

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

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Disclosures

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

I will be discussing investigational use of Pegzilarginase

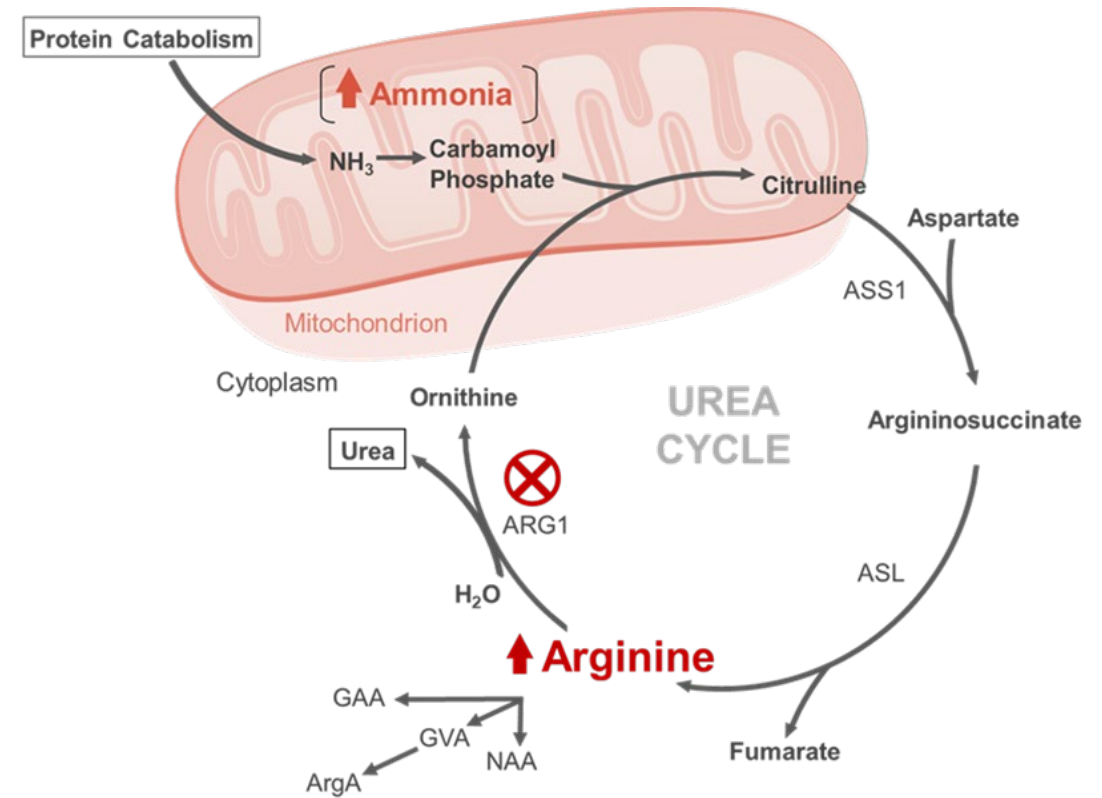
Arginase 1 Deficiency

- 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

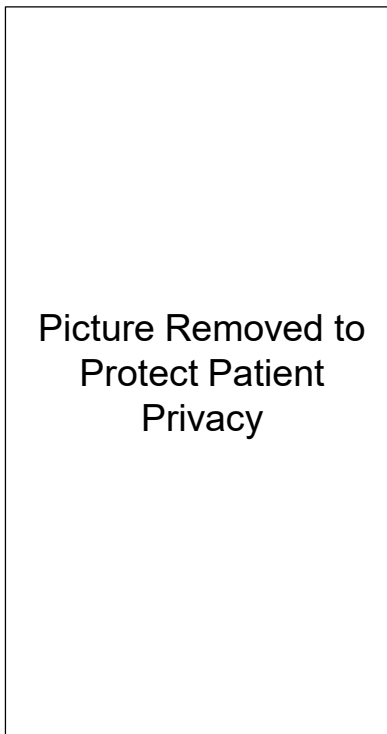
- Severe dietary protein restriction
- Essential amino acid supplementation
- Ammonia scavengers for hyperammonemia

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%



Baseline Study Assessments

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

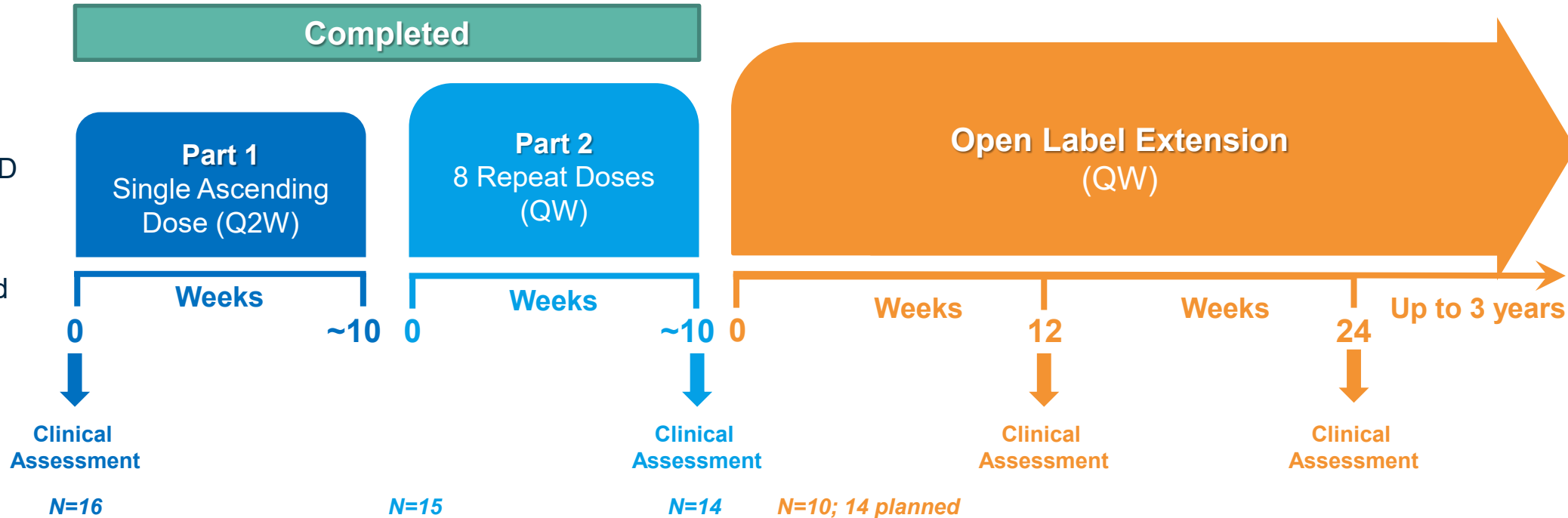
Open-Label, Multi-Center Phase 1/2 Study of IV Pegzilarginase in ARG1-D

Inclusion criteria:

- Diagnosis of ARG1-D
- >2 years old

Exclusion criteria:

- Severe, uncontrolled hyperammonemia



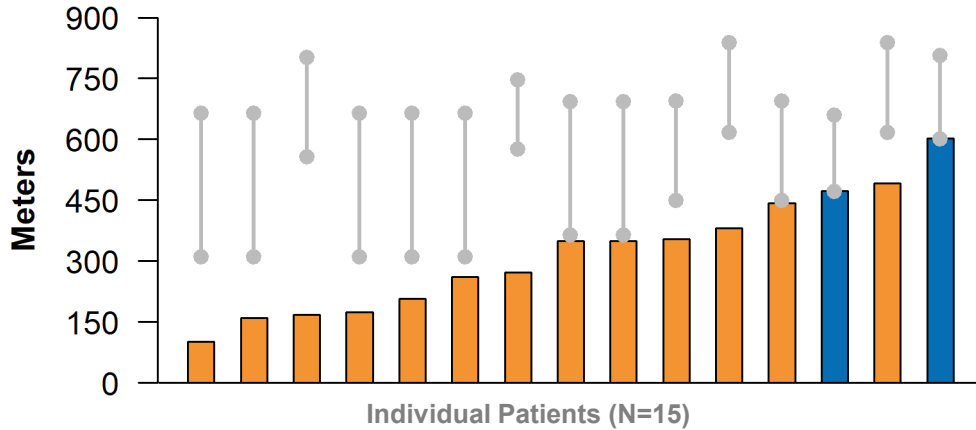
Clinical assessments:

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

Baseline Mobility Assessments

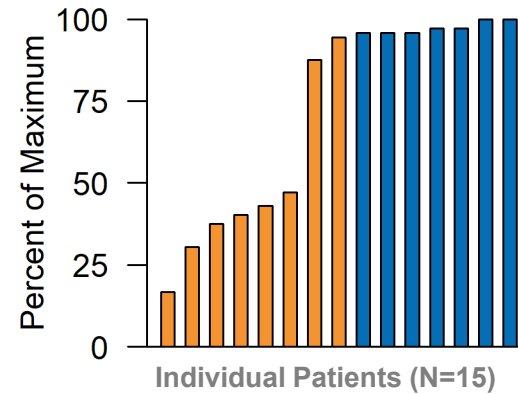
6-Minute Walk Test

Age/Gender Reference Limits

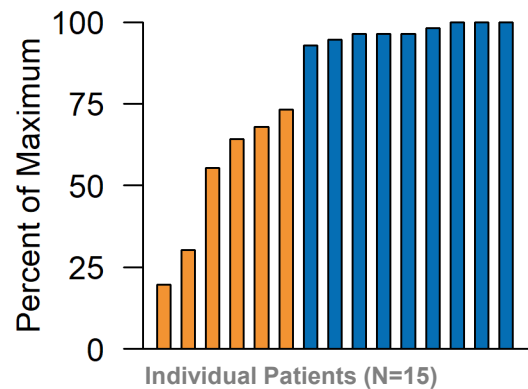


Gross Motor Function Measure

Part E

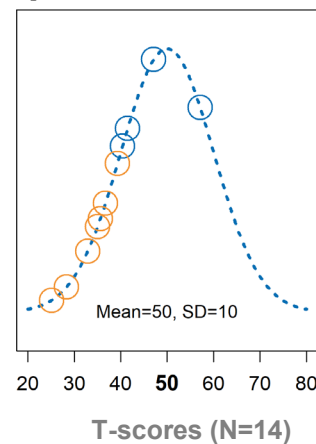


Berg Balance Scale



PROMIS

Physical Function / Mobility

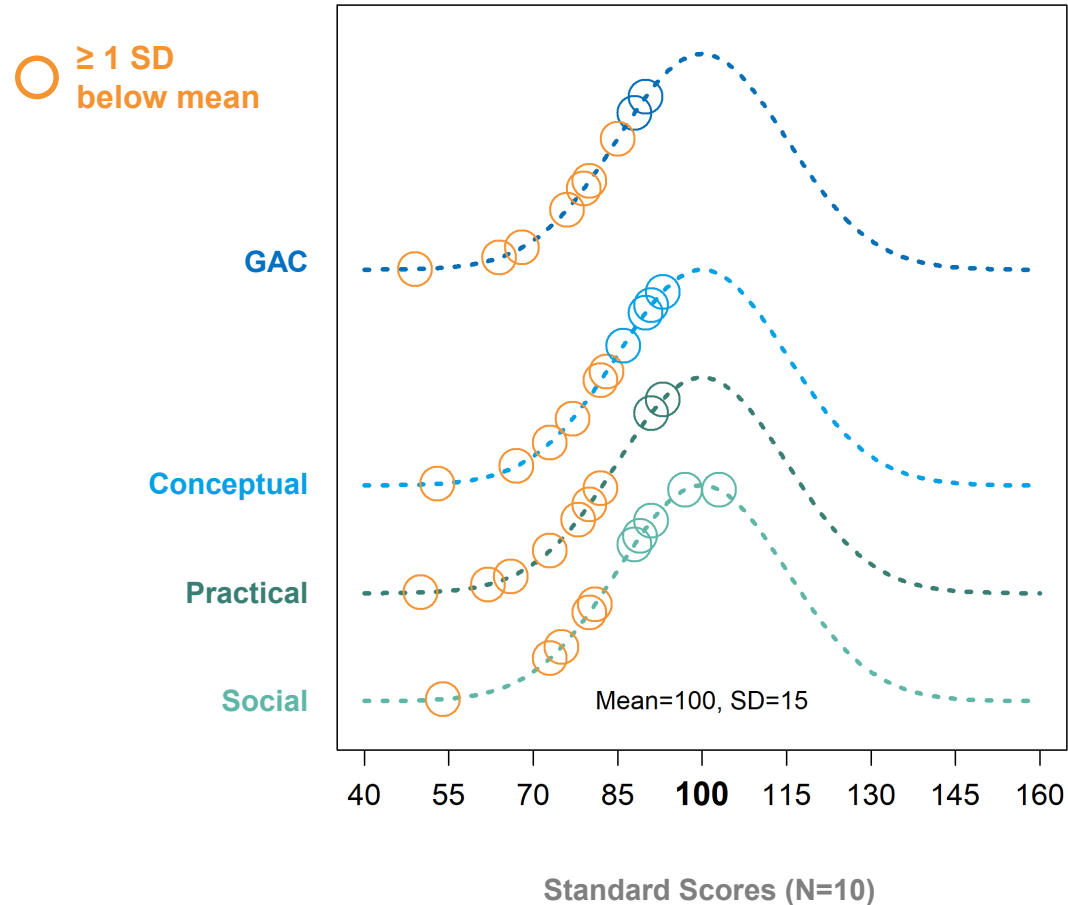


14 / 16 patients (88%) had a measurable deficit in mobility

- 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)

Baseline Adaptive Behavior Assessment

Adaptive Behavior Assessment System (ABAS)

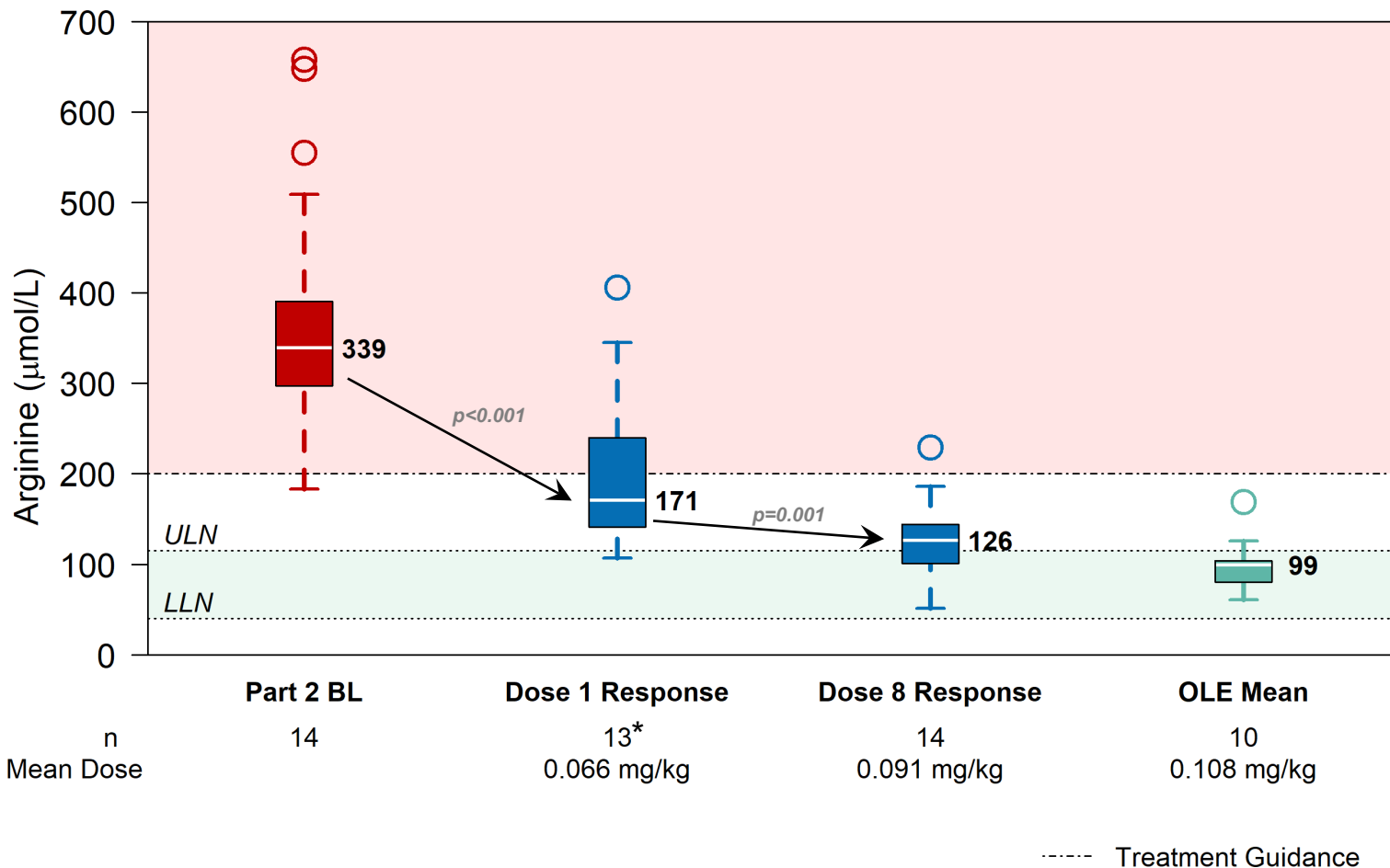


8/10 assessed patients had baseline deficiencies in one or more domains assessed by ABAS

- 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

Part 2 and Open-Label Extension (OLE)



- 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

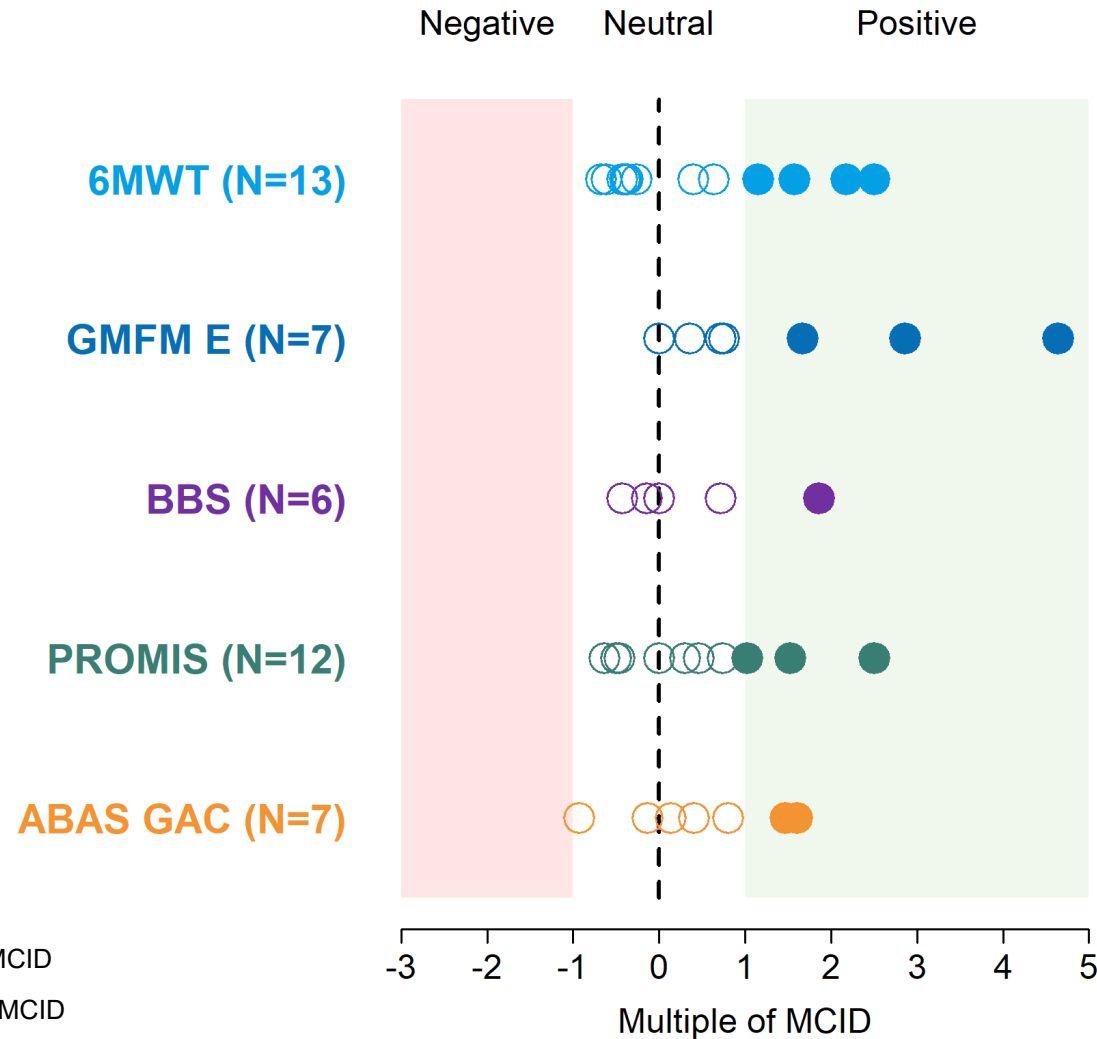
Safety Assessments

N=16 AE Term	Patients with Any AE		Patients with SAEs	
	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

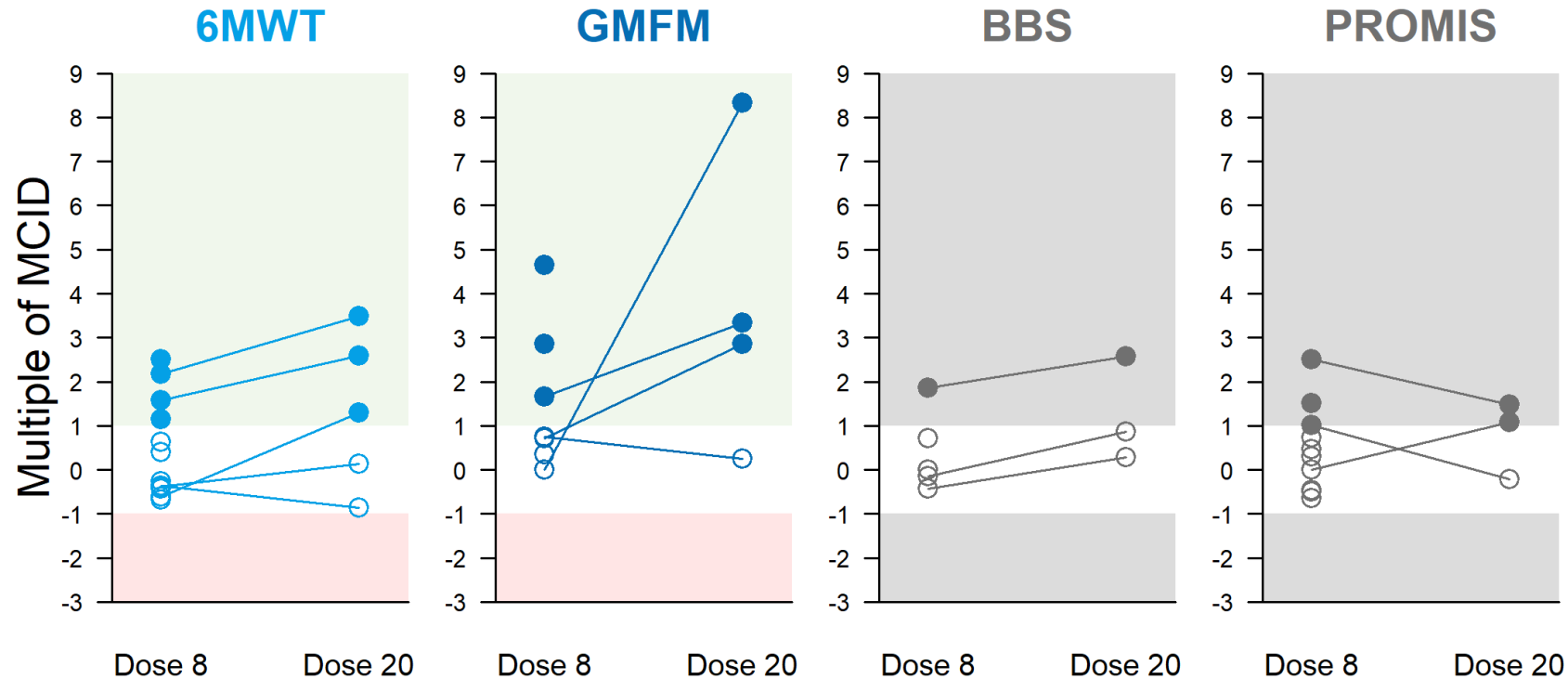


9 / 14 patients (64%) demonstrated clinically meaningful improvements in one or more clinical endpoints after only 8 weeks of dosing

● Exceeds MCID
○ Less than MCID

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

19 Year-Old Female with ARG1-D on Pegzilarginase

Clinical Presentation

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

Picture Removed to Protect Patient Privacy

Assessment	Normal Population	Baseline	After 20 doses (MCID)
Plasma arginine	40-115 μ M	363 μ M	93.1 μ M
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

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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and thank*

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*