

WORLD Symposium Presentation

An open-label, multicenter, ascending-repeat-dose study of the tolerability and safety of recombinant human acid sphingomyelinase (rhASM) in patients with ASM deficiency (ASMD)

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Abstract: Enzyme replacement therapy (ERT) with recombinant human acid sphingomyelinase (rhASM) is in clinical development for the treatment of the non-neurological manifestations of acid sphingomyelinase deficiency (ASMD). In a Phase 1a single-ascending-dose study in adult patients, the maximum tolerated starting dose of rhASM was 0.6 mg/kg.

The primary objective of this Phase 1b study (NCT01722526) was to determine the safety and tolerability of within-patient dose escalation of rhASM in five adult patients with non-neurological ASMD (Niemann–Pick disease type B). Each patient received a starting dose of intravenous rhASM at 0.1 mg/kg and advance dosing every two weeks according to a predetermined schedule to 3 mg/kg, or their maximum tolerated dose. The secondary objective was to study the pharmacokinetics, pharmacodynamics, and exploratory efficacy of rhASM administered intravenously every two weeks for 26 weeks. Study assessments included continuous adverse event (AE) reporting and periodic evaluations of safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy. Safety biomarkers included high-sensitivity C-reactive protein [hsCRP], bilirubin, IL-6, and IL-8. Plasma ceramide was used as a biomarker for the breakdown of sphingomyelin. Sphingomyelin content in liver was used as a pharmacodynamic endpoint. Exploratory efficacy evaluations included spleen and liver volumes, pulmonary assessments, hematology and lipid profiles, and health/disease-related questionnaires. The dose escalation regimen was well tolerated, with all patients reaching the maximum dose of 3 mg/kg. No serious or severe adverse events or deaths were reported. Related AE consisted predominantly of infusion associated reactions, the majority of which were mild, occurred between 3 and 72 h post-infusion, and resolved without sequelae. Two patients experienced acute phase responses at the 1 or 2 mg/kg doses that were associated with constitutional symptoms and increases in inflammatory biomarkers. None of the five patients developed IgG antibodies to rhASM. Plasma ceramide levels transiently increased following each infusion, but trended downward over time.

Mean liver sphingomyelin content by metamorph analysis decreased by 87% (from 33.3% to 4.3% of the microscopic field). Mean spleen and liver volumes decreased by 25.3% and 17.1%, respectively, and liver function tests normalized. Radiographic improvement of interstitial lung disease occurred in all patients, and mean % predicted DLCO increased by 6 percentage points (13% relative to baseline). Treatment with rhASM resulted in a shift to a less pro-atherogenic profile in the majority of lipid parameters analyzed (total cholesterol, HDL, LDL, VLDL, total triglycerides, and apolipoprotein B-100), and there were also trends for improvement in quality of life assessments. Within-patient dose escalation of rhASM was well tolerated. Repeat-dose safety, pharmacodynamics, and exploratory efficacy of rhASM support its continued development for the treatment of the non-neurological manifestations of ASMD. This study was funded by Genzyme Corporation.
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