Sponsor: Sanofi **Drug substance(s):** BIVV001 - efanesoctocog alfa	**Study Identifiers:** NCT04161495 EudraCT: 2019-002023-15 U1111-1223-4867 **Study code:** EFC16293

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 Patients ≥12 Years of Age With Severe Hemophilia A

Study center(s):

This study was conducted at 51 centers that screened participants in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, South Korea, Spain, Taiwan, UK, and USA.

Study period:

From 19 November 2019 to 03 February 2022

Study Status: Completed

Phase of development: Phase 3

Objectives:

Primary:

• To evaluate the efficacy of BIVV001 as a prophylaxis treatment

Secondary:

Efficacy objectives

• 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 the 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

Safety objective

• To evaluate the safety and tolerability of BIVV001 treatment

PK objective

• 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 Phase 3 open-label study was comprised of 2 arms: Arm A and Arm B. Participants who were on a prophylaxis treatment regimen with FVIII prior to the study entered Arm A and received BIVV001 50 IU/kg IV once weekly for up to 52 weeks. The majority of study participants enrolled in Arm A had previously completed study OBS16221 (an observational study of patients receiving a marketed FVIII replacement therapy for up to 12 months). Participants who were on an on-demand treatment regimen prior to the study entered Arm B and received BIVV001 50 IU/kg IV as on-demand treatment of bleeding episodes for 26 weeks before switching to BIVV001 50 IU/kg IV once weekly as a prophylaxis treatment regimen for another 26 weeks.

PK assessments at Day 1 were performed after a washout period of at least 4 to 5 days, depending on prior FVIII therapy. At least 16 participants in Arm A at selected sites were included in the Sequential PK subgroup and underwent PK sampling over 2 weeks (336 hours) after the first dose of BIVV001 (Baseline) and again at Week 26 (study drug was withheld on Week 2 and Week 27 to allow for this sampling). All other participants underwent abbreviated PK sampling at Baseline up to 7 days (168 hours). In addition, peak and trough FVIII measurements was performed in all participants throughout the study.

FVIII activities 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.

Participants from either arm who had major surgery after the first dose of BIVV001 were included in the surgery subgroup. A minimum of 10 major surgeries in at least 5 patients was targeted to assess the control and prevention of bleeding during use of BIVV001 in the surgical setting.

Number of study participants:

Number of participants planned: approximately 150 participants

- Arm A: approximately 124 participants to have at least 104 evaluable participants with at least 50 exposure days (EDs)
  - At least 75 participants with at least 6 months of participation in Study OBS16221 (an observational study of patients receiving a marketed FVIII replacement therapy for up to 12 months) prior to baseline
  - At least 16 participants included in the sequential PK subgroup
- Arm B: approximately 26 participants

Number of participants analyzed:

In total, 82 participants rolled over from OBS16221 to Arm A and 10 rolled over to Arm B.

- Efficacy (Full Analysis Set [FAS]): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
- Safety (Safety Analysis Set): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
- Pharmacokinetics
  - PK analysis Set (PKAS): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
  - Sequential PK subgroup: 17 (Arm A)
- Surgery subgroup: 13 (overall)

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 12 years or older. In addition, participants from Arm B (on-demand regimen) had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment. Previous treatment for hemophilia A (prophylaxis or on-demand regimen) was defined as any treatment with any recombinant and/or plasma derived FVIII, or cryoprecipitate for at least 150 EDs.

Study products

• Formulation: Recombinant coagulation factor VIII Fc-von Willebrand Factor XTEN Fusion Protein.
• Route of administration: Intravenous
• Dosing regimen:
• Arm A: prophylactic treatment regimen with once weekly injection of 50 IU/kg BIVV001 for 52 weeks
• Arm B: on-demand regimen with BIVV001 for 26 weeks followed by prophylactic treatment regimen with once weekly injection of 50 IU/kg BIVV001 for 26 weeks
All bleeding episodes (during either prophylaxis or on-demand treatment regimen) were to be treated with a single dose of 50 IU/kg BIVV001 (on clinical indication additional 30 or 50 IU/kg doses every 2-3 days could 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 on clinical indication.

Duration of study intervention:

Participants in Arm A received prophylaxis treatment regimen with BIVV001 for up to 52 weeks. Participants in Arm B received BIVV001 as on-demand treatment for 26 weeks before switching to prophylaxis treatment regimen for another 26 weeks.

Criteria for evaluation:

Primary

• Annualized bleeding rate (ABR) in Arm A

Secondary

• Intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A who participated in Study 242HA201/OBS16221, an observational study (**key secondary endpoint)**
• ABR by type and location for prophylaxis treatment per study arm
• Intra-patient comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B
• Intra-patient comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B
• Percentage of participants who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A
• Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen
• Percentage of bleeding episodes treated with a single injection of BIVV001 per study arm and treatment regimen
• Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale per study arm and treatment regimen
• Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale per study arm and treatment regimen
• Total annualized BIVV001 consumption per participant per study arm and treatment regimen
• Change from baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS) in Arm A
• Annualized Joint Bleeding Rate (AJBR) per study arm and treatment regimen
• Target joint resolution at Week 52, based on ISTH criteria in Arm A
• Changes in Haem-A-QoL (≥17 years old) total score and physical health score measures from baseline to Week 52 in Arm A
• Changes in PROMIS Pain Intensity 3a from baseline to Week 52 in Arm A
• Changes in PROMIS-SF Physical Function (≥18 years old) measures from baseline to Week 52 in Arm A
• 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
- Development of inhibitors (neutralizing antibodies directed against factor VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay
- The occurrence of embolic and thrombotic events
- 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 (CLss), accumulation index (AI), area under the activity time curve (AUC), volume of distribution at steady state (Vss), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels

Statistical methods:

Primary efficacy endpoint: Annualized bleeding rate (ABR) in Arm A. The confidence interval (CI) of the mean ABR was estimated using a negative-binomial model. If the upper limit of the one-sided 97.5% CI was ≤6, the weekly prophylaxis treatment regimen was considered to provide adequate bleeding control.

The selected secondary efficacy endpoints included in the hierarchical test procedure were Haem-A-QoL (≥17 years old) Physical Health score, PROMIS Pain intensity 3a past 7 days intensity of pain at its worst score (PAINQU6) and Hemophilia Joint Health Score (HJHS) total score. The adjusted mean change in each of the 3 endpoints from baseline to Week 52 in Arm A, along with its 95% CI, was estimated by the mixed-effects model repeated measures (MMRM) model. The multiplicity was adjusted through a fixed sequence procedure in the order of appearance above.

Analysis of safety endpoints: The incidence, seriousness, severity, and relatedness of AEs were assessed by study arm, treatment regimen, and overall. Incidence of inhibitor development was assessed using an exact 95% confidence interval based on the binomial distribution.

Analysis of PK endpoints: Plasma FVIII activity was corrected for baseline using predose FVIII activity at Day 1. Summary statistics were computed for baseline and Week 26 and mean (+SD) baseline-corrected FVIII activity level-time profiles are presented.

Summary Results:

Preliminary results presented in this document are limited to selected efficacy, safety and PK endpoints.

Demographic and other baseline characteristics:

One female participant was enrolled; all other participants were male. The mean (standard deviation, SD) age of the participants was 35.4 (15.1) years with:

- 12 to 17 years: 25 (15.7%) participants
- 18 to 64 years: 129 (81.1%) participants, all in Arm A
- 65 years or older: 5 (3.1%) participants

The 3 main geographic regions in the study were represented: Europe (81 [50.9%] participants), Asia/Pacific (33 [20.8%] participants), and North America (26 [16.4%] participants).

Baseline disease characteristics were representative of an adult and adolescent population with severe hemophilia A. The median and mean (SD) age at start of first prophylaxis was 1.0 and 3.6 (6.0) years for participants in Arm A, and 3.0 and 10.8 (15.1) years for participants in Arm B. The mean (SD) number of bleeding episodes reported in the 12 months prior to the study was 3.2 (5.4) in Arm A (pre-study on prophylaxis regimen) and 35.7 (22.2) in Arm B (pre-study on-demand treatment).

Exposure:
Of the 159 participants who received at least 1 dose of BIVV001, 115 (72.3%) had 50 or more EDs. The mean (SD) number of EDs was 48.4 (10.5) in the overall population; 50.9 (9.1) in Arm A, 11.9 (4.3) during on-demand treatment in Arm B and 23.8 (6.1) during prophylaxis treatment in Arm B.

Efficacy results:
The study met the primary endpoint, key secondary endpoint, as well as all secondary endpoints prespecified as part of the hierarchical testing model as shown in the table below.

Results of the primary and secondary efficacy endpoints analyzed as part of the hierarchical testing procedure demonstrating efficacy of BIVV001

ABR			
Primary endpoint		**Arm A (N=133)**	
ABR	Total number of treated bleeding episodes	86	
	Total participant-years followed	121.2	
	Mean ABR (SD)	0.71 (1.43)	
	Mean ABR, model based [a] (95% CI)	0.71 (0.52; 0.97)	
Key secondary endpoint (hierarchical testing procedure)		**Arm A**	
Intra-participant comparison of ABR between BIVV001 prophylaxis and pre-study FVIII prophylaxis: non-inferiority analysis based on PPS	Comparison groups	**Historical prophylaxis (OBS16221) (N=77)**	**BIVV001 prophylaxis (EFC16293) (N=77)**
	Mean ABR (95% CI) [b]	2.99 (2.03; 4.42)	0.69 (0.43; 1.12)
	Mean difference (95% CI) [b]		-2.30 (-3.49; -1.11)
Intra-participant comparison of ABR between BIVV001 prophylaxis and pre-study FVIII prophylaxis: superiority analysis based on FAS	Comparison groups	Historical Prophylaxis (OBS16221) (N=78)	BIVV001 Prophylaxis (EFC16293) (N=78)
	Mean ABR (95% CI) [b]	2.96 (2.00; 4.37)	0.69 (0.43; 1.11)
	Rate ratio (95% CI) [b]		0.23 (0.13; 0.42)
	p-value (superiority) [c]		<0.0001
Physical functioning and pain (QoL)			
Secondary endpoints analyzed as part of the hierarchical testing procedure		**Arm A (N=133)**	
Haem-A-QoL Physical Health	Baseline: mean (SD), number	37.02 (23.83), n=104	
	Week 52: mean (SD), number	29.66 (23.40), n=104	
	Change from B to Week 52:		
	Mean (SD), number	-6.79 (18.59), n=98	
	LS Mean (SE) [d]	-6.74 (1.71)	
	95% CI	(-10.13, -3.36)	
	p-value	0.0001	
PROMIS Pain Intensity 3a past 7 days intensity of pain at its worst score	Baseline: mean (SD), number	2.47 (1.15), n=125	
	Week 52: mean (SD), number	2.21 (1.21), n=127	
	Change from B to Week 52		
	Mean (SD), number	-0.21 (1.20), n=119	
	LS Mean (SE) [d]	-0.21 (0.10)	
	95% CI	(-0.41, -0.02)	
	p-value	0.0276	
Joint health			
Secondary endpoint analyzed as part of the hierarchical testing procedure		**Arm A (N=133)**	
HJHS total score	Baseline: mean (SD), number	18.1 (18.4), n=116	
	Week 52: mean (SD), number	16.5 (17.6), n=110	
	Change from B to Week 52:		
	Mean (SD), number	-1.5 (6.4), n=107	
	LS Mean (SE) [d]	-1.54 (0.59)	
	95% CI	(-2.70, -0.37)	
	p-value	0.0101	

a Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

b Estimated using a negative binomial regression model with treatment (BIVV001 prophylaxis vs historical prophylaxis) as covariate.

c P-value relates to the null hypothesis:rate ratio (BIVV001 prophylaxis/historical prophylaxis) =1.

d The LS mean (SE) and 95% CI are estimated by mixed-effect model with repeated measures (MMRM) with visit as)fixed effect, and baseline score as covariate.

Prevention of bleeding:
• The study **met the primary endpoint**, ARB in Arm A: the estimated mean ABR was 0.71 (95% CI: 0.52 to 0.97); the median (Q1; Q3) ABR was 0.00 (0.00; 1.04). The upper limit of the 1-sided 97.5% CI was less than the prespecified value of 6, demonstrating that the weekly prophylaxis treatment regimen with BIVV001 provided highly effective protection against bleeds and clinically meaningful treatment effect.
• The study **met the key secondary endpoint**: Intra-participant comparison demonstrated the non-inferiority of BIVV001 prophylaxis as compared with prestudy prophylaxis on estimated mean ABR with an estimated mean difference in ABR (BIVV001 prophylaxis versus prestudy FVIII prophylaxis) of -2.30 (95% CI: -3.49 to -1.11). Superiority of BIVV001 prophylaxis as compared with standard of care prestudy prophylaxis was also demonstrated with a rate ratio of 0.23 (95% CI: 0.13; 0.42) and p-value <0.0001, showing a reduction of 77% in estimated mean ABR.
• 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 all subgroups studied including in participants aged 12 through 17 years.
• In Arm B, intra-participant comparison of ABR showed a clinically important reduction of 97% (95% CI: 93% to 98%) in ABR with prophylaxis treatment as compared to on demand treatment with BIVV001, resulting in an ABR similar to the one observed with weekly prophylaxis in Arm A.
• While a single dose of 50 IU/kg BIVV001 maintained mean FVIII activity levels in the normal to near-normal range for 3 to 4 days, 99.0% of participants maintained FVIII activity levels at 7 days postdose >5% throughout the study duration. In 83.5% and 40.8% of participants, FVIII activity levels of >10%, and >15%, respectively, were maintained.
Treatment of bleeds:
• A total of 362 bleeding episodes were treated with BIVV001. Most of the bleeding episodes (96.7%) were controlled by a single injection of BIVV001. The mean dose per injection to treat a bleeding episode was 49.56 IU/kg and the mean number of injections for resolution of a bleeding episodes was 1.0.
• The hemostatic response was rated by the participants as excellent or good in 94.9% for all evaluable injections for treatment of a bleed.
• Physician's global assessment of the participant's response to BIVV001 treatment throughout the study was rated as excellent in 95.7% of all study visits in Arm A.
BIVV001 consumption
• The mean (SD) annualized BIVV001 consumption per participant during the efficacy period was 3131.75 (4113.19) IU/kg for participants in Arm A, 1135.32 (404.94) IU/kg for participants in Arm B with on-demand treatment and 2751.54 (88.26) IU/kg following switch to prophylaxis treatment.
Joint health:
• BIVV001 prophylaxis demonstrated a statistically significant improvement in joint health with reduction in **HJHS** score (LS mean decrease between baseline and Week 52 of -1.54 [95% CI: -2.70 to -0.37]; p value=0.0101 [**hierarchical testing procedure**]).
• The AJBR was low with BIVV001 prophylaxis and, in participants who switched from on demand to prophylaxis treatment with BIVV001, there was a clinically important reduction in AJBR (rate ratio: 0.04 [95% CI: 0.01 to 0.08]) resulting in an AJBR close to the one observed with weekly prophylaxis in Arm A.
• A total of 26 study participants presented with at least one target joint at baseline. Among these 26 participants, the 14 participants who had at least 1 year prophylaxis treatment with BIVV001 all achieved resolution of their target joints (n=45).
Physical functioning and pain:
• Prophylaxis with BIVV001 demonstrated a clinically meaningful improvement in physical health with a statistically significant decrease in the **Haem-A-QoL physical health score** between baseline and Week 52 in adults of -6.74 (95% CI: -10.13 to -3.36; p value=0.0001 [**hierarchical testing procedure**]).
• In participants receiving BIVV001 prophylaxis (Arm A), the adjusted mean change from baseline to Week 52 in **PROMIS Pain Intensity first item score** (past 7 days intensity of pain at its worst score) was -0.21 (95% CI: -0.41 to -0.02, p-value = 0.0276 [**hierarchical testing procedure**]) demonstrating a statistically significant improvement in pain. This was supported by an improvement in the overall pain intensity as measured by the PROMIS pain intensity 3a with a reduction of -1.94 (95% CI: -3.26 to 0.63) from baseline to Week 52.
Perioperative management: Efficacy during perioperative management was assessed in 12 major surgical procedures in 11 participants.
• Hemostatic responses were rated as excellent by the Investigators/Surgeons in all 12 surgeries, indicating that intraoperative

and postoperative blood loss was estimated by the Investigators/Surgeons as comparable to what would have been expected for a patient who does not have hemophilia.

• A single loading of BIVV001 was sufficient to maintain hemostasis during surgery. The mean dose per injection was 41.65 IU/kg (range: 12.7 to 51.7 IU/kg).

• No participant needed blood component transfusion during the surgical period.

• The mean estimated blood loss was 143.33 mL during major surgery and 65.56 mL postoperatively.

Safety results:

All 159 participants enrolled in the study received at least 1 dose of BIVV001 and were included in the Safety Analysis Set. The mean total number of EDs per participant was 48.4 (range: 2 to 63) and 115 (72.3%) participants had at least 50 EDs.

Overview summary of treatment-emergent adverse events - Safety analysis set

	Arm A	Arm B			
n (%)	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Surgery subgroup[a] (N=13)	Overall (N=159)
Total number of TEAEs	358	22	11	3	394
Participants with at least one TEAE	108 (81.2)	12 (46.2)	8 (30.8)	1 (7.7)	123 (77.4)
Participants with at least one related TEAE	8 (6.0)	0	0	0	8 (5.0)
Total number of TESAEs	16	2	0	0	18
Participants with at least one TESAE	13 (9.8)	2 (7.7)	0	0	15 (9.4)
Participants with at least one related TESAE	1 (0.8)	0	0	0	1 (0.6)
Total number of TEAESIs	1	0	1	0	2
Participants with at least one TEAESI	1 (0.8)	0	1 (3.8)	0	2 (1.3)
Participants with at least one related TEAESI	0	0	0	0	0
TEAEs leading to death	0	1 (3.8)	0	0	1 (0.6)
TEAEs leading to treatment discontinuation	2 (1.5)	0	0	0	2 (1.3)

Note 1: Percentages are based on the number of participants in the Safety Analysis Set.

2: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each participant is counted only once in the overall column.

3: AEs with missing causality assessment are included in the related TEAE, TESAE, or TEAESI.

a Includes AEs occurring during a major surgical/rehabilitation period. But AEs which occur on the day of the major surgical/rehabilitation period starts will be included in the columns treatment arm and regimen, they will not be included in the column of surgery subgroup.

Abbreviations: TESAE = treatment-emergent serious adverse event; TEAESI = treatment emergent adverse events of special interest; TEAE = treatment-emergent adverse event; AE = adverse event.

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• BIVV001 was well tolerated and reported TEAEs were generally consistent with what is anticipated in an adult and adolescent population with severe hemophilia A.

• Of the 159 participants who received at least one dose of BIVV001, 123 participants (77.4%) had at least one TEAE, with a total of 394 TEAEs reported.

• The most frequently reported (>3% of participants overall) TEAEs were: headache (32 [20.1%] participants), arthralgia (26 [16.4%] participants), fall (10 [6.3%] participants), back pain (9 [5.7%] participants), COVID-19 and fatigue (7 [4.4%] participants, each), contusion, haemophilic arthropathy, and nasopharyngitis (6 [3.8%] participants, each), and joint injury, pain in extremity and toothache (5 [3.1%] participants, each).

• The majority of TEAEs were assessed by the Investigator as mild in severity and not related to BIVV001. Subgroup analyses of TEAEs by predefined intrinsic and extrinsic factors were generally consistent with TEAEs in the overall population. No unique

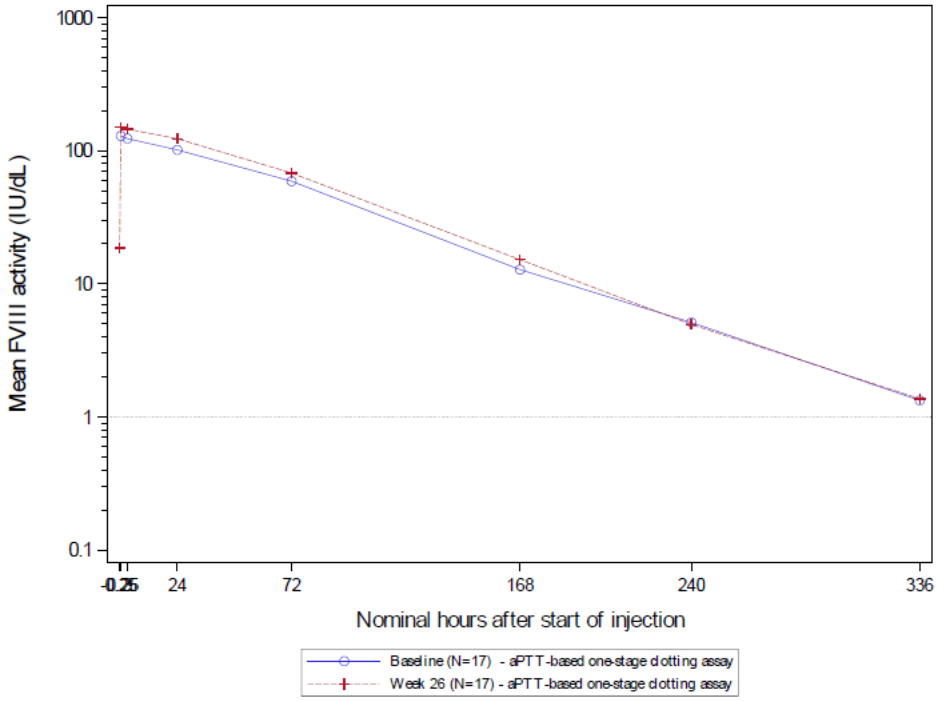
patterns or trends were identified in any subgroup.

- There were no unique safety findings identified during the major surgery/rehabilitation period.
- Fifteen (9.4%) participants experienced a total of 18 TESAEs. Haemophilic arthropathy was reported in 2 (1.3%) participants and all other TESAEs were reported in 1 (0.6%) participant each.
- Inhibitor development to FVIII was not detected and there were no reports of serious allergic reaction, anaphylaxis, or vascular thrombotic events.
- There were no clinically meaningful patterns or trends identified in laboratory or vital sign parameters.

Pharmacokinetic results:

- A single BIVV001 dose of 50 IU/kg resulted in mean FVIII activities in the normal to near-normal range (>40 IU/dL) for 3 to 4 days and mean FVIII activity of 11.92 IU/dL at the end of the 7-day dosing interval.
- After a 50 IU/kg of BIVV001, the majority of participants showed peak FVIII activities (mean C_{max} 131 IU/dL) below the upper physiological limit of 150 IU/dL.
- The mean (SD) half-life of BIVV001 was 47.6 (8.86) hours and the mean (SD) incremental recovery (IR) was 2.60 (0.648).
- Once weekly 50 IU/kg regimen showed minimal accumulation (mean accumulation index: 1.17).
- An effect of age on PK was observed with slightly lower AUC and half-life in adolescents as compared to adults.
- Four participants had transient treatment-emergent ADAs with no effect on peak and trough FVIII activity levels.

Semi-log plot of mean baseline-corrected FVIII activity over time based on OSC assay - Sequential PK subgroup (Arm A)- PK analysis set



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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