Sustained Lowering of High Plasma Arginine Levels in ARG1-D With Pegzilarginase is Accompanied by Improvements in Disease Manifestations

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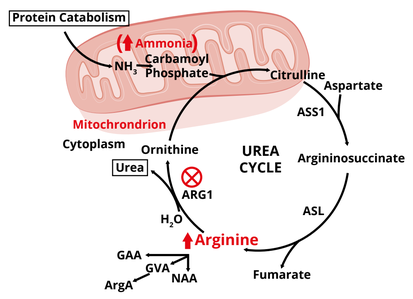
P-232

BACKGROUND

- ARG1-D is a serious, progressive disease with early mortality and high unmet medical need due to an autosomal recessive disorder of arginine metabolism (**Figure 1**)[1,2]
- Clinical presentation is typically in childhood, with spasticity, impaired mobility, developmental delay, and intellectual disability[1,3–5]
- Current disease management approaches utilising severe protein restriction have a limited impact on both plasma arginine levels and disease manifestations, with continued disease progression[1,3,5–7]
- Pegzilarginase is a pegylated, cobalt-substituted human arginase 1, currently in development for the treatment of patients with ARG1-D

Figure 1. Urea Cycle



METHODS

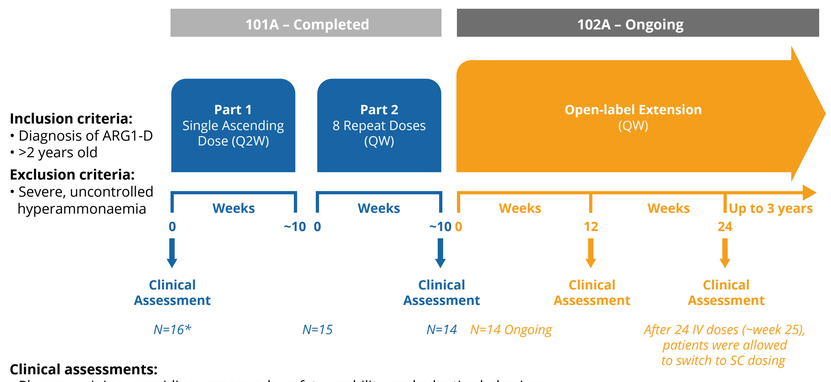
Phase 1/2 Trial Design

- 101A: Part 1, single ascending dose escalation; Part 2, repeat dosing with 8 weekly doses (NCT02488044) (**Figure 2**)
- 102A: Long-term OLE trial for patients who completed Part 2 of 101A (NCT03378531) (**Figure 2**)
  - Treatment with 24 weekly IV doses with the option to switch to subcutaneous dosing for the remainder of the 3-year OLE period

Key Endpoints

- Primary endpoint: Safety and tolerability
- Secondary endpoints: Effect on plasma arginine and plasma GC levels
- Other endpoints: Evaluation of clinical outcome assessments in capturing clinical benefit, including:
  - 6MWT, GMFM Parts D and E, and ABAS

Figure 2. Trial Design



Clinical assessments:
- Plasma arginine, guanidino compounds, safety, mobility, and adaptive behaviour
- Pharmacokinetics analysis occurred at week 8 of the OLE

*2 patients withdrew for personal reasons

DEMOGRAPHICS / BL CHARACTERISTICS

- 16 patients (11 paediatric and 5 adult) were enrolled into 101A Part 1, and 15 patients advanced into 101A Part 2 (**Table 1**)
  - 2 patients withdrew from the trial for personal reasons (1 patient after Part 1 Dose 3 and 1 patient after Part 2 Dose 3)
  - All 14 patients completing 101A Part 2 advanced into the OLE trial
- 7 novel *ARG1* mutations not previously reported in the literature were identified in 4 patients
  - c.371A>G; c.807_811delACTCT; c.611A>G; c.468-1G>C; c.787G>T; c.3G>A; c.92T>G

Table 1. BL Characteristics

Age, years, median (range)	15 (5–31)
Female, n (%)	11 (69)
Arginine, µM, median (range)	389 (238–566)
Ammonia, µM, median (range)	38 (9–77)
ALT (U/L), median (range)	34 (15–171)
ARG1 mutation, n (%) Homozygotes Compound heterozygotes	 11 (68.8) 5 (31.2)

Baseline Deficits

Mobility

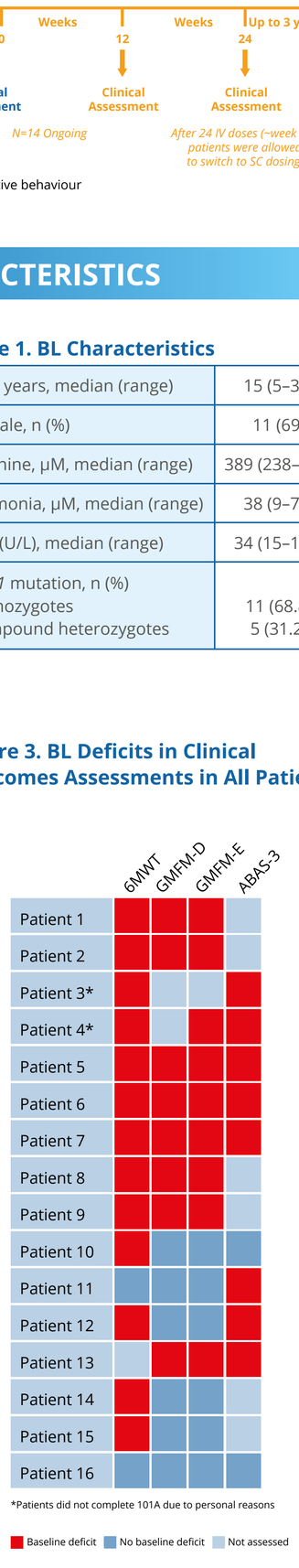
- 15 of 16 patients completed all mobility assessments at BL (patient 13 was confined to a wheelchair) (**Figure 3**)
  - 88% (14 of 16) of patients had at least 1 mobility deficit at BL
  - 88%, 50%, and 56% of the 16 patients were classified as having a BL deficit in the 6MWT, GMFM-D, and GMFM-E, respectively

Adaptive Behaviour

- ABAS-3 assessments were available for 10 patients at BL (**Figure 3**)
  - 6 patients were not tested for technical reasons, including constraints due to language, age, and cognitive impairment
  - 8 of 10 (80%) patients had baseline deficiencies in 1 or more domains assessed by ABAS-3

Deficits defined as:
6MWT: less than the lower fifth percentile; GMFM-D: <35 of 39; GMFM-E: <68 of 72; ABAS-3: ≤85

Figure 3. BL Deficits in Clinical Outcomes Assessments in All Patients



*Patients did not complete 101A due to personal reasons

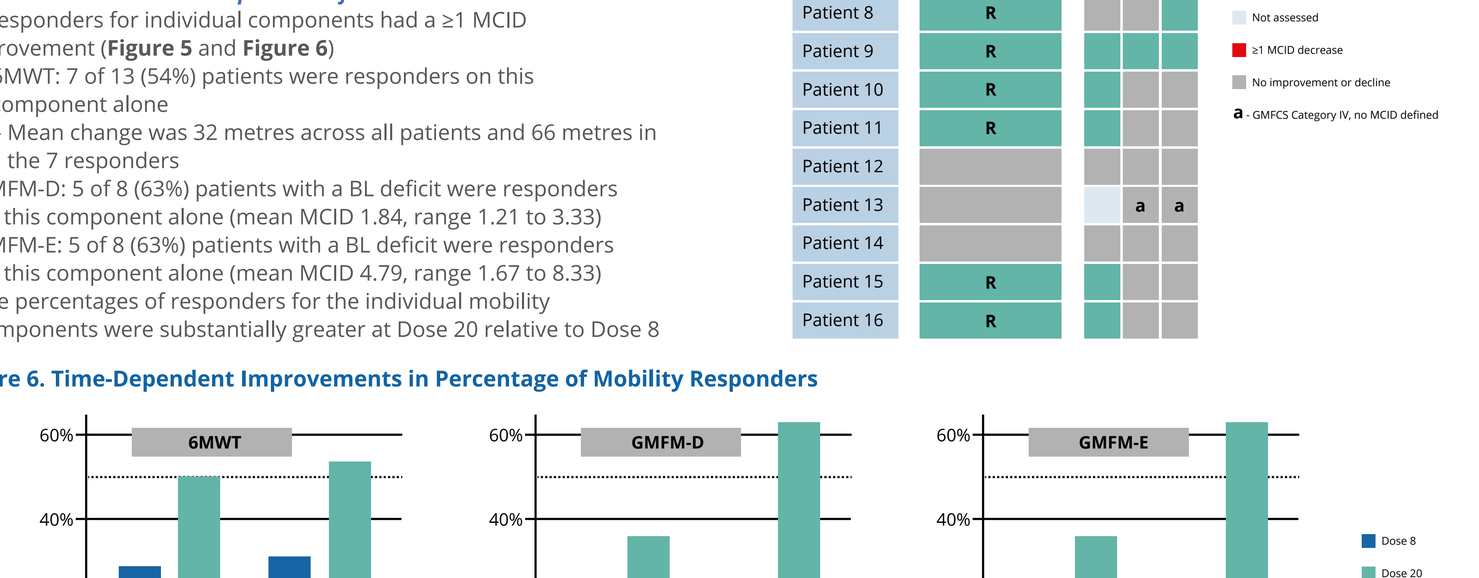
RESULTS

Efficacy

Plasma Arginine and GC Levels

- Marked and sustained reductions in plasma arginine levels (**Figure 4**) were demonstrated with a median reduction of 274 µM from BL after 20 doses of pegzilarginase
- Reductions in plasma arginine from BL to Dose 1, Dose 8, and OLE were statistically significant ($p<0.001$)
- Plasma arginine reductions were accompanied by decreases in plasma GC levels

Figure 4. Plasma Arginine and GC Levels from 101A and OLE



**Current treatment guidance

Clinical Responses in Key Disease Manifestations

Overall Clinical Response

- 11 of 14 patients (79%) were defined as responders at Dose 20 based on a ≥1 MCID improvement in at least one of the 6MWT, GMFM-D, or GMFM-E assessments (**Figure 5**)
  - 20-dose data demonstrated that 6MWT, GMFM-D, and GMFM-E are sufficiently sensitive to change for capturing clinical benefit in ARG1-D patients
- The percentage of overall responders increased substantially from Dose 8 to Dose 20
- All 5 patients (100%) who reached Dose 44 maintained their Dose 20 overall clinical response status as responders

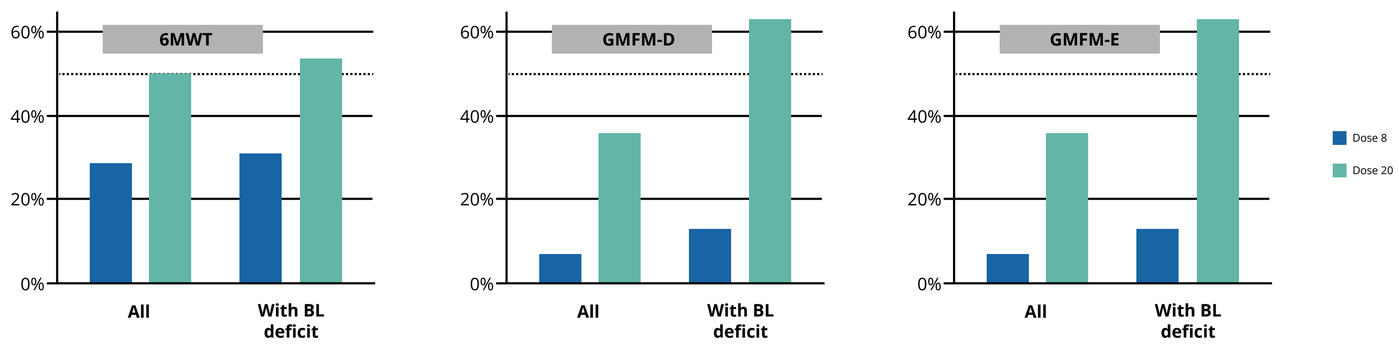
Response in Individual Components After 20 Doses

All responders for individual components had a ≥1 MCID improvement (**Figure 5** and **Figure 6**)

- 6MWT: 7 of 13 (54%) patients were responders on this component alone
  - Mean change was 32 metres across all patients and 66 metres in the 7 responders
- GMFM-D: 5 of 8 (63%) patients with a BL deficit were responders on this component alone (mean MCID 1.84, range 1.21 to 3.33)
- GMFM-E: 5 of 8 (63%) patients with a BL deficit were responders on this component alone (mean MCID 4.79, range 1.67 to 8.33)
- The percentages of responders for the individual mobility components were substantially greater at Dose 20 relative to Dose 8

Figure 5. Heat Map of Overall Clinical Responses and Individual Assessment Responses

Figure 6. Time-Dependent Improvements in Percentage of Mobility Responders



Safety

- Pegzilarginase was well tolerated, and the majority of treatment-related AEs were mild
  - More than 650 doses were administered to 16 patients (mean of 41 doses per patient)
  - More than 200 injections were administered to 10 patients subcutaneously
- The majority of all AEs and all treatment-related SAEs were observed in the first trial (101A)
  - Hypersensitivity and hyperammonaemia were the most common treatment-related SAEs in the Phase 1/2 101A trial, and were expected and manageable
- Reported treatment-related AEs included vomiting (31.3%), hypersensitivity (25.0%), hyperammonaemia (18.8%), pruritus (18.8%) and abdominal pain (18.8%)
- 4 mild treatment-related injection-site reactions were reported in 2 patients who were dosed subcutaneously

SUMMARY

- Data from all patients following 20 doses of pegzilarginase demonstrated marked and sustained reductions in plasma arginine, improvements in important disease manifestations, and a clinical responder rate of 79%
- The Phase 1/2 and OLE trials demonstrate the value of utilising the 6MWT, GMFM-D, or GMFM-E as tools for capturing the clinical benefit of pegzilarginase
- Pegzilarginase was well tolerated and the rates of treatment-related AEs decreased over time
- The improvements in arginine control and evidence of clinical benefit following pegzilarginase treatment provide further validation of the key endpoints and design elements of the pivotal Phase 3 PEACE trial (NCT03921541)

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Abbreviations
6MWT = 6-minute walk test; ABAS = Adaptive Behaviour Assessment Scale; ABAS-3 = Adaptive Behaviour Assesment Scale third edition; AE = adverse event; ALT = alanine amino transferase; ARGA = argininic acid; ARG1-D = arginase-1 deficiency; ASL = argininosuccinate lyase; ASS1 = argininosuccinate synthase 1; BL = baseline; CFB = change from baseline; GAA = guanidinoacetic acid; GC = guanidino compound; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GMFM-D, Gross Motor Function Measure Part D; GMFM-E, Gross Motor Function Measure Part E; GVA = α-keto-δ-guanidinovaleric acid; IV = intravenous; LLN = lower limit of normal; MCID = minimum clinically important difference; NAA = N-α-acetyl-L-arginine; OLE = open-label extension; Q2W = twice weekly; QW = once weekly; SAE = serious adverse event; SC = subcutaneous; ULN = upper limit of normal.

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