Initial Results of a Phase 1 Open Label Study of AEB1102 Enzyme Replacement Therapy in Adult Patients with Arginase I Deficiency

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Introduction

Arginase I deficiency (AID) is a rare urea cycle disorder characterized by deficiency of the arginase I enzyme leading to the accumulation of arginine and its metabolites. Arginase I is the final enzyme of the urea cycle, catalyzing the hydrolysis of arginine to ornithine and urea.

AID typically presents in early childhood and is associated with significant morbidity, including progressive and devastating neurological and neurocognitive decline and mortality in affected patients. Case reports have shown that patients have significant clinical symptoms by the age of 9, though when effective therapy is started early in life, symptoms may be delayed or ameliorated. However, as with other inborn errors of metabolism, a broad spectrum of disease severity may exist.

Objectives

• Evaluate the safety and tolerability of intravenous administration of AEB1102 in patients with AID.
• Assess the pharmacokinetic (PK) and pharmacodynamic effects of single ascending doses of AEB1102, including plasma arginine levels.

Methods

This is a multi-center, single-arm, phase 1 study in adult patients (≥ 18 years old) diagnosed with AID. Key Inclusion Criteria:
• Plasma arginine > 250 µM (screening), and either known ARG1 gene mutation or RBC arginase activity < 5%.
• Current ammonia <100 µM; no hospitalizations for hyperammonemia in the prior month.
• Adequate bone marrow, hepatic and renal function.

Enrolled patients receive up to 4 intravenous doses of AEB1102 starting at 0.015 mg/kg, with dose escalation at 2-week intervals. Subsequent escalating doses are 0.03, 0.06, and 0.1 mg/kg.

Safety is assessed with regular physical exams, laboratory tests, ECGs and at least 24-hour monitoring within the research unit. AEB1102 serum laboratory tests, ECGs and at least 24-hour monitoring within the research unit. AEB1102 serum and plasma arginine levels were measured frequently.

Stopping criteria:
• Hyperammonemia requiring hospitalization;
• Any severe or life-threatening adverse event related to AEB1102;
• Plasma arginine < 40 µM.

Results

Demographics
• Two adult female patients, ages 24 and 25 years old, enrolled and completed dosing. These patients are siblings with non-consanguineous parentage.
• Both patients are on maximal dietary therapy (protein restriction and supplementation) and oral nitrogen scavengers.
• Both have moderate to severe neurocognitive and neurological deficits.
• Both have homozygous ARG1 mutations (c.466-1G>C).
• Screening plasma arginine levels were 408 – 496 µM for subject A, and 300 – 362 µM for subject B.

Plasma Arginine

Subject A

Subject B

Dose Escalation
• Subject A stopped after the third dose (0.06 mg/kg) for plasma arginine < 40 µM.
• Subject B stopped after the second dose (0.03 mg/kg) for plasma arginine < 40 µM.

Safety
• Adverse Events
– There were no serious adverse events.
– There were no related or possibly related adverse events.
• Vital Signs
– No vital signs result was deemed to be clinically significant.
– No clinically notable trend was seen in the vital signs.
• Laboratory Data
– No abnormal results were listed as clinically significant.
– No clinically significant or notable laboratory trends were seen.
• ECG Data
– There were no clinically significant or notable ECG findings after the dosing.

PK/PD
• Plasma arginine levels decreased in a dose-proportional manner after AEB1102 infusions.
• At 168 hours after each dose, plasma arginine levels remained suppressed by 25 to 49% compared to the pre-dose values.
• AEB1102’s PK profile indicated dose linearity.

Oncology Results
Dose escalation is ongoing at 0.40 mg/kg and 0.48 mg/kg in two studies in patients with advanced solid tumors or AML/MDS, respectively. One SAE (nausea/vomiting) was related to AEB1102. No other SAE has been related to AEB1102.

Conclusions
• Single, intermittent doses of AEB1102 can be administered safely and tolerably to patients with AID to lower plasma arginine levels.
• Further study is needed to evaluate repeated dosing of AEB1102 and its effects on biochemical and functional measures of adult and pediatric patients with AID.

Discussion

AID is an ultra-rare urea cycle disorder. The natural history remains incompletely understood, though it is clear that the current standard of care rarely prevents the clinical sequelae. The development and progression of AID symptoms are attributed to subtle interindividual variations, including host factors and environmental factors that interact to produce the disease phenotype and determine disease progression. Additional studies are required to gain a better understanding of the disease natural history, as well as discovering the clinical consequences of sustained control of plasma arginine levels.

References

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