Title: Safety and efficacy of pegunigalsidase alfa vs agalsidase beta on renal function in Fabry disease: 24-month results from the phase III randomized, double-blind, BALANCE study

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Background: Pegunigalsidase alfa (PA) is a novel PEGylated α-Gal A enzyme replacement therapy in development to treat Fabry disease (FD)—designed to offer enhanced bioavailability, prolonged half-life, lower immunogenicity, and potential tolerability benefits over current treatments. The objective of this Phase III study was to evaluate the safety and efficacy of PA compared to agalsidase beta (AB) in patients with FD and deteriorating renal function.

Methods: BALANCE (NCT02795676) is a 24-month, randomized, double-blind, active-controlled study of PA in adults with FD. Enrolled patients were previously treated with AB for ≥1 year with an estimated glomerular filtration rate (eGFR) slope at screening of -2.0 mL/min/1.73 m^2/y or lower. Patients were randomized 2:1 to receive 1.0 mg/kg PA or 1.0 mg/kg AB, administered every two weeks. The primary efficacy analysis was noninferiority based on the median annualized eGFR slope difference between groups, meeting the prespecified noninferiority margin. Treatment-emergent adverse events (TEAEs) and anti-drug antibodies (ADAs) were endpoints for safety, tolerability, and immunogenicity profile.

Results: 77 patients with FD were treated with PA (n=52) or AB (n=25); at baseline, mean (range) age was 44.3 (18-60) y; 47 (61%) were men. Discontinuations: 5 (9.4%) patients receiving PA (1 drug-related, 4 drug unrelated) and 1 (4%) patient receiving AB (drug unrelated). At baseline, mean ± SD eGFR was 73.3 ± 19.8 mL/min/1.73 m^2 with a mean± SD eGFR slope of -8.2 ± 5.9 mL/min/1.73 m^2/y. At 24 months, eGFR slope CI overlapped: median (95% CI) of -2.5 mL/min/1.73 m^2/y (-3.8, -1.2) for PA and -2.2 mL/min/1.73 m^2/y (-3.8, -0.51) for AB; median difference between the two groups was -0.36 with a lower 95% CI of -2.4, meeting the prespecified noninferiority margin. Infusion-related reactions (IRRs): 11 (21%) patients on PA had 13 IRRs (0.5 events/100 infusions) vs 6 (24%) patients on AB had 51 IRRs (3.9 events/100 infusions). TEAEs occurred in 21 (40%) patients on PA (43 events/100 patient-years) vs 11 (44%) patients on AB (153 events/100 patient-years). Treatment-emergent ADAs: 6 (11.5%) patients on PA (3 titer booster; 3 induced) vs 4 (16.0%) patients on agalsidase beta (1 titer boosted; 3 induced). The % ADA+ patients with neutralizing antibodies declined in the PA arm from 94% at baseline to 64% at 24 months vs an increase from 88% to 100% in the AB arm. There were no deaths.

Conclusions: Pegunigalsidase alfa (PA) showed noninferiority to AB based on the rate of eGFR decline, a key measure of Fabry disease (FD) progression. No new additional safety concerns were identified. Overall, the tolerability and immunogenicity profiles were favorable for PA, with a lower rate of TEAEs and treatment-emergent ADAs than those receiving agalsidase beta (AB).

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