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Safety and Tolerability of Pegzilarginase for Arginase 1 Deficiency in the PEACE Pivotal Phase 3 Clinical Trial

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Background

- Pegzilarginase is a human enzyme therapy in advanced development for Arginase 1 Deficiency (ARG1-D),[1,2] a rare inborn error of metabolism with an estimated prevalence of 1:726,000[3]
- Defective or absent enzymatic activity of arginase 1 in ARG1-D results in persistent hyperargininemia, leading to progressive impairments and debilitating manifestations including spasticity, developmental delay, intellectual disability, seizures, and early mortality[4-8]
- Current management of ARG1-D relies on severe dietary protein restriction, which is inadequate to lower plasma arginine to therapeutic guideline-recommended levels and is insufficient to prevent disease progression[9-11]
- In an open-label Phase 1/2 trial of 16 patients with ARG1-D, pegzilarginase produced substantial plasma arginine reductions and meaningful clinical improvements, and demonstrated a favorable safety and tolerability profile[2]
- The safety and tolerability of pegzilarginase is being further characterized in a larger cohort of pegzilarginase-naïve patients with ARG1-D in the pivotal PEACE Phase 3 trial

Objective

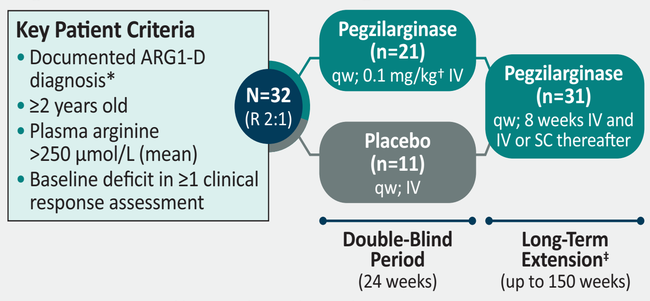
- To describe the safety and tolerability of pegzilarginase in the randomized double-blind period and ongoing open-label long-term extension (LTE) of the PEACE trial (**P**egzilarginase **E**ffect on **A**rginase 1 Deficiency **C**linical **E**ndpoints; NCT03921541)

Methods

Study Design

- The current analysis includes data from the 24-week double-blind period and the LTE, through an interim data cutoff of March 24, 2022, with all patients enrolled in the LTE completing ≥24 weeks of open-label pegzilarginase treatment (**Figure 1**)
- Treatment emergent adverse events (AEs), serious AEs (SAEs), AEs of special interest, immunogenicity, and laboratory investigations were assessed

Figure 1. **PEACE Trial Design**



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

Study Treatment

- Based on the Phase 1/2 trial experience,[2] pegzilarginase (or volume-matched placebo) was administered via a 30-minute intravenous (IV) infusion in the double-blind period, with a pegzilarginase starting dose of 0.1 mg/kg and dose modifications made as necessary to target maintenance of plasma arginine at the end of the dosing interval (168 hours post-dose) in the range of 50–150 µmol/L
  - All patients continued their current individualized disease management regimen for the duration of the trial
- In the LTE, pegzilarginase patients received their optimized dose from the double-blind period (pegzilarginase/pegzilarginase) and placebo patients transitioned to pegzilarginase (placebo/pegzilarginase)
- Patients had the option to switch to SC administration after completion of the first 8 weeks of treatment in the LTE, using the same pegzilarginase formulation and their last IV dose level
  - If considered safe and appropriate after a minimum of 4 SC doses, dose administration could be performed by home health care

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

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Results

Patients

- The PEACE cohort (N=32) has been described elsewhere.[1] The clinical manifestations and biochemical profile of these patients is consistent with patients in the prior Phase 1/2 study[2] and is representative of the broader ARG1-D population
- Most patients had prior history of hyperammonemia or liver function test abnormalities, with several patients also having a history of seizures (**Table 1**)
- The double-blind period was completed by 31 patients, with 1 patient randomized to pegzilarginase discontinuing at Week 6 for personal reasons unrelated to study treatment. All 31 patients continued into the LTE

Table 1. **Key Baseline Clinical Characteristics**

Patient Information	Pegzilarginase (n=21)	Placebo (n=11)	Overall (n=32)
Age at enrollment, y			
Mean ± SD	9.6 ± 6.16	12.9 ± 6.77	10.7 ± 6.47
Range	2–28	5–29	2–29
Sex, n (%)			
Male	12 (57.1)	7 (63.6)	19 (59.4)
Female	9 (42.9)	4 (36.4)	13 (40.6)
Plasma Arginine, µmol/L			
Mean ± SD	365.4 ± 93.7	471.9 ± 79.9	402.0 ± 101.8
Median (range)	368.2 ± (202–572)	483.7 ± (294–573)	398.2 ± (202–573)
Select Clinical Characteristics, n (%)			
History of hyperammonemia	12 (57.1)	6 (54.5)	18 (56.3)
History of liver test abnormalities	14 (66.7)	9 (81.8)	23 (71.9)
History of seizures	7 (33.3)	4 (36.4)	11 (34.4)

Treatment Exposure

- Overall, pegzilarginase doses ranged from 0.05–0.20 mg/kg; all 31 patients switched from IV to SC administration of pegzilarginase in the LTE
- Patients received pegzilarginase for a median duration of 24 weeks (double-blind period) followed by 55 weeks (78 weeks overall) in the pegzilarginase/pegzilarginase arm and for 53 weeks in the placebo/pegzilarginase arm in the LTE (**Table 2**)
- On average, patients received 92–94% of expected pegzilarginase doses and 98% of expected placebo doses (**Table 2**)
  - Three patients in the pegzilarginase arm and one in the placebo arm missed one or more scheduled doses during the double-blind period (taking place during the COVID-19 pandemic); however, no doses were missed because of safety or tolerability and no other patients missed pegzilarginase dosing during the LTE through the data cutoff

Table 2. **Treatment Exposure**

Treatment Exposure	24-Week Double-blind Period		24-Week Long-term Extension		Overall	
	Pegzilarginase (n=21)	Placebo (n=11)	Pegzilarginase/ Pegzilarginase (n=20)	Placebo/ Pegzilarginase (n=11)	Pegzilarginase/ Pegzilarginase (n=21)	Placebo/ Pegzilarginase (n=11)
Treatment exposure, weeks						
Median	24	24	55	53	78	77
Range	6–25*	22–25	24–97	24–125	6–121*	46–149
Expected doses						
Median	24	24	55	53	79	77
Range	7–29*	24–26	24–97	24–122	7–121*	48–146
Taken doses						
Median	23	24	50	41	70	64
Range	6–26*	22–26	21–95	22–112	6–118*	44–136
Number of taken/expected doses, %						
Mean (±SD)	94 (7.1)	98 (2.9)	94 (4.8)	92 (10.4)	94 (4.6)	93 (7.1)

*One pegzilarginase patient withdrew from the study for personal reasons at Week 6 of the double-blind period.
†Included placebo (double blind period) and pegzilarginase treatment (LTE).

Safety and Tolerability

Table 3. **Overall Summary of Adverse Events**

Adverse Events, n (%)	24-Week Double-blind Period		≥24-Week Long-term Extension		
	Pegzilarginase (n=21)	Placebo (n=11)	Pegzilarginase/ Pegzilarginase (n=20)	Placebo/ Pegzilarginase (n=11)	All (n=31)
Any treatment-emergent AE	18 (85.7)	11 (100.0)	19 (95.0)	11 (100.0)	30 (96.8)
Mild	10 (47.6)	5 (45.5)	8 (40.0)	4 (36.4)	12 (38.7)
Moderate	7 (33.3)	6 (54.5)	11 (55.0)	4 (36.4)	15 (48.4)
Severe	1 (4.8)	0	0	3 (27.3)	3 (9.7)
AE leading to discontinuation	0	0	0	0	0
AE leading to dose reduction	0	0	1 (5.0)	0	1 (3.2)
AEs of special interest					
Hypersensitivity reaction	2 (9.5)	0	0	0	0
Hyperammonemic episodes*	3 (14.3)	4 (36.4)	2 (10.0)	5 (45.5)	7 (22.6)
Injection site reaction	0	0	2 (10.0)	0	2 (6.5)
SAEs†	4 (19.0)	4 (36.4)	5 (25.0)	7 (63.6)	12 (38.7)
Leading to fatal outcome	0	0	0	0	0
Pegzilarginase-related‡	1 (4.8)	0	0	1 (9.1)	1 (3.2)

*Hyperammonemic episodes include preferred terms of hyperammonemia, hyperammonemic crisis, and hyperammonemic encepalopathy. †See text for details. ‡Considered possibly related to pegzilarginase by the investigator.
AE, adverse event.

Double-blind Period: Common (≥15%) Treatment Emergent Adverse Events

- Pegzilarginase was well tolerated, with AEs generally being self-limiting or manageable and resolving with standard medical care
- AEs were mostly mild to moderate in severity and none led to drug discontinuation or dose reduction in either treatment arm (**Table 3**)
- Vomiting was a common AE and occurred at a similar frequency in both treatment arms (pegzilarginase, 29%; placebo, 27%) (**Table 4**)
- Pyrexia was reported in the pegzilarginase arm only (19%). Cough was reported in 19% and 9% of patients randomized to pegzilarginase or placebo, respectively
  - Increased ammonia was reported with similar frequency in the pegzilarginase and placebo arms (14% and 18%, respectively)
  - Hyperammonemia was reported at a lower frequency in the pegzilarginase arm vs placebo (10% vs 27%). Nausea, abdominal pain, and decreased appetite were less frequent with pegzilarginase vs placebo
- There were no notable trends in laboratory investigations in either treatment arm, including liver function tests; the rates and magnitudes of laboratory changes were consistent with background rates in ARG1-D and baseline characteristics of the cohort

Table 4. **Common Adverse Events: Double-blind Period**

Adverse Events With ≥15 Incidence in Either Arm, n (%)	24-Week Double-blind Period	
	Pegzilarginase (n=21)	Placebo (n=11)
Vomiting	6 (28.6)	3 (27.3)
Pyrexia	4 (19.0)	0
Cough	4 (19.0)	1 (9.1)
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.

Interim LTE Period: Common (≥15%) Treatment Emergent Adverse Events

- A similar overall safety profile was observed in the LTE through the data cutoff compared with the double-blind period, with pegzilarginase being well-tolerated, no treatment discontinuations occurring due to AEs, and AEs generally mild to moderate in severity (**Table 3**); there were some minor differences:
  - A single pegzilarginase/pegzilarginase patient required dose reduction (**Table 3**); fatigue and gait disturbance were reported after increasing the patient's pegzilarginase dose from 0.1 mg/kg to 0.15 mg/kg (considered unlikely related) and the dose was reverted back to 0.1 mg/kg
  - More AEs with an incidence of ≥15% in either arm were reported in the LTE (**Table 5**), likely reflecting the longer duration of participation, than in the double-blind period
    - Fatigue was a relatively frequent AE reported in the LTE (26% of patients)
    - Increased ALT and AST were both reported as AEs in 23% of patients; this was consistent with background disease as observed in a Urea Cycle Disorder Consortium study[9] and no clinically meaningful trends were observed
    - Abdominal pain and amino acid level increased occurred in 16% of patients
    - COVID-19 illness occurred in 16% of patients; a further 23% had a positive SARS-CoV-2 test
    - Hyperammonemia occurred in 23% of patients in the LTE

Table 5. **Common Adverse Events: Interim LTE**

Adverse Events With ≥15 Incidence in Either Arm, n (%)	≥24-week Long-term Extension		
	Pegzilarginase/ Pegzilarginase (n=20)	Placebo/ Pegzilarginase (n=11)	All (n=31)
Vomiting	7 (35.0)	6 (54.5)	13 (41.9)
Pyrexia	6 (30.0)	3 (27.3)	9 (29.0)
Fatigue	6 (30.0)	2 (18.2)	8 (25.8)
Alanine aminotransferase increased	5 (25.0)	2 (18.2)	7 (22.6)
Aspartate aminotransferase increased	5 (25.0)	2 (18.2)	7 (22.6)
SARS-CoV-2 test positive	4 (20.0)	3 (27.3)	7 (22.6)
Nausea	4 (20.0)	2 (18.2)	6 (19.4)
Ammonia increased	3 (15.0)	4 (36.4)	7 (22.6)
COVID-19	3 (15.0)	2 (18.2)	5 (16.1)
Amino acid level increased	3 (15.0)	2 (18.2)	5 (16.1)
Gastroenteritis	3 (15.0)	0	3 (9.7)
Upper respiratory tract infection	3 (15.0)	0	3 (9.7)
Rhinorrhoea	3 (15.0)	0	3 (9.7)
Hyperammonemia	2 (10.0)	5 (45.5)	7 (22.6)
Abdominal pain	2 (10.0)	3 (27.3)	5 (16.1)
Headache	2 (10.0)	2 (18.2)	4 (12.9)
Oropharyngeal pain	2 (10.0)	2 (18.2)	4 (12.9)

Serious Adverse Events

- In the double-blind period, SAEs were reported in 19% of patients in pegzilarginase arm and 36% patients in placebo arm (**Table 3**)
  - SAEs of hyperammonemia (10% and 27%) and hyperammonemic encephalopathy (5% and 9%) were reported in patients randomized to pegzilarginase or placebo, respectively; vomiting was reported for 5% of patients in the pegzilarginase arm only
- In the LTE period, SAEs were reported in 39% of patients and included hyperammonemia (23%), vomiting (7%), and less commonly (3% of LTE patients for each event), abdominal pain constipation, acute cholecystitis, gastroenteritis, and increased ammonia, ALT, or AST
- SAEs reported as possibly related to pegzilarginase were moderate hyperammonemic encephalopathy in 1 patient in the pegzilarginase arm during the double-blind period and hyperammonemia in 1 patient in the placebo/pegzilarginase arm during the LTE

Adverse Events of Special Interest and Immunogenicity

- Two patients in the pegzilarginase arm, and no patients in the placebo arm, had mild/moderate hypersensitivity reactions in the double-blind period (IV administration) that were managed with antihistamines; no additional events were reported in the interim LTE period (**Table 3**)
- Injection site reactions (injection site pain) were reported in 2 patients in the LTE (SC administration) (**Table 3**)
- Hyperammonemic episode(s) (defined using prespecified preferred terms) were reported in 14% of patients in pegzilarginase arm and 36% in placebo arm during the double-blind period and in 23% of patients in the LTE (both groups combined) (**Table 3**)
- Transient, generally low-titer anti-drug antibodies were detected in both treatment arms in the double-blind period, without meaningful clinical or biochemical impact. Irrespective of treatment with pegzilarginase or placebo in the double-blind period, no patient who was previously negative developed anti-drug antibodies after switching to SC dosing

Summary

- Pegzilarginase was well-tolerated; there were no treatment discontinuations due to AEs
- AEs were transient, generally mild to moderate in severity, manageable, and self-limiting or resolved with standard care; many (eg, hyperammonemia) were known findings in ARG1-D
- Hypersensitivity reactions were infrequent and managed with routine care, occurring only during the double-blind period with IV administration; injection site reactions associated with SC administration were also uncommon
- Anti-drug antibodies were infrequent and without apparent impact
- Overall, pegzilarginase showed a favorable safety profile[2]

Conclusions

- Pegzilarginase was well tolerated and demonstrated an acceptable and manageable safety profile in the 24-week controlled, double-blind period of this Phase 3 trial, consistent with results of the previous Phase 1/2 trial[2]
  - No new safety signals were identified during long-term pegzilarginase treatment (up to 125 weeks of exposure in the Phase 3 LTE)
  - Overall, nearly 50 patients have received pegzilarginase in clinical trials to date
- Pegzilarginase is the first potential therapy to treat elevated plasma arginine levels in ARG1-D, and has consistently demonstrated favorable safety and tolerability