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Hepatic pathology of acid sphingomyelinase deficiency: Clearance of sphingomyelin with recombinant human acid sphingomyelinase administration is associated with improvement in pro-atherogenic lipid profiles

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Abstract: Acid sphingomyelinase deficiency (ASMD) is a lysosomal disorder characterized by abnormal sphingomyelin accumulation in multiple cell types, primarily within the liver, spleen, and lungs, leading to significant clinical disease. The clinical spectrum ranges from an infantile-onset visceral and neurodegenerative disease with death in early childhood (Niemann–Pick disease type A; NPD A) to a variableonset visceral disease with no neurodegeneration and prolonged survival (Niemann–Pick disease type B; NPD B). Liver manifestations of ASMD include hepatomegaly, fibrosis/cirrhosis, elevated liver function tests (LFTs) and a pro-atherogenic lipid profile. Recombinant human acid sphingomyelinase (rhASM) is in clinical development an enzyme replacement therapy for the non-neurological manifestations of ASMD. A Phase 1b study (NCT01722526) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of within-patient dose-escalation and repeat dosing of rhASM in adult patients. As plasma sphingomyelin levels in patients are normal, the measurement of sphingomyelin levels in liver biopsies was used as a pharmacodynamic biomarker. The association of reductions in biopsy sphingomyelin content with changes in liver volume, LFTs, and other lipid profiles after treatment with rhASM was examined. Five adult patients with nonneuropathic ASMD underwent within-patient dose escalation of intravenous rhASM every 2 weeks starting at 0.1 mg/kg and reaching the maximum targeted dose of 3 mg/kg. Liver biopsies obtained at baseline and 6 months post-treatment were evaluated for sphingomyelin content by morphometric analysis at the light microscopic level, and further examined by electron microscopy.

Patients also were assessed for changes in liver volume, LFTs, and lipid profiles. At baseline, sphingomyelin storage was present in both Kupffer cells and hepatocytes, and ranged from 9.8% to 53.8% of the microscopic field. Both light and electron microscopy demonstrated that sphingomyelin accumulation was predominant in the Kupffer cells of patients with low baseline levels of sphingomyelin, but equally distributed within Kupffer cells and hepatocytes in those with high levels. After 6 months of treatment, all 4 patients with evaluable liver biopsies (one of five post-treatment biopsies was insufficient for sphingomyelin evaluation) showed statistically significant reductions in sphingomyelin (p b 0.0001). Sphingomyelin storage in post-treatment biopsies ranged from 1.2% to 9.5% of the microscopic field, which corresponded to an 84% to 92% reduction from baseline. Residual substrate was present largely within hepatocytes, whereas Kupffer cells appeared completely clear. Improvements in liver volume, LFTs (ALT, AST), and pro-atherogenic lipid profiles (total cholesterol, LDL and VLDL subfractions, and triglycerides) were observed. There were also modest increases in anti-atherogenic markers, HDL and apolipoprotein A-I. These data demonstrate the histopathological clearance of hepatic sphingomyelin with rhASM enzyme replacement therapy and its association with improvements in pro-atherogenic markers. The study illustrates the utility of sphingomyelin content by liver biopsy as a pharmacodynamics biomarker. This study was sponsored by Genzyme Corporation.