Pegzilarginase in Arginase 1 Deficiency: Results of the PEACE Pivotal Phase 3 Clinical Trial

Gregory M. Enns, MB, ChB[1]; Rossana Sanchez Russo, MD[2]; Eric Bradford, MD, MSc, MBA[3]; Gillian Bubb, PhD[3]; Leslie S. Sloan, PhD[3]; Serena Gasperini, MD[4]; George A. Diaz, MD, PhD[5]

[1]Stanford University School of Medicine, Stanford, CA, USA; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]Aeglea BioTherapeutics, Inc., Austin, TX, USA; [4]Paediatric Department, Fondazione MBBM, Monza, Italy; [5]Icahn School of Medicine at Mount Sinai, New York City, NY, USA

Background

- Arginase 1 Deficiency (ARG1-D) is a rare inherited metabolic disorder with progressive, debilitating neurologic manifestations, including characteristic lower-limb spasticity and impaired mobility, driven by persistent high arginine levels[1-3]
- Treatment of ARG1-D currently relies on strict dietary protein restriction, which does not adequately lower plasma arginine and is not sufficient to prevent progression of disease[3-5]
- Pegzilarginase is a recombinant human enzyme therapy in development for treatment of ARG1-D. In a Phase 1/2 open-label trial, weekly pegzilarginase led to substantial plasma arginine reductions and clinically meaningful improvements in mobility that were sustained through 2 years of follow-up[6-8]

Objective

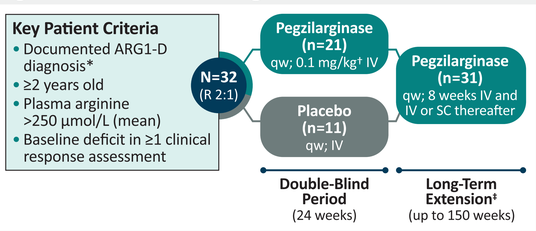
- To report the results of the pivotal Phase 3 PEACE clinical trial (**P**egzilarginase **E**ffect on **A**rginase 1 Deficiency **C**linical **E**ndpoints)

Methods

Study Design

- PEACE is an ongoing randomized, double-blind, placebo-controlled trial with an open-label extension (**Figure 1**)
- All patients are to remain on their current individualized disease management regimen for the duration of the trial

Figure 1. **PEACE Trial Design**



ARG1-D, Arginase 1 Deficiency; IV, intravenous; qw, weekly; R, randomized; SC, subcutaneous.
*Diagnosis through elevated plasma arginine, pathogenic *ARG1* variant, or diminished erythrocyte arginase activity.
†Dosing is weekly and, if needed, dose is modified based on plasma arginine levels with maintenance of blinding.
‡Blinding will be maintained for the first 8 weeks of the long-term extension.

Outcomes and Analyses

- ***Primary Efficacy:*** plasma arginine reduction from baseline at Week 24
- ***Key Secondary Efficacy:*** Gross Motor Function Measure part E (GMFM-E) and timed (2-minute) walk test (2MWT) change from baseline at Week 24
- ***Other Secondary Efficacy:*** plasma ornithine, guanidino compounds, and GMFM part D (GMFM-D)
- ***Prespecified Supportive Efficacy Analysis:*** patient-level analysis for those able to perform key mobility assessments (ie, Gross Motor Function Classification System [GMFCS] level <4) and with data at Week 24 for change from baseline in plasma arginine, GMFM-E, 2MWT, and GMFM-D
- ***Safety:*** adverse events (AEs)

References **1.** Carvalho DR, et al. *Gene.* 2012;509(1):124-130. **2.** Carvalho DR, et al. *Pediatr Neurol.* 2012;46(6):369-374. **3.** Diaz GA, et al. *Ann Neurol.* 2019;86:S137. **4.** Burrage LC, et al. *Hum Mol Genet.* 2015;24(22):6417-6427. **5.** Häberle J, et al. *J Inherit Metab Dis.* 2019;42(6):1192-1230. **6.** Diaz GA, et al. *Eur J Neurol.* 2020;27:1271. **7.** Aeglea BioTherapeutics, Inc. Data on File. 2022. **8.** Diaz GA, et al. *J Inherit Metab Dis.* 2020;27:1271. **9.** Oeffinger D, et al. *Dev Med Child Neurol.* 2008;50(12):918-925. **10.** Schrover R, et al. *Orphanet J Rare Dis.* 2017;12(1):78. **11.** Bohannon RW, et al. *Phys Occup Ther Pediatr.* 2018;38(1):39-45.

Disclosures **GME**, **SG**, and **GAD** have served on advisory boards for Aeglea; **GME**, **RSR**, **SG**, and **GAD** are PEACE trial investigators. **EB**, **GB**, and **LSS** are Aeglea employees.

Acknowledgments The authors thank the PEACE trial patients and their families. Medical writing support was provided by Heather Starkey, PhD, from The Curry Rockefeller Group, LLC (Tarrytown, NY), and was funded by Aeglea.

Results

Patients

- A total of 32 patients were enrolled (pegzilarginase, n=21; placebo, n=11; **Table 1**)
  - Patients were racially and ethnically diverse; approximately 30% were Hispanic or Latino
  - All patients were managed with dietary protein restriction; baseline plasma arginine was markedly elevated
  - Spasticity was evident in 65.6% of patients (n=21/32) and functional impairment of GMFCS level ≥2 was evident in >50% of patients

Table 1. **Key Demographics and Baseline Clinical Characteristics**

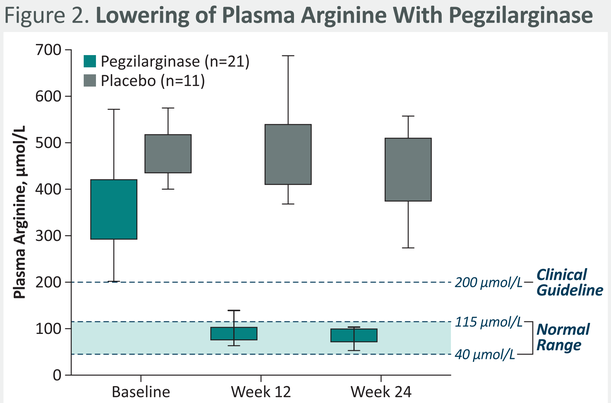
Patient Information	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Age at enrollment, y			
Mean ± SD Range	9.6±6.16 2–28	12.9±6.77 5–29	10.7±6.47 2–29
Sex, n (%)			
Male Female	12 (57.1) 9 (42.9)	7 (63.6) 4 (36.4)	19 (59.4) 13 (40.6)
Region, n (%)			
US Outside US (8 countries)	8 (38.1) 13 (61.9)	6 (54.5) 5 (45.5)	14 (43.8) 18 (56.3)
Plasma arginine, µmol/L			
Mean ± SD Median (range)	365.4±93.7 368.2 (202–572)	471.7±79.9 483.7 (294–573)	402.0±101.8 398.2 (202–573)
Spasticity, n (%)			
Any Moderate to severe	13 (61.9) 6 (28.6)	8 (72.7) 6 (54.5)	21 (65.6) 12 (37.5)
GMFCS level, n (%)			
1 ≥2	9 (42.9) 12 (57.1)	5 (45.5) 6 (54.5)	14 (43.8) 18 (56.3)
GMFM-E, points*			
Mean ± SD Median (range)	48.3±19.9 53 (5–71)	46.5±24.6 56 (0–72)	47.7±21 54 (0–72)
2MWT, m			
Mean ± SD Median (range)	109±55.7 122 (2–202)	99.9±49.0 102 (0–171)	105.8±52.8 118 (0–202)

2MWT, 2-minute walk test; GMFCS, Gross Motor Function Classification System; GMFM-E, Gross Motor Function Measure part E.
*GMFM-E possible score range, 0-72 points; higher scores indicate better performance.

Efficacy

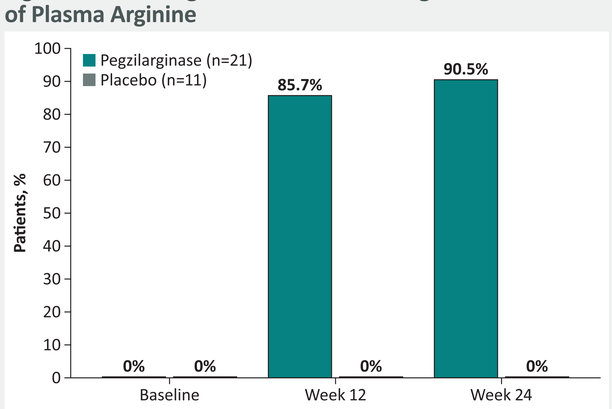
- Pegzilarginase significantly reduced mean plasma arginine from 365.4 µmol/L at baseline to 105.5 µmol at Week 24, representing a reduction of 76.7% relative to placebo (p<0.0001; **Figure 2**)
  - Mean plasma arginine was well below guideline-recommended levels and within the normal range by Week 12
  - No meaningful change was observed in the placebo arm (baseline, 471.7 µmol/L; Week 24, 448.8 µmol/L)
- Normalization of plasma arginine was achieved for 90.5% of patients at Week 24 (p<0.0001 vs placebo; **Figure 3**)

Figure 2. **Lowering of Plasma Arginine With Pegzilarginase**



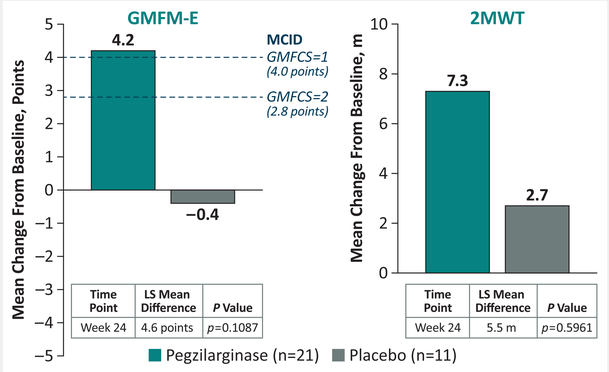
Data reflect arithmetic means (boxes reflect middle 50%; whiskers reflect 95% CIs). Significance based on mixed model for repeated measures using geometric means.

Figure 3. **Percentage of Patients Achieving Normalization of Plasma Arginine**



- Key secondary outcomes suggested meaningful improvements in mobility at Week 24 in the pegzilarginase arm (**Figure 4**)
  - GMFM-E score increased from baseline by 4.2 points with pegzilarginase and decreased by 0.4 point with placebo (least squares [LS] mean difference of 4.6 points; p=0.1087)
    - This improvement exceeds the minimum clinically important differences for patients with analogous neuromotor diseases,[9] which are applicable to ARG1-D based on psychometric analysis in patients with this disorder[7]
  - 2MWT distance increased by 7.3 m with pegzilarginase vs 2.7 m with placebo (LS mean difference of 5.5 m; p=0.5961)
- Other secondary endpoints are presented in **Table 2**

Figure 4. **Change From Baseline in Key Mobility Assessments**



2MWT, 2-minute walk test; GMFCS, Gross Motor Function Classification System; GMFM-E, Gross Motor Function Measure Part E; LS, least squares; MCID, minimum clinically important difference.
Significance based on mixed model for repeated measures using LS mean estimates and Hochberg multiplicity adjustment.

Table 2. **Change From Baseline in Other Secondary Efficacy Endpoints**

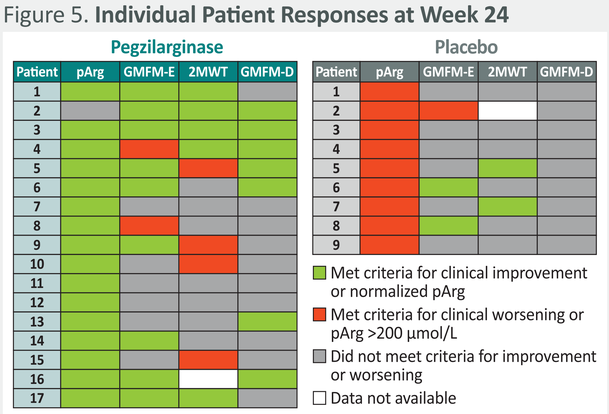
Endpoint*	Pegzilarginase (n=21)		Placebo (n=11)		Change From Baseline Relative to Placebo (95% CI)†
	Baseline	24 Weeks	Baseline	24 Weeks	
Ornithine, µmol/L*	38.6±1.64	67.7±1.43	30.6±1.16	32.8±1.23	**+106.9%** (56.7%, 173.1%); p<0.0001
Argininic acid, µmol/L*	2.4±1.54	0.7±1.82	3.2±1.50	3.2±1.47	**−69.5%** (−57.2%, −78.3%); p<0.0001
Guanidinoacetic acid, µmol/L*	3.4±1.87	1.7±1.60	3.6±1.63	3.7±1.62	**−53.3%** (−32.2%, −67.8%); p=0.0003
α-keto-δ-guanidinovaleric acid, µmol/L*	4.5±1.59	1.3±1.84	5.4±1.57	4.8±1.50	**−68.3%** (−54.6%, −77.9%); p<0.0001
α-N-acetylarginine, µmol/L*	1.0±1.94	0.3±2.12	1.5±1.90	1.3±1.73	**−69.8%** (−51.8%, −81.1%); p<0.0001
GMFM-D, points‡	28.0±9.61	30.5±10.09	29.5±12.42	28.2±13.28	**+2.25** (−0.37, 4.87); p=0.0896

GMFM-D, Gross Motor Function Measure part D.
*Ornithine and guanidino compounds presented as geometric mean ± SD; GMFM-D presented as mean ± SD. †Ornithine and guanidino compounds presented as estimated percentage change from baseline relative to placebo; GMFM-D presented as least squares mean difference vs placebo. Significance based on mixed model for repeated measures. ‡Reflects ad hoc analysis addressing data entry error in placebo arm; 1 patient had a missing baseline assessment that was originally scored as zero rather than a nonnumeric entry of "not assessed."

Patient-Level Outcomes

- In the patient-level analysis for individuals at GMFCS level <4 (pegzilarginase, n=17; placebo, n=9), clinically important differences between treatment arms were evident in arginine normalization and clinical responses (**Figure 5**)
  - Clinical response criteria[9,10] for ≥1 assessment were met by 11/17 patients receiving pegzilarginase (64.7%), compared with 4/9 patients receiving placebo (44.4%). Mean change from baseline for each assessment was also greater for patients meeting response criteria in the pegzilarginase arm vs placebo (data not shown)
  - Nearly half of the patients receiving pegzilarginase (n=8/17; 47.1%) met clinical response criteria on ≥2 outcomes, compared with 0% in the placebo arm
  - Six patients in the pegzilarginase arm met clinical response criteria on ≥2 outcomes *and* had no response of worsening on the other endpoints (**Table 3**)

Figure 5. **Individual Patient Responses at Week 24**



2MWT, 2-minute walk test; GMFM-D, Gross Motor Function Measure part D; GMFM-E, Gross Motor Function Measure part E; pArg, plasma arginine.

Table 3. **Pegzilarginase-Treated Patients Achieving Clinical Response on ≥2 Mobility Outcomes and No Worsening at Week 24**

Patient* (Age)	GMFM-E (Score Range, 0–72)	2MWT†	GMFM-D (Score Range, 0–39)
1 (6 y)	• **Improved** by 7 points • Total score: 69	• **Improved** by 34 m to 152 m • **Achieved normal** age-/sex-matched mean	• **Improved** by 2 points • Total score: 35
2 (6 y)	• **Improved** by 18 points • Total score: 45	• **Improved** by 46 m to 96 m (from 29% to 56% of normal age-/sex-matched mean)	• **Improved** by 4 points • Total score: 32
3 (12 y)	• **Improved** by 6 points • **Achieved maximum score**	• **Improved** by 43 m to 167 m (achieved 82% of normal age-/sex-matched mean)	• **Improved** by 5 points • **Achieved maximum score**
6 (14 y)	• **Improved** by 9 points • Total score: 62	• No worsening	• **Improved** by 8 points • Total score: 37
16 (2 y)	• **Improved** by 11 points • Total score: 52	• **Improved** by 44 m‡ to 150 m • **Exceeded normal** age-/sex-matched mean	• **Improved** by 8 points • Total score: 32
17 (3 y)	• **Improved** by 21 points • Total score: 62	• **Improved** by 95 m to 164 m • **Exceeded normal** age-/sex-matched mean	• No worsening

2MWT, 2-minute walk test; GMFM-D, Gross Motor Function Measure Part D; GMFM-E, Gross Motor Function Measure Part E.
*Patient numbers correspond to Figure 5. †Normalization defined as ±15% of age-/sex-matched mean distance.[11] ‡Reflects change from Week 12; distance at baseline not assessed owing to age.

Safety

- Pegzilarginase was well tolerated; AEs (**Table 4**) were generally mild to moderate in severity

Table 4. **Adverse Events**

AEs, n (%)	Pegzilarginase (n=21)	Placebo (n=11)
Any treatment-emergent AE	18 (85.7)	11 (100.0)
AEs leading to discontinuation	0	0
AEs of special interest		
Hypersensitivity reaction	2 (9.5)	0
Hyperammonemic episodes	3 (14.3)	4 (36.4)
Serious AEs*	4 (19.0)	4 (36.4)
AEs with incidence ≥15%		
Vomiting	6 (28.6)	3 (27.3)
Cough	4 (19.0)	1 (9.1)
Pyrexia	4 (19.0)	0
Ammonia increased	3 (14.3)	2 (18.2)
Hyperammonemia	2 (9.5)	3 (27.3)
Nausea	1 (4.8)	4 (36.4)
Abdominal pain	1 (4.8)	3 (27.3)
Decreased appetite	0	2 (18.2)

AE, adverse event.
*Serious AEs were hyperammonemia/hyperammonemia-related events and vomiting.

Long-Term Extension

- The majority of patients have reached LTE Week 24; continued benefit of pegzilarginase on biochemical and clinical endpoints observed to date (data not shown)

Summary

- ARG1-D is a progressive and debilitating disease, and despite standard-of-care treatment, substantial deficits were evident in the trial cohort at baseline (mean age, 10.7 years), demonstrating the inadequacy of current management
- With weekly pegzilarginase:
  - 76.7% reduction in plasma arginine at Week 24 (p<0.0001) and 90.5% of patients with plasma arginine levels in the normal range (previously unachievable for most patients)
  - Positive trend in GMFM-E score improvement (4.6-point increase vs placebo) and a numeric increase in 2MWT distance after 24 weeks of treatment
  - In the patient-level analysis (n=26), 64.7% of patients receiving pegzilarginase achieved clinical response on ≥1 mobility assessment, and nearly 50% achieved responses on ≥2 of these clinical outcomes (compared with none receiving placebo). Several patients receiving pegzilarginase achieved age- and sex-matched norms on the timed walk test
- Pegzilarginase was well tolerated, with a safety profile consistent with the previous Phase 1/2 study and no treatment discontinuations owing to tolerability

Conclusions

- Pegzilarginase is the first potential therapy to achieve normalization of plasma arginine levels in patients with ARG1-D; for a majority of patients, normalization of plasma arginine after 6 months of treatment was accompanied by clinical improvement in ≥1 mobility outcome
- The results of this pivotal Phase 3 trial suggest that pegzilarginase represents a potential transformative therapy for ARG1-D