1 Year Data from First in Human Study of Pegzilarginase for the Treatment of Arginase 1 Deficiency (ARG1-D)

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On behalf of the 101A/102A Investigators and Research Staff

Disclosures

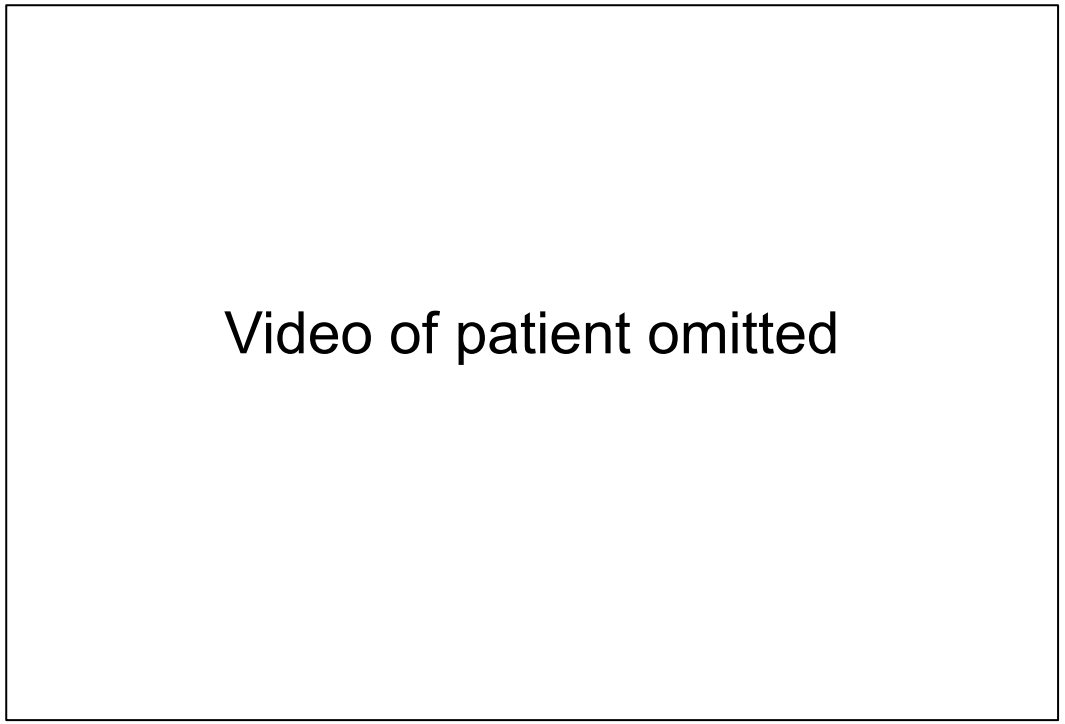
Bechter MW, Sloan LS, Rao RM are full time employees of Aeglea BioTherapeutics

Diaz GA, Zori RT have performed as consultants and received travel support from Aeglea BioTherapeutics

The investigational use of pegzilarginase will be discussed during this presentation

Arginase 1 Deficiency (ARG1-D)

- **Autosomal recessive disorder of arginine metabolism due to ARG1 enzyme deficiency**
  - Recent genetic prevalence data suggests > 2500 patients worldwide[1]
    - >700 patients in Europe
    - >250 patients in US
- **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]**
- **Suspected cases can be diagnosed reliably**
  - Plasma Arginine >300µM[5]
  - Red Blood Cell Arginase, Genetic testing[6]



May be initially misdiagnosed as Cerebral Palsy or Hereditary Spastic Paraplegia[7]

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.

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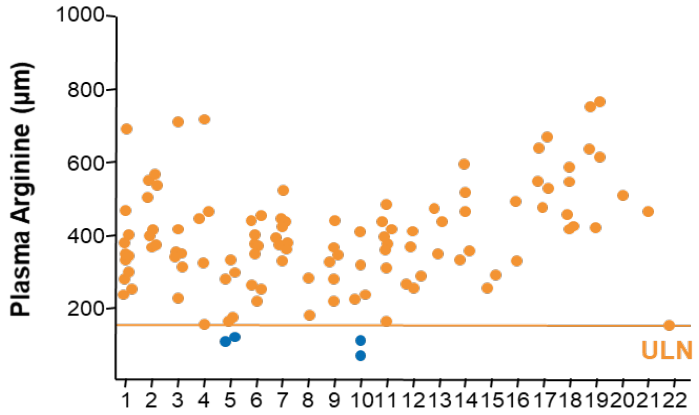
Current Disease Management Fails To Adequately Control Plasma Arginine Levels

- Even with strict dietary restriction, plasma arginine levels ≤200 µM are very difficult to achieve[1–3]
- Diet-related reductions in plasma arginine are not always accompanied by consistent reductions in guanidino compound levels[4]
- Current dietary strategies and use of ammonia scavengers are unable to fully alter disease progression and improve clinical status of patients[5,6]

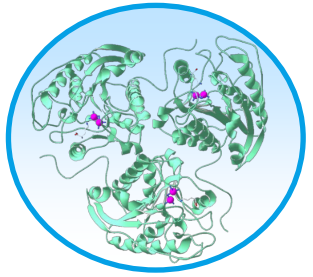
Elevated plasma arginine levels in patients with ARG1-D managed with standard of care (n=22)



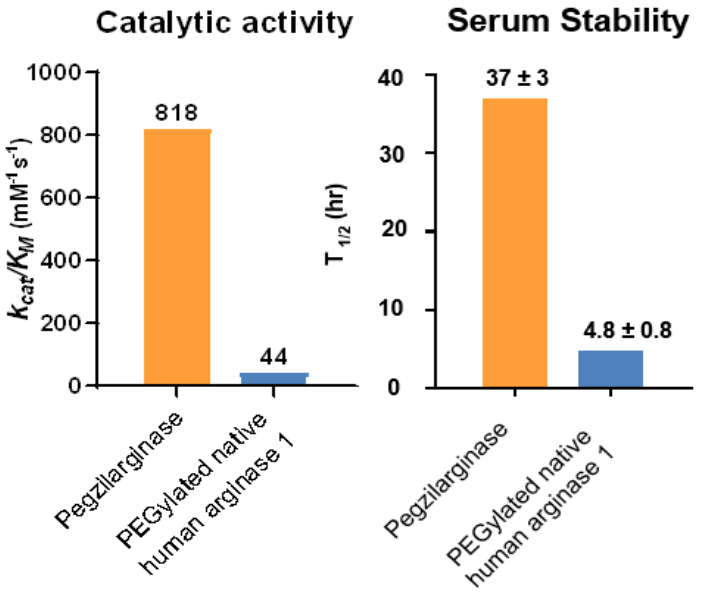
ULN, upper limit of normal

Pegzilarginase is Engineered to Robustly Control Plasma Arginine

Substituted metal cofactor (Mn^{2+} replaced with Co^{2+})

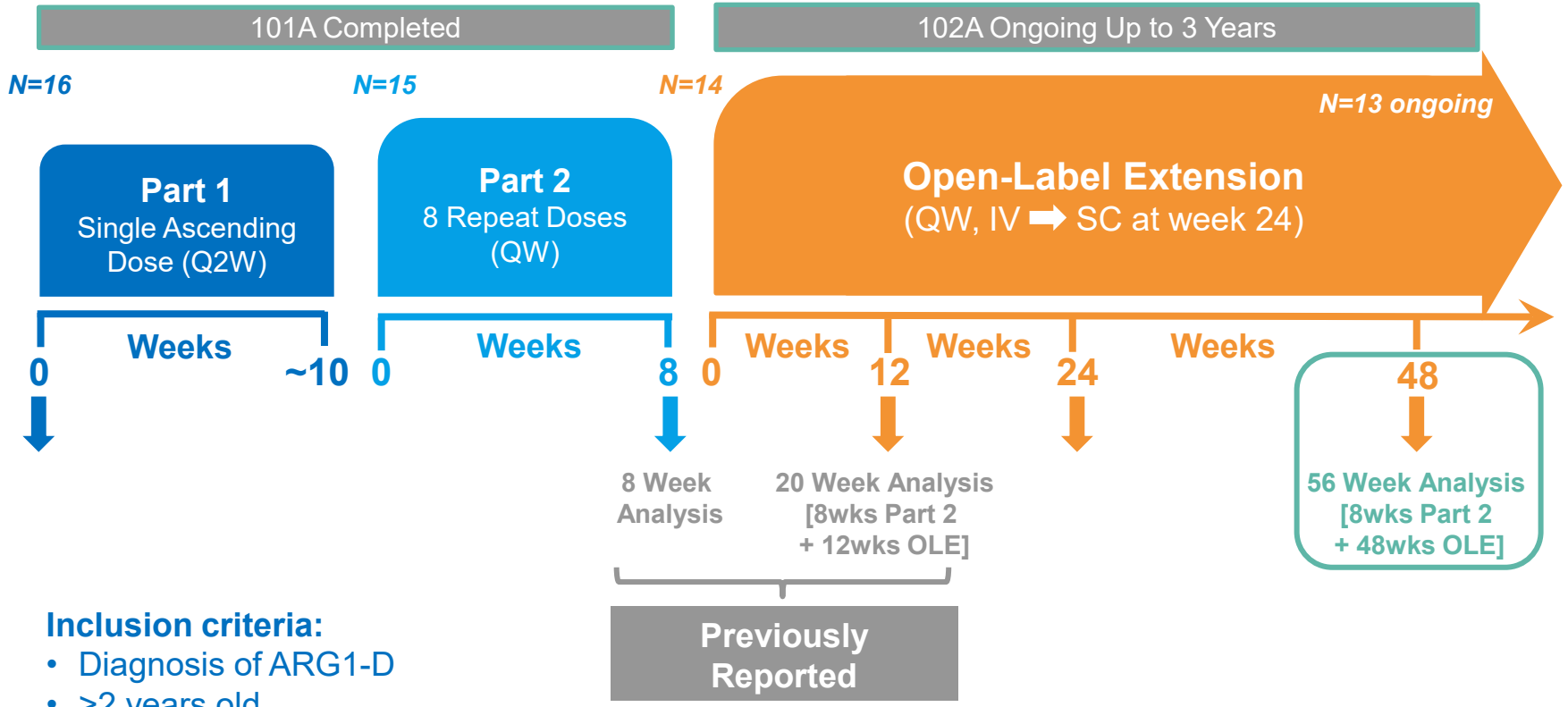


Improved catalytic activity and serum stability



1. Burrage LC, et al. *Hum Mol Genet.* 2015;24:6417–6427; 2. Huemer M, et al. *J Inherit Metab Dis.* 2016;39:331–340; 3. Diez-Fernandez C, et al. *Hum Mutat.* 2018;39:1029–1050; 4. Marescau B, et al. *Pediatr Res.* 1990;27:297–303; 5. Amayreh W, et al. *Dev Med Child Neurol.* 2014;56:1021–1024; 6. Uchino T, et al. *Hum Genet.* 1995;96:255–260.

Open-Label, Multi-Centre Phase 1/2 Study of Pegzilarginase in ARG1-D (101A and 102A Studies)



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

Exclusion criteria:
- Severe, uncontrolled hyperammonaemia

Key Objectives
- Primary endpoint:
  - Safety and tolerability
- Secondary endpoints: Effect on:
  - Plasma arginine (p[Arg])
  - Plasma guanidino compound (GC) levels
- Evaluation of clinical outcome assessments including:
  - 6 Minute Walk Test
  - GMFM Part D (standing)
  - GMFM Part E (walk, run, jump)
- A clinical Responder was defined as showing a 1 MCID or greater improvement in one of: 6MWT, GMFM Part D or Part E

↓ Clinical Assessments

ARG1-D = Arginase 1 Deficiency; IV = intravenous; QW = weekly; Q2W = every 2 weeks;
MCID = Minimal Clinically Important Difference, GMFM = Gross Motor Function Measurement, 6MWT = Six Minute Walk Test

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

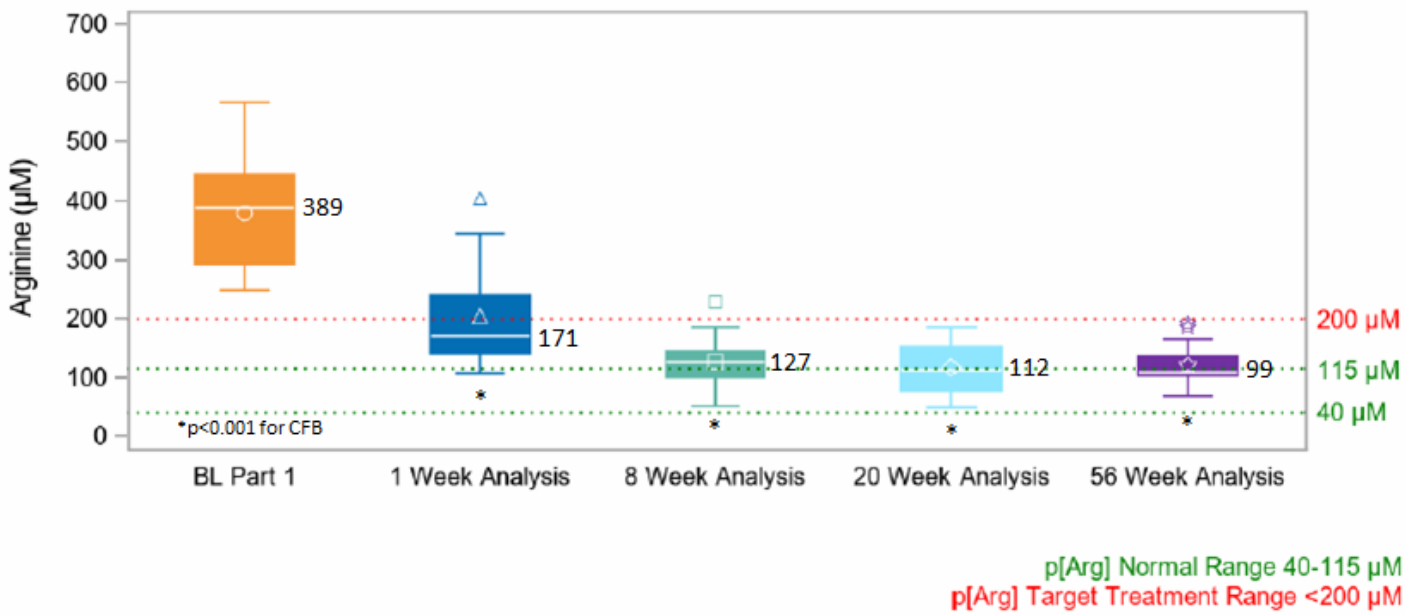
*Values are median (range) unless stated otherwise.
Arg, arginine; ARG1, arginase 1; BL, baseline; NH_3, ammonia; 6MWT, 6-minute walk test; GMFM-D/E, Gross Motor Function Measure Part D/E; Pt, patient
** 1 patient non-assessable (wheelchair bound)

Safety Summary

- Pegzilarginase has a favorable safety profile in ARG1-D patients
- More than 750 doses administered in 101A and 102A
  - Approximately 500 intravenous doses
- Most treatment-related adverse events were mild
- The frequency of treatment-related adverse events decreased over time
- Hypersensitivity and hyperammonaemia were the most common treatment-related serious adverse events; expected and manageable

Pegzilarginase Markedly Reduces and Sustainably Controls Plasma Arginine

Plasma Arginine in Response to Pegzilarginase



- Baseline p[Arg] on standard disease management was markedly elevated
- Significant and sustained reductions in p[Arg] were achieved from baseline to week 1, week 8, week 20 and week 56
- At the week 56 analysis:
  - the median p[Arg] was 99µM (40-115µM)
  - 10/13 patients achieved a p[Arg] within normal range (40-115uM)
  - 13/13 patients achieved a p[Arg] within target range (<200uM)
- p[Arg] reductions accompanied by expected decreases in plasma Guanidino Compounds

Clinically Impactful Improvements at Patient Level with Pegzilarginase

- Teenage girl diagnosed at age 1 (presented with hyperammonaemia)
- Developed severe lower limb spasticity, speech delay, intellectual disability
- Treated with severe protein restriction, essential amino acids, and ammonia scavengers
- Persistent hyperargininaemia
- Progressive worsening of lower extremity diplegia, walked with arm crutches at baseline (GMFCS II)

Assessment	Normal Population	Baseline	20 Week Analysis	56 Week Analysis
Plasma arginine	40 - 115µM	363µM	**108.5µM***	**88.2µM***
6MWT	310 - 664m	174m	176m	**209m***
GMFM-D	Max = 39	21	**27***	**28***
GMFM-E	Max = 72	27	**35***	**34***

*** Achieved MCID: 6MWT = 16m; GMFM-D = 3.3; GMFM-E = 2.8**

Patient 5:
Baseline

Unable to cross legs and dependent on walking aid

Patient 5:
20 Week Analysis

Able to cross legs and less dependent on walking aid

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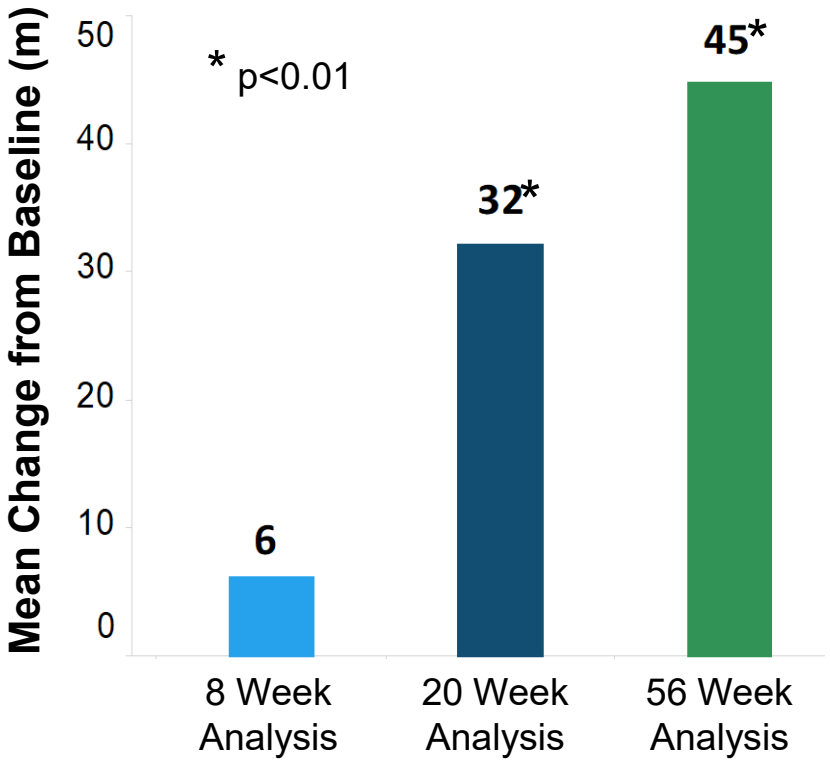
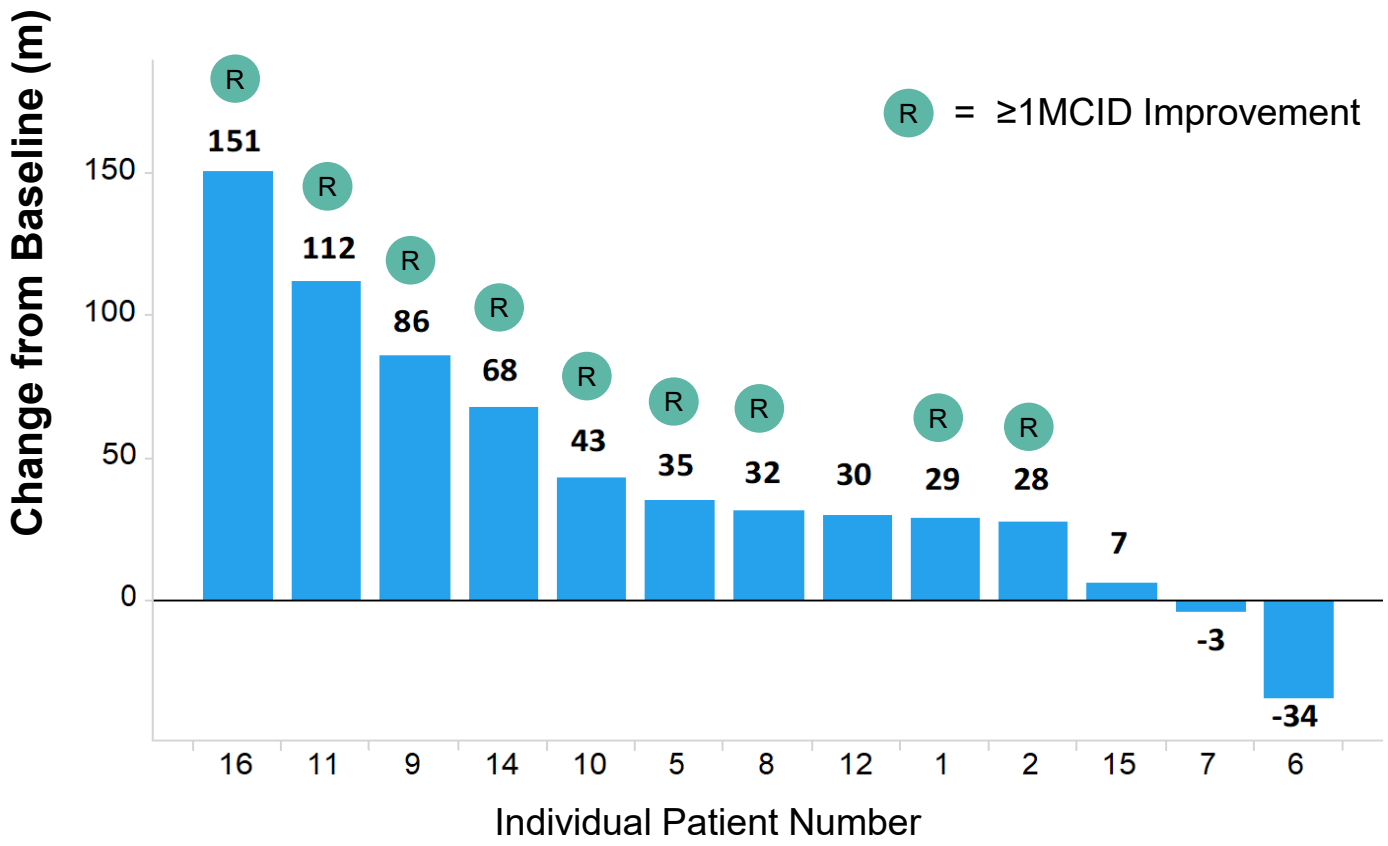
Pegzilarginase Demonstrates Sustained Improvements in 6 Minute Walk Test

Mean Change from Baseline in 6MWT



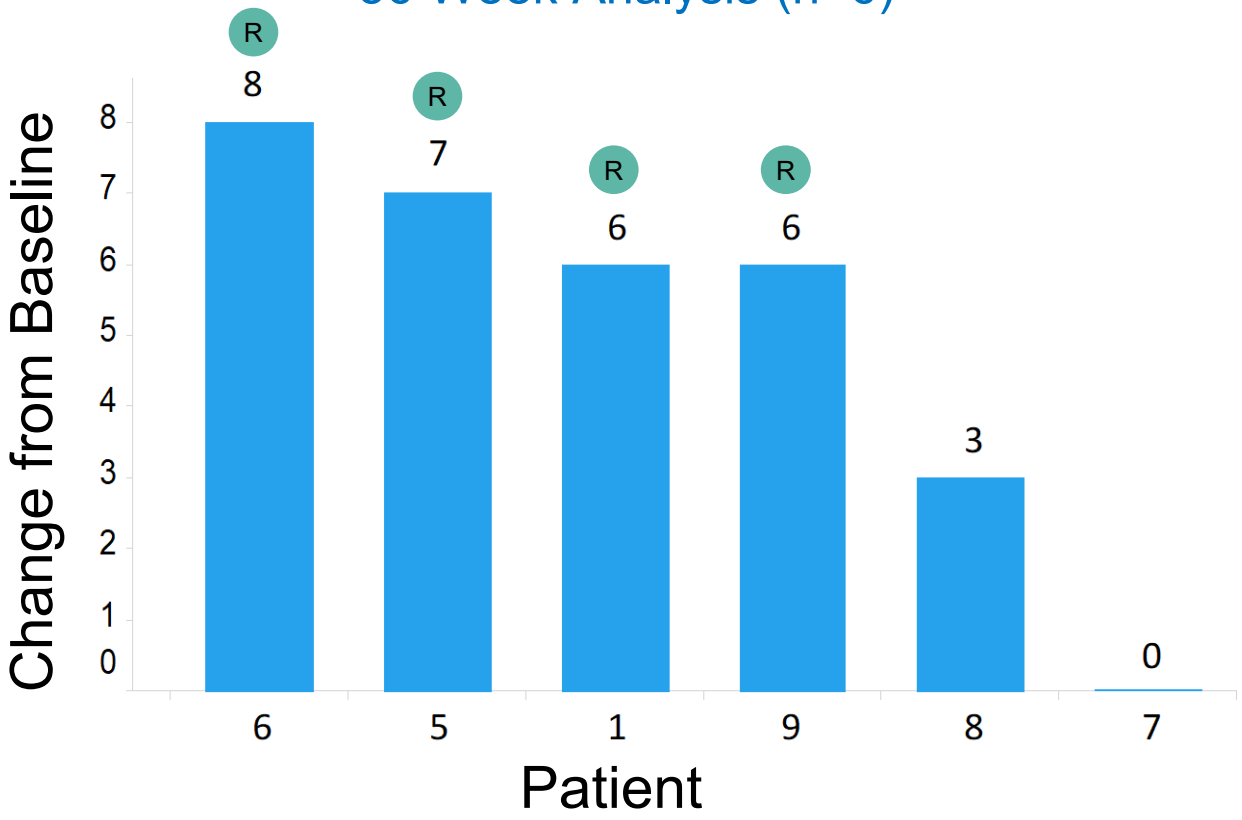
6MWT by Patient at 56 Week Analysis



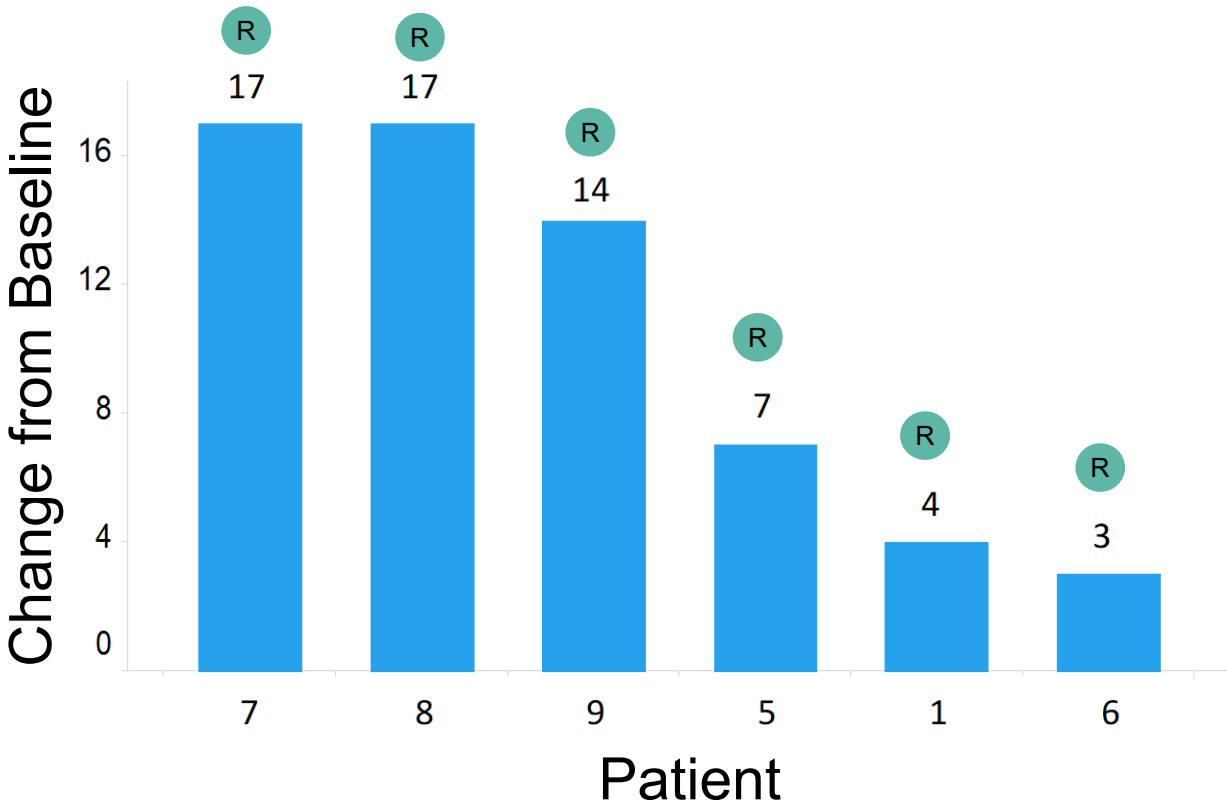
6MWT – Six Minute Walk Test; MCID=9%

Patients in GMFCS Levels II and III also Show Improvement in Mobility

GMFM-D Change from Baseline
56 Week Analysis (n=6)



GMFM-E change from Baseline
56 Week Analysis (n=6)



R = ≥1MCID Improvement

MCID for GMFM Part D is 3.3 and 1.5 for GMFCS Levels II and III, respectively; MCID for GMFM Part E is 2.8 and 1.8 for GMFCS Levels II and III, respectively. Maximum values for GMFM-D and GMFM-E are 39 and 72, respectively.

Pegzilarginase Demonstrates Durable Clinical Response at 56 Week Analysis

Overall clinical response rate:

20 Week Analysis: 11/14 (79%)

56 Week Analysis: 11/13 (85%)

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

	Overall Combined Response	6MWT	GMFM-D	GMFM-E	GMFCS
	56 Week Analysis (Change from Baseline)				BL
Patient 1	R	29m	6	4	III
Patient 2	R	28m	2	3	I
Patient 5	R	35m	7	7	II
Patient 6	R	(34m)	8	3	II
Patient 7	R	(3m)	0	17	III
Patient 8	R	32m	3	17	II
Patient 9	R	86m	6	14	II
Patient 10	R	43m	2	3	I
Patient 11	R	112m	0	0	I
Patient 12		30m	0	1	I
Patient 14	R	68m			I
Patient 15		7m			I
Patient 16	R	151m	0	0	I

Responder (≥1 MCID Increase) ≥1 MCID decrease Not assessed <1 MCID increase data not available

*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.

Conclusions

- Arginase 1 Deficiency (ARG1-D) is a debilitating, progressive, inherited, metabolic disease driven by the accumulation of arginine and its metabolites, which results in prominent neurological manifestations including progressive spastic diplegia and early mortality
  - Delays in diagnosis are common with some cases initially diagnosed as Cerebral Palsy or Hereditary Spastic Paraplegia

- Pegzilarginase was highly effective in sustainably lowering plasma arginine levels with a favorable safety profile and is now being further evaluated in an active Phase 3 study.

- Plasma arginine reduction was accompanied by improvements in disease manifestations within 8 weeks and a durable clinical response rate of 85% at 56 Week Analysis

- These marked improvements in important disease-related manifestations with pegzilarginase on a background of standard treatment suggests the potential for a substantial clinical improvement over current management of patients with ARG1-D

Acknowledgements

The 101A/102A Investigators and Research Staff wish to acknowledge and thank

the Patients, their Families, and Caregivers

for their dedication to these studies

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