Documents

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Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A

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Abstract
Background: Valoctocogene roxaparvovec delivers a B-domain-deleted factor VIII coding sequence with an adeno-associated virus vector to prevent bleeding in persons with severe hemophilia A. The findings of a phase 3 study of the efficacy and safety of valoctocogene roxaparvovec therapy evaluated after 52 weeks in men with severe hemophilia A have been published previously. Methods: We conducted an open-label, single-group, multicenter, phase 3 trial in which 134 men with severe hemophilia A who were receiving factor VIII prophylaxis received a single infusion of 6×1013 vector genomes of valoctocogene roxaparvovec per kilogram of body weight. The primary end point was the change from baseline in the annualized rate of treated bleeding events at week 104 after receipt of the infusion. The pharmacokinetics of valoctocogene roxaparvovec were modeled to estimate the bleeding risk relative to the activity of transgene-derived factor VIII. Results: At week 104, a total of 132 participants, including 112 with data that were prospectively collected at baseline, remained in the study. The mean annualized treated bleeding rate

decreased by 84.5% from baseline (P<0.001) among the participants. From week 76 onward, the trajectory of the transgene-derived factor VIII activity showed first-order elimination kinetics; the model-estimated typical half-life of the transgene-derived factor VIII production system was 123 weeks (95% confidence interval, 84 to 232). The risk of joint bleeding was estimated among the trial participants; at a transgene-derived factor VIII level of 5 IU per deciliter measured with chromogenic assay, we expected that participants would have 1.0 episode of joint bleeding per year. At 2 years postinfusion, no new safety signals had emerged and no new serious adverse events related to treatment had occurred. Conclusions: The study data show the durability of factor VIII activity and bleeding reduction and the safety profile of valoctocogene roxaparvovec at least 2 years after the gene transfer. Models of the risk of joint bleeding suggest that the relationship between transgene-derived factor VIII activity and bleeding episodes is similar to that reported with the use of epidemiologic data for persons with mild-to-moderate hemophilia A. © 2023 Massachusetts Medical Society.

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