Sponsor: Sanofi **Drug substance(s):** efanesoctocog alfa	**Study Identifiers:** U1111-1244-0558 NCT04759131 EudraCT Number: 2020-000769-18 **Study code:** EFC16295

Title of the study:

A Phase 3 open-label, multicenter study of the safety, efficacy, and pharmacokinetics of intravenous recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001) in previously treated pediatric patients <12 years of age with severe hemophilia A

Study center(s):

This study was conducted at 40 centers that screened participants in USA, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, UK, Turkey, Australia, and Taiwan.

Study period:

From 19 February 2021 to 18 January 2023.

Study Status: Completed

Phase of development: Phase 3

Objectives:

Primary

- To evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A

Secondary

- To evaluate the efficacy of BIVV001 as a prophylaxis treatment
- To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes
- To evaluate BIVV001 consumption for prevention and treatment of bleeding episodes
- To evaluate the effect of BIVV001 prophylaxis on joint health outcomes
- To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes
- To evaluate the efficacy of BIVV001 for perioperative management
- To evaluate the safety and tolerability of BIVV001 treatment
- To assess the PK of BIVV001 based on the one stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays

Methodology:

This was a multinational, multicenter, single-arm, open-label Phase 3 study of the safety, efficacy, and PK of BIVV001 administered as weekly prophylaxis in previously treated patients (PTPs) <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A).

The study was comprised of 2 age cohorts of children (<6 years and 6 to <12 years), and participants were to receive BIVV001 at a dose of 50 IU/kg IV once weekly for 52 weeks.

Safety assessments were conducted at every study visit, including the baseline visit and visits at weeks 4, 13, 26, 39, and 52 according to the study protocol.

PK assessments at Baseline were performed after a washout period of at least 3 to 4 days depending on age. At least the first 12 participants enrolled in each of the two age cohorts were to be included in the PK subgroup in which PK samples were to be collected after the first dose of BIVV001 at Baseline and up to 7 days (168 hours). In addition, peak and trough FVIII sampling were evaluated in all participants throughout the study.

FVIII activity levels were measured using WHO plasma standard with the aPTT-based one-stage clotting (OSC) assay as the primary evaluation of PK endpoints. The lower limit of quantification (LLOQ) for one stage clotting assay was 1 IU/dL. Plasma FVIII activity was corrected for baseline using predose FVIII activity at Day 1. Summary statistics were computed, and baseline-corrected FVIII activity level-time profiles are presented.

The participants who underwent major surgery during the study were included in the surgery subgroup.

An independent external Data Monitoring Committee (DMC) was responsible for evaluating and monitoring the safety and tolerability of BIVV001 on an ongoing basis during the study.

Number of study participants:

Number of participants planned: approximately 65 participants to have at least 50 participants (25 with at least 50 exposure days [Eds] per age cohort):

- 25 participants <6 years of age, at least 12 in the PK subgroup
- 25 participants 6 to <12 years of age, at least 12 in the PK subgroup

The planned number of enrolled participants was increased from 65 to 75 in order to have a sufficient number of fully evaluable PK profiles based on the study protocol and pediatric investigation plan requirements of participants in the <6 years age cohort. There was no risk to patient safety or data integrity. As this was a single-arm, uncontrolled study, an impact of this over enrollment on results was considered unlikely. The protocol was not amended and there were no changes to the planned statistical analyses.

Diagnosis and criteria for inclusion:

Participants enrolled in this study were previously treated patients (PTPs) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A) aged younger than 12 years. Previous treatment of hemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6 to <12 years and for at least 50 EDs for patients aged <6 years.

Study products

Investigational medicinal product: BIVV001

- Formulation: Recombinant coagulation factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein.
- Route of administration: Intravenous.
- Dosing regimen: once weekly injection of 50 IU/kg.

All bleeding episodes were to be treated with a single dose of 50 IU/kg BIVV001 (if clinically indicated, additional 30 or 50 IU/kg doses could be administered every 2-3 days). For mild/moderate bleeds within 2-3 days of a recent prophylactic dose, a 30 IU/kg dose could also be administered. All participants undergoing minor or major surgery were to receive a pre-operative loading dose of 50 IU/kg, followed by additional 30 or 50 IU/kg doses every 2-3 days based on clinical indication.

Duration of study intervention:

Study participants received the prophylaxis treatment regimen with BIVV001 for up to 52 weeks.

Criteria for evaluation:

Primary

• The occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen-modified Bethesda assay)

Secondary

• Annualized bleeding rate (ABR) (for treated bleeding episodes)

• ABR (for treated bleeding episodes) by type and location

• ABR for all bleeding episodes (including untreated bleeding episodes)

• Percentage of participants who maintain FVIII activity levels over 1%, 3%, 5%, 10%, 15%, and 20% at Day 7

• Number of injections and dose of BIVV001 to treat a bleeding episode

• Percentage of bleeding episodes treated with a single injection of BIVV001

• Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale

• Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale

• Total annualized BIVV001 consumption per participant

• Annualized joint bleeding rate (AjBR)

• Target joint resolution at Week 52, based on ISTH criteria

• Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS)

- Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score and physical health domain score from baseline to Week 52 (⩾4 years old) and via parent proxy version (⩾4 years old)
- Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment on the ISTH 4-point response for surgical procedures scale
- Number of injections and dose to maintain hemostasis during perioperative period for major surgery
- Total BIVV001 consumption during perioperative period for major surgery
- Number and type of blood component transfusions used during perioperative period for major surgery
- Estimated blood loss during perioperative period for major surgery
- The occurrence of adverse events (AEs) and serious adverse events (SAEs)
- The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests
- PK parameters including, but not limited to, maximum activity (C_{max}), elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}), area under the activity time curve (AUC), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels

Statistical methods:

Primary endpoint: occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen-modified Bethesda assay). Inhibitor development was defined as an inhibitor result of >0.6 BU/mL that was confirmed by a second test result from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both tests were to be performed by the central laboratory using the Nijmegen-modified Bethesda assay.

The efficacy endpoint of ABR was analyzed using the FAS. The mean and 95% CI of ABR was estimated using a negative binomial model. The model included the number of treated bleeding episodes during the efficacy period as the response variable, and the log-transformed duration of efficacy period as the offset variable to account for variable duration. One participant did not receive the weekly prophylaxis as specified in the protocol for an extended period of time; an ad hoc sensitivity analysis excluding this participant has therefore been performed.

Analysis of safety endpoints: the incidence, seriousness, severity, and relatedness of AEs were assessed by age (<6 years and 6 years to <12 years) and overall.

Analysis of PK endpoints: plasma FVIII activity was corrected for baseline using predose FVIII activity at Day 1. FVIII activity post start of injection was summarized by overall population and age cohort using descriptive statistics.

Summary Results:

Disposition of participants:

Overall, 74 participants were enrolled in the single-arm of this open-label study and received at least one dose of BIVV001: 38 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort. A total of 72 (97.3%) participants completed the study and 2 (2.7%) participants prematurely discontinued. The reason for study discontinuation was "other" in both participants and was related to extreme fear of blood drawing in one participant and a positive low-titer FVIII inhibitor test at Baseline (prior to first dose) in the other one.

Demographic and other baseline characteristics:

All participants were male. The mean (SD) age of the participants was 5.99 (2.91) years. In the <6 years of age cohort, the mean (SD) age was 3.69 (1.21) years (range: 1.4 to 5.0 years) and in the 6 to <12 years of age cohort, the mean (SD) age was 8.42 (2.08) years (range: 6.0 to 11.0 years).

Three geographic regions were represented in the study: North America (28 [37.8%] participants), Europe (27 [36.5%] participants), and Asia/Pacific (19 [25.7%] participants).

Baseline disease characteristics were representative of a pediatric population with severe hemophilia A. The mean (SD) age at the start of first prophylactic treatment was 1.0 (1.0) year. The mean (SD) total number of bleeding episodes reported in the 12 months prior to the study was 2.1 (4.2) across the overall study population. Twenty-seven (38.6%) participants reported no bleeding episodes and 39 [55.7%] participants experienced 1 to 5 bleeding episodes during the prior 12 months. In the 12 months prior to study entry, the mean (SD) number of reported joint bleeding episodes was 1.1 (3.9) across the study population. No target joints were reported at Baseline in 72 (97.3%) participants.

Exposure:

Of the 74 participants who received at least 1 dose of BIVV001, 66 (89.2%) achieved 50 or more EDs: 31 (81.6%) participants in the <6 years of age cohort and 35 (97.2%) participants in the 6 to <12 years of age cohort. The mean (SD) number of EDs was 52.5 (7.2) in the overall population; 51.2 (8.6) in the <6 years of age cohort and 53.9 (4.9) in the 6 to <12 years of age cohort. The mean (SD) total number of injections per participant was 52.6 (7.3).

Primary Endpoint

The primary endpoint of this study was the occurrence of inhibitor development (neutralizing antibodies directed against FVIII). Inhibitor development to FVIII was not detected. In all treated participants and participants with ⩾50 exposure days to BIVV001, the incidences of inhibitor development to FVIII were 0.0% (95% CI: 0.0 to 4.9) and 0.0% (95% CI: 0.0 to 5.5), respectively.

Efficacy Results

Prevention of bleeds

• BIVV001 was effective for routine prophylaxis in children under 12 years of age with severe hemophilia A. Once-weekly BIVV001 50 IU/kg routine prophylaxis resulted in an overall estimated mean ABR of 0.89 (95% CI: 0.56 to 1.42) in the study participants with an efficacy period and an overall estimated mean ABR of 0.61 [95% CI: 0.42 to 0.90] in the ad hoc sensitivity analysis excluding the participant who did not receive a prophylaxis treatment for an extended period of time); The observed median (Q1; Q3) ABR was 0.00 (0.00; 1.02). Low ABRs were observed in both age cohorts. The majority of the participants (63.5%) reported no bleeding episodes across both age cohorts (64.4% in the ad hoc sensitivity analysis).

• The ABRs were consistently low with BIVV001 weekly prophylaxis: across type and location of bleeding, when including untreated and treated bleeding episodes, as well as in the 3 subgroups studied (bleeding phenotype, number of targets joints, regimen compliance).

• Seven days after administration of BIVV001 at any study visit, all participants maintained FVIII activity levels >3% and the majority (86.9%) >5%. Trough FVIII activity levels >10% were maintained in 51.7% of children aged 6 to <12 years and 18.8% of children under 6 years.

• The physician's global assessment of the participant's response to their BIVV001 treatment was excellent for 96.6% of study visits.

Treatment of bleedings

・BIVV001 was effective for the treatment of bleeding episodes in children under 12 years of age with severe hemophilia A. Across the 2 age cohorts, 64 bleeds were treated with BIVV001. Analysis per bleeding episode showed that 81.3% of the bleeding episodes were controlled by only 1 injection. In the ad hoc sensitivity analysis excluding the participant who did not receive a weekly prophylaxis treatment for an extended period of time, 43 bleeds were treated with BIVV001 and 95.3% of the bleeding episodes were controlled by only 1 injection.

・The mean (SD) total dose per bleeding episode was 63.02 (33.26) IU/kg and in the ad hoc sensitivity analysis was 51.14 [11.10] IU/kg.

・Per protocol, only the first injections to treat a bleed were evaluated for response to BIVV001 treatment. Forty out of the 64 bleeding episodes were evaluated for response to BIVV001 treatment, with the majority (97.5%) rated as producing an excellent or good response (37 out of 43 bleeding episodes were evaluated in the ad hoc sensitivity analysis, with 97.3% having an excellent or good response).

BIVV001 consumption

The overall mean (SD) annualized BIVV001 consumption per participant during the efficacy period was 3003.24 (394.01) IU/kg. The mean (SD) annualized BIVV001 consumption was 3115.57 (488.64) IU/kg for participants in the <6 years of age cohort and 2884.67 (207.88) IU/kg in the 6 to <12 years of age cohort.

Joint health

BIVV001 prophylaxis maintained joint health:

・Prophylaxis with BIVV001 showed maintenance in joint health. The mean change (SD) in HJHS Total score from baseline to Week 52 was -0.6 (6.0).

・BIVV001 prophylaxis prevented joint bleeds: the estimated mean AJBR was low with BIVV001 prophylaxis. The majority (82.4%) of participants had no joint bleeds during the study.

・A total of 2 study participants (one in each cohort of age) presented with at least one target joint at Baseline. Among these 2 participants, 1 participant in the 6 to <12 years of age cohort (with 2 target joints at baseline) had at least 1 year prophylaxis treatment with BIVV001 and achieved resolution of the 2 target joints.

Quality of life:

Quality of life data were collected at Baseline, Week 26 and Week 52 in participants aged 4 to 7 years, in participants aged 8 to <12 years, and in respective caregivers via 4 separate Haemo-QoL questionnaires. Lower scores represent better QoL.

・In participants between 4 and 7 years of age, the mean (SD) change from baseline to Week 52 in Haemo-QoL total score (n = 14) was -2.46 (10.49).

・In Participants between 8 and 12 years of age, the mean (SD) change from baseline to Week 52 in Haemo-QoL total score (n = 10) of -9.79 (12.18), showing global improvements in quality of life.

Perioperative Management

A total of 2 major surgeries were performed in 2 participants, both in the <6 years of age cohort. These involved a dental restoration including one tooth extraction in one participant, and circumcision in the other. Investigator'/Surgeon's assessment of the participant's hemostatic response to BIVV001 was rated as excellent for both surgeries. A single loading dose of BIVV001 was sufficient to maintain hemostasis during surgery and the mean dose per injection was 61.13 IU/kg (range: 60.4 to 61.9 IU/kg).

Safety results:

All 74 participants enrolled in the study received at least 1 dose of BIVV001 and were included in the Safety Analysis Set. The mean (SD) total number of EDs per participant was 52.7 (7.2) and 66 (89.2%) participants had at least 50 EDs.

Overview summary of treatment-emergent adverse events - Safety Analysis Set

n (%)	Age cohort			
	<6 years (N=38)	6 to <12 years (N=36)	Surgical/rehab. period - Surgery subgroup[a] (N=2)	Overall (N=74)
Total number of TEAEs	146	108	1	255
Participants with at least one TEAE	33 (86.8)	29 (80.6)	1 (50.0)	62 (83.8)
Participants with at least one related TEAE	3 (7.9)	0	0	3 (4.1)
Total number of TESAEs	6	4	0	10
Participants with at least one TESAE	5 (13.2)	4 (11.1)	0	9 (12.2)
Participants with at least one related TESAE	0	0	0	0
Total number of TEAESIs	1	0	0	1
Participants with at least one TEAESI	1 (2.6)	0	0	1 (1.4)
Participants with at least one related TEAESI	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs leading to treatment discontinuation	0	0	0	0

Note 1: Percentages are based on the number of participants in the Safety Analysis Set.
2: AEs with missing causality assessment are included in the related TEAE, related TESAE or related TEAESI.
[a]Includes AEs emergent during the major surgical/rehabilitation period; these AEs are excluded from each age cohort column but are included in the overall column. Each participant is counted only once in the overall column.
Abbreviations: TEAESI = treatment-emergent adverse event with special interest; TESAE = treatment-emergent serious adverse event; TEAE = treatment-emergent adverse event; AE = adverse event.
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BIVV001 was well tolerated and reported treatment-emergent adverse events (TEAEs) were generally consistent with what is anticipated in a pediatric population with severe hemophilia A.

Of the 74 participants in the Safety Analysis Set, 62 (83.8%) experienced a total of 255 TEAEs: 33 (86.8%) participants in the <6 years of age cohort experienced 146 TEAEs and 29 (80.6%) participants in the 6 to <12 years of age cohort experienced 108 TEAEs. One TEAE was reported in 1 (50.0%) participant during the major surgical/rehabilitation period. The majority of TEAEs were assessed by the Investigator as mild in severity and not related to BIVV001. No TEAEs resulting in death or leading to treatment discontinuation were reported.

The most frequently reported TEAEs (>5% of participants overall) were SARS-CoV-2 test positive and upper respiratory tract infection (11 [14.9%] participants, each), pyrexia (9 [12.2%] participants), asymptomatic COVID-19 (7 [9.5%] participants), gastroenteritis viral, head injury, and nasopharyngitis (6 [8.1%] participants, each), arthralgia, pain in extremity, and vomiting (5 [6.8%] participants, each), contusion, diarrhoea, viral infection, and viral upper respiratory tract infection (4 [5.4%] participants, each).

Nine (12.2%) participants experienced a total of 10 TESAEs: 5 (13.2%) participants aged <6 years and 4 (11.1%) participants aged 6 to <12 years. All TESAEs were reported in 1 (1.4%) participant each, except vascular device infection which was reported in 2 (2.7%) participants. The majority of TESAEs were assessed by the Investigator as mild to moderate in severity. All TESAEs

were assessed by the Investigator as not related to BIVV001, no action was taken with BIVV001, and the outcomes were reported as recovered/resolved.

One unrelated TEAESI of urticaria was reported in 1 (1.4%) participant. There were no reports of Grade 3 or higher allergic reaction, anaphylaxis, embolic or thrombotic events during the study.

There were no clinically meaningful patterns or trends identified in laboratory or vital sign parameters.

Immunogenicity results:

Overall, 73 participants were evaluable for their anti-drug antibody (ADA) status (defined as those with at least one post-baseline ADA result). No treatment-emergent (treatment induced and/or treatment boosted) ADA responses were observed in these participants. A total of 3 (4.1%) participants had positive ADA samples at Screening and/or at Baseline but all tested negative during the on-treatment phase.

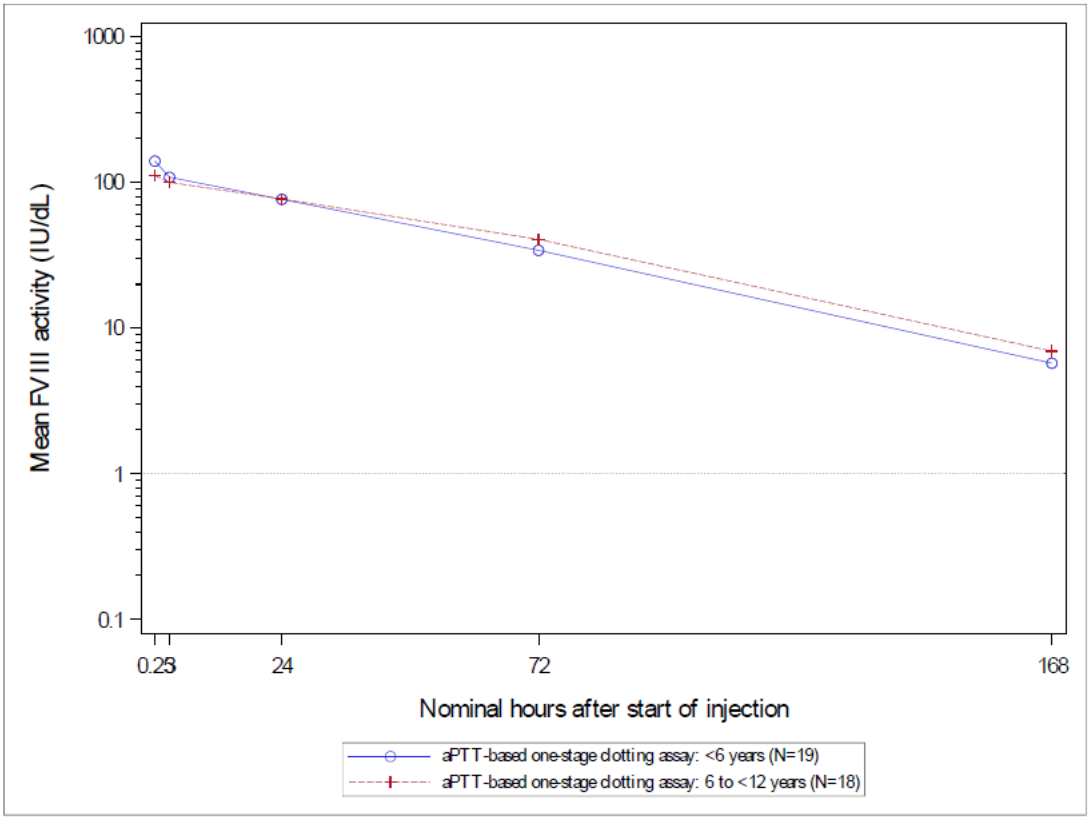
Pharmacokinetic results:

The first dose of BIVV001 50 IU/kg maintained mean FVIII activity in the normal to near-normal range (>40 IU/dL) for 2 to 3 days, and a mean FVIII activity >5 IU/dL 7 days after the first weekly dose, with similar PK profiles in both age cohorts (Figure 1). The majority of participants showed peak FVIII activity levels (mean C_{max} 128 IU/dL) below the upper physiological limit of 150 IU/dL. The mean (SD) terminal half-life of BIVV001 was 40.2 (4.29) hours. Mean (SD) incremental recovery (IR) was 2.53 (0.880) IU/dL per IU/kg. An effect of age on PK was observed with slightly lower $AUC_{0\text{-}tau}$ and half-life in participants in the <6 years of age cohort as compared to participants in the 6 to <12 years of age cohort.

At steady state, the analysis of time above specified FVIII activity levels showed a mean (SD) time above near-normal levels (>40 IU/dL) of 3 days and time above 10 IU/dL of approximately 7 days, indicating high sustained FVIII activity over a weekly dosing interval of BIVV001.

Mean trough (predose) FVIII activity levels ranged from 8.54 IU/dL at Week 4 to 13.68 IU/dL at Week 52/EOS and mean values at 15-min postdose were consistently below 150 IU/dL across all visits.

Figure 1 - Mean baseline-corrected FVIII activity after the first dose of BIVV001 by age cohort: aPTT-based one-stage clotting assay - PK Analysis Set (semi-log scale)



Note 1: For aPTT-based one-stage clotting assay, values below 1 IU/dL (i.e., LLOQ) are imputed as zero.
2: The horizontal dash line at y= 1 IU/dL represents LLOQ.
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