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Poster Abstract: Therapeutic

A Phase 4 Prospective Study in Patients with Adult Pompe Disease Treated with Alglucosidase Alfa

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Pompe disease is a rare, autosomal recessive disease caused by the deficiency of lysosomal acid α-glucosidase (GAA), an enzyme that degrades glycogen. The accumulated glycogen in tissues, especially cardiac, respiratory-specific, and major skeletal muscle groups, disrupts the cellular architecture and function leading to multisystem pathology and early mortality. The Exploratory Muscle Biopsy Assessment Study (EMBASSY; NCT01288027), sponsored by Genzyme, a sanofi company, was conducted to evaluate glycogen clearance in muscle tissue samples collected pre- and post-alglucosidase alfa treatment in patients with adult Pompe disease. Sixteen patients (44% male) were enrolled in this open-label, single arm, global, multicenter, Phase 4 study. Patients received IV alglucosidase alfa 20 mg/kg every other week for 26 weeks. The primary endpoint was percent reduction of tissue glycogen content from baseline in muscle biopsy samples at Week 24. Secondary endpoints included histology, MRI, and functional assessments. T1-weighted MRI was performed to assess muscle involvement in upper and lower leg using Mercuri classification. The mean age at baseline was 51.6 years (range: 24.5–70.7 years). Mean age at symptom onset was 40.0 years (range: 14.9–59.4 years). Mean baseline 6MWT was 449.9 meters (range: 173.0–997.0 meters). Mean baseline FVC was 76.4% predicted (range: 50.4–115.1% predicted). Mean baseline glycogen to muscle tissue ratio in quadriceps and deltoid muscles was 5.3% ($n=13$; range: 1.0–14.2%) and 2.4% ($n=10$; range: 1.2–5.9%), respectively. In 10/13 post-treatment quadriceps biopsies, glycogen was reduced or remained

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stable (mean: 3.1%; $p=0.19$). In 9/10 deltoid biopsies, glycogen was reduced or remained stable (mean: 1.4%; $p=0.01$). At baseline, glycogen was present within lysosomes and as free cytoplasmic glycogen outside lysosomes. Histopathology demonstrated post-treatment glycogen was predominantly in cytoplasm. Secondary changes were limited to occasional foci of autophagic debris. No fibrosis, inflammation, or fatty replacement was observed. Biopsies were MRI guided to enhance sampling from normal appearing muscle. The overall Mercuri score indicated mild muscle involvement, ranging from normal to moderate for individual patients. The upper leg (mean: 1.9; range: 1–3.5) was generally more affected than the lower leg (mean: 1.0; range: 1–1.2). Muscular fatty infiltration was quantified from a 3-point 3D Dixon acquisition ($n=5$). Percent fatty infiltration was normal or elevated (>10%) and in accordance with the Mercuri scoring degree. Muscle water T2, a marker of disease activity, was abnormally elevated (>39 ms) in approximately 1/3 of all muscles. No changes were observed from baseline on MRI parameters. Mean increase from baseline in the 6MWT was 37.3 meters ($p=0.02$). Eleven patients improved; 4 patients worsened. Mean improvement from baseline in percent predicted FVC was 1.8% ($p=0.67$). Seven patients improved; 8 patients worsened. No deaths or discontinuations due to AEs occurred. Fifteen patients (93.8%) reported at least one AE for a total of 90 events. The majority were infusion-associated reactions. Overall, this was consistent with the known safety profile for alglucosidase alfa. This study provides the first histopathological support for the expected biological activity of alglucosidase alfa in adult Pompe disease. Alglucosidase alfa reduced lysosomal glycogen, with cytoplasmic glycogen remaining. This treatment effect was associated with overall stabilization/improvement on functional assessments.

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