Session Information

Session Title: Therapy for Genetic Disorders **Session Type:** Poster

Session Location: Exhibit Hall, Ground Level, Convention Center **Session Time:** Sun 11:00AM-7:00PM

Abstract Information

Program Number: 2187S **Presentation Time:** Sun, Oct 19, 2014, 4:00PM-5:00PM

Keywords: Therapy for Genetic Disorders, KW051 - enzyme replacement therapy, KW099 - lysosomal diseases, KW108 - metabolic disorder

Abstract Content

An open-label, multicenter, ascending dose study of the tolerability and safety of recombinant human acid sphingomyelinase (rhASM) in patients with ASM deficiency (ASMD). *M. P. Wasserstein[1], S. A. Jones[2], H. Soran[2], G. Diaz[1], B. Thurberg[3], K. Culm-Merdek[3], A. Cunningham[3], T. Singh[3], A. C. Puga[3]* 1) Icahn School of Medicine at Mount Sinai, New York, NY, USA; 2) Manchester Centre for Genomic Medicine, St. Marys Hospital, CMFT, University of Manchester, Manchester, UK; 3) Genzyme, a Sanofi company, Cambridge, MA, USA.

Background: 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 determined to be 0.6 mg/kg. Objectives: The primary objective of this phase 1b study was to determine the safety and tolerability of within-patient dose escalation of rhASM in five adult patients with Niemann-Pick Disease type B (NPD B), the non-neuronopathic form of ASMD. Each patient was to receive a starting dose of intravenous rhASM at 0.1 mg/kg and advance every two weeks according to a predetermined schedule to 3.0 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. Methods: Study assessments included continuous adverse event (AE) reporting and periodic evaluations of safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy. Safety biomarkers (e.g., C-reactive protein, bilirubin, IL-6, IL-8) were evaluated; plasma ceramide was used as a biomarker for the breakdown of sphingomyelin. Sphingomyelin content in liver was used as a pharmacodynamic endpoint. Results: The dose escalation regimen was well tolerated, with all patients reaching the maximum dose of 3.0 mg/kg. No serious or severe adverse events or deaths were reported. Related AEs consisted predominantly of infusion-associated reactions, the majority of which were mild and resolved without sequalae. A positive response to treatment with rhASM was observed in liver sphingomyelin content and several exploratory efficacy parameters, including spleen and liver volumes, pulmonary function testing, lung imaging, lipid profile, and quality of life assessments. Results will be presented. Conclusions: Within-patient dose escalation of rhASM was well tolerated. Repeat-dose safety 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, a Sanofi company.

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