Title: Tolerability and Infusion Duration of Pegunigalsidase Alfa in Patients With Fabry Disease: Data From 5 Completed Clinical Trials

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Background: Pegunigalsidase alfa (PA) is a novel PEGylated α-Gal A enzyme replacement therapy (ERT) in development for Fabry disease (FD) that was designed to offer enhanced bioavailability, prolonged half-life, and lower immunogenicity with potential tolerability benefits. We characterize PA tolerability in clinical trials completed by 2021, with a focus on the incidence of infusion-related reactions (IRRs) and change in infusion duration over time.

Methods: Patients were included from 5 PA clinical trials: 2 Phase 1/2 studies (F01; NCT01678898, F02; NCT01769001), their extension (F03; NCT01981720), and 2 Phase 3 studies (BRIDGE [NCT03018730] and BRIGHT [NCT03180840]). The following outcomes are described: incidence of IRRs, mean duration of infusion at beginning and end of study, number of pts achieving the minimum duration of infusion allowed per protocol, and time to achieve the minimum per protocol infusion duration.

Results: In the Phase 1/2 studies, 18 treatment-naïve pts received PA once every 14 days. 5 (28%, n=3 female) pts experienced 24 IRRs (1 hypersensitivity reaction [bronchospasm] during the first infusion). The extension study (F03, completed n=15) had initial infusion of PA 0.2 mg/kg, 1 mg/kg, and 2 mg/kg with mean infusion durations of 4.0h (n=6, SD 0.13), 5.2h (n=5, SD 1.7), and 6.4h (n=4, SD 0.34), respectively, and were reduced at 12 months to mean durations of 1.5h (n=6, SD 0.03), 3.6h (n=5, SD 1.4), and 3.1h (n=4, SD 0.09), respectively ($p<0.001$). In BRIDGE, PA 1 mg/kg was given once every 14 days with initial mean infusion of 2.9h (n=22, SD 0.9). 5 male pts (22.7%) experienced 9 IRRs (7 mild; 2 severe). 2 pts discontinued due to type 1 hypersensitivity reactions; 1 positive for IgE antidrug antibodies at baseline. All other pts reached minimum protocol-allowed infusion of 1.5h (± 10 min, n=20, SD 0.05) by 12 months ($p<0.001$ vs baseline). In BRIGHT, 30 pts initially received PA 2 mg/kg once a month; 5 (17%, all male) pts experienced 27 IRRs (17 mild; 10 moderate) who all completed the study. Mean infusion duration decreased from 4.8h (n=30, SD 0.59) at baseline to 2.3h (n=29, SD 0.7, $p<0.001$) by month 12. At BRIGHT completion, most pts reached targeted infusion duration of 3h (mean 2.97h, SD 0.24) for pts >100kg (n=5, 100% reached target) and 2h (mean 2.1h, SD 0.13) for pts ≤100kg (n=24, 96% reached target); 1 pt discontinued due to motor vehicle accident and 1 patient did not reach target.

Conclusion: This analysis of trials completed by 2021 supports good tolerability of PA. Mean infusion duration at study end and IRR incidence (17% to 28%) compares favorably to other ERTs (14% to 55%). Additional data from the PA clinical program may further characterize its potential to offer both tolerability and quality-of-life benefits for patients with FD.

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