Sponsor: Sanofi **Drug substance(s):** BIVV001	**Study Identifiers:** **Study code:** 242HA102 (TDR16219)

Title of the study:

A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001

Study center(s):

This study was conducted in a single center in Bulgaria.

Study period:

Date first subject enrolled: 10 October 2018

Date last subject completed: 12 April 2019

Study Status: Completed

Phase of development: Phase 1

Objectives:

The **primary objective** was to assess the safety and tolerability of a total of 4 once-weekly doses of intravenous (IV) BIVV001 at a dose of 50 IU/kg or 65 IU/kg in adult male previously treated patients (PTPs) 18 to 65 years of age (inclusive) with severe hemophilia A.

The **secondary objective** was to characterize the pharmacokinetics (PK) of BIVV001 after a total of 4 once-weekly IV doses for each cohort, with factor VIII (FVIII) activity determined by the one-stage (activated partial thromboplastin time [aPTT]) clotting assay.

Methodology:

This was a Phase 1, open-label, single-site study to evaluate the safety, tolerability, and PK of a total of 4 once-weekly doses of 50 IU/kg or 65 IU/kg BIVV001 in adult male PTPs 18 to 65 years of age (inclusive) with severe hemophilia A who have received at least 150 exposure days (EDs) of prior FVIII treatment.

The study comprised a **Screening Period**, a **Dosing Period**, and a **Safety Observation Period** as follows:

- **Screening Period** (approximately 21 days not to exceed 56 days): Subjects were screened for determination of eligibility. Subjects underwent a washout period prior to Screening assessments of FVIII activity and the inhibitor test.
- **Dosing Period** (22 days): Subjects received 4 once-weekly doses of BIVV001 on Days 1, 8, 15 and 22. During this period, subjects also underwent safety and PK assessments. A predose PK sample was taken on Day 1. In addition, there were multiple PK samples taken after dosing on Days 1 and 22, and a trough (168h) sample occurring prior to dosing on Days 8, 15, and 22.
- **Safety Observation Perio**d (28 days): The Safety Observation Period began on the day the subject received the last dose of BIVV001 (Day 22) and overlapped with the PK sampling period for the subject's last dose. Subjects could resume treatment with prestudy FVIII product during the 28-day Safety Observation Period after completing the Visit 16 (Day 36) activities, including the 14-day inhibitor test. For subjects who completed all 4 once-weekly doses of BIVV001, the Safety Observation Period ended with the End-of-Study Visit at Day 50. For subjects who discontinued treatment early, the Safety Observation Period ended with the Early Termination Visit 28 days after the last dose of BIVV001.

Number of subjects:

Planned: up to 25 subjects (10 subjects in the 50 IU/kg cohort and up to 15 subjects in the 65 IU/kg cohort)

Enrolled: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort)

Treated: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort)

Evaluated:

Efficacy/pharmacodynamics: Not applicable

Safety: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort)

Pharmacokinetics: 23 subjects (9 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort)

Diagnosis and criteria for inclusion:

Adult male PTPs 18 to 65 years of age (inclusive) with severe hemophilia A who have received at least 150 EDs of prior FVIII treatment.

Study products

Investigational medicinal product(s): BIVV001
Formulation: lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent) at the time of dosing. Each vial of drug product included 1000 IU of BIVV001 along with the following excipients: L histidine, L arginine hydrochloride, sucrose, calcium chloride dihydrate, polysorbate 80, sodium hydroxide, and hydrochloric acid.
Route(s) of administration: IV

Dose regimen: 4 once-weekly doses at 50 IU/kg or 65 IU/kg

Duration of treatment:
The study included a Dosing Period of 22 days during which subject received 4 once-weekly doses of BIVV001 (Days 1, 8, 15 and 22).
Duration of observation:
The duration of study participation for any individual subject was anticipated to be approximately 71 days: an anticipated Screening Period of 21 days, a Dosing Period over 22 days, and a Safety Observation Period of 28 days after the last dose of BIVV001. The actual duration of study participation depended on the length of the Screening Period, which was not to exceed 56 days.

Criteria for evaluation:

Efficacy/pharmacodynamics: Not applicable.
Safety: Safety and tolerability of repeat doses of BIVV001 was assessed through the monitoring of the occurrence of adverse events (AEs) and serious adverse events (SAEs) as well as 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.
Pharmacokinetics: For the secondary objective, FVIII activity following repeat doses of BIVV001 was assessed using the one-stage (activated partial thromboplastin time [aPTT]-based) clotting assay. Estimated PK parameters, included but were not limited to the following: maximum activity (C_{max}), half-life ($t_{½}$), total clearance at steady state (CL_{ss}), accumulation index (AI), area under the activity-time curve from hour 0 over the dosing interval ($AUC_{0\text{-}tau}$), volume of distribution at steady state (V_{ss}), mean residence time (MRT), incremental recovery (IR), lowest (trough) concentration that a drug reaches before the next dose is administered (C_{trough}), and time to 1% above baseline for FVIII activity.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

FVIII activity was assessed using a one-stage (aPTT-based) clotting and two-stage chromogenic coagulation assays.
The PK sampling schedule was as follows:

- Day 1: PK assessments occurred pre-dose and at the following post-dose timepoints: 30 (±3) minutes, 3 hours (±15 minutes), 24 hours (±1 hour), 48 hours (±2 hours), 72 hours (±2 hours), and 120 hours (±2 hours).
- Day 8: PK assessment occurred pre-dose and served as the Day 1 168 hours timepoint.
- Day 15: PK assessment occurred pre-dose and served as the Day 8 168 hours timepoint.
- Day 22: PK assessments occurred pre-dose (Day 15 168 hours timepoint) and at the following post-dose timepoints: 30 (±3) minutes, 3 hours (±15 minutes), 24 hours (±1 hour), 48 hours (±2 hours), 72 hours (±2 hours), 120 hours (±2 hours), 168 hours (±5 hours), 240 hours (±5 hours), and 336 hours (±5 hours)

Statistical methods:

No formal statistical hypothesis was tested. In general, the following approaches were used in the analysis in the summary of safety and PK endpoints. Safety and PK data were summarized using standard summary statistics for continuous and categorical data. Continuous variables were summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Where specified, the 25th and 75th percentiles were also provided. Pharmacokinetic parameters were also summarized using the geometric mean and 95% confidence interval, and percent coefficient of variation (%CV). Categorical variables were summarized by counts and percentages.
One interim analysis was performed after at least 8 subjects in Cohort 1 had completed their PK assessments. As of 07 February 2019, the cutoff date of the interim analysis, 15 subjects had enrolled, of whom 13 received at least one dose of BIVV001 ([50 IU/kg, n=10], [65 IU/kg, n=3]). The analysis focused on baseline demographic information, PK data, and adverse events and was of descriptive nature. No formal hypothesis testing was performed.

Summary Results:

Safety results:

- Repeat doses of BIVV001 were well tolerated and no safety concerns were identified.
- No inhibitor development to FVIII was detected and there were no reports of hypersensitivity, anaphylaxis, or vascular thrombotic events.
- Of the 24 subjects included in the Safety Analysis Set, 12 subjects (50.0%) were reported to have experienced at least one treatment-emergent adverse events (TEAE), with a total of 25 TEAEs reported.
- No study drug-related TEAEs, TEAEs leading to study discontinuation, treatment-emergent serious adverse events or deaths were reported during the study.
- Treatment-emergent adverse events were most commonly (≥2 subjects overall) reported in the following system organ classes: infections and infestations (5 subjects [20.8%]), musculoskeletal and connective tissue disorders (3 subjects [12.5%]), gastrointestinal disorders (2 subjects [8.3%]), nervous system disorders (2 subjects [8.3%]) and respiratory, thoracic and mediastinal disorders (2 subjects [8.3%]). The most common (≥2 subjects overall) TEAEs reported were rhinitis (4 subjects [16.7%]), arthralgia (2 subjects [8.3%]), upper respiratory tract infection (2 subjects [8.3%]), and headache (2 subjects [8.3%]). All other TEAEs were reported in 1 subject (4.2%), each. The reported TEAEs were generally consistent with those anticipated in a population of adult subjects with severe hemophilia A.
- Of the 25 TEAEs reported overall the majority (23 TEAEs) were assessed as mild with 2 TEAEs assessed as moderate and none assessed as severe.
- No clinically meaningful changes from baseline, patterns or trends were observed in any hematology, clinical chemistry, or coagulation parameter. Review of all potentially clinically significant laboratory abnormalities did not reveal an adverse effect of BIVV001 treatment.
- All 24 subjects in the Safety Analysis Set had a valid inhibitor test and no subject developed an inhibitor to FVIII. The overall estimated inhibitor incidence was 0% (95% CI: 0.00%, 14.25%).
- Of the 23 subjects considered evaluable for anti-drug antibodies (ADAs), 22 (95.7%) remained negative at all on study assessments. One subject ([4.3%]; Subject 170-020) developed a positive ADA at the Day 50 (EOS) visit. Further characterization testing was negative for antibodies specific to FVIII, D'D3, and XTEN.
- No clinically meaningful changes from baseline, patterns or trends were observed for any vital sign parameter. Review of all potentially clinically significant vital sign measurements did not reveal an adverse effect of BIVV001 treatment.

Pharmacokinetic results:

- The mean FVIII activity profiles on Day 22 were comparable to Day 1 following once-weekly BIVV001 treatment at both 50 and 65 IU/kg supporting minimal accumulation.
- On Day 22 following once-weekly 50 IU/kg BIVV001 treatment, the mean FVIII activity was 46.28% and 30.46% at 72 hour; 22.30% and 14.48% at 120 hour; and 9.83% and 6.74% at 168 hour with the one-stage clotting and chromogenic assay, respectively.
- On Day 22 following once-weekly 65 IU/kg BIVV001 treatment, the mean FVIII activity was 69.31% and 37.63% at 72 hour; 27.21% and 16.51% at 120 hour; and 11.81% and 7.64% at 168 hour with the one-stage clotting and chromogenic assay, respectively.
- The geometric mean $t_{1/2}$ based on one-stage clotting and chromogenic assays, respectively, was 41.25 and 43.87 hour following 50 IU/kg; and 37.31 and 42.51 hour following 65 IU/kg.
- On Day 22 following once-weekly 50 IU/kg BIVV001 treatment, the geometric mean C_{max} was 131 and 115 IU/dL; the geometric mean IR was 2.43 and 2.15 IU/dL per IU/kg; the geometric mean $AUC_{0\text{-}tau}$ was 8290 and 5860 hr*IU/dL with one-stage clotting and chromogenic assay, respectively.
- On Day 22 following once-weekly 65 IU/kg BIVV001 treatment, the geometric mean C_{max} was 171 and 172 IU/dL; the geometric mean IR was 2.45 and 2.52 IU/dL per IU/kg; the geometric mean $AUC_{0\text{-}tau}$ was 11200 and 7870 hr*IU/dL with one-stage clotting and chromogenic assay, respectively.
- The C_{max} and IR for one-stage and chromogenic assays were comparable on Days 1 and 22 indicating consistent recovery within dose level (50 and 65 IU/kg once-weekly treatment).
- The AI for one-stage and chromogenic assays at steady state was close to unity. The one-stage and chromogenic FVIII activity AI at steady state was 1.07 and 1.08, respectively at 50 IU/kg; and 1.05 and 1.07, respectively at 65 IU/kg.
- Across the 50 and 65 IU/kg dose levels, the one-stage and chromogenic FVIII activity dose-normalized $AUC_{0\text{-}tau}$ was comparable supporting dose proportionality in $AUC_{0\text{-}tau}$ with once-weekly dosing.
- The geometric mean C_{avg} was >35% with 50 IU/kg once-weekly dosing; and >47% with 65 IU/kg once-weekly dosing.
- The geometric mean C_{trough} of one-stage and chromogenic assay FVIII activity at steady state was 9.16 and 6.51 IU/dL with 50 IU/kg once-weekly dosing, respectively; and 10.8 and 7.37 IU/dL with 65 IU/kg once-weekly dosing, respectively.
- On Day 22, the geometric mean one-stage and chromogenic FVIII activity was maintained above 40% for 76.18 and 55.84 hour, respectively at 50 IU/kg; and 91.87 and 68.92 hour, respectively at 65 IU/kg.
- On Day 22, the geometric mean one-stage and chromogenic FVIII activity was maintained above 10% for 162.75 and 141.16 hour, respectively at 50 IU/kg; and 172.53 and 146.70 hour, respectively at 65 IU/kg.

Issue date: 21-Nov-2023