Reimagining The Potential Of Human Enzyme Therapeutics

August 2020

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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 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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Advancing Programs Set Stage for Transformative 2021

Pegzilarginase in Arginase 1 Deficiency

Enhanced human arginase that enzymatically lowers levels of the arginine

PEACE – pivotal Phase 3 trial enrolling

ACN00177 in Homocystinuria

Novel recombinant human enzyme that degrades the amino acid homocysteine

Phase 1/2 trial ready for initiation

Enzyme Therapeutics Platform

Rare metabolic-disease, monogenic focus

Most advanced program in Cystinuria

2020 Momentum

- ☑ 1-year OLE data
- ❑ Pivotal Ph 3 enrollment completion
- ❑ Topline Ph 3 data (1Q21)

- ☑ CTA approved by MHRA
- ☑ Ph 1/2 trial initiated
- ❑ Ph 1/2 first patient dosed

- ☑ $138m financing to support clinical and platform programs; runway through 2022

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Looking Beyond the Conventional with Next Generation Human Enzyme Therapeutics



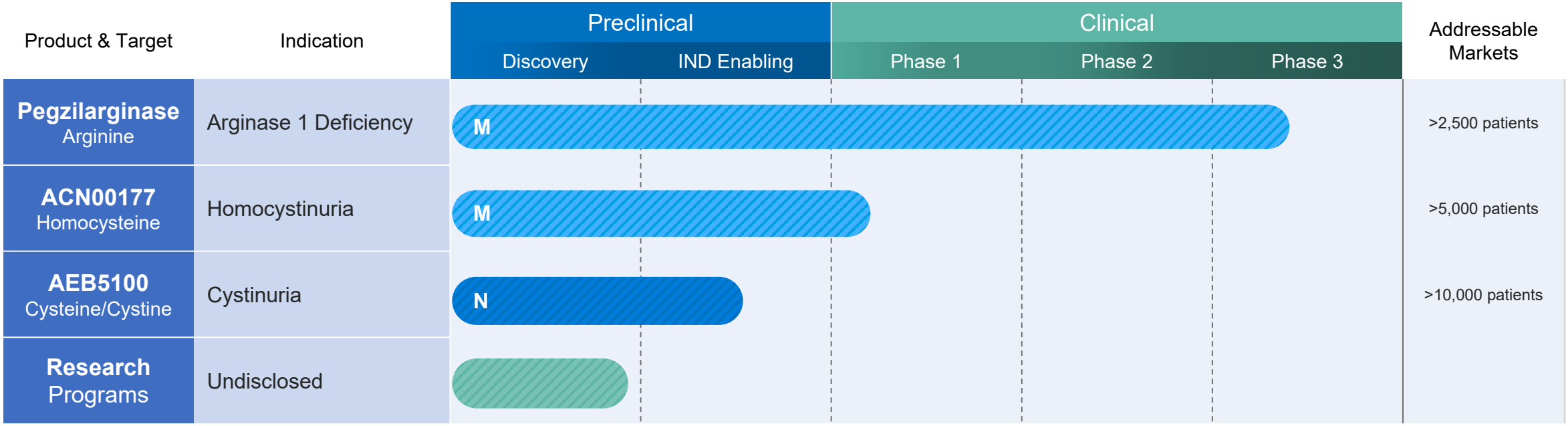
- Distinctive disease selection approach
- Validated metabolite targets
- Human enzyme scaffolds
- Translatable disease models
- Reduced toxicology risk

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

- Efficient and targeted commercialization model
- Attractive reimbursement potential
- Substantial barriers to entry

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Rethinking the Potential of Human Enzyme Therapeutics



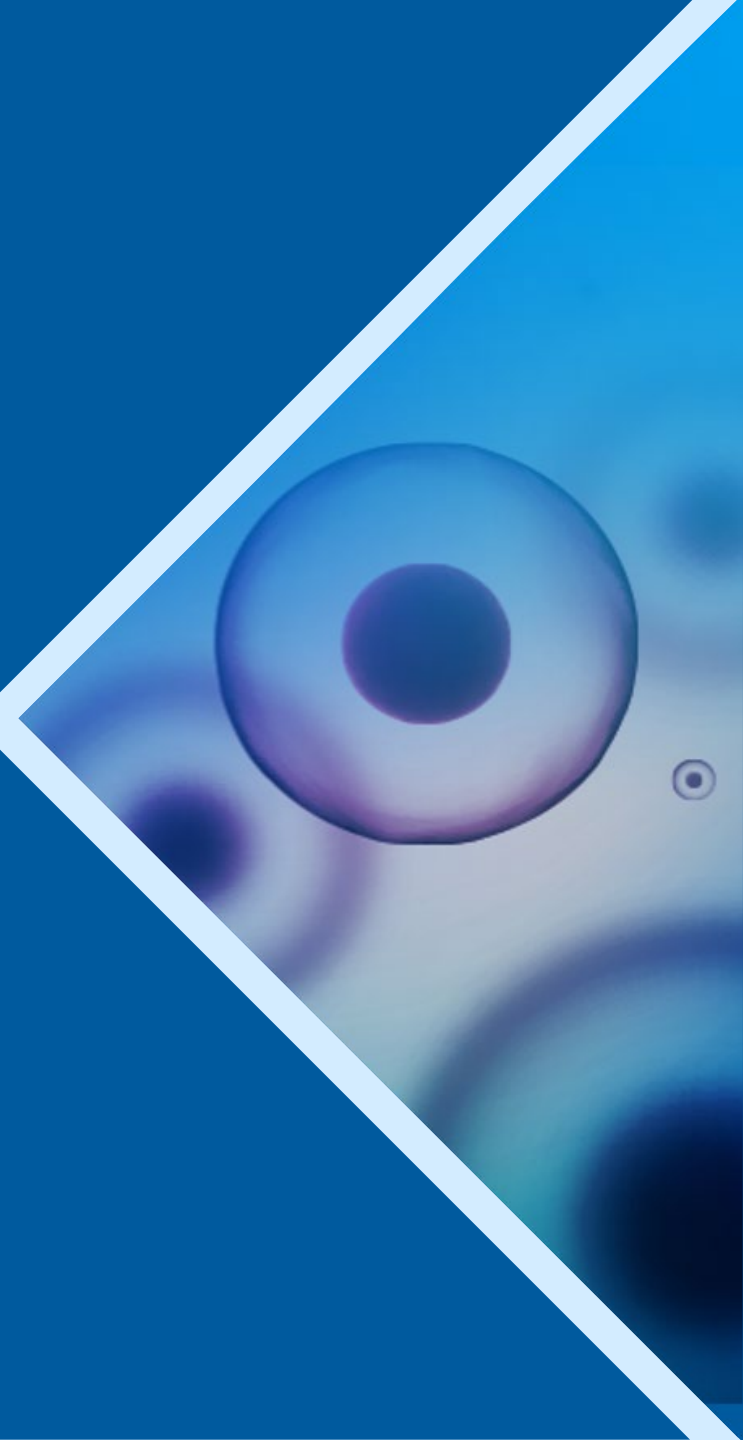
Worldwide commercial rights to entire pipeline

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Pegzilarginase

A novel recombinant human arginase which rapidly and sustainably reduces plasma levels of arginine in patients with Arginase 1 Deficiency

Rare Pediatric, Breakthrough Therapy and Fast Track Designations



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Pegzilarginase: Arginase 1 Deficiency

Novel plasma arginine metabolizing enzyme

Unmet Medical Need	• Very high - no effective therapy
	• Early mortality and serious complications with continued disease progression
	  • Severe progressive spasticity
	  • Developmental delay and intellectual disability
	  • Seizures
	  • Episodic hyperammonemia

Patient Population (Addressable Markets)	• **Genetic prevalence estimates >2,500** patients in addressable markets • **>240** patients identified to date • >50% of U.S. and >30% of EU5 genetic prevalent population identified
Diagnosis	• Plasma arginine level/enzyme activity assay and/or mutation analysis • Newborn screening: currently available in 34 of 50 U.S. states

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Arginase 1 Deficiency (ARG1-D)

- **Typically presents at ~2-4 years of age, can be later[2,3]**
  - Developmental delay with increasing intellectual disability
  - Failure to thrive and short stature
- **Prominent and progressive neurological manifestations[4]**
  - Impaired mobility due to characteristic spastic diplegia
  - Seizures are a common feature
- **Additional abnormalities due to impairment urea cycle**
  - Hyperammonemia but less prominent than other urea cycle disorders
  - Protein aversion, food refusal and self-restriction of protein
- **Low disease awareness leads to delay in diagnosis[2]**



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1. Aeglea Data on File 2. Huemer M, et al. *J Inherit Metab Dis.* 2016;39:331–340 3.Burrage LC, et al. *Hum Mol Genet.* 2015;24:6417–6427 4. Carvalho DR, et al. *Pediatr Neurol.* 2012;46:369–374 5.Haberle J et al *J Inherit Metab Dis,* 2019, 6.Diez-Fernandez C, et al. Hum Mutat. 2018;39:1029–1050, 7.Carvalho DR et al. Gene 2012; 509(1): 124-130.

1-Year Data from Phase 1/2 + Open-Label Extension Study of Pegzilarginase in Arginase 1 Deficiency Patients

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 (40-115)	389 (238–566)
NH_3*, µM (range)	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

Safety Summary

- Pegzilarginase was shown to have a favorable safety profile
- More than 750 doses administered in the Phase 1/2 clinical trial (101A) and Phase 2 OLE study (102A)
  - Approximately 500 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

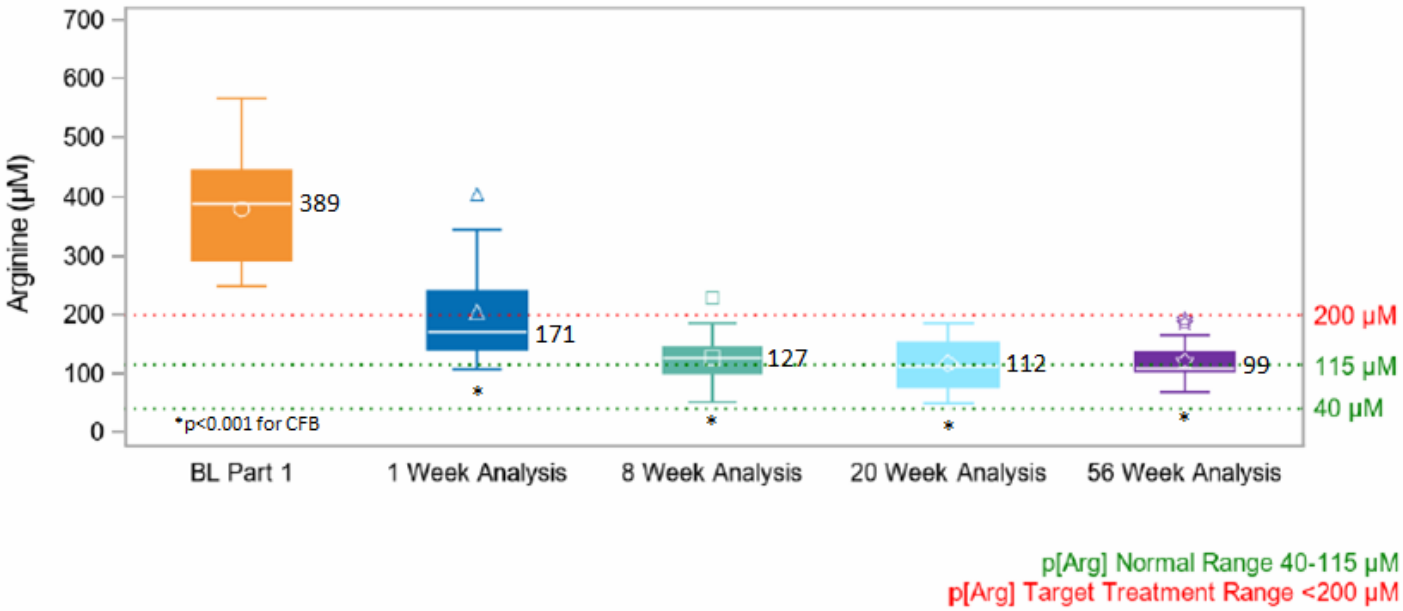
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*Values are median (range) unless stated otherwise.
Arg, arginine; ARG1, arginase 1; BL, baseline; NH_3, ammonia; 6MWT, 6-minute walk test; GMFM-D/E, Gross Motor Function Measure Part D/E; Pt, patient
** 1 patient non-assessable (wheelchair bound)

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Pegzilarginase Markedly Reduces and Sustainably Controls Plasma Arginine

Plasma Arginine in Response to Pegzilarginase



- Baseline plasma arginine on standard disease management was markedly elevated
- Significant and sustained reductions in plasma arginine were achieved from baseline to week 1, week 8, week 20 and week 56
- At the week 56 analysis:
  - The median plasma arginine was 99μM (40-115μM)
  - 10/13 patients achieved plasma arginine within normal range (40-115uM)
  - 13/13 patients achieved plasma arginine within target range (<200uM)

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#'s are medians

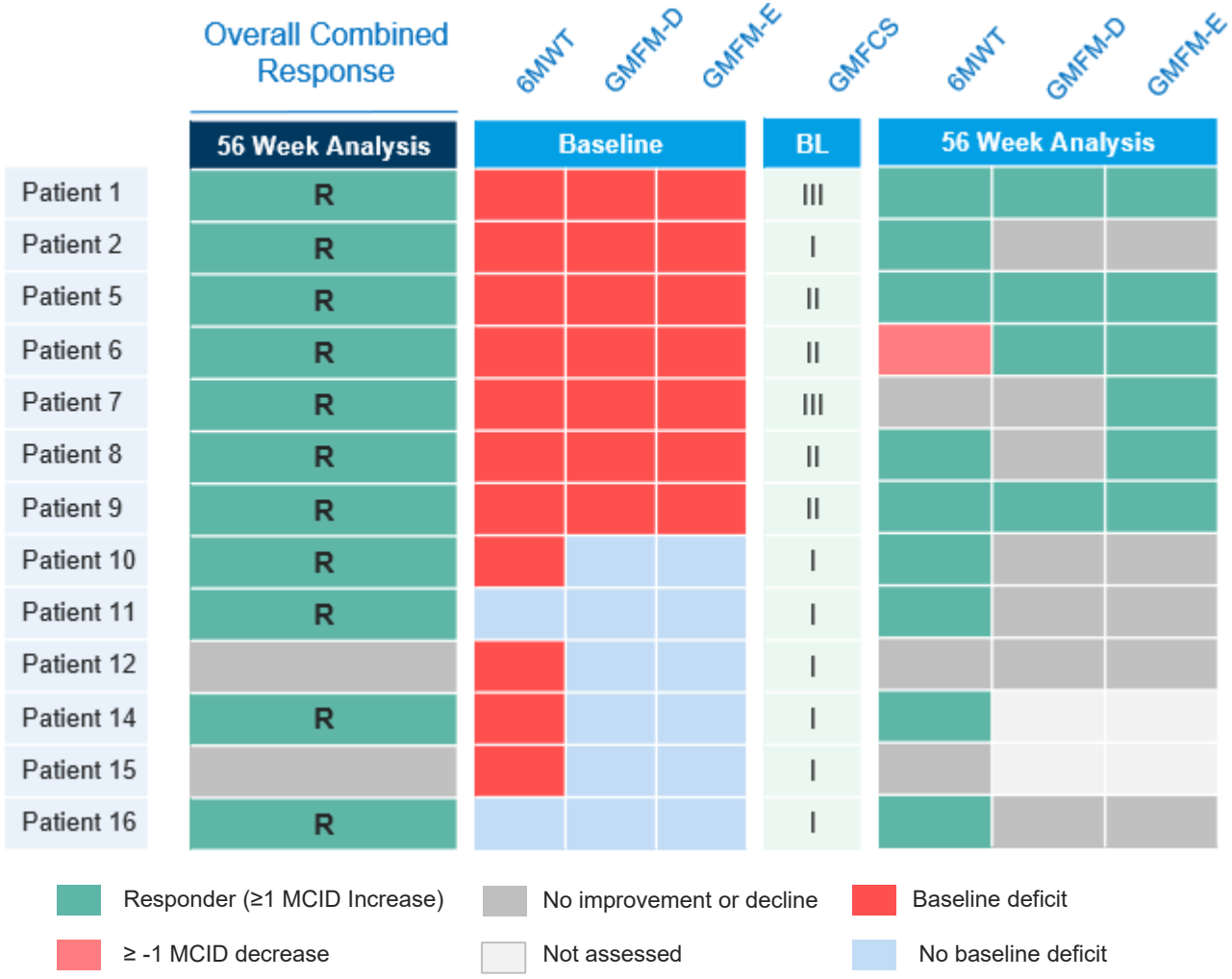
Pegzilarginase Demonstrates Durable Clinical Response at 56 Week Analysis

Overall clinical response rate:

56 Week Analysis: 11/13 (85%)

20 Week Analysis: 11/14 (79%)

Clinical Responder defined by achievement in one or more of three mobility assessments



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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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Rare Disease Trial Design: Learn & Adapt Along the Way

Disease Burden

In a disease with no natural history study or previous clinical trials, how do you:

- Quantify the disease burden?
- Measure the patient benefit?

Known Impact

- Start with known and measurable manifestations that have an impact on the patient's life – mobility and spasticity.

"Look A-Like" Condition

- Leverage outcomes assessments validated in other conditions which show similar disease manifestations. Spastic diplegia in ARG1-D closely resembles manifestations in cerebral palsy.

Patient Feedback

- Gather and listen to patient, caregiver and physician feedback to refine assessments and inform future trial design.

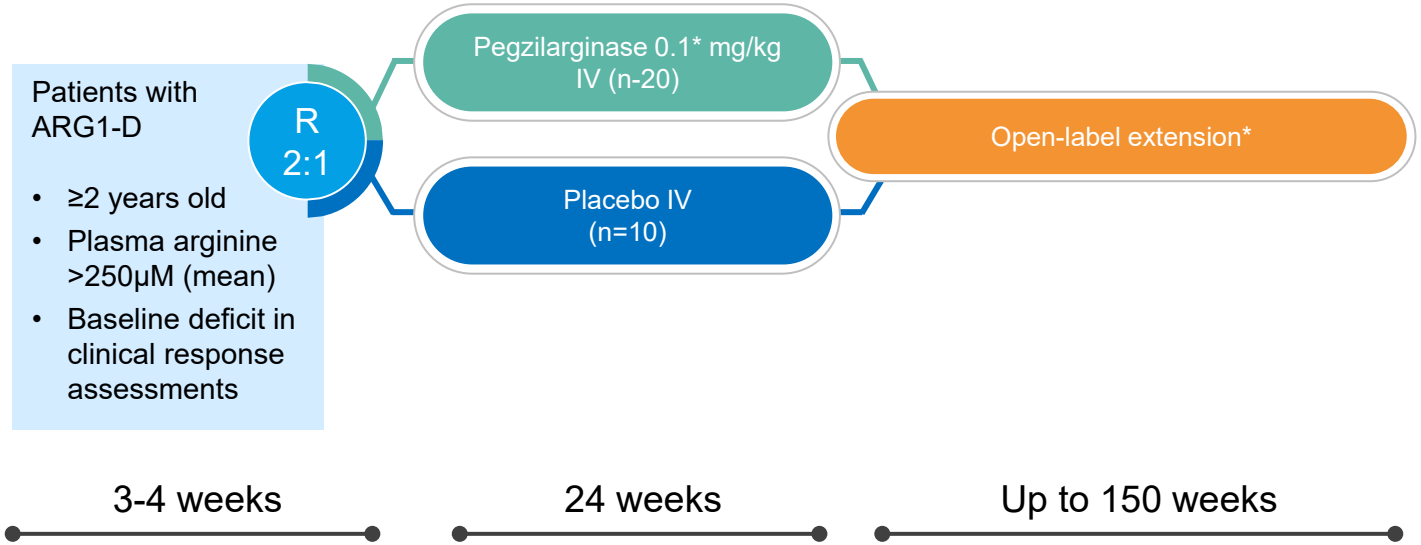
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Pivotal Phase 3: PEACE Trial Design

Key Endpoints

- **Primary:** plasma arginine reduction
- **Secondary:** clinical responder endpoint
  - Timed Walk Test (2MWT)
  - GMFM-D (Standing)
  - GMFM-E (Walking, Running & Jumping)

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



*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.

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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

Finding Arginase 1 Deficiency Patients

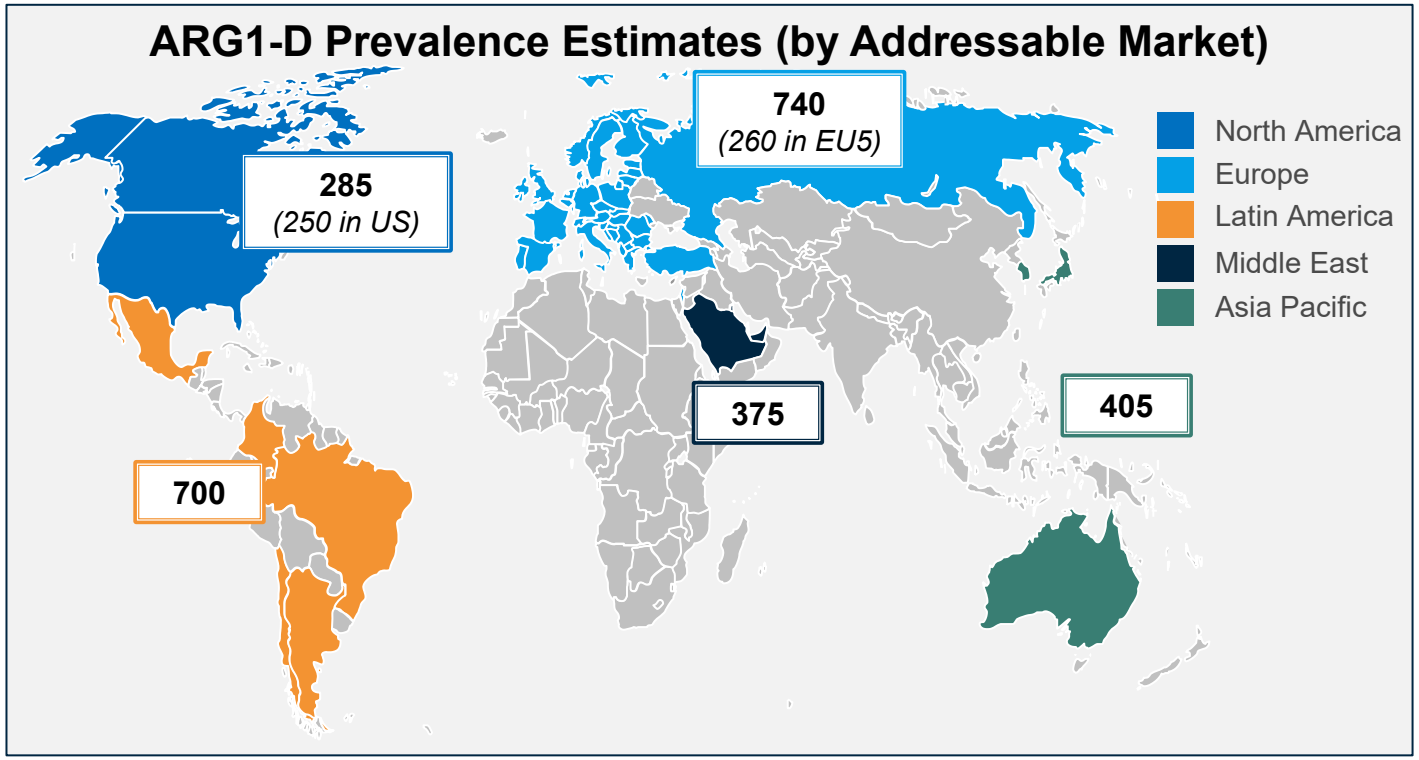
Genetic analysis indicates a prevalence of ~2,500 in select geographies.

ARG1-D Genetic Prevalence

Estimates based on ARG1 genetic mutations identified in published literature and in Aeglea clinical development program

Advantages of Genetic Prevalence

- Widely available
- Applicable to multiple populations
- More accurate than NBS-based approaches



To date, Aeglea has identified more than 240 ARG1-D patients, the majority of which are in the U.S. and EU5

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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 Lean & Efficient Commercial Organization to Serve as Foundation for Future Rare Disease Portfolio

Key Pillars

Patient Identification



Scientific Communications



Access & Reimbursement



Commercial Planning

- Worldwide commercial rights with ongoing ex-U.S. partnering discussions
- Strategic, senior commercial leadership team in place
- Plans to establish a U.S. commercial organization
  - Field-based sales (~10 FTEs) and patient access (~5 FTEs) teams
  - Additional commercial functions, e.g., marketing, patient services, trade, market access, and analytics

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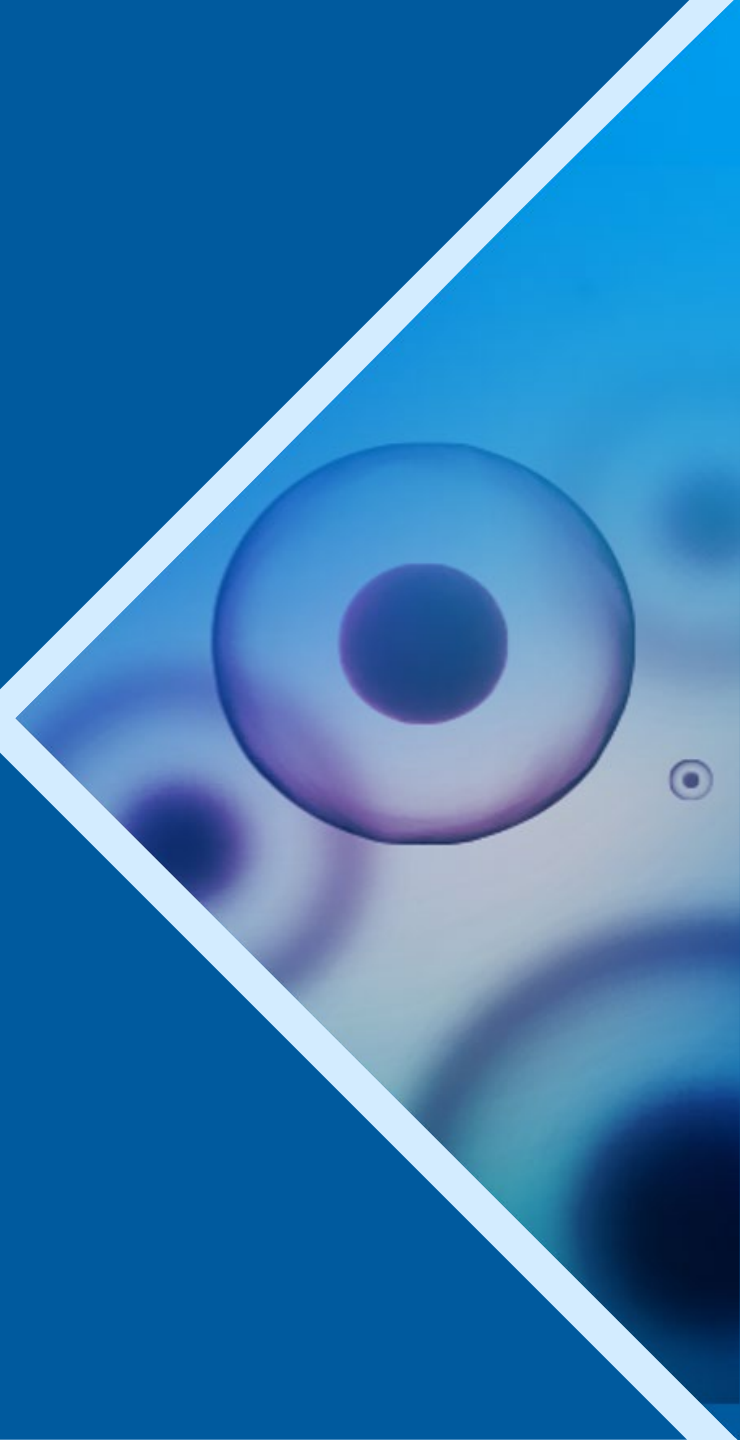
Arginase 1 Deficiency Key Highlights and Opportunity

Phase 1/2 & OLE data demonstrates clinical impact	PEACE: A single, global pivotal trial designed with input from FDA and EMA	Opportunity
• 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	• Primary endpoint: arginine reduction; secondary endpoints: clinical outcomes, safety and PK • 30 patients, randomized 2:1 (pegzilarginase:placebo) • 24 weeks dosing period • Enrollment completion in 3Q2020; topline results in 1Q2021	• Estimated >2,500 patients worldwide • >240 patients identified worldwide (>125 patients in U.S.) • Worldwide commercial rights with ongoing ex-U.S. partnering discussions

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ACN00177

Novel recombinant human enzyme in clinical development to treat homocystinuria due to cystathionine beta synthase (CBS) deficiency



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ACN00177: Homocystinuria

Novel homocysteine/homocystine metabolizing enzyme

Unmet Medical Need	• Very high - no effective therapy for many patients
	• Early mortality and serious complications
	  • Lens dislocation, glaucoma and severe short-sightedness
	  • Skeletal abnormalities including osteoporosis
	  • Learning problems, developmental delay/intellectual disability
	  • Vascular abnormalities including thromboembolism

Patient Population (Addressable Markets)	• >**5,000** patients with B6 non-responsive CBS Deficiency • Additional opportunity in B6 responsive patients (>5,000)
Diagnosis	• Plasma total homocysteine level/enzyme activity assay and/or mutation analysis • Newborn screening in all U.S. states

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Homocystinuria Patient Needs Not Adequately Addressed

Limited impact of approved therapies for Homocystinuria

Current standard of care:

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

Current disease management is inadequate:

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

Key areas:

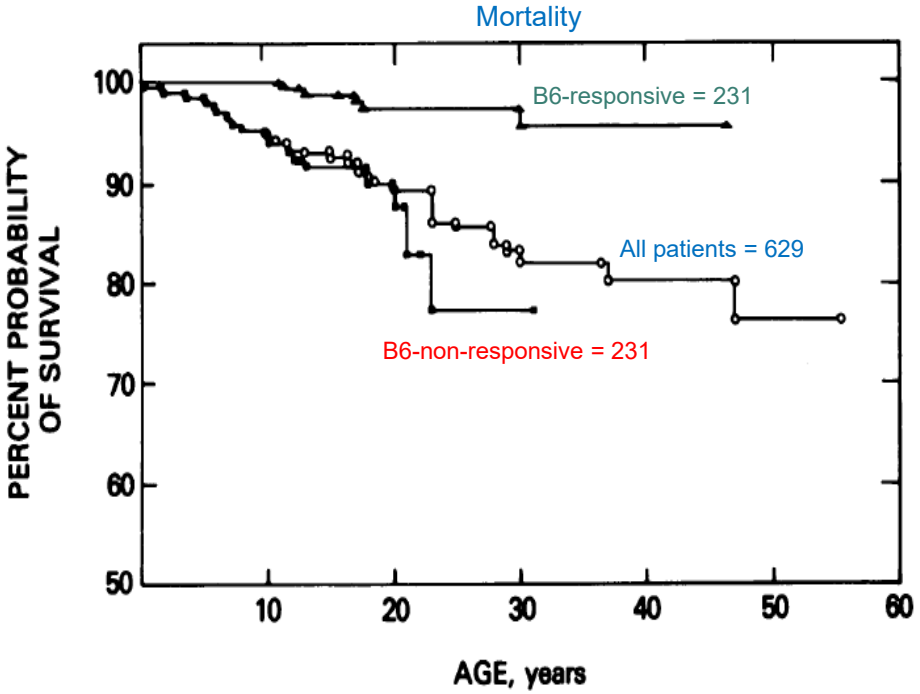
1. **Therapy-resistant patients** on standard disease management
2. **Patients who are at high risk of non-compliance** which places them at increased risk of severe complications
3. **Patients intolerant of available adjunctive therapies** due to either safety issues or other adverse reactions

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Increased Mortality and Severe Complication Risk in Patients with Homocystinuria

Complication risk is dependent on severity of metabolic defect (B6 responsive vs non-responsive) and homocysteine levels

Natural History Study of Untreated CBS Deficient Patients



Natural History

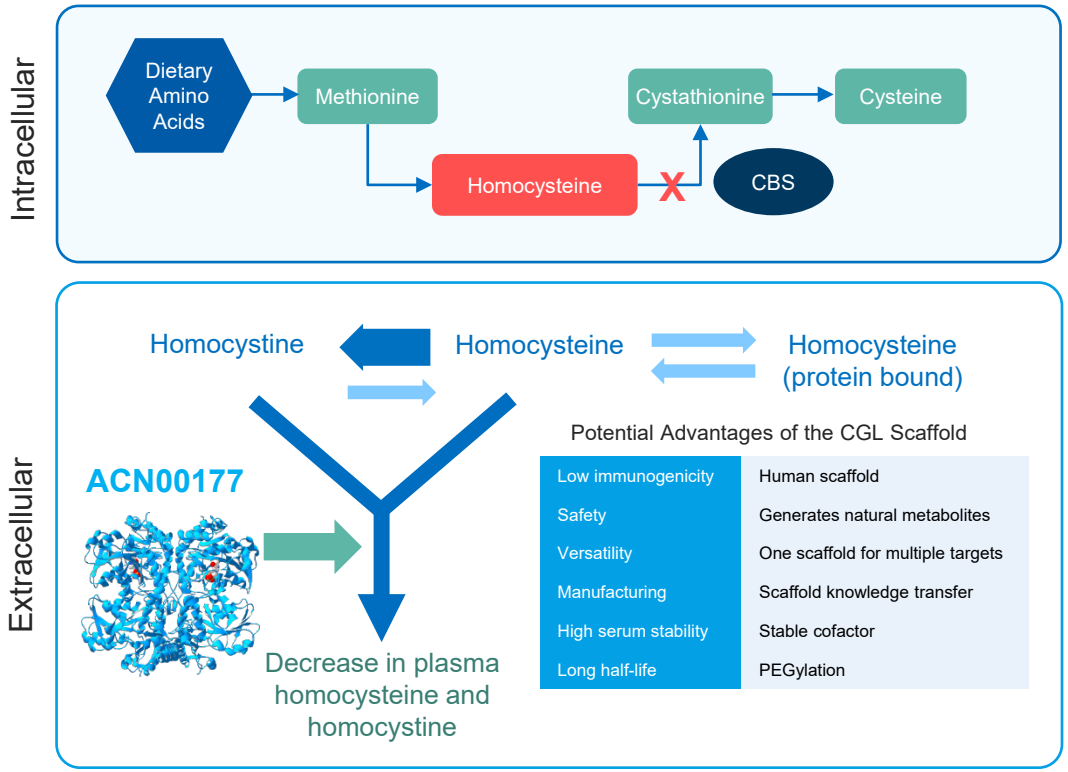
	B6-non-responsive	B6-responsive
Elevated levels of Homocysteine	⊕ ⊕ ⊕	⊕
Mortality by age 30	23%	4%
Most common cause of death	**Thromboembolism**	
Lens Dislocation in 50%	Age 6	Age 10
Median IQ	56	78
Chance of thrombosis by age 15	27%	12%

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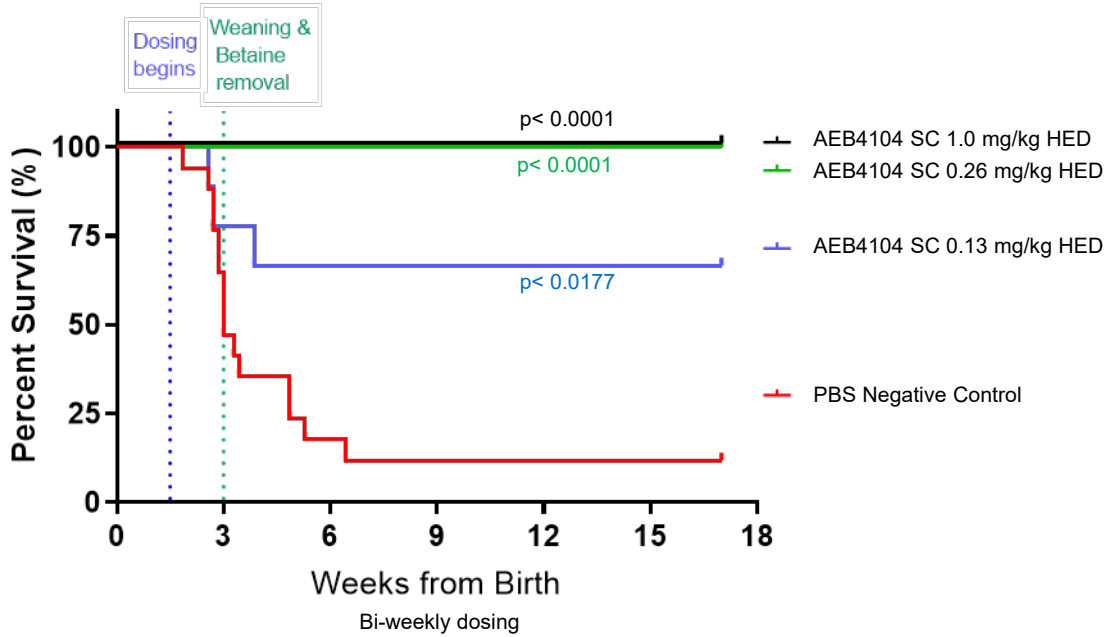
[1] Mudd et al, 1985
Kluijtmans et al, Am. J. Hum. Genet. 65,59-67, 1999, CBS – Cystathionine β-synthase

Therapeutic Approach to Improve Survival in Preclinical Model of Homocystinuria

Engineered CGL enzyme designed to change its native substrate specificity from cystathionine to both homocysteine and homocystine



100% Survival at 18 Weeks Following Subcutaneous Treatment CBS -/-



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Survival preclinical study conducted with AEB4104 program candidate

ACN00177 for Homocystinuria – Phase 1/2 Trial

Dose dependent reduction in tHcy establishes proof of concept

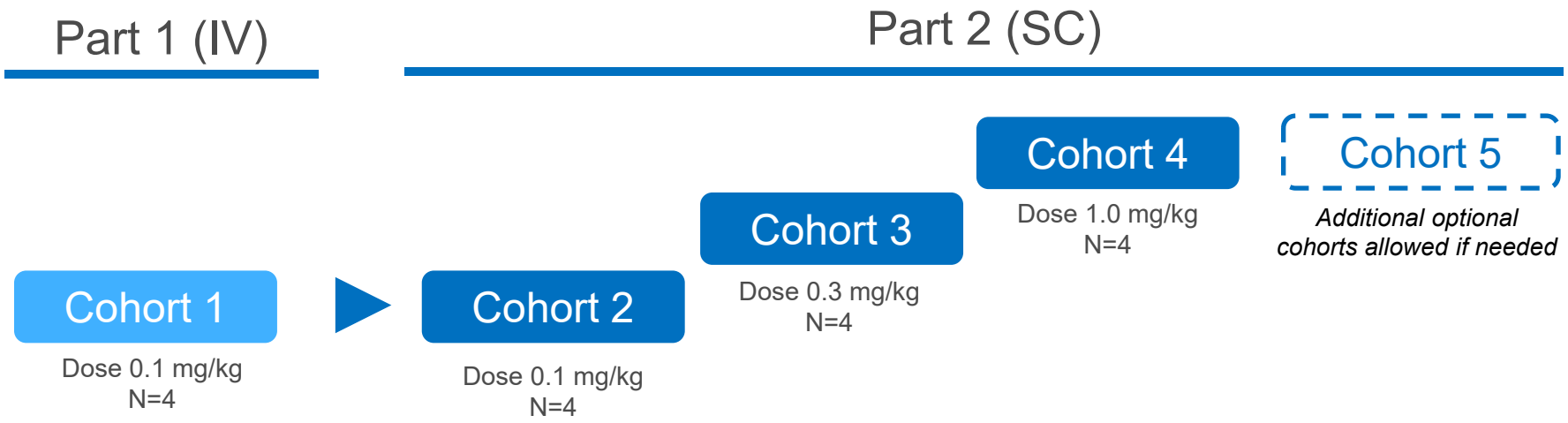
Key Inclusion Criteria

- Plasma tHcy >80 µm
- ≥12 yrs of age

Endpoints

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

- *Anticipate enrolling 16-20 pts*
- *Weekly dosing for 4 weeks*

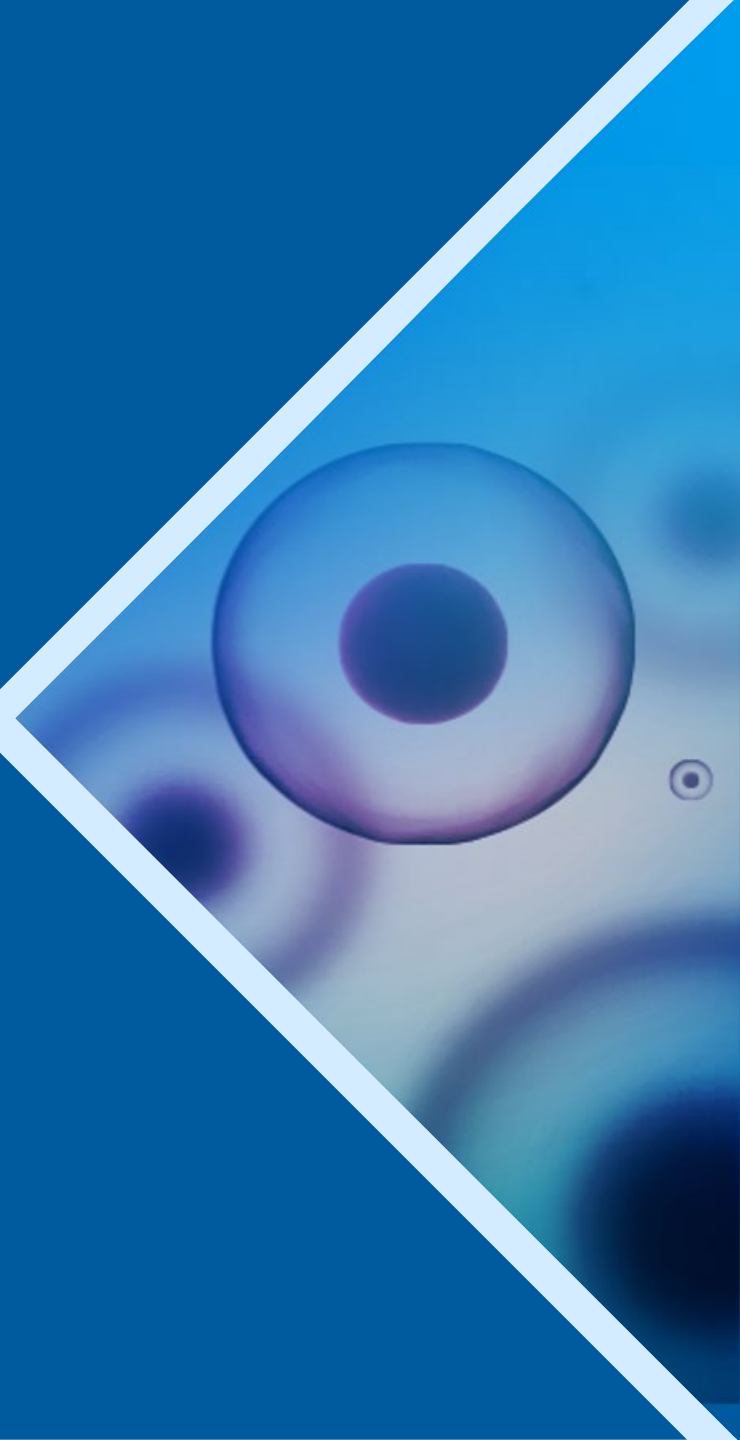


Phase 1/2 Trial Initiated in June 2020

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AEB5100 Program

With our platform to reengineer enzymes, we are designing solutions for a range of rare and high-burden diseases. Our most advanced research program looks to lower cystine levels in patients with Cystinuria.



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AEB5100 Program: Cystinuria

Novel cystine metabolizing enzyme

Unmet Medical Need	• Very high - no effective therapy for many patients
	• Serious complications and high treatment burden
	  • Severe, recurrent flank/abdominal pain and hematuria from an early age
	  • Multiple hospitalizations and invasive procedures including surgical interventions
	  • Increased risk of hypertension and chronic kidney failure

Patient Population (Addressable Markets)	• >**10,000** patients
Diagnosis	• Urine cystine concentration and/or mutation analysis

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Cystinuria Patient Needs Not Adequately Addressed

Limited impact of approved therapies for Cystinuria

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
- Impractical high fluid intake requirements that can 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. **Patients' inability to maintain high urine volume or to comply with high fluid intake**

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)

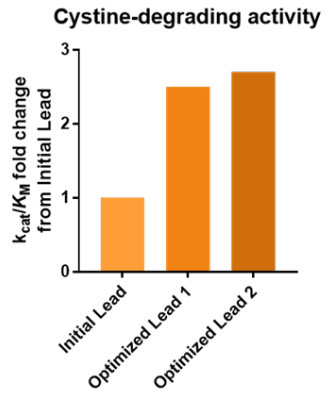
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Pearle, Goldfarb et al. 2019

AEB5100 Program: Novel Human Enzyme Solution for Cystinuria

There are no naturally occurring human enzymes that efficiently degrade cystine

Protein Engineering

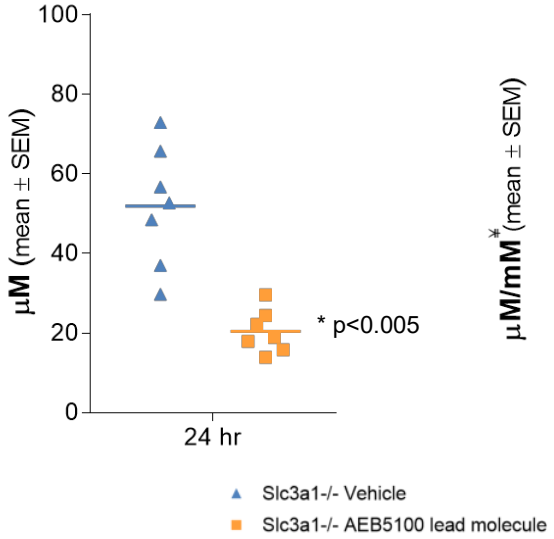
Creating Novel Cystine Degrading Activity[1]



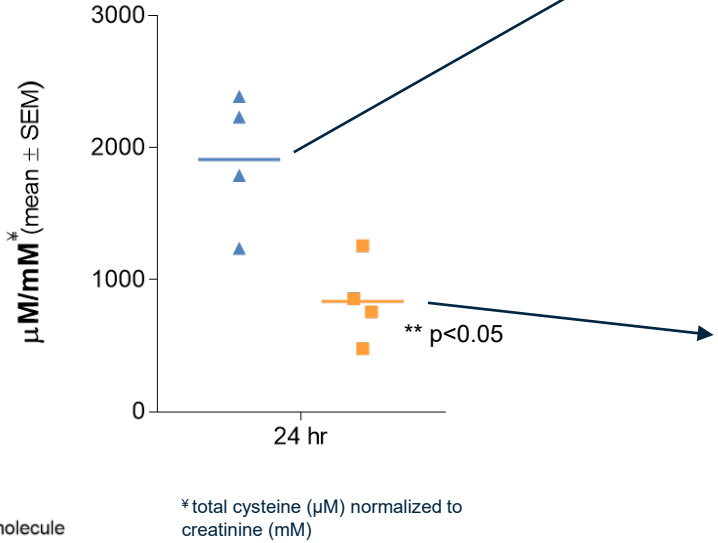
- Increase catalytic activity
- Increase serum stability
- Improve manufacturability

Proof of Concept Determination in Cystinuria Disease Model

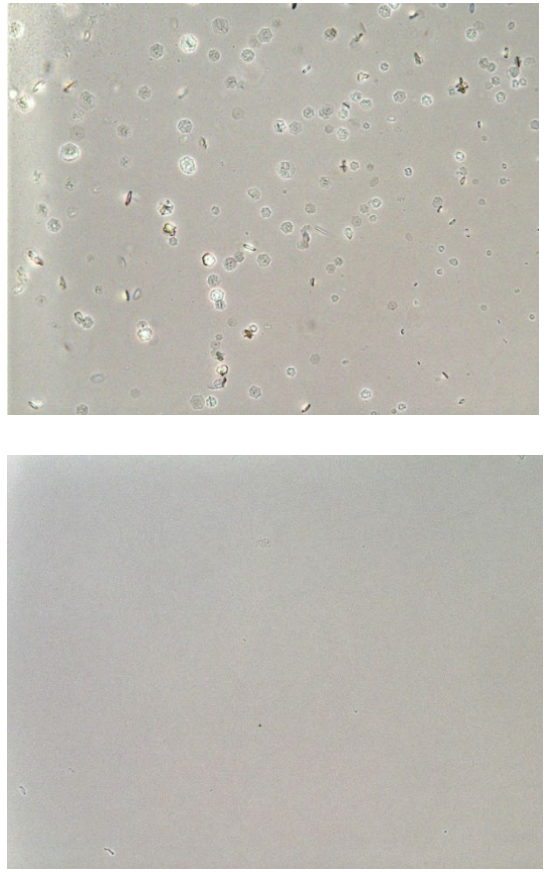
Plasma Cystine & Cysteine



Urine Cystine & Cysteine



Slc3a1 -/- mouse urine cystine crystals



Before Dosing

After Dosing

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

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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

Pegzilarginase — Metabolism

Pivotal Phase 3

Arginase 1 Deficiency

ACN00177

Homocystinuria

AEB5100 — Nephrology

Cystinuria

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