A Phase 1 Trial of Recombinant Human Acid Sphingomyelinase (rhASM) Enzyme Replacement Therapy in Adults with ASM Deficiency (ASMD)

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Introduction

Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive, lysosomal storage disorder that results when sphingomyelin is not normally hydrolyzed to ceramide and phosphorylcholine. Consequences of sphingomyelin accumulation occur within cells of the reticuloendothelial system, resulting in hepatosplenoencephalomegaly, anemia, thrombocytopenia, and nephrotic syndrome. RhASM activity is reduced in the majority of patients, and their clinical course is often characterized by neurocognitive decline, sphincteric incontinence, and cardiac, hepatic, and renal disease.

Methods and Study Design

Design

This was a single-center, single-dose, dose-escalation Phase 1 trial conducted at Mount Sinai Medical Center in New York City, NY from December 2006 to April 2009. The primary trial objectives were to evaluate the safety and pharmacodynamics of single doses of rhASM in adults with non-neuropathic ASMD (Niemann-Pick B). Single doses of 0.3, 0.6, 1.0, 1.5, and 2.0 mg/kg of rhASM were infused sequentially by dose cohort. The original trial design called for a minimum of 15 patients (5 cohorts of 3 patients each) per dose. Due to difficulties with patient enrollment, the protocol was amended such that the first 2 cohorts enrolled 3 patients each and the last 3 cohorts were enrolled 2 patients each. An independent data monitoring committee oversaw the conduct of the trial and all study procedures were approved by the IRB.

Patients

To be eligible for the study patients had to be 18-65 years of age and have deficient ASM enzyme activity (a spleen volume >2x normal; ALT 250-500 U/L; bilirubin >3.0 mg/dL; INR >1.5; Gln >300 predicted and platelets >200,000/µL). Patients were excluded if they had cirrhosis (by liver biopsy), significant cardiac disease, total splenectomy, or were taking medications or herbal supplements that were potentially hepatotoxic, promoted bleeding, or inhibited rhASM.

Visits

Once screening was completed and eligibility was confirmed, patients were admitted to the cardiac care unit (CCU) overnight for baseline telemetry and infused the following morning with rhASM. Patients were monitored for 72 hrs post-dose while on telemetry (4 hrs in the CCU and 48 hrs in the General Clinical Research Center). Patients returned for an overnight visit on Day 14 and an outpatient visit on Day 28.

Screening/Baseline

Final assessments

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Substrate and Product

Plasma ceramide levels showed a dose-dependent rise by 4 hrs and peaked at 10-15 hrs.

Assessments

• Physical exam – Days 0, 1, 2, 14, and 28
• Chemistry, hematology, and urinalysis – predose, then 24, 48, 72 hrs: Days 14, 28
• Liver function tests – predose, then at 2 hrs through 72 hrs; Days 14, 28
• Adrenalite, cortisol, aldosterone-androstenedione – predose, then every 2 hrs through 72 hrs
• ACTH stimulation test – Screening, Day 14
• Telemetry – continuous through 72 hrs
• ECG, echocardiogram, and abdominal ultrasound – Day 14
• CRP (mg/dL) – Screen, Days 14, 28
• Ferritin (ng/mL) – Screen, Days 14, 28
• C-reactive protein (CRP) – Predose, Days 14, 28
• CRP (mg/dL) – Post-infusion, Days 14, 28
• Ferritin (ng/mL) – Post-infusion, Days 14, 28
• CRP (mg/dL) – Day 28

ACPHase Response (Infarct)

CPR showed a transient dose-related rise by 24 hrs, peaked at 48-72 hrs, and returned to normality Day 14. Other acute phase reactants also showed increases (% neutrophils, % monocytes, fibrinogen, ferritin, and NT-proBNP).

Preliminary Safety Observations

• Dose-related clinical and lab adverse events began of 0.3 mg/kg

1. Hypersensitivity

• No dose-related clinical or lab detectable
• No consistent markers of liver damage (ALT, AST, AP) in patients who received the highest dose (1mg/kg), although increased CRP (1.0 mg/kg, #12013) was noted (0.03 mg/kg, #11509) doses. There was no indication of hemolysis as hemoglobin and hematocrit were stable.

2. Acute phase response (Infarct)

• Plasma ceramide levels showed a dose-dependent rise by 4 hrs and peaked at 10-15 hrs.

• No evidence of cytokine release syndrome, cardiovascular changes, or hormonal abnormalities

Conclusions

• This trial describes the first experience with enzyme replacement therapy in adult patients with ASMD. At biweekly doses in humans, rhASM did not cause significant cytokine elevations or cardiovascular changes.

• The maximum tolerated dose of rhASM was 0.6 mg/kg.

• Based on the hypersensitivity findings, the maximum tolerated starting dose of rhASM may be 0.3 mg/kg. Further dose escalation may be an option for higher repeat doses of rhASM.