Patient Characteristics in the Pivotal Phase 3 PEACE Trial of Pegzilarginase Human Enzyme Therapy for Arginase 1 Deficiency

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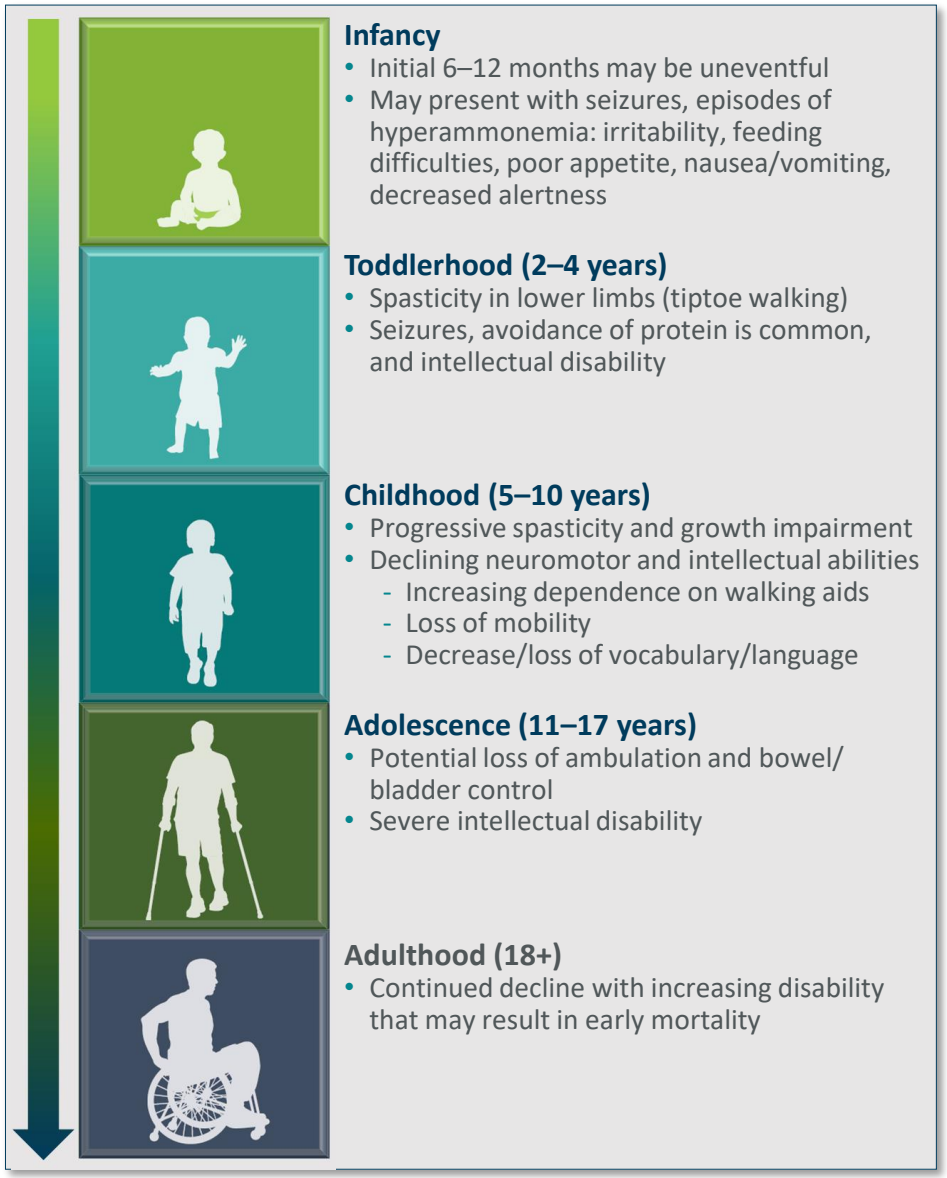
ARG1-D Disease Background

- Arginase 1 Deficiency (ARG1-D) is a rare, debilitating inherited metabolic disorder caused by mutations in the *ARG1* gene and characterized by a marked reduction in arginase 1 activity that leads to significant accumulation of arginine[1,2]
- Affected patients demonstrate a distinct, progressive neurologic phenotype with prominent lower-limb spasticity that leads to impaired mobility including difficulties in walking and climbing stairs; patients may ultimately become reliant on assistive devices[1,3-5] **(Figure 1)**
- Current disease management includes dietary protein restriction to minimize arginine intake and, in some patients, nitrogen scavengers to reduce the risk of hyperammonemia
- Dietary protein restriction is largely inadequate to sufficiently reduce arginine levels and prevent progression
  - The normal plasma arginine range is estimated to be 40–115 µmol/L based on analysis of data from the Framingham cohort[6]
  - Current guidelines for managing ARG1-D recommend reducing plasma arginine to ≤200 µmol/L[3]
  - In an analysis of Urea Cycle Disorder Consortium data (22 patients with 1–13 data points per patient), <10% of plasma arginine assessments were ≤200 µmol/L[7]

Figure 1. **ARG1-D Disease Progression**



1. Diez-Fernandez C, et al. *Hum Mutat*. 2018;39(8):1029-1050. **2.** Sun A, et al. Arginase deficiency. *GeneReviews® [Internet]*. 2004 [Updated 2020]. **3.** Häberle J, et al. *J Inherit Metab Dis*. 2019;42(6):1192-1230. **4.** Carvalho DR, et al. *Pediatr Neurol*. 2012;46(6):369-374. **5.** Huemer M, et al. J *Inherit Metab Dis*. 2016;39(3):331-340. **6.** Luneburg N, et al. *J Nutr*. 2011;141(12): 2186-2190. **7.** Burrage LC, et al. *Hum Mol Genet*. 2015;24(22):6417-6427.

Pegzilarginase and Insights from a Phase 1/2 Clinical Trial (Study 102A)

Pegzilarginase

- Pegzilarginase is an investigational arginine-lowering recombinant human enzyme therapy with 20-fold greater catalytic activity and a 10-fold longer half life than wild-type arginase[8,9]

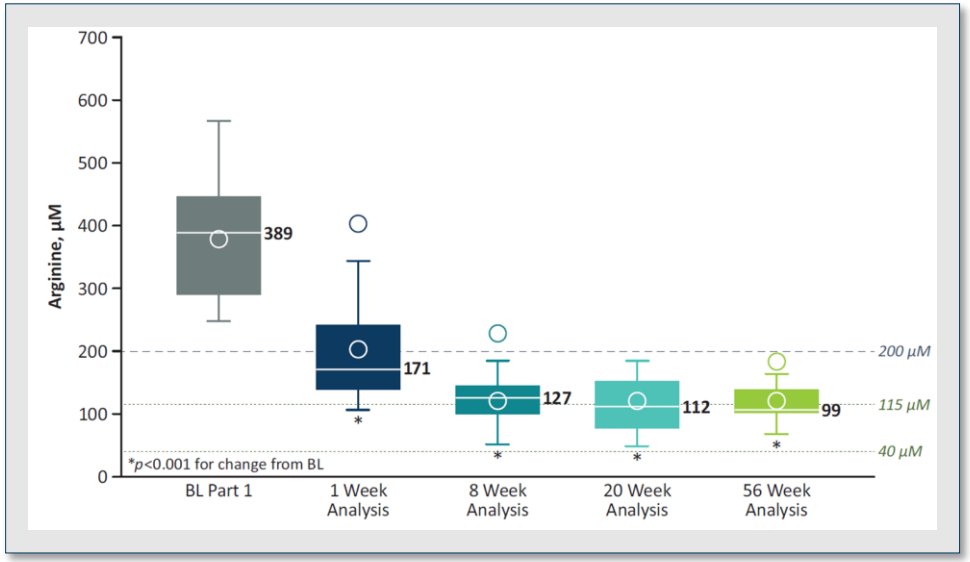
Study Design

- Study 102A was a Phase 1/2 open-label trial in 14 patients with ARG1-D[10]
- Patients received weekly pegzilarginase treatment administered by intravenous infusion with an option to switch to subcutaneous injection after 24 doses[10]

Control of Plasma Arginine

- Marked elevation of plasma arginine levels at baseline was consistent with published observations on the failure of standard-of-care treatment to adequately lower arginine[10]
- Pegzilarginase treatment resulted in rapid, substantial, and sustained reductions in plasma arginine levels[10,11] **(Figure 2)**
- Meaningful and durable improvements in mobility assessments were achieved in 79% of patients at week 20 and were sustained through week 56[10,11]

Figure 2. **Plasma Arginine Control With Pegzilarginase[11]**



Potential Utility of Clinical Outcome Assessments of Mobility in Capturing Disease Burden and Clinical Impact of Lowering Plasma Arginine

- Study 102A provided the first important insights into the potential utility of clinical outcome assessments of mobility in patients with ARG1-D
  - Plasma arginine reductions were accompanied by meaningful mobility improvements
  - The Gross Motor Function Measure part E (GMFM-E; unaided walking, running, jumping tasks) and 6-minute walk test (6MWT; aided timed walk test) provided complementary insights about patients' baseline mobility impairments and pegzilarginase-related mobility improvements
    - GMFM-E was effective in capturing improvement in mobility. Patients with less severe impairment at baseline (and therefore higher baseline scores) demonstrated smaller improvements due to a ceiling effect
    - The 6MWT was also useful in capturing mobility improvements, particularly in patients who were at or close to the ceiling of GMFM-E

8. Stone E, et al. *J Control Release*. 2012;158(1):171-179. **9.** Stone EM, et al. *ACS Chem Biol*. 2010;5(3):333-342. **10.** Diaz GA, et al. *J Inherit Metab Dis*. 2020;doi:10.1002/jimd.12343. **11.** Diaz GA, et al. *Eur J Neurol*. 2020;27:1271.

PEACE Trial Design

- The Phase 3 PEACE trial (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints, NCT03921541) is a pivotal randomized, double-blind, placebo-controlled study of weekly pegzilarginase treatment added to standard-of-care management **(Figure 3)**

- Key eligibility criteria were: documented diagnosis of ARG1-D and high baseline arginine (on standard of care; **Table 1**)

- Dosing of the first patient occurred in June 2019 and patient randomization was completed in Q2 2021

- Key efficacy endpoints are:
  - Primary: plasma arginine reduction
  - Key secondary: GMFM-E and 2MWT*

Figure 3. **PEACE Trial Design**

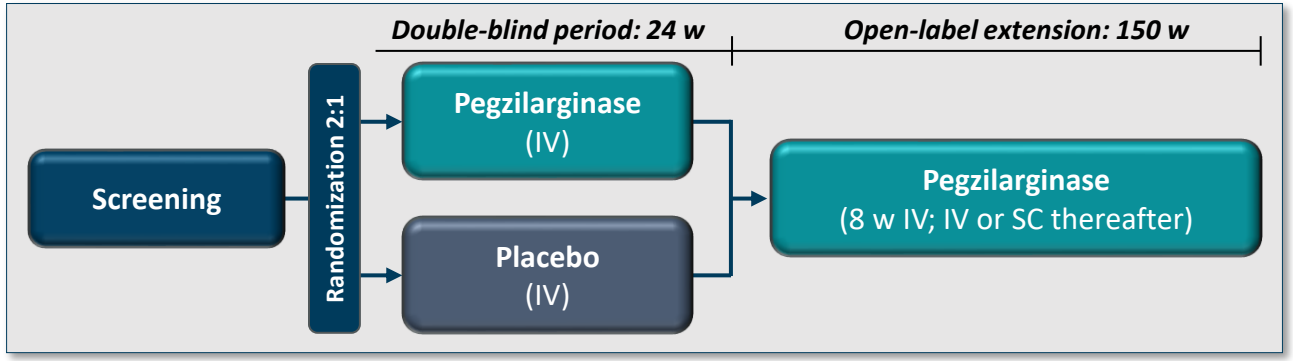


Table 1. **Patient Eligibility Criteria**

Inclusion
• Documented ARG1-D diagnosis with ≥1 of the following: - Elevated plasma arginine - Pathogenic ARG1 variant - Diminished erythrocyte arginase activity
• Baseline plasma arginine ≥250 µmol/L
• Age ≥2 years
• Baseline impairment in ≥1 clinical response assessment
Exclusion
• Symptomatic hyperammonemia (ammonia ≥100 µmol/L and requiring acute care or hospitalization) ≤6 w before first dose of pegzilarginase
• Extreme mobility impairment (inability to complete assessments)
• Participation in a prior pegzilarginase study
• Prior liver or hematopoietic transplant

2MWT, 2-minute walk test; GMFM-E, Gross Motor Function Measure part E; IV, intravenous; SC, subcutaneous; w, weeks.
*Due to its shorter duration, the 2MWT was used to avoid a potential confounding effect of distraction owing to age and/or intellectual disability.

PEACE Baseline Characteristics

- A total of 44 patients were screened; 32 patients were randomized to treatment **(Table 2)**, exceeding the target enrollment of 30
- Median plasma arginine was 407 µmol/L, which is similar to levels observed in the Phase 1/2 study (median, 389 µmol/L)[10]
- All patients were managed with a restricted protein diet; a large proportion were receiving EAA supplementation
- Only 25% of patients were identified by newborn screening

Table 2. **PEACE Patient Demographics and Baseline Disease Characteristics**

Characteristic	Value (N=32)
Age at enrollment, y	
Mean ± SD	11±6.5
Range	2–29
Sex, n (%)	
Male	19 (59)
Female	13 (41)
Management approach, n (%)	
Restricted protein diet	32 (100)
EAA supplementation	27 (84)
Nitrogen scavenger therapy	23 (72)
Restricted protein diet, EAA supplementation, and nitrogen scavenger therapy	19 (59)
Plasma arginine, µmol/L	
Median	407.3
Range	230–617
Age at onset of manifestations, y	
Mean ± SD	2±2.5
Range	0–10
Key medical history, n (%)	
Spasticity	21 (66)
Moderate-to-severe	12 (38)
Hyperammonemia history	17 (53)
Seizure history	11 (34)

EAA, essential amino acid.

10. Diaz GA, et al. *J Inherit Metab Dis*. 2020;doi:10.1002/jimd.12343.

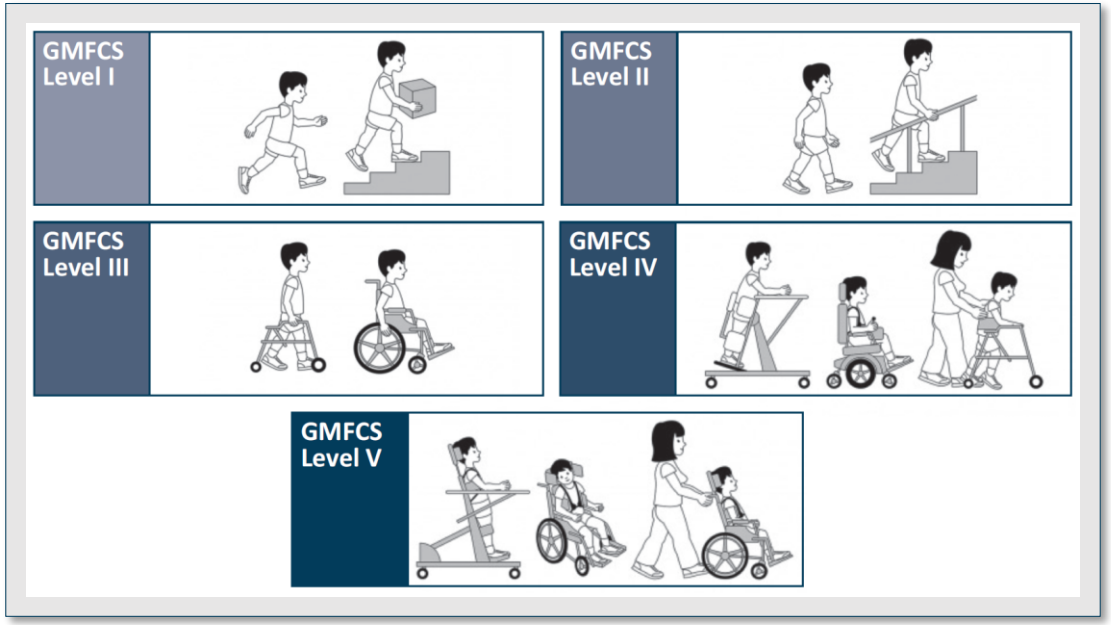
Baseline Functional Impairment

- The Gross Motor Function Classification System (GMFCS; **Figure 5**) was originally developed for cerebral palsy, which, like ARG1-D, is characterized by impaired mobility due to spasticity

- GMFCS evaluates self-initiated movement with emphasis on sitting, walking, ascending stairs, and wheeled mobility
  - Level 1 indicates ability to walk, climb stairs without use of a railing, and perform gross motor skills (eg, running, jumping), but with limited speed, balance, and coordination
  - Levels ≥2 indicate progressively greater mobility impairment and reliance on assistive devices

- In PEACE, 41% of patients (n=13) were classified as GMFCS Level 1 and 56% (n=18) were GMFCS ≥2 (indicating more significant functional impairment)*
  - More patients in PEACE were classified as GMFCS ≥2 than in the Phase 1/2 study (46%)[10]
  - No patients at GMFCS Level 5 were enrolled

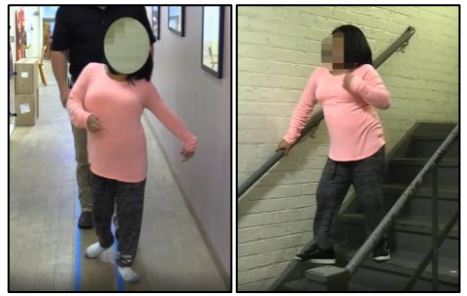
Figure 5. **GMFCS Scoring**[12,13]



Adapted with permission from The Royal Children's Hospital, Melbourne, Australia.

10. Diaz GA, et al. *J Inherit Metab Dis*. 2020;doi:10.1002/jimd.12343. **12.** Palisano R, et al. *Dev Med Child Neurol*. 1997;39(4):214-223. **13.** The Royal Children's Hospital, Melbourne, Australia. GMFCS Descriptors and Illustrations. Accessed October 13, 2021.
*Baseline GMFCS score is missing for 1 patient.

Baseline Mobility Impairment



- The GMFM is an instrument designed to evaluate motor function, including changes over time and/or with intervention. Notably, the GMFM is performed without any needed bracing or assistive devices
- GMFM-E evaluates 24 tasks involving walking forward/backward, running, jumping, and ascending/descending stairs. Possible scores range from 0–72, with lower scores indicating greater impairment
  - Median score was 54 points
  - 84% of patients demonstrated a mobility deficit on GMFM-E, defined as a score of <68 points. In comparison, 56% of patients were classified as having a GMFM-E deficit in Study 102A[10]
  - As expected, patients at GMFCS ≥2 demonstrated lower baseline GMFM-E scores compared with patients at GMFCS =1 (41 vs 67 points)
- 72% of patients demonstrated baseline impairment on the supportive GMFM part D (GMFM-D; standing, balancing, squatting, transitioning from sitting to standing). Median score was 31 of a possible 39 points; deficit was defined as a score <35 points

- The 2MWT evaluates aided mobility, through distance traveled in 2 minutes with any needed bracing or assistive devices
  - 84% of patients demonstrated a mobility deficit on the 2MWT, defined using age- and sex-based criteria from the NIH Toolbox dataset. In comparison, 88% of patients in Study 102A had a deficit on the 6MWT[10]
  - Median distance traveled was 118 meters; in comparison, the median 6MWT distance traveled in 102A was 272 meters
  - Patients at GMFCS ≥2 demonstrated a reduced baseline distance compared with those at GMFCS =1 (81 vs 150 meters)

Assessment*	GMFM-E (points)	2MWT (meters)
Percent impaired	84%	84%
Median score (range)	54 (0–72)	119 (0–202)

*Data have been updated to include a patient without available data at the time of abstract development.
Each GMFM task is scored as: 0 (does not initiate), 1 (initiates), 2 (partially completes), 3 (completes), or NT (not tested; no score).

2MWT, 2-minute walk test; 6MWT, 6-minute walk test; GMFCS, Gross Motor Function Classification System; GMFM-E, Gross Motor Function Measure Part E.

10. Diaz GA, et al. *J Inherit Metab Dis*. 2020;doi:10.1002/jimd.12343.

Summary and Conclusions

- The Phase 3 PEACE study is the first randomized placebo-controlled clinical trial in ARG1-D

- Baseline characteristics of PEACE study participants provide important demographic and disease insights in a well-studied cohort of 32 ARG1-D patients and are consistent with information provided by the previous Phase 1/2 trial cohort. These patients appear to be representative of the broader ARG1-D population

- Baseline plasma arginine measurements on current standard of care are markedly elevated
  - The observed median arginine level of >400 µmol/L clearly demonstrates the inadequacy of standard-of-care management in reducing arginine to prevent disease progression and functional impairment

- The PEACE cohort provides further evidence of the utility of GMFM-E and timed walk test in capturing disease burden and providing complementary insights on the impact of ARG1-D on mobility

- Top-line PEACE data are anticipated in Q4 2021

Thank You

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- Related ARG1-D posters
  - **62:** Diagnosis and Long-term Management of Arginase 1 Deficiency
  - **63:** Diagnosis of Arginase 1 Deficiency In a Patient With Cerebral Palsy
  - **65:** Gait Improvement in Pegzilarginase-treated Patients with Arginase 1 Deficiency: A Blinded Kinematic Analysis
  - **116:** Arginase 1 Deficiency Presenting with Clotting Abnormalities
  - **118:** Arginine: The Key Driver of Pathophysiology and Progression in Arginase 1 Deficiency
  - **126:** Management and Progression of Arginase 1 Deficiency Over 2 Decades of Follow-up

- For more information: **aeglea.com**

References: **1.** Diez-Fernandez C, et al. *Hum Mutat*. 2018;39(8):1029-1050. **2.** Sun A, et al. Arginase deficiency. *GeneReviews® [Internet]*. 2004 [Updated 2020]. **3.** Häberle J, et al. *J Inherit Metab Dis*. 2019;42(6):1192-1230. **4.** Carvalho DR, et al. *Pediatr Neurol*. 2012;46(6):369-374. **5.** Huemer M, et al. J *Inherit Metab Dis*. 2016;39(3):331-340. **6.** Luneburg N, et al. *J Nutr*. 2011;141(12): 2186-2190. **7.** Burrage LC, et al. *Hum Mol Genet*. 2015;24(22):6417-6427. **8.** Stone E, et al. *J Control Release*. 2012;158(1):171-179. **9.** Stone EM, et al. *ACS Chem Biol*. 2010;5(3):333-342. **10.** Diaz GA, et al. *J Inherit Metab Dis*. 2020;doi:10.1002/jimd.12343. **11.** Diaz GA, et al. *Eur J Neurol*. 2020;27:1271. **12.** Palisano R, et al. *Dev Med Child Neurol*. 1997;39(4):214-223. **13.** The Royal Children's Hospital, Melbourne, Australia. GMFCS Descriptors and Illustrations. Accessed October 13, 2021.