Sponsor: Sanofi **Drug substance(s):** BIVV001 - efanesoctocog alfa	**Study Identifiers:** U1111-1256-9661 NCT05042440 EudraCT Number: 2021-000228-37 **Study code:** PKM17085

Title of the study:

A Phase 1, Single-Site, Open-Label Study to Assess Pharmacokinetics of efanesoctocog alfa (BIVV001), Standard Half-Life and Extended Half-Life FVIII after each Single Intravenous Injection in a Fixed Sequence, in Previously Treated Adults with Severe Hemophilia A

Study center(s):

This study was conducted at 1 study center in Bulgaria.

Study period:

Study initiation date: 11 August 2021

Study completion date: 24 November 2021

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary

· To assess the half-life of BIVV001, SHL rFVIII and EHL rFVIII after a single intravenous (IV) injection

Secondary

• To characterize additional PK parameters of BIVV001, SHL rFVIII and EHL rFVIII after a single IV injection

• To evaluate the safety and tolerability of a single IV injection of BIVV001

Methodology:

This was a Phase 1, single-center, single-arm, nonrandomized, open-label, 3-period, fixed sequence, PK comparison study assessing the PK profiles of BIVV001, SHL and EHL rFVIII after a single IV injection in previously treated patients with severe hemophilia A.

Number of study participants:

Approximately 12 participants were planned to be enrolled in order to have at least 10 to 12 hemophilia A patients who completed the study for PK analysis.

In total, 14 participants were screened with 13 enrolled for treatment of whom:

· 13 participants received at least 1 dose of study intervention;

· 13 participants were included in the safety population;

· 13 participants were included in the PK population; and

· 13 participants were included in the anti-drug antibodies (ADA) population.

Diagnosis and criteria for inclusion:

Participants were male; 18 to 65 years of age (inclusive) at the time of informed consent; with documented severe hemophilia A (defined as < 1 IU/dL [< 1%] endogenous FVIII) with prior treatment, of at least 150 days, with any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products; and a platelet count of ≥100 000 cells/ μ L at Screening.

Study products:

Investigational medicinal product(s):

・Recombinant coagulation factor VIII Fc-VWF-XTEN fusion protein (BIVV001, efanesoctocog alfa)

・Full length recombinant coagulation factor VIII (Advate®)

・Antihemophilic factor (recombinant), PEGylated (Adynovi®)

Formulation(s):

・BIVV001: lyophilized powder in a sterile vial (1000 IU) that requires reconstitution with sterile water for injection (diluent)

・Advate: lyophilized powder in single-use vials containing 1000 IU. It comes with 2 mL of sterile water for injection (included in the commercial package)

・Adynovi: lyophilized powder in single-use vials containing 1000 IU. The solvent vial contains 2 mL of sterile water for injections (included in the commercial package)

Route of administration: IV

Dose regimen: a single dose of 50 IU/kg for each study intervention

Non-investigational medicinal product(s):

・None

Duration of study intervention:

Participants in this study were planned to receive 3 rFVIII study interventions (Advate, Adynovi, and BIVV001; the first 2 are marketed and BIVV001 is in development at the time of reporting). Each participant received a single dose of each rFVIII study intervention in the following fixed sequence: Advate, Adynovi, and subsequently BIVV001. Administration of Advate and Adynovi was separated by a washout period (dependent on the prestudy FVIII) of at least 4 days (96 hours) for conventional products or 5 days (120 hours) for an EHL product. Administration of Adynovi and BIVV001 was separated by a washout period of at least 7 days (168 hours).

Criteria for evaluation:

Primary

- Half-life of BIVV001, SHL rFVIII and EHL rFVIII, as assessed by FVIII activity determined by the one-stage activated partial thromboplastin time (aPTT) clotting assay

Secondary

- Additional PK parameters, including but not limited to the following: maximum activity (C_{max}); clearance (CL); volume of distribution at steady state (V_{ss}); area under the activity time curve extrapolated to infinity (AUC_{∞}); mean residence time (MRT); incremental recovery (IR), assessed with FVIII activity measurement by one-stage aPTT clotting assay
- The occurrence of adverse events (AEs) and serious adverse events (SAEs).
- The occurrence of clinically significant abnormalities in laboratory tests, including development of inhibitors (neutralizing antibodies directed against FVIII) as determined via the Nijmegen-modified Bethesda assay.

Statistical methods:

Pharmacokinetics:

Pharmacokinetic parameters were computed and analyzed using baseline corrected FVIII activity values.

Pharmacokinetic parameters were summarized by study intervention group (treatment) using descriptive statistics.

Log-transformed terminal half-life ($t_{1/2z}$), C_{max}, AUC, and CL were analyzed with a linear model with fixed terms for treatment and a random term for participant, using the Statistical Analysis Software (SAS) Proc Mixed® procedure. Point estimates and 90% confidence intervals for the geometric means of each treatment was provided for $t_{1/2z}$, C_{max}, AUC, and CL. As an exploratory analysis, point estimates and 90% confidence intervals for the geometric means ratio between treatments (BIVV001 versus Advate [SHL] and BIVV001 versus Adynovi [EHL]) were also provided.

Safety:

Safety analysis was based on the review of individual values and descriptive statistics.

The safety analysis focused on the treatment emergent (TE) period, defined as the time from the first study intervention administration of a study period up to the next study period (excluded) or up to the end of study (EOS) visit (included) for the last study period.

All AEs were coded according to the Medical Dictionary for Regulatory Activities version 24.1. The number (%) of participants experiencing TEAEs were summarized.

Potentially clinically significant abnormalities (PCSAs) for laboratory and vital signs variables were flagged and summarized using frequency tables.

Inhibitor development to FVIII was summarized in a frequency table.

Summary Results:

Demographic and other baseline characteristics:

All 13 participants were white males with a mean (SD) age of 36.8 (6.5) years and body weight of 87.77 (18.91) kg. Participant BMIs were varied with the largest proportion having a BMI of 25 to <30 kg/m2 (6 participants [46.2%]).

Participants were diagnosed with severe hemophilia A at a mean (SD) age of 1.5 (1.3) years. A mean (SD) of 38.0 (25.8) bleeding events during the 12 months preceding screening was reported. No participant had a family history of FVIII inhibitor development. Factor VIII genotyping information was available for none. Most participants (76.9%) were on 'on-demand' therapy, with the remaining participants receiving prophylactic therapy (23.1%). All participants had been exposed to FVIII products for ⩾150 exposure days (ED).

Exposure:

All participants received single, sequential, IV, 50 IU/kg administrations of Advate (SHL FVIII), Adynovi (EHL FVIII), and BIVV001 after appropriate washout periods, as per the protocol.

Safety results:

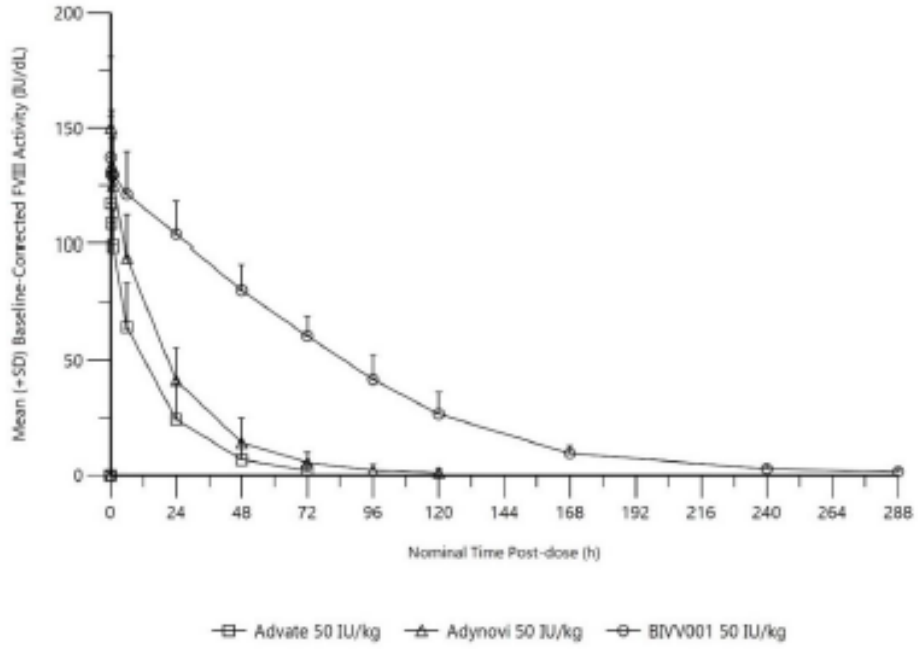
BIVV001 was well tolerated and no safety concerns were identified. Inhibitor development to FVIII was not detected and there were no reports of serious allergic reaction, anaphylaxis, or vascular thrombotic events.

Of the 13 participants included in the safety analysis set, 1 participant (7.7%) experienced 3 TEAEs during the BIVV001 treatment period. There were no TEAEs reported during the Advate or Adynovi treatment periods. There were no serious or severe TEAEs reported and no TEAEs leading to permanent discontinuation of study intervention or withdrawal from the study.

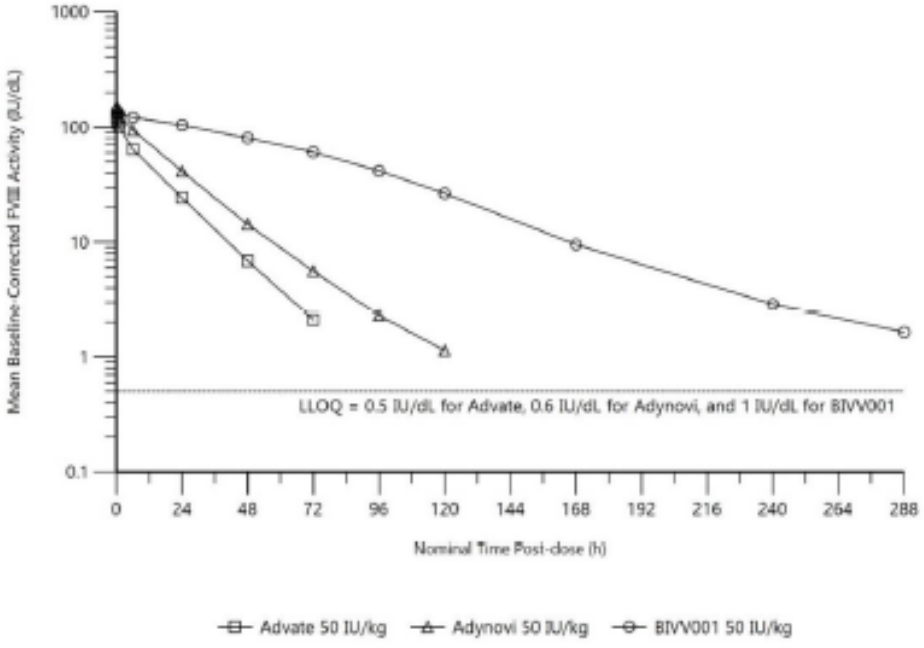
Reported TEAEs included events of headache, cough, and SARs-CoV-2 test positive. All TEAEs were assessed by the Investigator as non-serious, mild to moderate in severity, and not-related to BIVV001. In addition, the outcome of all 3 events was reported as recovered/resolved.
There were no clinically meaningful patterns or trends identified in laboratory or vital signs parameters throughout the study. Consistent with what is anticipated in a population of adults with severe hemophilia A, all abnormalities in physical examination findings involved the musculoskeletal system.
Potentially clinically significant abnormalities in laboratory or vital signs parameters were not identified during the Advate or Adynovi treatment periods. The PCSAs were identified during the BIVV001 treatment period for white blood cell parameters of monocytes > 0.7 × 109/L and eosinophils >0.5 × 109/L or >ULN (if ULN > 0.5 × 109/L) in a single participant. Both PCSAs were detected 14 days after administration of BIVV001 and resolved at the EOS visit, 28 days after administration of BIVV001. There were no other PCSAs identified in any laboratory or vital signs parameter during the BIVV001 treatment period.
Pharmacokinetic results:
As presented in Figure 1, BIVV001 maintained a mean FVIII activity level > 40 IU/dL up to 96 hours (4 days) whereas Advate and Adynovi maintained up to 6 hours (< 1 day) and up to 24 hours (1 day), respectively.
BIVV001 maintained a mean FVIII activity level >10 IU/dL approximately up to 168 hours (7 days) whereas Advate and Adynovi maintained up to 24 hours (1 day) and up to 48 hours (2 days), respectively.
BIVV001 maintained a mean FVIII activity level >1 IU/dL up to 288 hours (12 days) whereas Advate and Adynovi maintained up to 72 hours (3 days) and up to 120 hours (5 days), respectively.

Figure 1 - Mean (+SD) baseline-corrected factor VIII activity-time profiles following single dose administration of Advate, Adynovi, and BIVV001 in participants with severe hemophilia A (linear and semi-logarithmic scales)

Linear Scale



Semi-Logarithmic Scale



Notes: Mean baseline-corrected FVIII activity for BIVV001 was below LLOQ by 336 hours (14 days) post-dose. LLOQ for Advate was 0.5 IU/dL, Adynovi was 0.6 IU/dL, and BIVV001 was 1 IU/dL.

Following a single 50 IU/kg IV dose of Advate, Adynovi, and BIVV001, the median t_{max} of the baseline-corrected FVIII activity generally occurred at the first collected sample (0.17 hours postdose) across all participants and treatments (range 0.17 to 1.00 hours) (Table 1). The C_{max} and IR values indicated consistent recovery across the 3 FVIII products.

Table 1 - Mean ±SD (geometric mean) [CV%] pharmacokinetic parameters for baseline-corrected factor VIII activity following a single dose of Advate, Adynovi, and BIVV001 in participants with severe hemophilia A

PK Parameters	Advate	Adynovi	BIVV001
N	13	13	13
IR ((IU/dL)/(IU/kg))	2.37 ± 0.295 (2.36) [12]	3.02 ± 0.605 (2.96) [20]	2.80 ± 0.338 (2.78) [12]
C_{max} (IU/dL)	119 ± 14.7 (118) [12]	151 ± 30.3 (148) [20]	140 ± 16.9 (139) [12]
t_{max}[a] (h)	0.17 (0.17, 0.50)	0.17 (0.17, 1.00)	0.17 (0.17, 1.00)
AUC (IU·h/dL)	1820 ± 748 (1670) [41]	2950 ± 905 (2820) [31]	10200 ± 1560 (10100) [15]
$t_{1/2z}$ (h)	11.7 ± 4.55 (11.0) [39]	16.3 ± 5.63 (15.4) [35]	44.4 ± 10.4 (43.3) [24]
CL (mL/(h*kg))	3.26 ± 1.48 (2.99) [45]	1.86 ± 0.618 (1.77) [33]	0.503 ± 0.0974 (0.496) [19]
V_{ss} (mL/kg)	40.1 ± 6.82 (39.5) [17]	34.5 ± 6.60 (33.9) [19]	31.3 ± 3.44 (31.1) [11]
MRT (h)	14.6 ± 6.76 (13.2) [46]	20.4 ± 7.73 (19.2) [38]	63.4 ± 9.41 (62.7) [15]

a Median (Min, Max), CV – coefficient of variation

A single 50 IU/kg dose of BIVV001 exhibited reduced CL (0.17- and 0.28-fold), which resulted in a longer $t_{1/2z}$ (3.94 -and 2.82-fold) and a higher exposure (AUC, 6.03- and 3.57-fold) compared with Advate and Adynovi, respectively (Table 2).

Table 2 - Comparison of Advate, Adynovi, and BIVV001 pharmacokinetic parameters for baseline-corrected factor VIII activity based on one-stage activated partial thromboplastin time clotting assay

Parameter	Comparison	Point estimate	90% CI
$t_{1/2z}$ (h)	BIVV001 vs Advate	3.94	(3.47 to 4.48)
	BIVV001 vs Adynovi	2.82	(2.48 to 3.20)
C_{max} (IU/dL)	BIVV001 vs Advate	1.18	(1.10 to 1.26)
	BIVV001 vs Adynovi	0.94	(0.88 to 1.01)

Parameter	Comparison	Point estimate	90% CI
AUC (h*IU/dL)	BIVV001 vs Advate	6.03	(5.32 to 6.83)
	BIVV001 vs Adynovi	3.57	(3.15 to 4.05)
CL (mL/h/kg)	BIVV001 vs Advate	0.17	(0.15 to 0.19)
	BIVV001 vs Adynovi	0.28	(0.25 to 0.32)

CI: confidence interval

PGM = pk_te_k_t.sas OUT = pk_te_k_t_i.rtf (01FEB2022 12:21)

Other results:

Most participants (11 participants) tested negative for ADAs at baseline, while 2 participants had pre-existing ADAs. These 2 participants had titer measurements of 20 that persisted at all assessments. One participant was negative for all tested ADA subtypes (VWF D'D3, FVIII, IgG1 Fc, and XTEN) while the other tested positive for ADAs against FVIII at most assessments except at the Adynovi period Day 1 assessment. Neither of these 2 participants had an ADA result deemed as treatment-boosted. All participants who had an ADA negative assessment at baseline were also ADA-negative at the screening visit.

One participant with a negative ADA assessment at baseline had a treatment induced/emergent ADA result during the study. This participant tested as negative up to the BIVV001 period Day 1 assessment then had a positive result (titer of <20 [1/dil]) on Day 16. The positive ADA sample was negative for the ADA subtypes assessed (VWF D'D3, FVIII, IgG1 Fc, and XTEN). The participant subsequently had a negative ADA assessment at the EOS assessment. There were no TEAEs reported for this participant.

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