Long-term Safety and Efficacy of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease

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Study Question
Is avalglucosidase alfa safe and effective during long-term treatment in adults with late-onset Pompe disease (LOPD)?

What Is Known and What This Paper Adds
Pompe disease is a rare, progressive neuromuscular disorder caused by lysosomal acid α-glucosidase (GAA) deficiency and resultant glycogen accumulation. Alglucosidase alfa has improved survival and quality of life in LOPD; however, unmet needs in respiratory and motor function remain, and disease progression is partly attributed to suboptimal enzyme replacement therapy uptake. Avalglucosidase alfa is designed with increased mannose-6-phosphate (M6P) content compared with alglucosidase alfa, to improve cation-independent M6P receptor-mediated uptake, glycogen clearance, and thus clinical efficacy. This study provides Class IV evidence of long-term tolerability and sustained efficacy of avalglucosidase alfa in patients with LOPD after ≤6.5 years.

Methods
NEO-EXT is an open-label, multicenter, multinational, long-term extension study of NEO1, a 24-week safety and pharmacokinetic study of avalglucosidase alfa in adults with LOPD, either treatment-naive or previously treated with alglucosidase alfa for ≥9 months. Of the 21 participants who completed NEO1, 19 entered NEO-EXT and continued on their same NEO1 dose (5, 10, or 20 mg/kg every other week) until, between weeks 105 and 156, those on 5 or 10 mg/kg switched to 20 mg/kg. Safety and exploratory efficacy were assessed over ≤6.5 years of avalglucosidase alfa treatment. The primary objective was to assess long-term tolerability of avalglucosidase alfa in adults with LOPD.

Results and Study Limitations
Avalglucosidase alfa’s safety profile during NEO-EXT was consistent with that in NEO1. No deaths/treatment-related life-threatening serious adverse events occurred. Antidrug antibodies developed in 18 participants without apparent impact on clinical outcomes. The data provide evidence of long-term and overall maintained avalglucosidase alfa effect on respiratory and motor function in LOPD. Upright forced vital capacity (FVC) % predicted and 6MWT % predicted remained stable in most participants during the follow-up (repeated-measure mixed model slopes of change [95% CIs] in naive and switch groups, respectively: FVC: −0.473/y [−1.188, 0.242] and −0.648/y [−1.061, −0.236]; 6MWT: −0.701/y [−1.571, 0.169] and −0.846/y [−1.567, −0.125]). Study limitations include relatively small population, lack of a comparator group, potential influence of lower doses (5 and 10 mg/kg) on outcomes, and baseline age variation. In addition, the baseline FVC (51%–116% predicted) indicated participants’ respiratory impairment was not severe, which could limit room for short-term improvement.

Registration, Study Funding, and Competing Interests
This study was registered at ClinicalTrials.gov: NCT01898364 (NEO1) and NCT02032524 (NEO-EXT) and was funded by Sanofi. The authors report additional competing interests. Go to Neurology.org/N for full disclosures.
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