Sponsor: Sanofi **Drug substance(s):** rFVIIIFc-VWF-XTEN (BIVV001)	**Study Identifiers:** NCT03205163 **Study code:** 242HA101 (TDU16220)

Title of the study:

A Phase 1/2a Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A.

Study center(s): 7 sites in the United States of America and Japan

Study period:

Date first subject enrolled: 28 August 2017

Date last subject completed: 12 November 2018

Study Status: Completed

Phase of development: Phase 1/2a

Objectives:

The primary objective of this study was to assess the safety and tolerability of a single Intravenous (IV) administration of BIVV001 in adult previously treated patients (PTPs) with severe hemophilia A.

The associated endpoints were:

- The occurrence of adverse events (AEs)
- The occurrence of clinically significant abnormalities in laboratory tests, including development of inhibitors (neutralizing antibodies directed against FVIII) as determined by the Nijmegen-modified Bethesda assay

The secondary objective was to characterize the PK (pharmacokinetics) of BIVV001 after a single IV administration compared with the PK of Advate®, with FVIII activity determined by the one-stage activated partial thromboplastin time (aPTT)-based clotting assay with Actin® FSL as activator.

The endpoints associated with the secondary objectives were PK parameters, including but not limited to the following: maximum concentration (C_{max}), half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), area under the concentration time curve from time 0 to infinity (AUC_{∞}), mean residence time (MRT), incremental recovery (IR), and time to 1% above baseline for FVIII activity.

Methodology:

This was a Phase 1/2a, open-label, dose-escalation, multicenter study designed to evaluate the safety, tolerability, and PK of a single IV dose of BIVV001 in PTPs with severe hemophilia A.

After a brief washout (if applicable), subjects were dosed with a single IV dose of Advate followed by a PK sampling period. After another brief washout period, each subject was to be administered a single dose of BIVV001 followed by a PK sampling period. Subjects were also to undergo safety observation for 28 days following BIVV001 administration, which included inhibitor assessments 14 and 28 days after BIVV001 dosing.

Two BIVV001 doses were evaluated in this study: 25 IU/kg single dose (low-dose cohort) and 65 IU/kg single dose (high-dose cohort). A step-wise dosing and dose-escalation procedure was utilized.

Number of study participants: Planned: 18 Enrolled: 16 Treated with Advate: 16 Treated with BIVV001: 15 **Evaluated:** Safety: 16 Pharmacokinetics: 16
Diagnosis and criteria for inclusion: Adult male subjects (18 to 65 years of age) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII) who have had at least 150 exposure days (EDs) to FVIII products.
Study products: **Investigational medicinal product(s):** BIVV001 Formulation: The drug product was provided as lyophilized material in vials, to be reconstituted with sterile water for injection at the time of dosing. Route(s) of administration: IV Dose regimen: Single dose of either 25 or 65 IU/kg
Noninvestigational medicinal product(s) (if applicable): Advate Formulation: The drug product was provide as lyophilized material in vials, to be reconstituted with sterile water for injection at the time of dosing. Route(s) of administration: IV Dose regimen: Single dose of either 25 or 65 IU/kg
Duration of treatment: The total duration of study participation for each subject was expected to range from approximately 60 to 156 days, depending on the length of the Screening Period and the cohort to which the subject was assigned. The study consisted of 3 periods: A 28-day Screening Period (extendable to 120 days); an Advate dosing and PK sampling period (which also included an Advate washout that overlapped with PK sampling); a BIVV001 dosing and PK sampling period; and a 28 day Safety Observation Period (in which PK sampling and safety observation overlapped during the first 10 to 14 days of this period). **Duration of observation:** Final assessments for Study 242HA101 were performed in the End of Study (EOS)/Early Termination (ET) evaluations. Subjects who withdrew from Study 242HA101 (for reasons other than withdrawal of consent) prior to BIVV001 administration were asked to participate in a post Advate follow-up safety telephone call. Subjects who were administered BIVV001 and either completed the 28 day Safety Observation Period or withdrew from Study 242HA101 (for reasons other than withdrawal of consent) prior to completion of the Safety Observation Period were asked to submit to Visit 15 (EOS) procedures.

Criteria for evaluation:

Safety:

All safety analyses were performed based on the Safety Analysis Set and included all subjects who received at least one dose of Advate or BIVV001.

A treatment-emergent AE (TEAE) was defined as any adverse event that began on or after the study treatment (Advate or BIVV001) and within 28 days after BIVV001 administration. AEs with missing start dates were assumed to be treatmentemergent, unless the stop date was before the dosing date. In general, adverse events were summarized by subject incidence by dose level and overall for the Advate treatment period and separately for the BIVV001 treatment period. An AE starting on or after the single dose of study-administered Advate but before the single dose of study-administered BIVV001 was counted in the Advate treatment period. An AE starting on or after the single administration of study-administered BIVV001 and up to the end of study was counted in the BIVV001 treatment period.

Immunogenicity analyses:

All subjects were assessed for inhibitor development and anti-rFVIIIFc-VWF-XTEN antibodies at Screening, Advate dosing visit, BIVV001 dosing visit, Visit 14 and EOS visit (Visit 15). Testing for inhibitors was performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returned as $\geqslant$0.6 BU/mL, a separate sample must have been collected and tested for confirmation of inhibitor development within 2 to 4 weeks. Testing for potential antibody formation was performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific anti-drug antibody assay. Confirmed positive samples were further characterized for antibodies specific to Fc, FVIII, D'D3, or XTEN.

The number and percentage of subjects who tested positive for inhibitor development and the number and percentage of subjects who tested positive for anti-rFVIIIFc-VWF-XTEN antibodies were summarized by dose level using the Safety Analysis Set.

Pharmacokinetics:

All PK analyses were performed based on the PK analysis set (PKAS) and included all subjects who had adequate blood sample collections (following Advate or BIVV001 administration), to assess the key PK parameters.

FVIII activity was summarized by study drug, dose level and visit for both FVIII activity assays. FVIII activity versus time profiles were plotted in both original and log scale by study drug for both FVIII activity assays.

Individual PK parameter estimates were listed for each subject and summarized descriptively by drug and dose level group for both FVIII activity assays. An analysis of variance model with factors for drug and subject was used to compare BIVV001 to Advate. Analyses were performed for each dose level separately. PK parameters were log-transformed for these analyses, and estimated means, mean differences, and confidence intervals on the log scale were exponentiated to obtain estimates for geometric means, geometric mean ratios, and confidence intervals, respectively, on the original scale.

All individual PK parameter calculations were performed using actual timepoints calculated relative to the time of starting administration of Advate or BIVV001. Individual PK parameter estimates were listed for each subject and summarized descriptively by drug and dose level group for both FVIII activity assays. Summary descriptive statistics include the number of observations, arithmetic and geometric means, standard deviation, coefficient of variation, minimum, and maximum

Measured FVIII activity in predose samples was used to calculate baseline-corrected FVIII activity post treatment. Baseline-corrected FVIII activity post Advate or BIVV001 treatment is presented as FVIII activity. The units for FVIII activity are IU/dL or %.

FVIII activity post start of injection (SOI) was summarized by study drug, dose level, visit, and assay (one-stage clotting assay). Summary descriptive statistics include number of non-missing values, mean, geometric mean, standard deviation, percent coefficient of variation, minimum, and maximum.

Pharmacokinetic sampling times:

FVIII activity for Advate (one-stage clotting assay) was assessed prior to the administration of Advate (predose of 25 or 65 IU/kg) and at 0.5, 1, 6, 24, 48, and 72 hours post injection.

FVIII activity for BIVV001 (one-stage clotting assays) was assessed just prior to the administration of BIVV001 and at 0.17, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, and 240 hours (10 days) post injection for all subjects administered the low dose of BIVV001 and additionally at 288 and 336 hours (14 days) post injection for those subjects administered the high dose of BIVV001 and at the EOS/ET Visit.

Statistical methods:

No statistical hypothesis testing was planned.

In general, safety and PK data were summarized using standard summary statistics for continuous and categorical data. Data was summarized by study drug and dose level.

Continuous variables were summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Pharmacokinetic parameters were also summarized using geometric mean and percent coefficient of variation (%CV). Categorical variables were summarized by counts and percentages.

Summary Results:

Population characteristics:

A total of 16 subjects were enrolled in Study 242HA101. Seven subjects enrolled in the low-dose (25 IU/kg) cohort. Six subjects in the low dose cohort received both Advate and BIVV001 and completed Study 242HA101. One subject discontinued due to complications from a motor vehicle accident prior to receiving BIVV001. In addition, all 9 subjects enrolled in the high-dose (65 IU/kg) cohort received both Advate and BIVV001 and completed Study 242HA101.

Of the 16 subjects enrolled, 14 were enrolled in the United States and 2 were enrolled in Japan. All subjects were male. The median age was 36 years (range: 19 to 63 years) and the majority of subjects (81.3%) were white. The median weight was 79.0 kg (range: 59.9 to 100.7 kg) and the median BMI was 25.9 kg/m2 (range: 21.0 to 34.2 kg/m2).

Safety results:

- Single dose BIVV001 was well tolerated and no safety concerns were identified. No inhibitor development to FVIII was detected and there were no reports of serious hypersensitivity or anaphylaxis.
- During the Advate treatment period, 8 TEAEs were reported in 3 subjects. This included 4 treatment emergent serious adverse events (TESAEs) that occurred in the setting of a motor vehicle accident, after which the subject was withdrawn from the study. The most common TEAE during the Advate treatment period was thrombin-antithrombin III complex increased (2 subjects, 1 from each cohort). Three TEAEs reported in 2 subjects were assessed by the Investigator as related to study treatment: thrombin-antithrombin III complex increased (2 subjects) and Fibrin D dimer increased (1 subject). There were no associated adverse events reported in either subject.

- During the BIVV001 treatment period, 18 TEAEs were reported in 9 subjects. This included 1 TESAE of a small intestinal obstruction; the Investigator attributed the event to complications from a prior appendectomy and assessed the event as unrelated to BIVV001. The most common TEAEs during the BIVV001 treatment period were thrombin-antithrombin III complex increased and headache (2 subjects each, 1 from each cohort). Three TEAEs assessed by the Investigator as treatment-related were reported in the same 2 subjects as during the Advate treatment period. Identical to the Advate treatment period, these were Thrombin-antithrombin III complex increased (2 subjects) and Fibrin D dimer increased (1 subject). There were no associated adverse events reported in either subject. No pattern of clinically meaningful abnormalities in laboratory values was observed.
- The higher number of TEAEs reported during the BIVV001 treatment period compared to the Advate treatment period was likely attributable to the longer duration of the BIVV001 treatment period (approximately 28 days versus approximately 3-4 days). TEAEs were generally similar during the BIVV001 treatment period between the low and high dose cohorts. The majority of TEAEs were assessed by the Investigator as unrelated to study treatment. Related TEAEs included elevations in coagulation parameters reported in the Advate and BIVV001 treatment periods with no corresponding clinical sequelae reported. Overall, single dose BIVV001 was well tolerated and no safety concerns were identified.

Pharmacokinetic results:

- PK comparison between Advate and BIVV001 at 25 and 65 IU/kg was conducted using geometric mean for parameters and geometric mean ratios (fold change) of BIVV001 relative to Advate.
- Following Advate treatment, FVIII activity based on the one-stage clotting assays on Day 3 (72 hours) was 0.66% at 25 IU/kg and 2.33% at 65 IU/kg. Following BIVV001 treatment at 25 IU/kg, FVIII activity based on the one-stage clotting assays on Day 3 was 26.20% and, on Day 5 (120 hours) was 12.23%, and on Day 7 (168 hours) was 5.32%, respectively. Following BIVV001 treatment at 65 IU/kg, FVIII activity based on the one-stage clotting assays on Day 3 was 78.21%, on Day 5 was 37.79%, and on Day 7 was 17.04%, respectively. Taking into account the data, FVIII activity on Day 7 after 65 IU/kg indicates C_{trough} in the range of 10% to 17% with once weekly dosing with BIVV001 treatment.
- Compared to Advate treatment, FVIII activity AUC_{∞} was higher (p-value < 0.001) following BIVV001 treatment by 7.0-fold at 25 IU/kg and 6.54-fold at 65 IU/kg, respectively.
- FVIII activity declined slowly following BIVV001 treatment with a $t_{1/2}$ of 37.61 hours at 25 IU/kg and 42.54 hours at 65 IU/kg, respectively. Compared to Advate treatment, $t_{1/2}$ was longer following BIVV001 treatment by 4.13- at 25 IU/kg and 3.24-fold at 65 IU/kg, respectively.
- Consistent with prolonged half-life, the time to 10% and 40% FVIII activity was also longer following BIVV001 treatment.
- Following Advate treatment, FVIII activity was maintained above 10% for 23.59 hours, at 25 IU/kg and 41.27 at 65 IU/kg. Following Advate treatment, FVIII activity based on the one-stage clotting assays was maintained above 40% for 1.66 hours at 25 IU/kg and 19.18 at 65 IU/kg.
- Following BIVV001 treatment, FVIII activity was maintained above FVIII activity levels of 10% over a longer period compared to Advate.

- FVIII activity, as measured by the one stage clotting assay was maintained above 10% for 126.10, respectively, at 25 IU/kg and 201.58, respectively, at 65 IU/kg.

- FVIII activity, as measured by the one stage clotting, was maintained above 40% for 24.89 hours at 25 IU/kg and 111.61 hours at 65 IU/kg.

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