CRA 59

Three-year efficacy and safety results from a phase 1/2 clinical study of AAV5-hFVIII-SQ gene therapy (valoctocogene roxaparvovec) for severe hemophilia A (BMN 270-201 study)

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Abstract

Objective: Hemophilia A (HA) is an X-linked disorder caused by mutations in the gene encoding Factor VIII protein (FVIII). Gene therapy is increasingly being viewed as a viable treatment option for hemophilia. Herein, long-term clinical safety and efficacy are presented from a Phase 1/2 study of an AAV-mediated gene therapy for severe HA. Methods: Valoctocogene roxaparvovec is an adeno-associated virus-mediated gene therapy that delivers a functional, codon-optimized, B domain-deleted, human FVIII gene under the control of a liver-specific promoter (AAV5-hFVIII-SQ). An ongoing Phase 1/2 study continues to evaluate the safety and efficacy of valoctocogene roxaparvovec in thirteen males with severe HA. Study participants received a single intravenous injection of valoctocogene roxaparvovec at one of two dose levels (6×1013vg/kg, n=7; 4×1013vg/kg, n=6). Summary: Participants who received 6×1013vg/kg valoctocogene roxaparvovec showed a reduction in annualized bleeding rate (ABR) of 96%, from a pre-treatment median(mean) of 16.5(16.3) to 0.0(0.7) at year three. Participants demonstrated an absence of target joints and target joint bleeds, with 86% experiencing zero bleeds requiring FVIII treatment. ABR diminished by 92% in 4×1013vg/kg participants, from a pre-treatment median(mean) of 8(12.2) to 0(1.2) at year two. Sixty-seven percent of 4×1013vg/kg participants experienced zero bleeds requiring FVIII treatment. FVIII usage demonstrated a reduction from pre-treatment median(mean) of 139(137) infusions to 0(5.5) at year three in 6×1013vg/kg participants, and from 156(147) to 0.5(6.8) at year two in 4×1013vg/kg participants. In 6×1013vg/kg participants, FVIII levels reported by chromogenic assay reached a median(mean) of 60.3(64.3), 26.2(36.4), and 19.9(32.7) IU/dL at the end of one, two, and three years post-infusion, respectively. In 4×1013vg/kg participants, FVIII levels reported by chromogenic assay reached a median(mean) of 22.9(21.0) IU/dL and 13.1(14.7) IU/dL at the end of one and two years post-infusion, respectively. Although FVIII levels were measured and will be presented using both the chromogenic substrate assay and the one-stage assay, chromogenic assay results appear to more accurately represent the true level of circulating FVIII. The safety profile of valoctocogene roxaparvovec remains favorable and unchanged, with transient, asymptomatic ALT elevations and no FVIII inhibitor development reported to-date. Conclusions: Following a single administration of valoctocogene roxaparvovec, participants showed sustained, clinically relevant FVIII activity that reduced self-reported bleeding and exogenous FVIII replacement use at 156 weeks and 104 weeks post-administration in 6×1013vg/kg and 4×1013vg/kg dose cohorts, respectively.