CRA 80

Four-year safety and efficacy of N8-GP (ESPEROCT®) in previously treated adolescents/adults with hemophilia A in the completed pathfinder 2 trial

Escobar, Miguel; Wheeler, Allison P; Geybels, Milan S; Cooper, David L; Lentz, Steven

Submission Group

Clinical Research/Clinical Trials

Abstract

Objective: The adolescent/adult pivotal phase 3 pathfinder 2 trial assessed N8-GP (turoctocog alfa pegol, ESPEROCT®) use for routine prophylaxis and treatment of bleeds in previously treated patients (PTPs). Methods: pathfinder 2 was a multi-center, multi-national, single-arm study evaluating safety, efficacy and pharmacokinetics. Adolescents/adults (aged ≥12 y) with severe hemophilia A were administered prophylaxis (50 IU/kg Q4D) in the main phase with option for eligible patients (0-2 bleeds in prior 6 months) to randomize (2:1) to 75 IU/kg Q7D or 50 IU/kg Q4D during extension 1 (24 weeks) and continue treatment into extension 2. An on-demand group was included throughout. Current analysis covers January 2012 through December 2018. Summary: Of the 186 PTPs (including 46 [25%] from the US) enrolled in the main phase, 150 (81%) started extension 1, 139 (75%) completed extension 1, and 128 (69%) completed the study. Mean age was 31.1 years, weight 75 kg and BMI 24.3. The complete trial covers 785 patient-years of treatment (66,577 exposure days [ED]) during which there were 2,758 bleeds, including 1,807 (66%) spontaneous bleeds and 1,735 (63%) joint bleeds. Twelve patients treated on-demand for a mean 3.1 years reported nearly half of all bleeds (1,270, 46%), including 971 (54%) spontaneous bleeds and 627 (36%) joint bleeds. Hemostatic efficacy was rated excellent/good in 2,470 (90%) episodes; 2,614 bleeds (95%) were treated with 1-2 injections. Of 175 patients on prophylaxis, 55 of 110 eligible were randomized in extension 1. For 177 patients treated with 50 IU/kg Q4D prophylaxis for 613 years (57,723 ED), 126 (71%) experienced 1,312 bleeds. For 61 low-bleed patients with 134 years (7,255 ED) on 75 IU/kg Q7D prophylaxis, 53 (87%) experienced 176 bleeds. Median ABRs are shown in the TABLE . 50 IU/kg Q4D 75 IU/kg Q7D n 177 61 Mean treatment 3.5 years 2.2 years Median ABR 0.8 1.7 N8-GP mean trough levels were 3.1 IU/dL on 50 IU/kg Q4D and 1.0 IU/dL on 75 IU/kg Q7D. A total of 1,827 adverse events were reported over 785 exposure years, including 63 serious adverse events. One patient with an intron 22 inversion developed a low-titer inhibitor at 93 ED and was withdrawn when it progressed to >5 BU. Non-neutralizing anti-PEG antibodies were seen at baseline in 12 patients (6.5%) prior to first N8-GP exposure and 11 (5.9%), who had negative anti-PEG at baseline, had positive antibodies after exposure. Conclusion: These data support the safety and efficacy of N8-GP in a controlled phase 3 trial setting in adolescents/adults. Prophylaxis with N8-GP with a consistent dose/interval (50 IU/kg Q4D) was effective in preventing bleeds; extended dosing was evaluated as successful for a subgroup of low-bleed patients. No significant safety issues were identified.