Sustained Reductions in Plasma Arginine Following Pegzilarginase Administration in Patients with Arginase-1 Deficiency are Accompanied by Improvements in Mobility and Adaptive Behavior

Diaz GA[1], Schulze A[2], McNutt MC[3], Teles EL[4], Merritt II JL[5], Enns GM[6], Batzios SP[7], Conway RL[8], Bechter M[9], Eckert S[9], Bubb G[9], Wooldridge JE[9], Zori RT[10]

[1]Icahn School of Medicine at Mt. Sinai, New York City, NY, USA, [2]University of Toronto and The Hospital for Sick Children, Toronto, ON, Canada, [3]UT Southwestern Medical Center, Dallas, TX, USA, [4]Centro Hospitalar de São João, Porto, Portugal, [5]University of Washington, Seattle, WA, USA, [6]Stanford University, Stanford, CA, [7]Great Ormond Street Hospital NHS Trust, London, UK, [8]Children's Hospital of Michigan, Detroit, MI, USA, [9]Aeglea BioTherapeutics, Austin, TX, USA, [10]University of Florida, Gainesville, FL, USA

Disclosures

- **Grant/Research Support:**
  Urea Cycle Disorders Consortium, NYCKidSeq Consortium, N-Carbamylglutamate Consortium

- **Consultant:**
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- **Major Shareholder:** ***None***

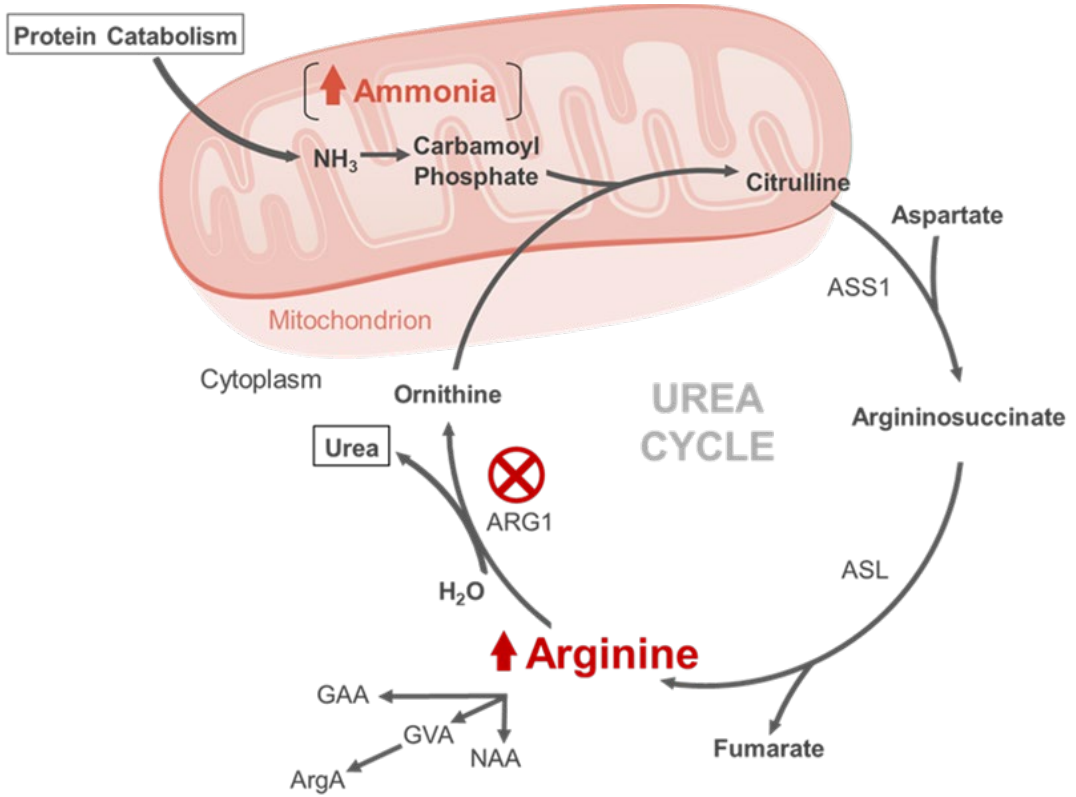
I will be discussing investigational use of Pegzilarginase

Arginase 1 Deficiency

- ARG1-D Causes Two Key Metabolic Effects
  - High levels of arginine and arginine-derived metabolites
  - Impairment of the Urea Cycle

- **Key Disease Manifestations**
  - **Chronic hyperargininemia-related**:
    - spasticity, loss of mobility, deficits in adaptive behavior, intellectual disability, seizures
  - **Episodic hyperammonemia-related:**
    - food refusal, protein aversion, encephalopathy

- Diagnosis:
  - **Biochemical:** Elevations in plasma arginine, reduced RBC arginase activity
  - **Molecular:** ARG1 mutation analysis



Disease Management

- Severe dietary protein restriction
- Essential amino acid supplementation
- Ammonia scavengers for hyperammonemia

19 Year-Old Female with ARG1-D at Baseline

Clinical Presentation

- Diagnosed age 1 after presentation with hyperammonemia
- Developed severe lower limb spasticity, speech delay, intellectual disability
- Treated with severe protein restriction, essential amino acids, and ammonia scavengers
- Progressive worsening of lower extremity spastic diplegia, ambulates with arm crutches

- C.371A>G (single point active site mutation D124G)
- Arginase activity 0%

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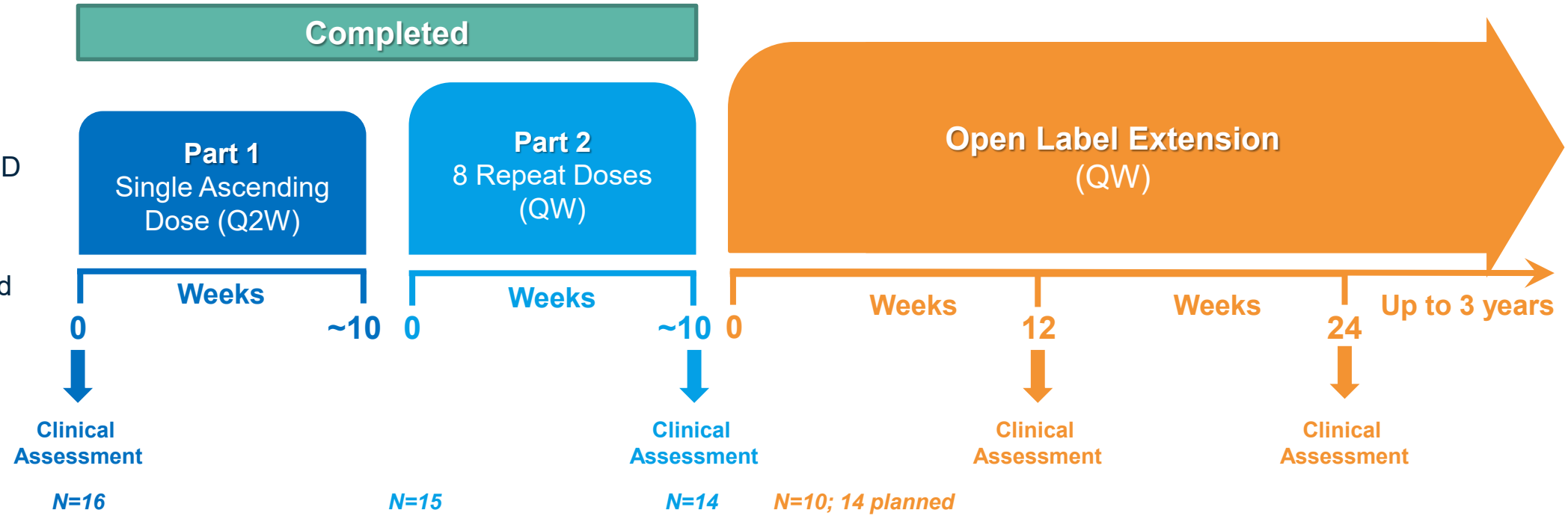
Baseline Study Assessments

Assessment	Normal Population	Patient Baseline
Plasma arginine	40 – 115 µM	389 µM
6MWT	Reference Interval: 310 – 664 meters	174 meters
GMFM-E	Max = 72	27
ABAS GAC	Mean = 100, SD=15	64

Open-Label, Multi-Center Phase 1/2 Study of IV Pegzilarginase in ARG1-D

Inclusion criteria:
- Diagnosis of ARG1-D
- >2 years old

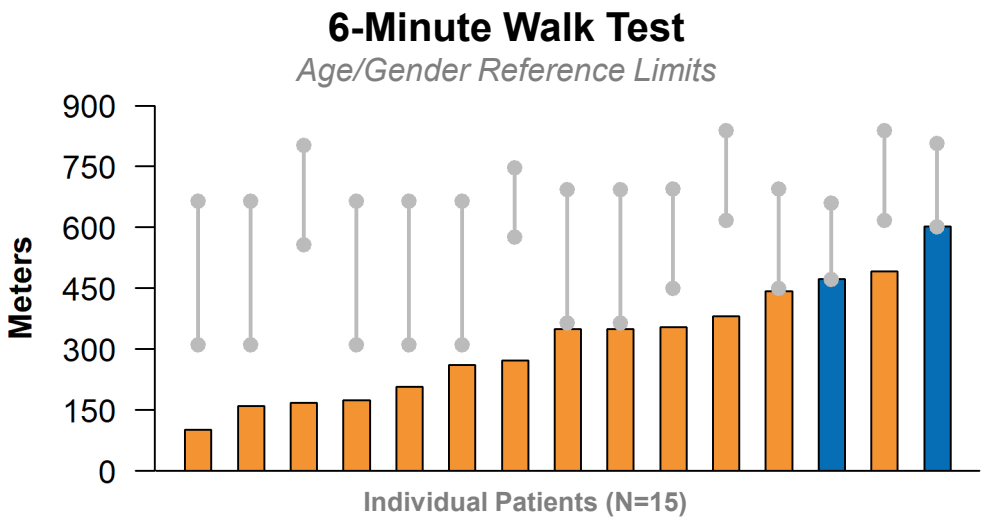
Exclusion criteria:
- Severe, uncontrolled hyperammonemia

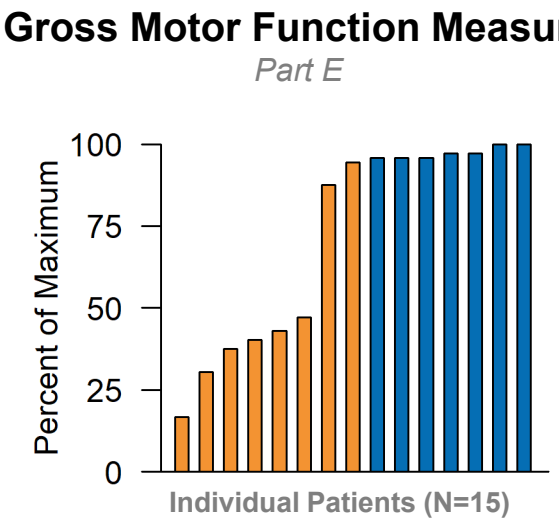


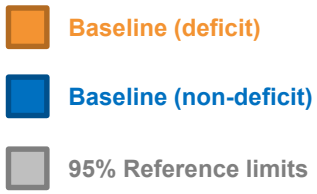
Clinical assessments:
- Plasma arginine, guanidino compounds, safety, mobility, and adaptive behavior
- Pharmacokinetics analysis occurred at week 8 of the open label extension

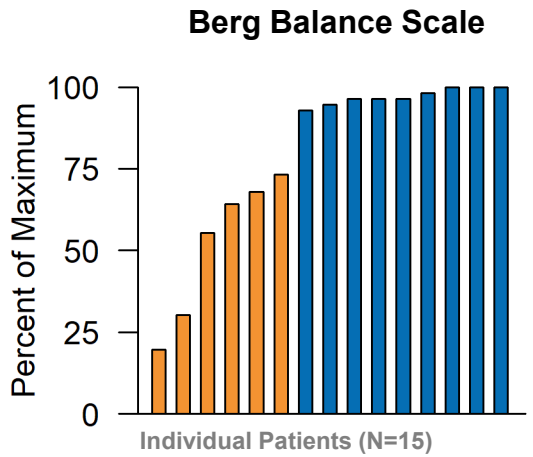
IV = intravenous; QW = weekly; Q2W = every 2 weeks

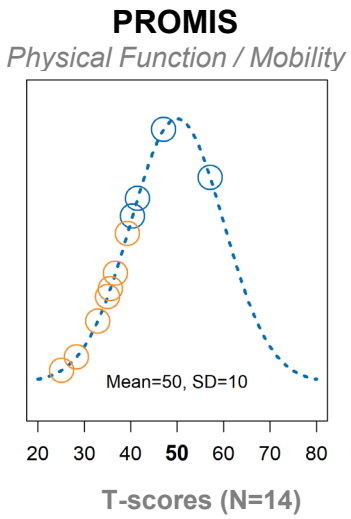
Baseline Mobility Assessments









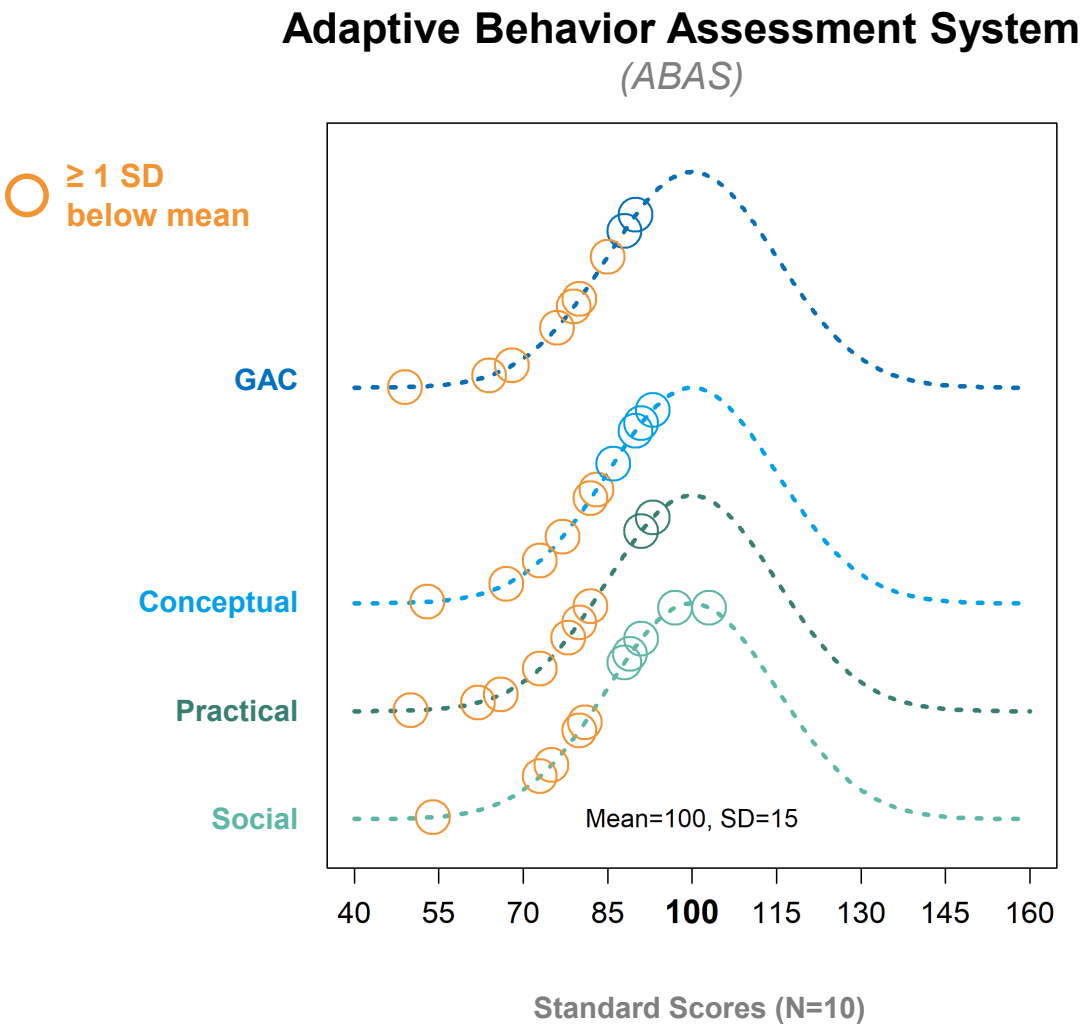


14 / 16 patients (88%) had a measurable deficit in mobility

- Baseline deficits observed in
  - 13/15 (87%) on 6MWT
  - 8/15 (53%) on GMFM Part E
  - 6/15 (40%) on Berg Balance Scale
  - 10/14 (71%) on PROMIS Physical Function (adults) or Mobility (pediatric)

1 patient was wheelchair bound. 2 patients were non-English speaking and not assessed for PROMIS

Baseline Adaptive Behavior Assessment

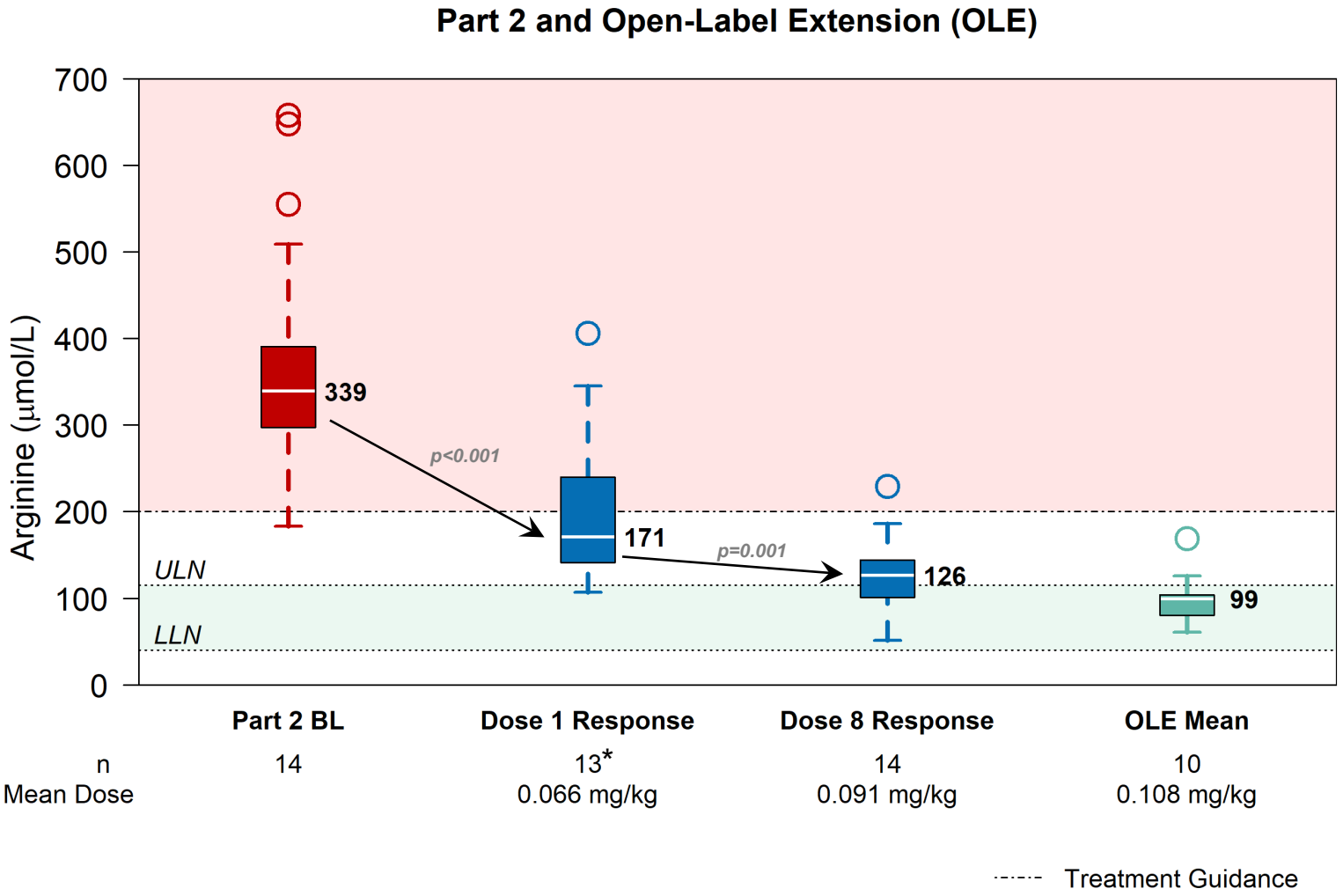


8/10 assessed patients had baseline deficiencies in one or more domains assessed by ABAS

Captured deficits in activities of daily living, including:

- General Adaptive Composite (GAC): All skills
  - *70% ≥ 1 SD below the mean*
- Conceptual: communication, functional, and self-direction
  - *60% ≥ 1 SD below the mean*
- Practical: Community use, home living, health, safety, self-care
  - *80% ≥ 1 SD below the mean*
- Social: Leisure and social
  - *50% ≥ 1 SD below the mean*

Pegzilarginase Rapidly Reduced and Sustainably Controlled Plasma Arginine



- **Arginine reduction statistically significant after 1 dose**
  - ***(n=13 with paired data)***
- **Plasma arginine control improved over time with further significant reduction after 8 weeks of dosing**

**1-week sample not collected in 1 patient*
Arginine responses are shown for patients who completed Part 2 and were determined from the sample drawn 1 week after a dose (immediately prior to the next dose).
OLE Mean shows the means of each patient's last 4 responses (determined 1 week after a dose), excluding samples following missed doses.
BL = baseline; LLN/ULN = Lower/Upper Limit of Normal

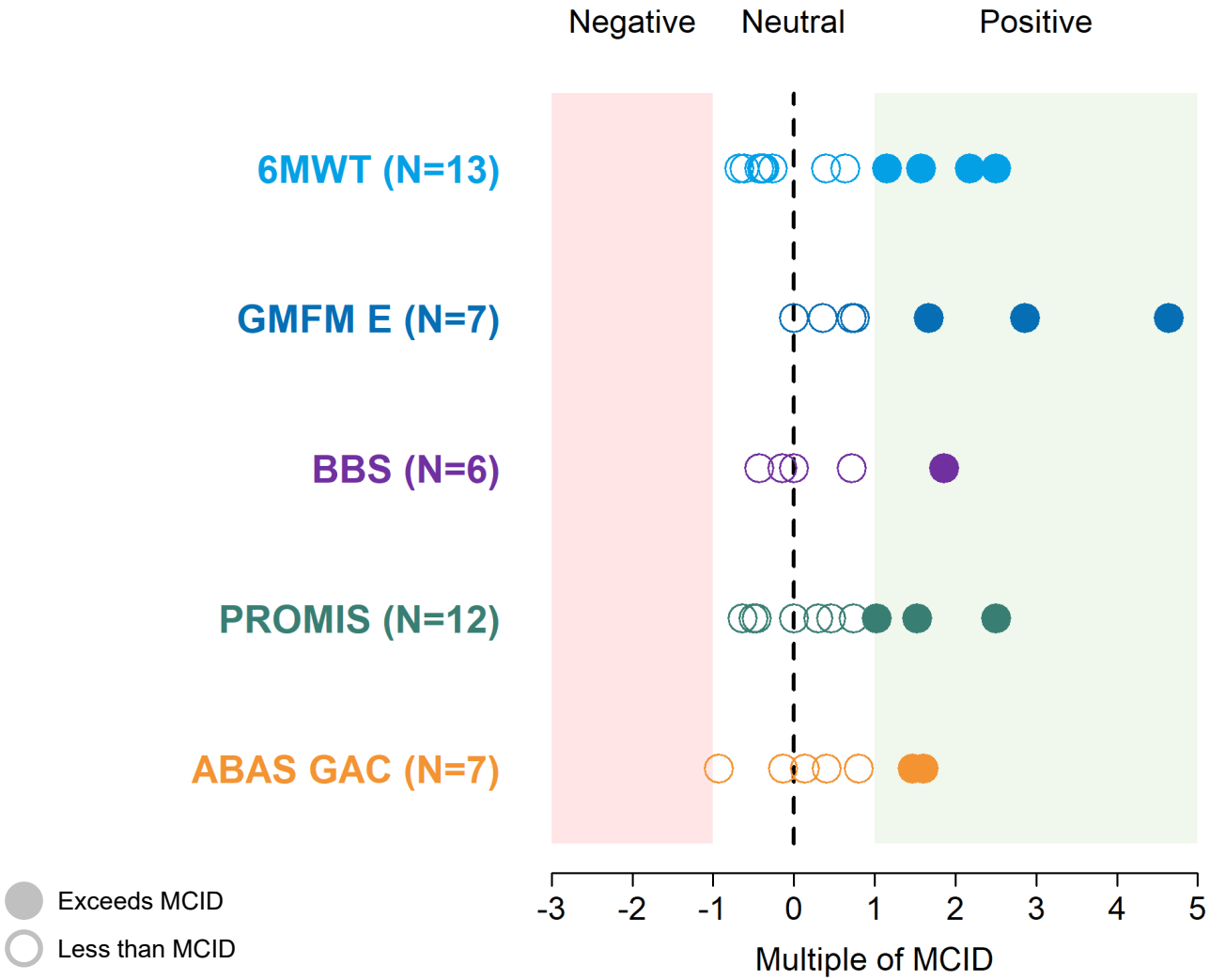
Safety Assessments

N=16	Patients with Any AE		Patients with SAEs	
AE Term	Related	Unrelated	Related	Unrelated
Vomiting	5 (31%)	3 (19%)	0	0
Hypersensitivity	4 (25%)	0	3 (19%)	0
Abdominal Pain	3 (19%)	2 (13%)	1 (6%)	0
Pruritus	3 (19%)	1 (19%)	0	0
Hyperammonemia	2 (13%)	4 (25%)	2 (13%)	4 (25%)
Dry Skin	2 (13%)	0	0	0

Includes all terms reported in ≥2 patients as treatment-related, or in ≥1 patient as both treatment-related and serious. Patients with both related and unrelated episodes of a specific AE term are counted in the related column(s) for that term.

- **Pegzilarginase was generally well tolerated**
  - **> 300 infusions administered**
  - **83% of infusions were ≤ 30 minutes duration**
- **Hypersensitivity reactions were manageable with standard measures and did not lead to treatment discontinuation**
- **Low-titer, emergent ADAs were detected in 8/16 patients; all titers became undetectable by end of study**

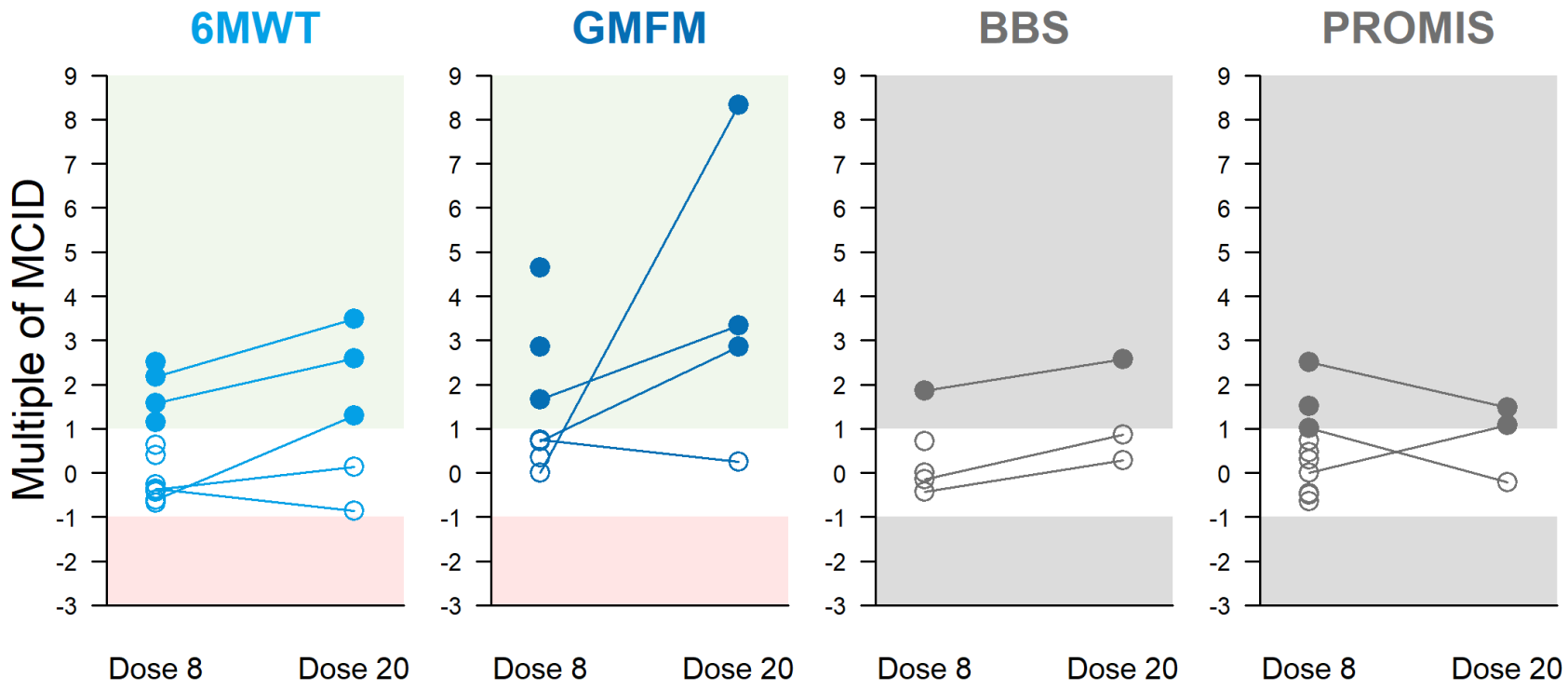
Clinically Important Improvements After Only 8 Weeks of Dosing



9 / 14 patients (64%) demonstrated clinically meaningful improvements in one or more clinical endpoints after only 8 weeks of dosing

Data is for patients who completed Part 2; patients who were within 1 MCID of the maximum score for GMFM and BBS are not shown.
MCID = minimal clinically important difference; 6MWT = 6-minute walk test; GMFM = Gross Motor Function Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; BBS = Berg Balance Scale; ABAS GAC = Adaptive Behavior Assessment System® General Adaptive Composite

Continued Improvements in Mobility were Observed at Dose 20



5 / 5 (100%) patients demonstrated clinically meaningful improvements in one or more clinical endpoints at 20 weeks of dosing

GMFM enhances the ability to capture objective improvements in mobility

14 patients have completed Part 2, and 5 patients have completed 20 weeks of dosing.
MCID = minimal clinically important difference

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Clinical Presentation

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Assessment	Normal Population	Baseline	After 20 doses (MCID)
Plasma arginine	40-115 µM	363 µM	**93.1 µM**
6MWT	Reference Interval: 310 – 664 meters	174 meters	176 meters
GMFM-E	Max = 72	27	**35 (2.9X)**
ABAS GAC	Mean = 100, SD=15	64	**76 (1.6X)***

Marked improvement in plasma arginine control

Clinically meaningful improvements in GMFM-E and ABAS align with observed impact on walk quality and interpersonal interactions

** Measured after 8 doses*

Conclusions

- **Pegzilarginase was highly effective in sustainably lowering plasma arginine**, a key driver of ARG1-D disease manifestations and progression

- **Plasma arginine reductions were accompanied by improvements in mobility and adaptive behavior after only 8 weeks of repeat dosing** with additional improvements after longer dosing

- **Pegzilarginase was well tolerated;** hypersensitivity reactions were manageable with standard measures and did not lead to treatment discontinuation

- **Mobility and adaptive behavior assessments effectively captured** treatment related clinical improvements

Acknowledgements

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the Patients, their Families, and Caregivers

for their dedication to these studies

Information on the Phase 3 Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints (PEACE) Study for patients with Arginase 1 Deficiency is available at ARG1Dstudy@aegleabio.com