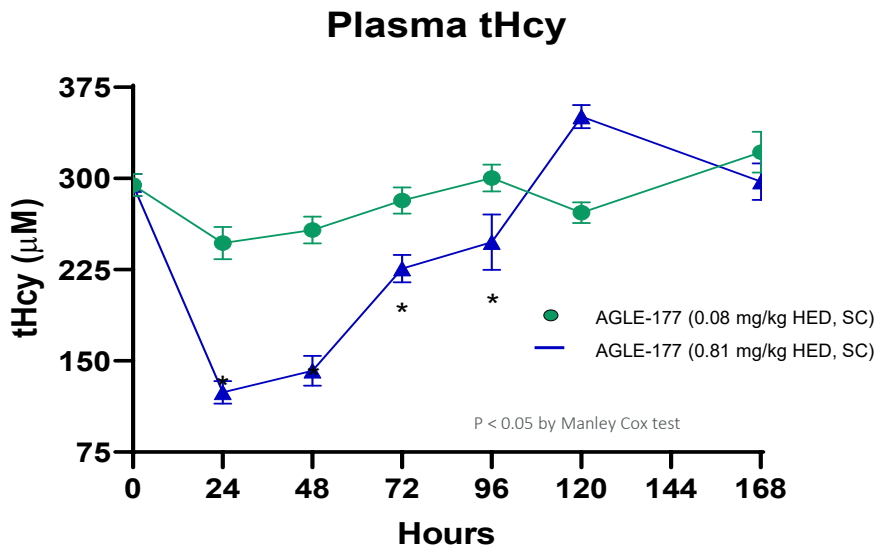
Degrading both homocysteine and homocystine is likely to enable more efficient lowering of plasma homocysteine levels

[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

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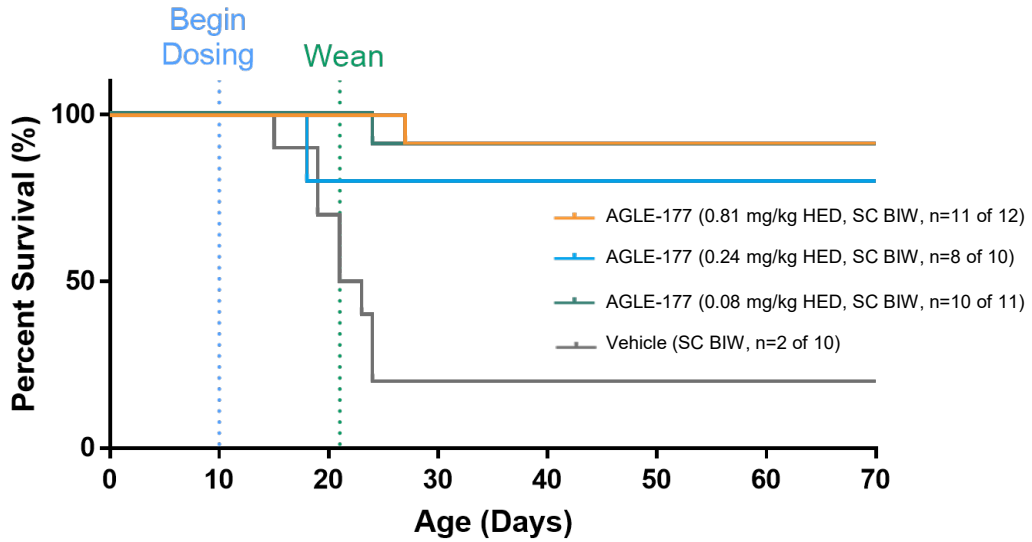
Subcutaneous Dosing Reduces Total Plasma Homocysteine and Improves Survival in Preclinical Model

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



AGLE-177 statistically significant reduction in total plasma homocysteine

In Vivo Efficacy at Multiple SC Dose Levels[2]



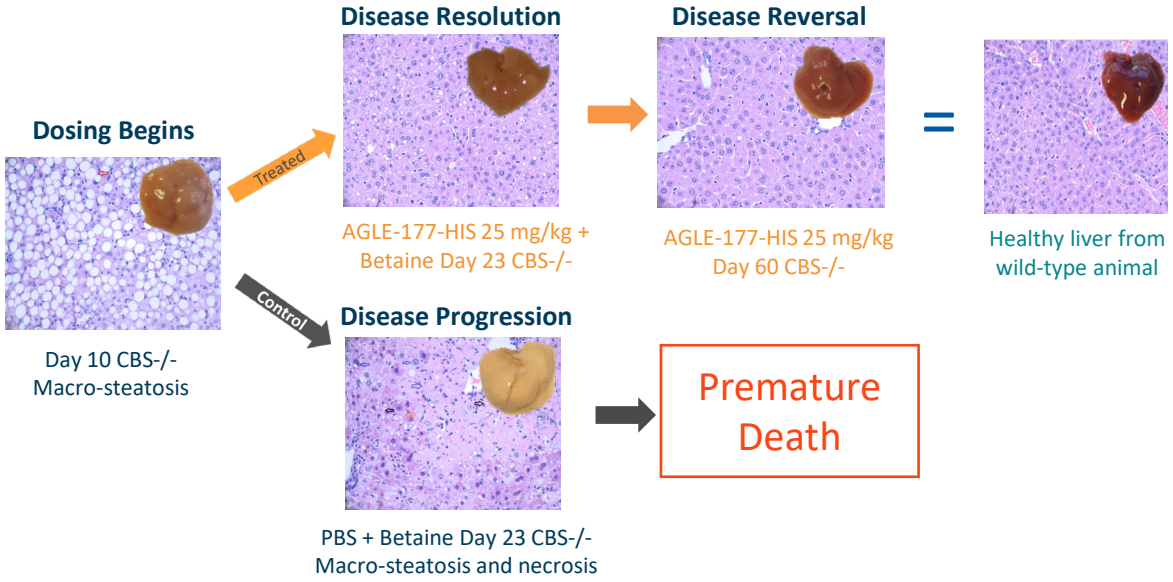
Improvement in survival following subcutaneous treatment in CBS-/- mouse model

[1] CBS -/- mice were dosed twice per week (BIW) starting at D10 with 0.81 mg/kg HED, 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. [2] Animals dosed SC BIWx3.
tHcy = total Homocysteine, HED = human equivalent dose

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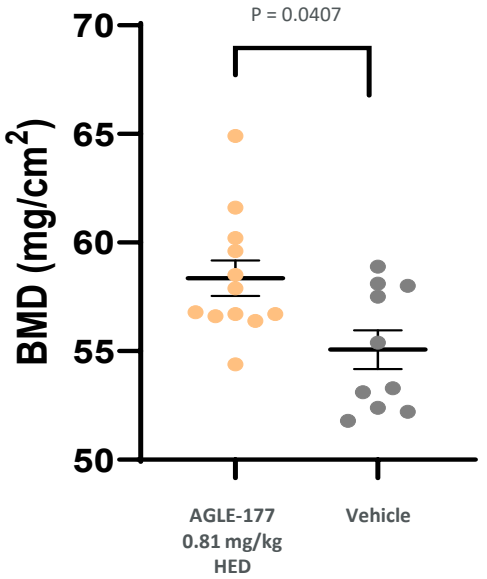
AGLE-177 Improves Pathologies and Correction of Disease Manifestations in a Preclinical Model of Homocystinuria

Reversal of Severe Liver Abnormalities in CBS-/- Mouse Model



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

Effects on the Long-term Pathologies of Osteoporosis[1]



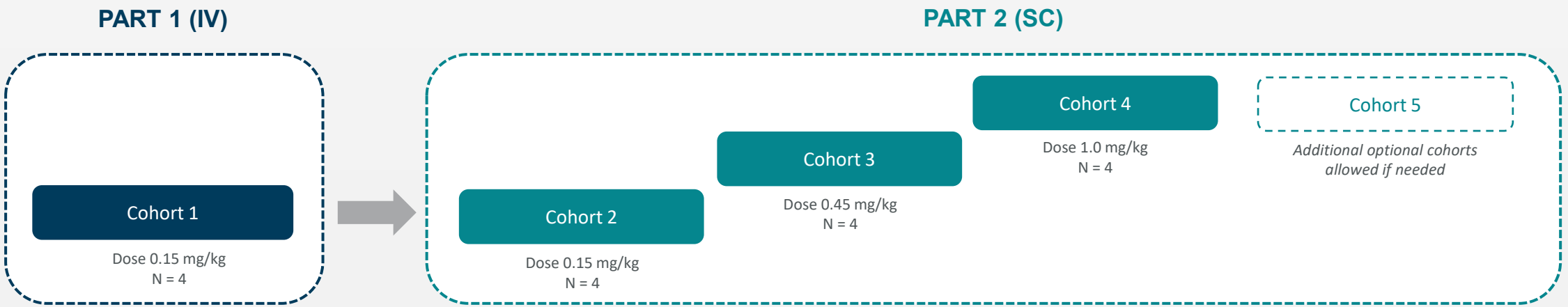
Increased BMD in preclinical model of Homocystinuria with multiple doses of AGLE-177

BMD = bone mineral density, HED = human equivalent dose. [1] 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 – Proof-of-Concept Phase 1/2 Trial

Development timeline to rapidly progress to Phase 3 trial pending trial results



Endpoints

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

Key Inclusion Criteria

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

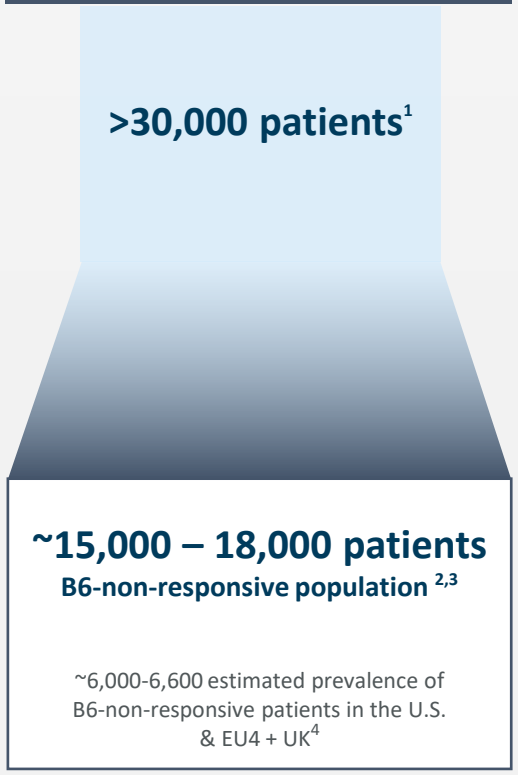
Enrollment & Dosing

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

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Homocystinuria

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

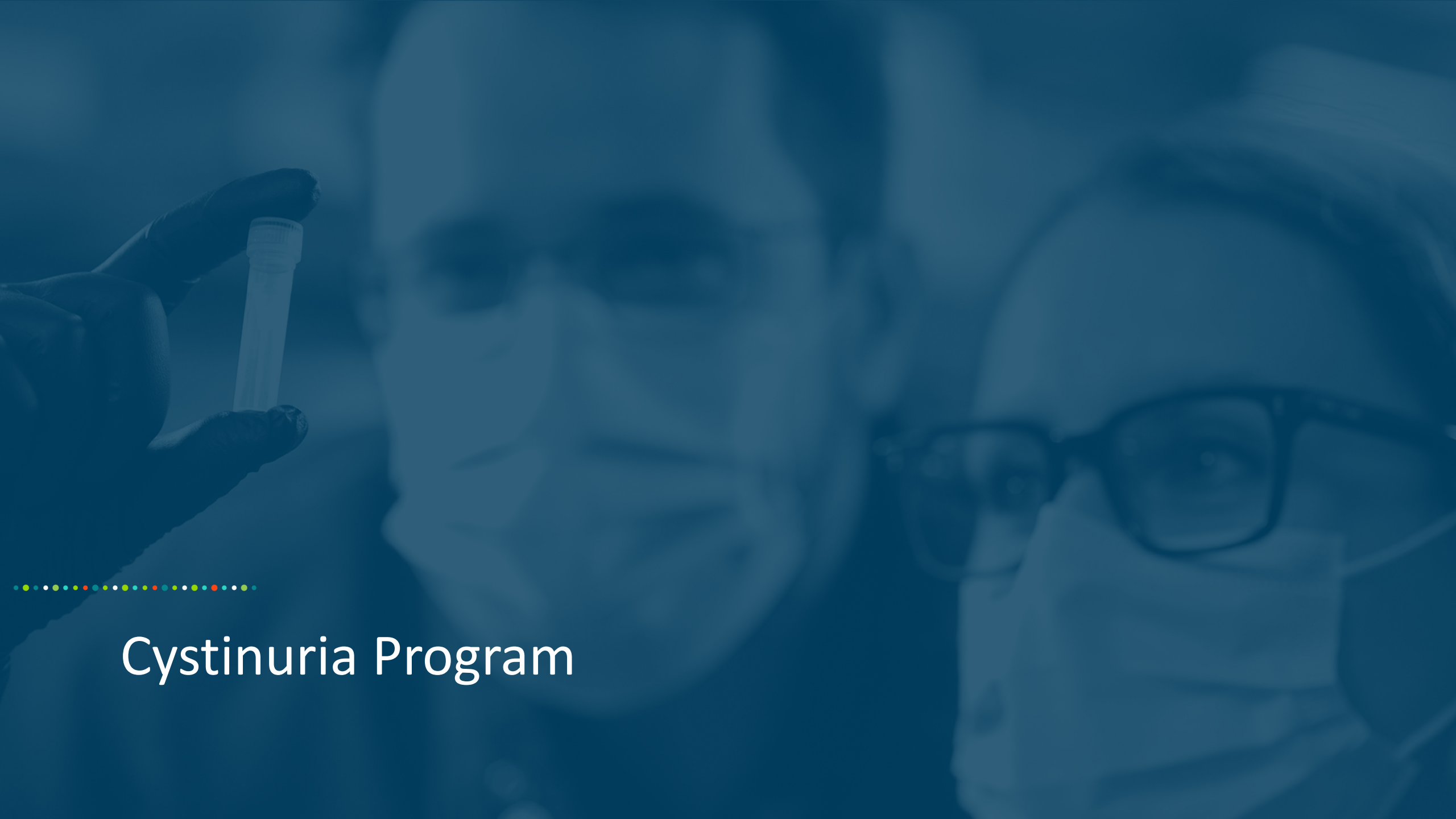
AEGLEA'S APPROACH

- Natural History study illustrates the toxic build up of homocysteine levels leads to a wide range of life-altering and worsening complications
- 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

PRV – Priority Review Voucher

[1] >30,000 represents estimated prevalence of Classical Homocystinuria (including B6-responsive and B6-non-responsive) 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. [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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Cystinuria Program

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

Cystinuria Impact to Patients

- Episodes of severe abdominal pain
- Obstructive syndromes like hydronephrosis
- Hematuria and infective syndromes like pyelonephritis
- Chronic pain (opioid addiction risk)
- Hypertension, chronic kidney disease & reduced life expectancy

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), >10,000 patients in addressable markets represents potential treatable patient population

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Cystinuria Patient Needs Not Adequately Addressed

Current standard of care:

- Very high fluid intake (>3.5 liters/day)
- Diet modification to reduce cystine consumption
- Urine alkalization to improve cystine solubility
- Thiol binding drugs (e.g. tiopronin)

Current disease management is inadequate

- Limited effectiveness
- High fluid intake requirements impractical and adversely impact QOL
- Serious side effects and/or poor tolerability of oral therapies

KEY AREAS:

1. **Therapy-resistant patients** on optimal standard disease management
2. **Patients intolerant of available adjunctive therapies**
3. **Patient circumstances where ability to maintain high urine volume or comply with high fluid intake is challenging**

Kidney obstructed with cystine stones



(Image courtesy of Stuart Wolf, UT Austin)

Untreated cystine stone



(Bazin et al. J. Appl. Cryst. (2014). 47, 719–725)

Cystine stone after alkali and/or thiol treatment



(Bazin et al. J. Appl. Cryst. (2014). 47, 719–725)

Unmet Need: Therapy that addresses both disease and treatment burden

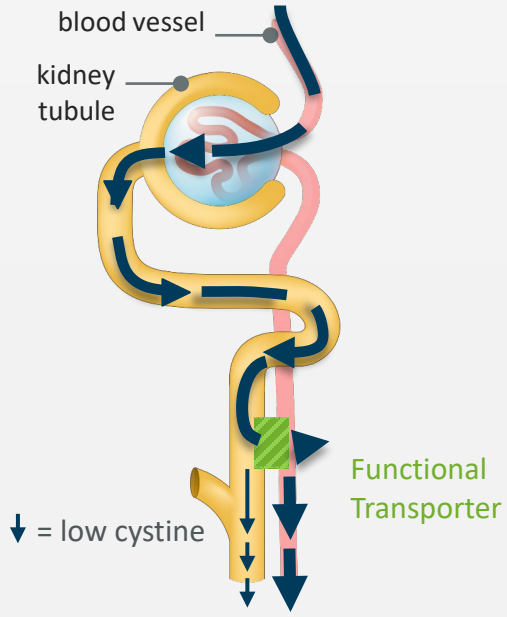
Pearle, Goldfarb et al. 2019

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Novel Therapeutic Approach for Cystinuria – Enzymatic Reduction of Cystine

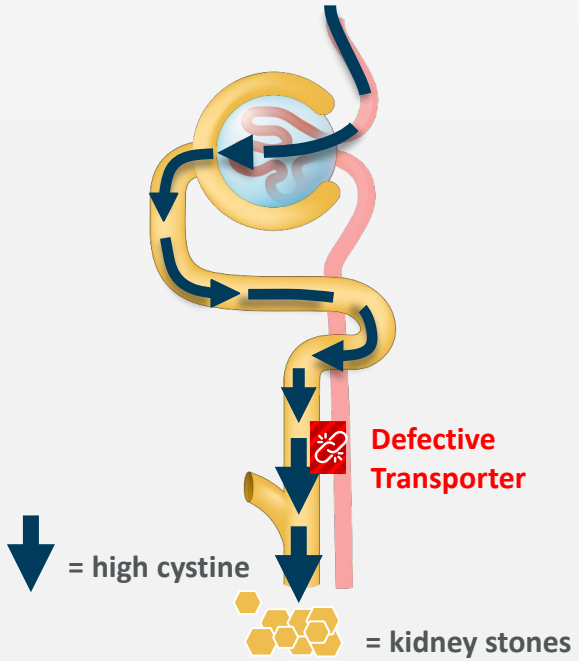
HEALTHY



Low cystine in urine

Healthy

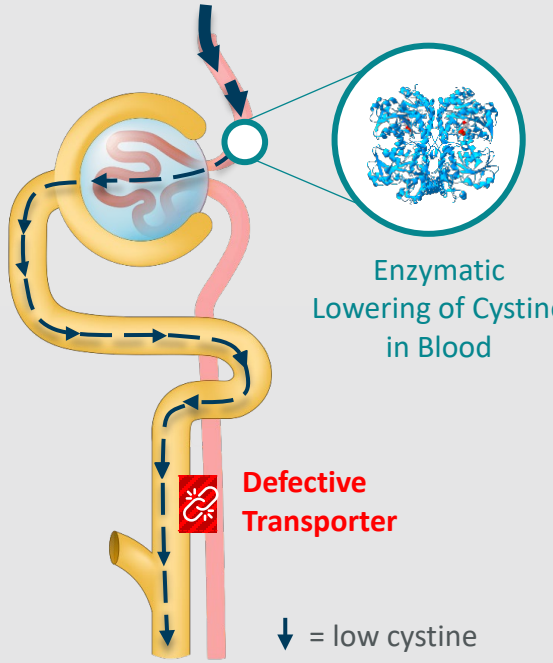
CYSTINURIA



High cystine in urine → cystine precipitates → stone formation

Severe pain, surgical interventions, kidney failure

INNOVATIVE ENZYME APPROACH



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

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

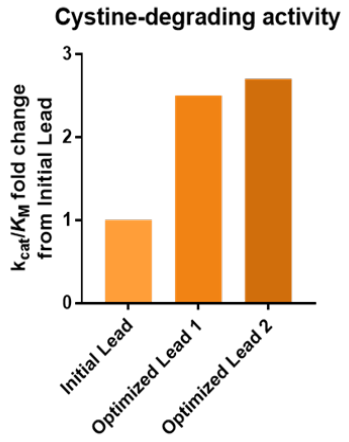
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Cystinuria Program: Novel Human Enzyme Solution for Cystinuria

Protein Engineering

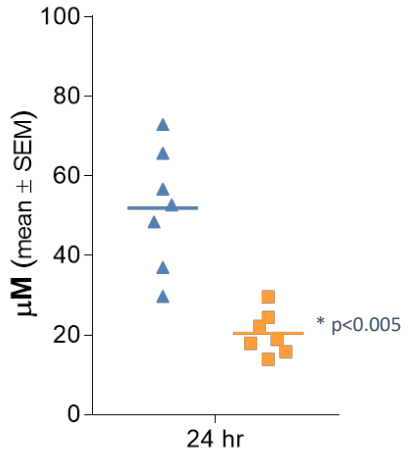
Creating Novel Cystine Degrading Activity[1]



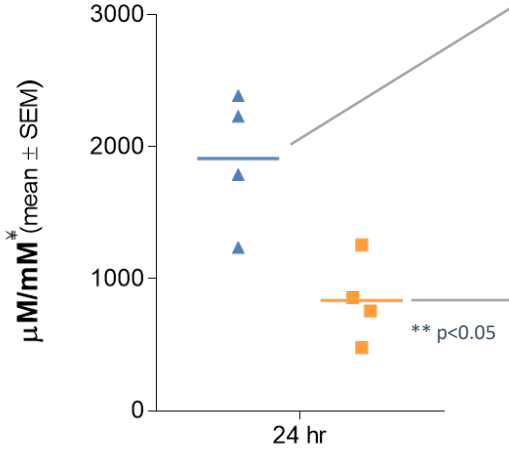
- Increase catalytic activity
- Increase serum stability
- Improve manufacturability

Proof of Concept Determination in Cystinuria Disease Model

Plasma Cystine & Cysteine



Urine Cystine & Cysteine

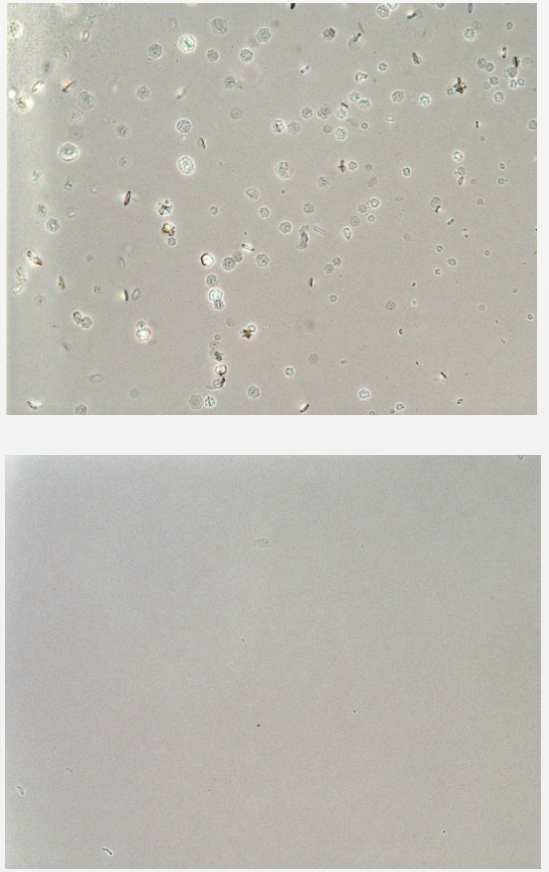


▲ Slc3a1 -/- Vehicle

■ Slc3a1 -/- Cystinuria program lead molecule

¥ total cysteine (µM) normalized to creatinine (mM)

Slc3a1 -/- mouse urine cystine crystals



Before Dosing

After Dosing

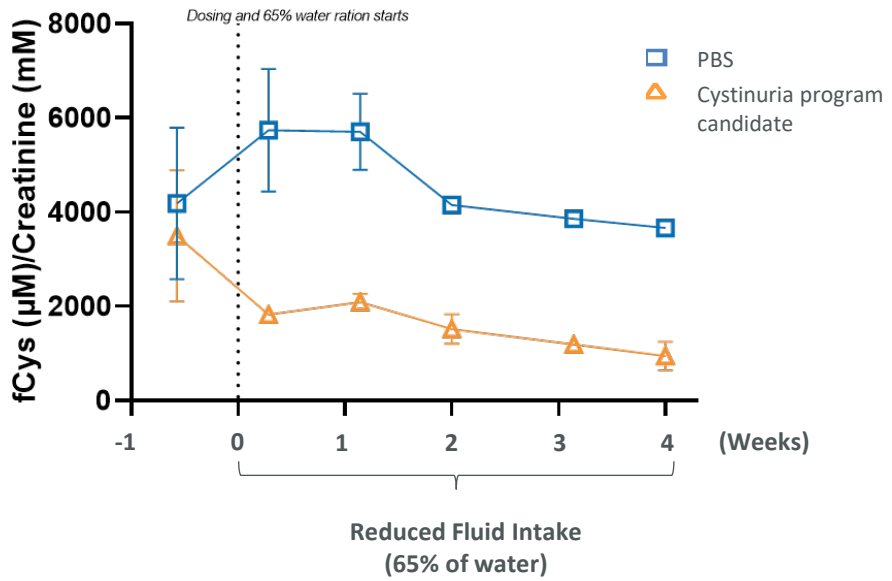
[1] Cramer SL et al, 2017 Nature Medicine 23:120-7

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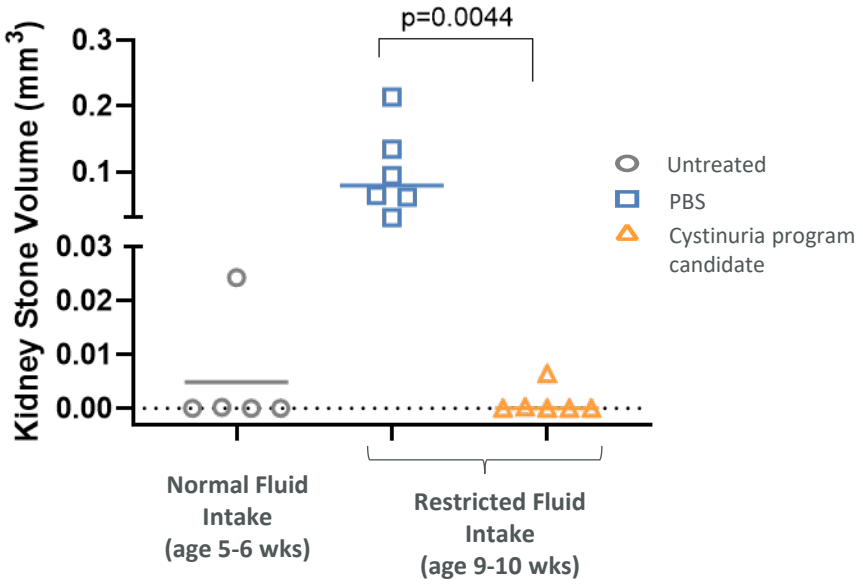
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Prevention of Kidney Stone Formation in Cystinuria Mouse Model

Urine Cystine



Volume of Kidney Stones



Agnello, et al American Society of Nephrology #TH-P0815

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Human Enzyme Platform

Leveraging Aeglea's Next Generation Human Enzyme Platform

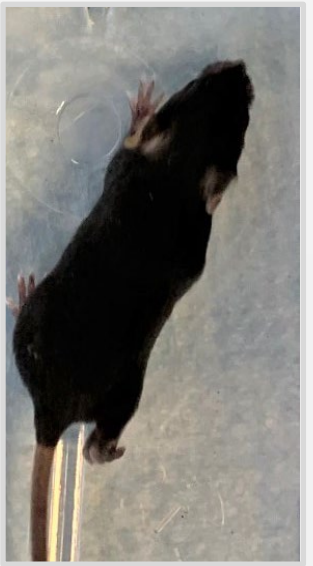
Therapeutic Approach	**Pegylated enhanced human enzyme** • Enzymatic control of high levels of a metabolite considered important in disease pathogenesis
Unmet Medical Need	• Very high - no effective therapy • Early mortality and serious complications with continued disease progression
Patient Population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

ACCOMPLISHMENTS

Pegzilarginase: ARG1-D

- 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%
- First patient dosed in pivotal Phase 3 PEACE trial
- Breakthrough Therapy Designation (BTD)
- PRV eligible: Rare Pediatric Disease Designation (RPD)
- Subcutaneous dosing; all eligible patients in OLE

AGLE-177: Homocystinuria

- Phase 1/2 trial initiated in June 2020
- 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
- Natural history study shows clear link between reductions in homocysteine levels and improvement

Cystinuria Program

- Novel 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

TARGETED MILESTONES

Pegzilarginase: ARG1-D

- Completion of enrollment: March 2021
- Topline pivotal Phase 3 data: 4Q2021

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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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Financial Summary

Cash, cash equivalents and marketable securities as of December 31, 2020: $148.1 million[1] (no debt)

As of March 12, 2021, 65.6 million[2] common shares and pre-funded warrants outstanding

$ Millions	Three Months Ended 12/31/20	Twelve Months Ended 12/31/20
R&D Expense	$15.8	$59.6
G&A Expense	$7.0	$21.8
Net Loss	$22.7	$80.9

Expected funding runway: into 2023

[1]Includes $1.8mm of restricted cash. [2]Includes 48.0 million common shares outstanding and 17.6 million pre-funded warrants

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Baseline Demographics and Patient Characteristics

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

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

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

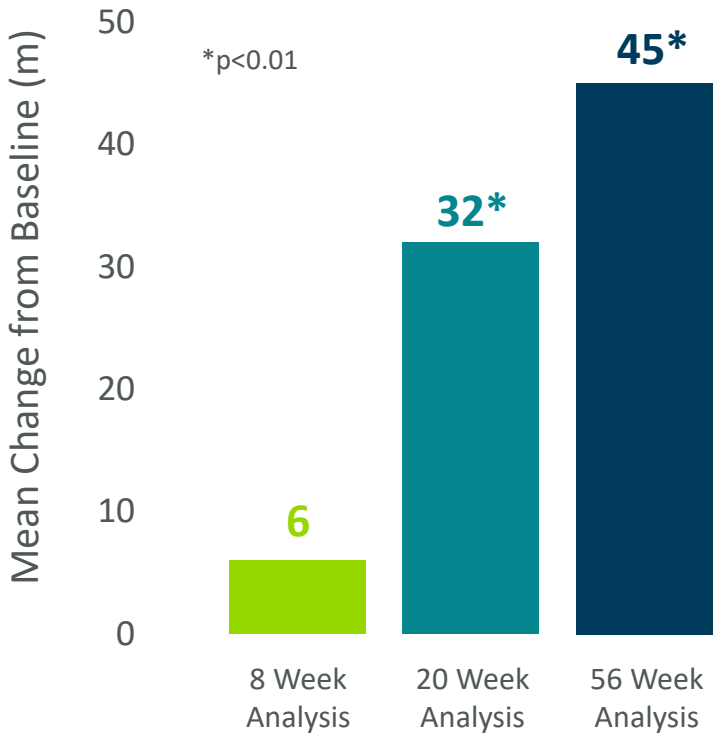
*Clinically meaningful response defined as an improvement in Minimal Clinically Important Difference (MCID) MCID for 6MWT = 9%; MCID for GMFM Part D is 2.4, 3.3, and 1.5 for GMFCS Levels I, II and III, respectively; MCID for GMFM Part E is 4.0, 2.8, and 1.8 for GMFCS Levels I, II and III, respectively.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

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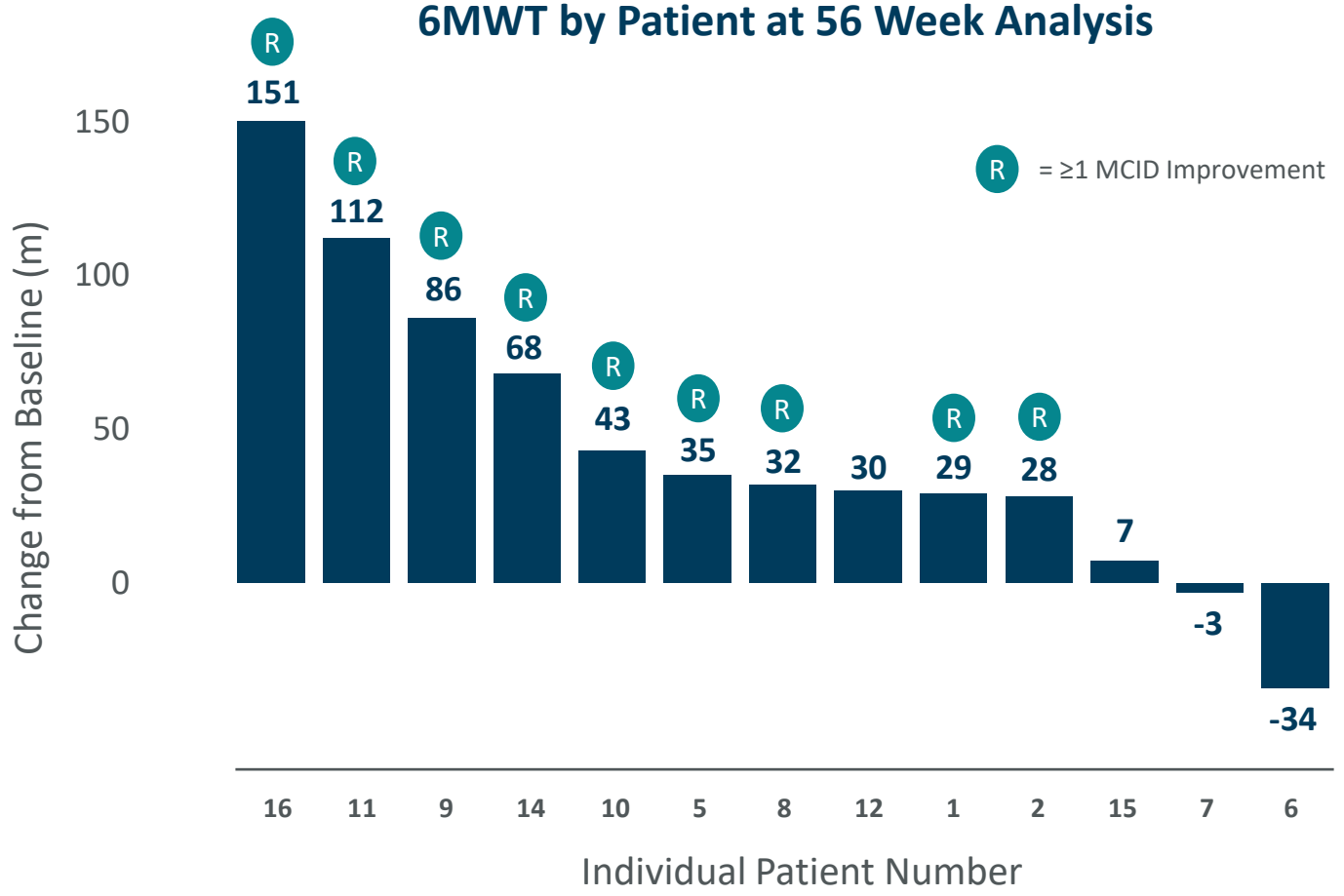
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Pegzilarginase Demonstrates Sustained Improvements in 6 Minute Walk Test

Mean Change from Baseline in 6MWT



6MWT by Patient at 56 Week Analysis



6MWT – Six Minute Walk Test

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Clinically Impactful Improvements at Patient Level with Pegzilarginase

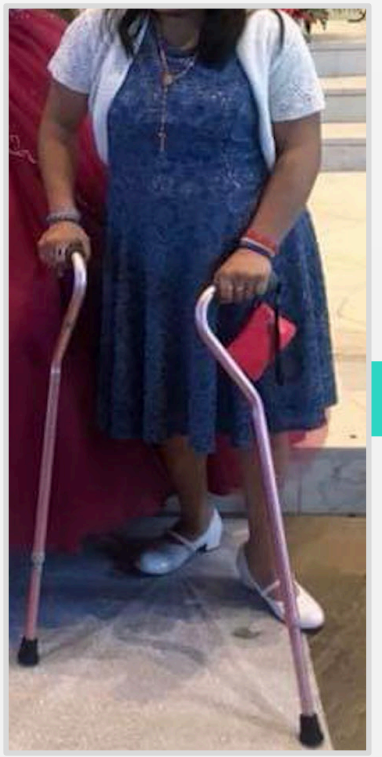
Patient Background

- Teenage girl diagnosed at age 1 (presented with hyperammonaemia)
- Developed severe lower limb spasticity, speech delay, intellectual disability
- Treated with severe protein restriction, essential amino acids, and ammonia scavengers
- Persistent hyperargininaemia
- Progressive worsening of lower extremity diplegia, walked with arm crutches at baseline (GMFCS II)

Assessment	Normal Population	Baseline	20 Week Analysis	56 Week Analysis
Plasma Arginine	40 - 115µM	363µM	**108.5µM***	**88.2µM***
6MWT	310 - 664m	174m	176m	**209m***
GMFM-D	Max = 39	21	**27***	**28***
GMFM-E	Max = 72	27	**35***	**34***

*Achieved MCID 6MWT = 16m; GMFM-D = 3.3; GMFM-E = 2.8

Patient 5:
Baseline



Unable to cross legs and dependent on walking aid

Patient 5:
20 Week Analysis



Able to cross legs and less dependent on walking aid

Images by kind permission of Dr GA Diaz

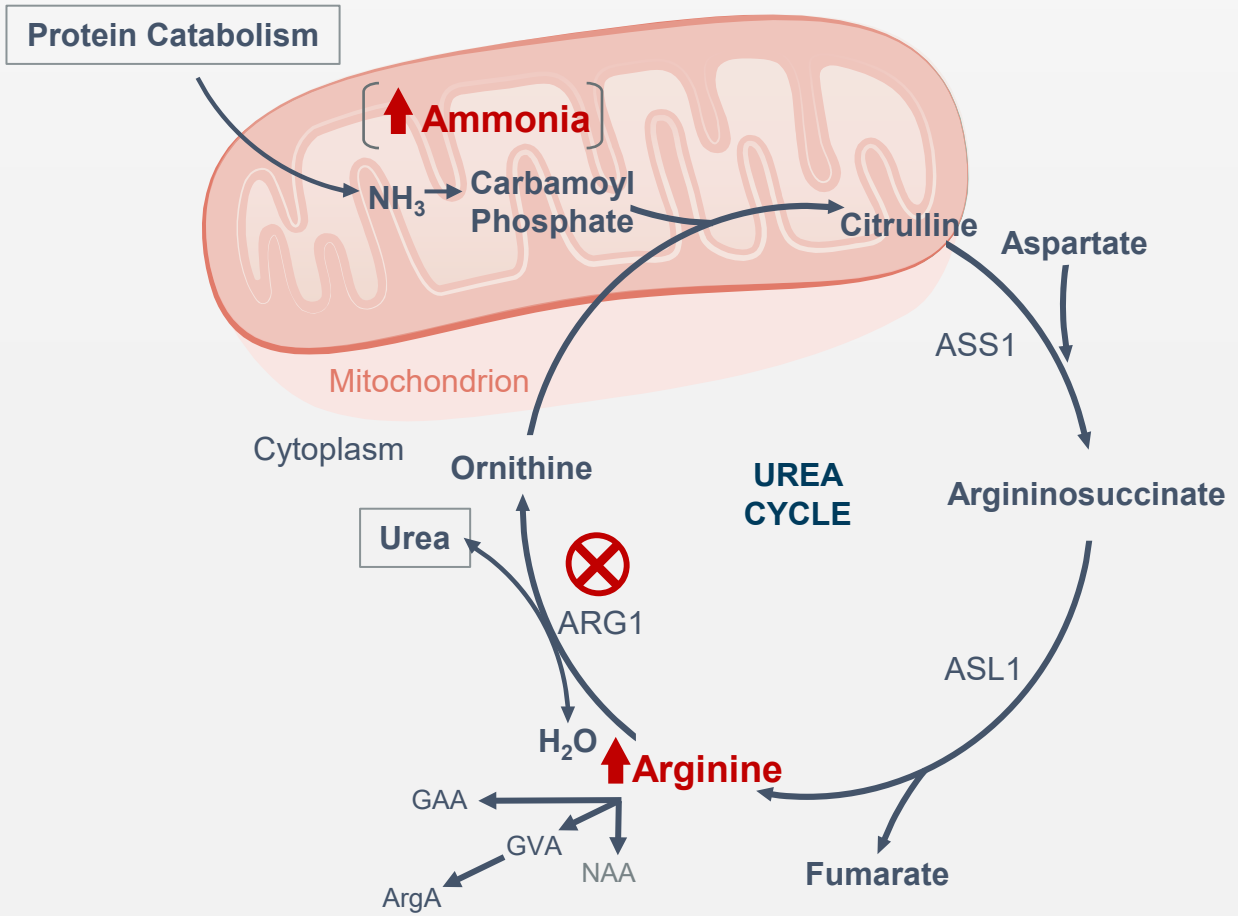
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Arginase 1 Deficiency (ARG1-D)

Progressive metabolic disease with significant morbidity and early mortality

Typically presents in childhood with spasticity, neurocognitive impairment, seizures, growth delay and hyperammonemic episodes

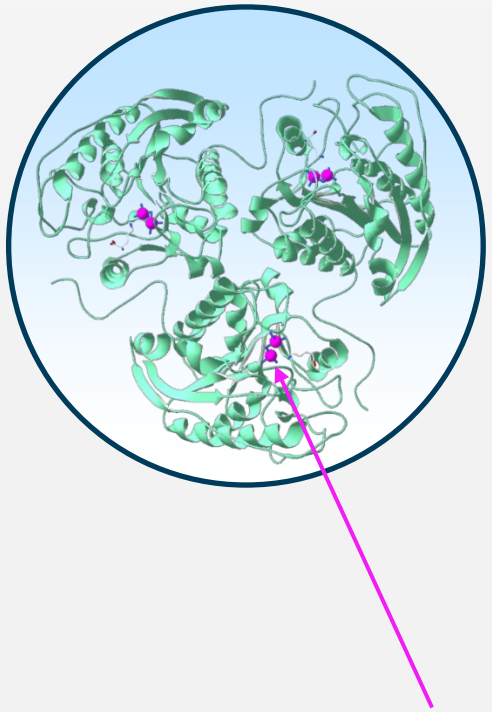
- Deficiency of Arginase-1 leads to:
  - Elevated plasma arginine and related metabolites, which are responsible for the spasticity, developmental delay and seizures
  - Slowing of the urea cycle, which leads to elevated ammonia levels, and hyperammonemic episodes in times of stress
- Current treatment is inadequate:
  - Dietary protein restriction is the best available therapy for lowering plasma arginine
  - Compliance is challenging resulting in disease progression and early death

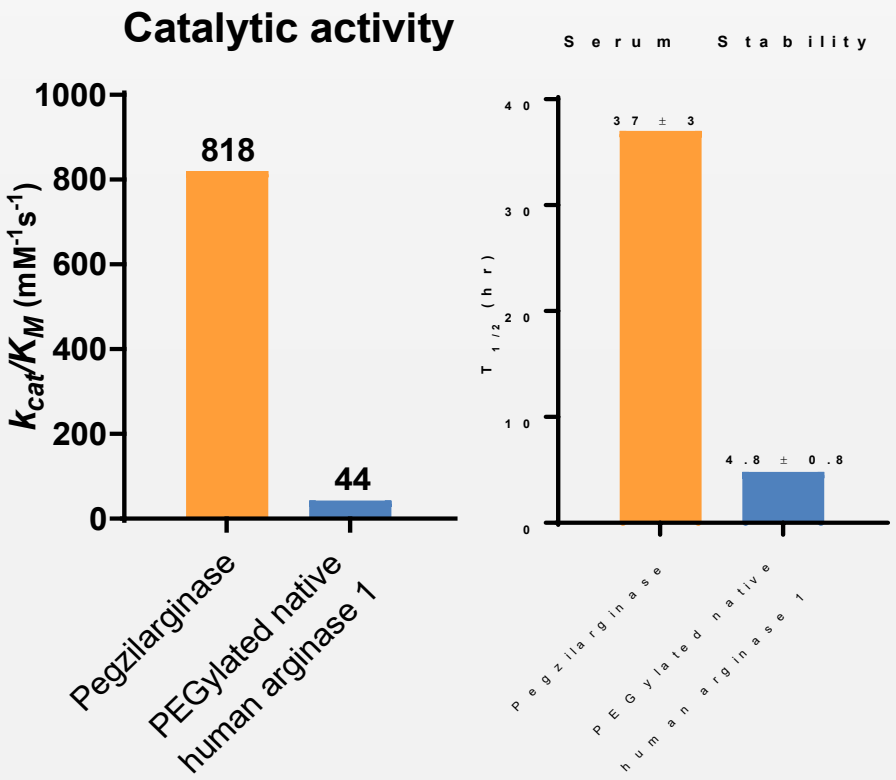


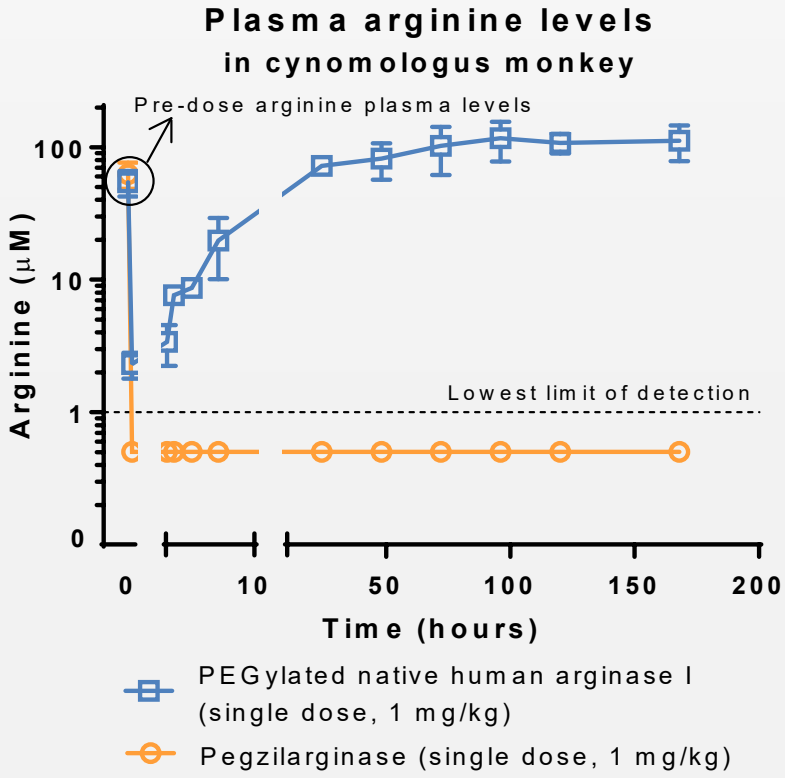
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Designing Enzyme Therapeutics - Pegzilarginase

Pegzilarginase







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

Improved Catalytic Activity & Serum Stability

Reduced Circulating Arginine levels

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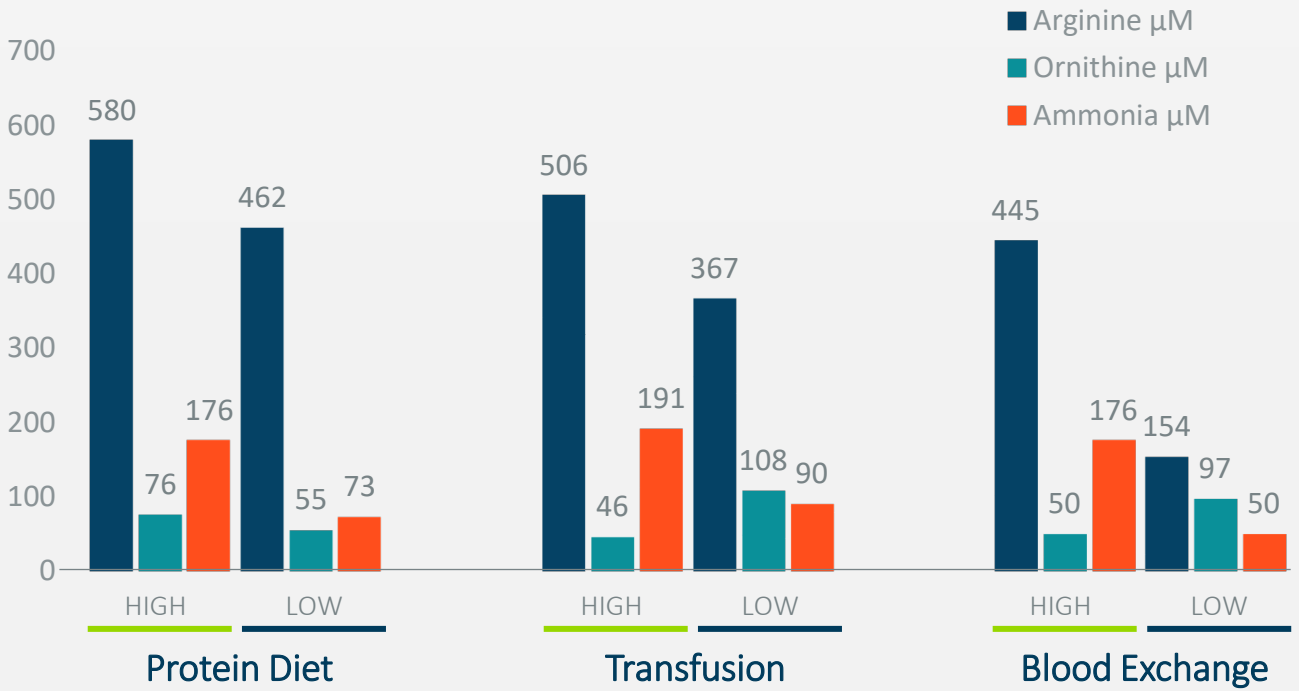
Pegzilarginase: Clinical Benefit Associated With Extra-Hepatic Enhancement of Arginase 1 Enzyme Activity



Clinical Description

- 5 y.o. male
- Spastic quadriplegia
- Hyperreflexia
- Mental retardation
- Loss of speech
- Unable to sit or crawl

Red blood cell exchange improved clinical presentation



Protein Diet

No change in condition

Transfusion

Slight improvement in spasticity

Blood Exchange

Improved clinical condition

- Able to sit and roll over on his own
- Decreased spasticity

Adapted from Sakiyama et al (1984) "A successful trial of enzyme replacement therapy in a case of Argininemia" J Exp Med.

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