Sponsor: Sanofi **Drug substance(s):** BIVV001	**Study Identifiers:** IND: 017464 EudraCT/EU trial number: 2020-004947-10 NCT: NCT04770935 WHO: U1111-1255-4463 **Study code:** PKM16978

Title of the study:

A Phase 1, Open-Label Study to Assess the Pharmacokinetics, and Safety and Tolerability of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Adults with type 2N and 3 von Willebrand disease (VWD)

Study center(s):

This study was conducted at 4 sites (2 in the United States of America [US] and 2 in France), of which 3 sites screened participants (1 in the US and 2 in France), however, only 2 sites enrolled participants (both in France).

Study period:

Study initiation date: 03 May 2021 (first participant signed informed consent)

Study completion date: 20 December 2022 (last participant completed)

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary

・To characterize the PK of BIVV001 after a single intravenous (IV) administration, with factor VIII (FVIII) activity determined by the 1-stage activated partial thromboplastin time (aPTT) clotting assay, as well as BIVV001 capture chromogenic Coatest FVIII activity assay.

Secondary

・To assess the safety and tolerability of a single IV dose of BIVV001 in adults with type 2N and 3 VWD.

Methodology:

This was a Phase 1, multicenter, open-label, single-arm, single-dose, nonrandomized study in adult participants with type 2N or 3 VWD. A single IV dose of BIVV001 was administered to each participant.

Number of study participants:

Approximately 9 participants were planned to be enrolled in order to have at least 6 evaluable participants who completed the study for PK analysis. The actual number of participants analyzed per analysis population is as follows:

Safety: 6 participants

Pharmacokinetic: 6 participants

Antidrug antibody (ADA): 6 participants

Diagnosis and criteria for inclusion:

Adult male and/or female patients between 18 and 65 years of age (inclusive) with type 2N or 3 VWD (with a medical history of at least 25 exposure days to VWF- and FVIII-containing coagulation factor concentrates) without any other coagulation disorder (hereditary or acquired), any VWF or FVIII inhibitors, abnormal renal function, or any condition which in the judgement of the Investigator made the participant unsuitable for enrollment were eligible for the study.

Study products

Investigational medicinal product

• BIVV001 - Recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN).

• Formulation: BIVV001 drug product was supplied as a lyophilized powder in a sterile vial that required reconstitution with Sterile Water for Injection (diluent).

• Route of administration: IV infusion with an injection duration of 8 ±2 minutes.

• Dose regimen: Single dose (25 IU/Kg) administration on Day 1.

Duration of study intervention:

The overall duration of the study for each participant was up to approximately 57 days which included a screening period (up to 28 days), a treatment period (single administration of BIVV001 on Day 1), and a safety observation period of up to approximately 28 days.

Criteria for evaluation:

Primary

• PK parameters, assessed as FVIII activity by 2 assay methods, and including but not limited to the following: maximum activity (C_{max}); terminal half-life ($t_{1/2z}$); 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).

Secondary

• 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:

Safety analysis was based on the review of individual values and descriptive statistics. The safety analysis focused on the treatment-emergent period, defined as the time from the first BIVV001 administration up to the end-of-study visit (included). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of participants experiencing treatment-emergent adverse events (TEAEs) was summarized.

Potentially clinically significant abnormalities (PCSAs) for laboratory and vital signs parameters were flagged and summarized using frequency tables. Inhibitor development was summarized in a frequency table.

Pharmacokinetic parameters were summarized using descriptive statistics.

Summary Results:

Demographic and other baseline characteristics:

Six participants including 5 females (83.3%) with a mean (± standard deviation [SD]) age of 46.5 (6.6) years and baseline body weight of 90.43 (18.34) kg were enrolled. Four participants (66.7%) had a body mass index of $\geqslant$30 kg/m^2.

The median age of participants at diagnosis of their VWD was 7.0 years with all participants being diagnosed between the ages of 1 and 41 years. Two participants (33.3%) had type 2N VWD and 4 participants (66.7%) had type 3 VWD.

A mean (±SD) of 2.3 (1.9) bleeding events during the 12 months preceding screening was reported. In total, 3 participants (50.0%) had previously experienced a joint bleed while no participant had a bleeding event related to gastrointestinal dysplasia.

Four participants (66.7%) had previously been treated with prophylaxis against bleeds.

Exposure:

All 6 participants enrolled in the study received a single 25 IU/kg dose of BIVV001.

Safety results:

A single dose of 25 IU/kg 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.

There were no serious or severe TEAEs, AEs of special interest, or TEAEs leading to permanent discontinuation of study intervention or withdrawal from the study reported. Of the 6 participants included in the safety analysis set, 3 participants (50.0%) experienced 8 TEAEs during the study (headache, gastrointestinal motility disorder, nausea, and arthropod bite). All TEAEs were assessed by the Investigator as mild in severity and not related to BIVV001. The outcome of most TEAEs was reported as recovered/resolved except for the TEAEs of gastrointestinal motility disorder and nausea.

There were no clinically meaningful patterns or trends identified in laboratory or vital signs parameters throughout the study. No PCSAs were reported in the laboratory or vital signs parameters during the study.

Other than a skin abnormality (insect bites on right arm), which was considered clinically significant and reported as a TEAE (arthropod bite), all other physical examination findings were not clinically significant.

Pharmacokinetic results:

Plasma FVIII activity was measured by 2 bioanalytical methods: (1) 1-stage aPTT-based FVIII activity assay using Actin-FSL reagent (referred to as '1-stage clotting assay'). The 1-stage aPTT assay was calibrated using World Health Organization (WHO) 6th international FVIII standard and its lower limit of quantification (LLOQ) value was 1% FVIII activity (1 IU/dL). (2) BIVV001 capture chromogenic Coatest FVIII activity assay (referred to as 'capture chromogenic assay'). In the capture chromogenic assay, an anti-XTEN antibody was used to capture BIVV001 and the activity of the captured BIVV001 was then tested using a chromogenic assay. The 1-stage aPTT assay measures the activity of both endogenous FVIII and BIVV001, while the capture chromogenic assay measures only BIVV001 activity. As the capture chromogenic assay could not detect WHO plasma FVIII standard, it was calibrated using BIVV001 (ie, self or product specific standard). The LLOQ of capture chromogenic assay was 0.4% (0.4 IU/dL) FVIII activity.

Baseline-corrected FVIII activity levels and actual collection time were used to calculate the PK parameters by noncompartmental analysis.

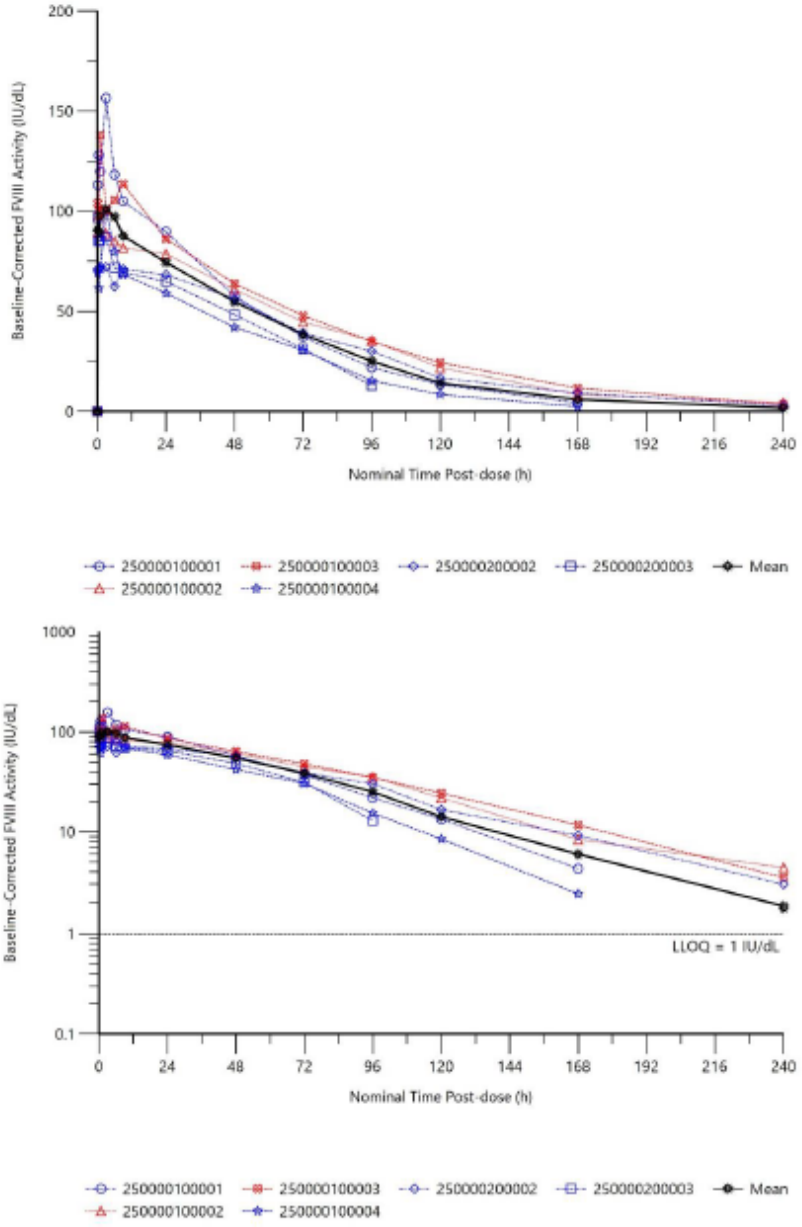
Plasma baseline-corrected factor VIII activity levels

Mean and individual participant plasma baseline-corrected FVIII activity level-time profiles, quantified by the 1-stage clotting assay and capture chromogenic assay are presented in Figure 1 and Figure 2, respectively.

As quantified by the 1-stage clotting assay, BIVV001 maintained a mean baseline-corrected FVIII activity level of >40 IU/dL (normal to near normal level) up to nearly 72 hours (3 days) postdose (38.5 IU/dL at 72 hours), >10 IU/dL up to 120 hours (5 days) postdose, and >1 IU/dL up to the last sampling time point of 240 hours (10 days) postdose.

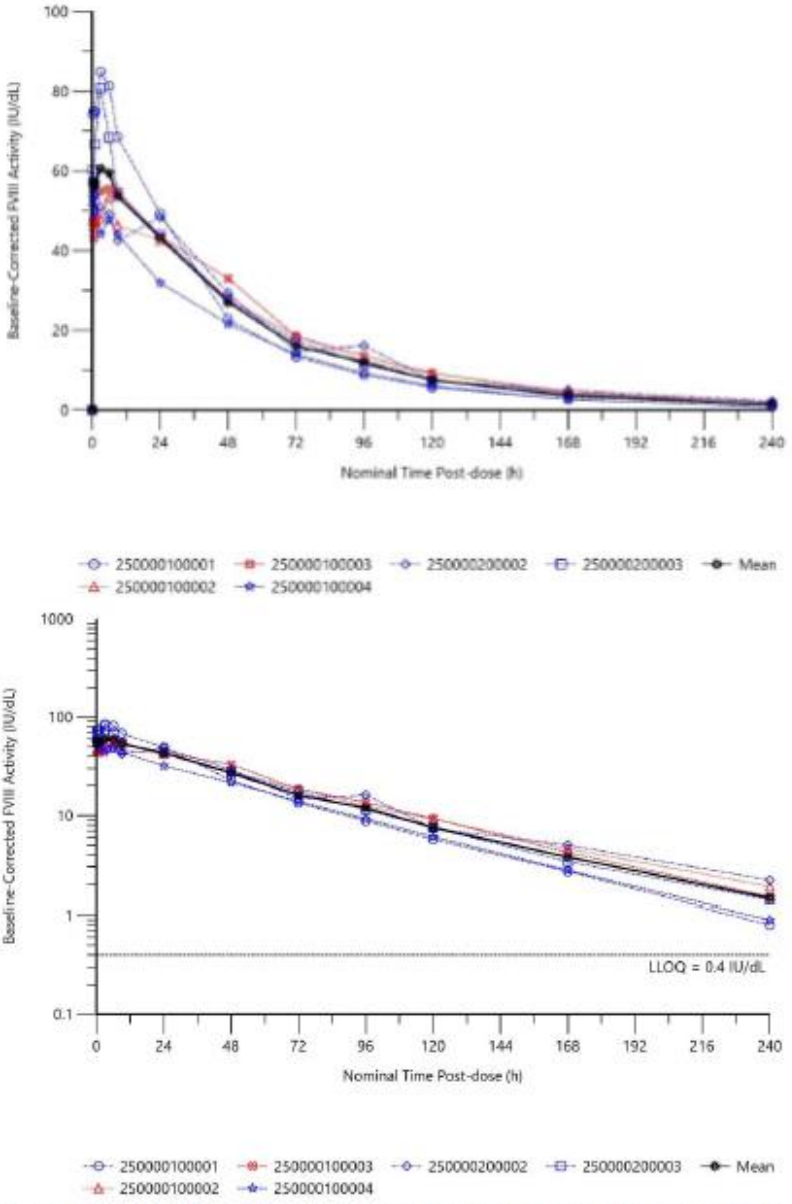
As quantified by the capture chromogenic assay, BIVV001 maintained a mean baseline-corrected FVIII activity level of >40 IU/dL (normal to near normal level) up to 24 hours (1 day) postdose, >10 IU/dL up to 96 hours (4 days) postdose, and >1 IU/dL up to the last sampling time point of 240 hours (10 days) postdose.

Figure 1 - Mean and individual participant plasma baseline-corrected factor VIII activity-time profiles, quantified by the 1-stage clotting assay, following a single 25 IU/kg dose of BIVV001 (upper panel: linear scale; lower panel: semi-logarithmic scale)



Note: participants with type 2N von Willebrand disease are displayed with red symbols and lines, and participants with type 3 von Willebrand disease are displayed with blue symbols and lines.

Figure 2 - Mean and individual participant plasma baseline-corrected factor VIII activity-time profiles, quantified by the capture chromogenic assay, following a single 25 IU/kg dose of BIVV001 (upper panel: linear scale; lower panel: semi-logarithmic scale)



Note: participants with type 2N von Willebrand disease are displayed with red symbols and lines, and participants with type 3 von Willebrand disease are displayed with blue symbols and lines.

Pharmacokinetic parameters for baseline-corrected factor VIII activity

A summary of plasma PK parameters for baseline-corrected FVIII activity is presented in Table 1.

The data obtained from the 1-stage clotting assay appeared to be higher than those obtained from the capture chromogenic assay. The reason for this discrepancy is not entirely clear, however, in this patient population the capture chromogenic assay results may be most accurate as interference from endogenous FVIII is avoided by use of a self-standard.

Table 1 - Mean ±SD (geometric mean) [CV%] pharmacokinetic parameters following a 25 IU/kg dose of BIVV001 in participants with type 2N or 3 von Willebrand disease

PK Parameters	1-Stage Clotting Assay	Capture Chromogenic Assay
N	6	6
C_{max} (IU/dL)	111 ± 30.9 (107) [28]	63.8 ± 14.8 (62.5) [23]
t_{max}[a] (h)	1.09 (0.17, 2.95)	2.96 (0.50, 6.00)
IR ((IU/dL)/(IU/kg))	4.41 ± 1.24 (4.27) [28]	2.55 ± 0.596 (2.49) [23]
AUC_{last} (IU·h/dL)	6620 ± 1630 (6440) [25]	3620 ± 387 (3600) [11]
AUC (IU·h/dL)	6910 ± 1550 (6760) [22]	3730 ± 419 (3710) [11]
$t_{1/2z}$ (h)	39.1 ± 8.70 (38.2) [22]	49.0 ± 10.2 (48.3) [21]
MRT_{inf} (h)	59.9 ± 11.7 (59.0) [20]	61.3 ± 9.74 (60.6) [16]
CL (mL/(h*kg))	0.380 ± 0.0910 (0.371) [24]	0.681 ± 0.0926 (0.677) [14]
V_{ss} (mL/kg)	22.1 ± 3.50 (21.9) [16]	41.5 ± 6.78 (41.0) [16]

CV = coefficient of variation

a Median (Min, Max)

Other results:

Factor VIII inhibitor development:

Factor VIII inhibitor development was not detected during this study.

Antidrug antibodies:

No treatment-emergent ADA response against BIVV001 was observed as no participant had treatment-induced or -boosted ADAs.

Issue date:24-Oct-2024