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Clinical experience with BIVV001, the first investigational factor VIII (FVIII) therapy to break through the von Willebrand factor (VWF) ceiling in hemophilia A

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Abstract

Objective: Factor replacement therapy remains the only option for comprehensive care in hemophilia. While extended half-life recombinant FVIII (rFVIII) therapies have reduced the frequency of prophylactic dosing, weekly or greater dosing intervals remain an unmet need because endogenous VWF limits the half-life of current FVIII replacements. BIVV001 (rFVIIIFc-VWF-XTEN) is a novel investigational rFVIII therapy with single-chain FVIII, the Fc domain of human immunoglobulin G1, two XTEN polypeptides, and the FVIII-binding D′D3 domain of VWF, designed to circulate independently of VWF, thereby breaking the VWF half-life ceiling. Higher sustained FVIII levels have demonstrated improved protection from bleeds and preservation of joint health. BIVV001 has the potential to achieve higher sustained FVIII levels, with less frequent administration. Here we present BIVV001 clinical experience to date. Methods: Males (aged 18−65 years) with severe hemophilia A (<1 IU/dL [<1%] endogenous FVIII) with ≥150 exposure days of prior FVIII treatment were included in two separate open-label studies. In the Phase 1/2a EXTEN-A study (NCT03205163), subjects received a single dose (25 or 65 IU/kg) of rFVIII. After a 3- to 4-day washout period, subjects received a single dose of BIVV001 at the same dose level as rFVIII. In the Phase 1 repeat-dosing study (EudraCT No: 2018-001535-51), subjects received four once-weekly doses of 50 IU/kg or 65 IU/kg of BIVV001.In both studies, safety, tolerability, and pharmacokinetic parameters were assessed, and 28-day safety observation periods followed the last dose of BIVV001.Summary: In EXTEN-A, 7 subjects were enrolled in the 25 IU/kg cohort and 9 subjects in the 65 IU/kg cohort, with 6 and 9 subjects receiving BIVV001, respectively. Geometric mean half-life of BIVV001 was longer than rFVIII for both cohorts (37.6 vs 9.1 hours and 42.5 vs 13.2 hours, respectively; P<0.001). Mean (SD) FVIII activity (one-stage assay) at 5 and 7 days following single-dose 65 IU/kg BIVV001 was 38 (10)% and 17 (5)%, respectively. BIVV001 was well tolerated. No inhibitors were detected through 28 days after BIVV001 dosing. In the repeat-dosing study, an interim analysis was conducted when ≥8 subjects from cohort 1 completed PK assessments. As of February 7, 2019, 10 of 10 subjects enrolled to cohort 1 have received 50 IU/kg BIVV001. Three of 5 subjects enrolled to cohort 2 have received 65 IU/kg BIVV001. Data from the interim analysis will be presented. Conclusions: In EXTEN-A, BIVV001 was well tolerated and no safety concerns were identified. BIVV001 half-life was three- to four-fold higher than rFVIII, demonstrating a breakthrough in the VWF-imposed half-life ceiling. The BIVV001 repeat-dosing study provides an opportunity to assess safety, tolerability, and

pharmacokinetics over multiple infusions. BIVV001 may provide less frequent dosing while maintaining high FVIII levels, resulting in extended protection against bleeds for most individuals with severe hemophilia A.