STATISTICAL ANALYSIS PLAN

Protocol title:	**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**
Protocol number:	**EFC16295**
Compound number (INN/Trademark):	**BIVV001**
Study phase:	**Phase 3**
Short title:	**Safety, efficacy and PK of BIVV001 in pediatric patients with hemophilia A (XTEND-Kids)**
Statistician:	[redacted]
Statistical project leader:	
Date of issue:	**23-Aug-2021**

Regulatory agency identifier number(s):

IND:	017464
EudraCT:	2020-000769-18
WHO:	U1111-1244-0558
NCT:	NCT04759131

Total number of pages: 53

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

VERSION HISTORY

This statistical analysis plan (SAP) for Study EFC16295 is based on the protocol dated 15-May-2020.

The first participant was enrolled on 22-Mar-2021.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	Current version	Not Applicable	Original version

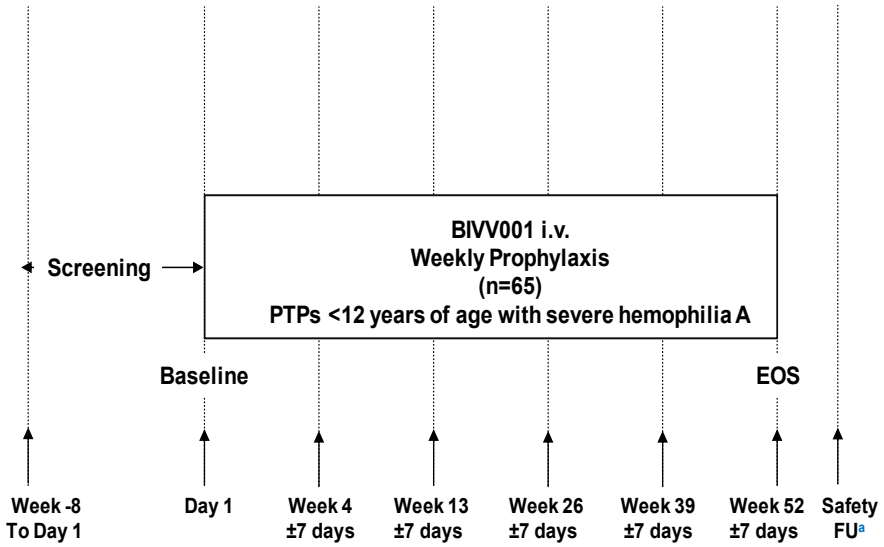
1 INTRODUCTION

1.1 STUDY DESIGN

This is a multinational, multicenter, open-label Phase 3 study of the safety, efficacy and pharmacokinetics (PK) of BIVV001 in previously treated patients (PTPs) <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII).

The study is comprised of <6 years and 6 to <12 years age cohorts, where participants will receive BIVV001 at a dose of 50 IU/kg IV QW for 52 weeks. Approximately 65 participants will be enrolled to achieve at least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 exposure days (EDs). Enrollment in a planned open-label extension study will be offered to participants after completion of this study.

Figure 1 - Study schema



Abbreviations: EOS = end of study; FU = follow-up; IV = intravenous; PTP = previously treated patient.

a The safety follow-up call or visit will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study.

All enrolled participants will come in to scheduled visits at Baseline (Day 1), Week 4, Week 13, Week 26, Week 39 and Week 52.

Following a washout period (at least 3 to 4 days, depending on age), the first 24 participants from the 2 age cohorts (at least 12 participants <6 years of age and at least 12 participants 6 to <12 years of age) will undergo PK sampling after their first dose of BIVV001 (Baseline).

In addition, participants who undergo major surgery during the study will be included in the surgery subset to assess control and prevention of bleeding during use of BIVV001 in the surgical setting.

Participants will be offered enrollment in an open-label extension study after completion of this study based on eligibility criteria.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A	• The occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen modified Bethesda assay
Secondary	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) (for treated) • ABR 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%
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• 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
• To evaluate BIVV001 consumption for prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• 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)
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• 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)

Objectives	Endpoints
• To evaluate the efficacy of BIVV001 for perioperative management	• 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
• To evaluate the safety and tolerability of BIVV001 treatment	• 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 • The occurrence of embolic and thrombotic events
• To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	• 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
Tertiary/Exploratory	
• To assess the impact of BIVV001 treatment on caregiver- and/or patient-reported clinical outcome assessments measurements and health resource utilization	• Changes in PROMIS-SF Physical Function measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in PROMIS Pain Intensity measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in PROMIS Pediatric-SF Pain Interference measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in EuroQoL 5-dimension 5-level Youth (EQ-5D-Y) from Baseline to Week 52 (≥8 years old) and via parent proxy version (4-7 years old) • Caregiver interviews at Week 52 (or subsequent post-study follow-up visit) • Changes in healthcare resource utilization

2 SAMPLE SIZE DETERMINATION

The determination of the number of participants is based on clinical rather than statistical considerations. Taking into consideration the guideline from Committee for Medicinal Products for Human Use (EMEA/CHMP/BPWP/144533/2009 rev.2), approximately 65 PTPs will be enrolled to obtain at least 50 participants with at least 50 EDs at the end of the study. All eligible participants completing or remaining at the end of study will be offered participation in the planned extension trial.

At least 12 participants in each age cohort need to have completed adequate blood sample collection to assess key PK parameters.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
All-Enrolled Analysis Set	All participants who were enrolled in the study, regardless of whether they were dosed with study drug or not. Participants will be considered enrolled when the Investigator has verified that they are eligible according to the criteria in Section 5 of the protocol. Participant disposition and enrollment summaries will be based on the All-Enrolled Analysis Set.
Full Analysis Set	All participants who take at least 1 dose of study intervention. All analyses of demographics, baseline characteristics, and efficacy will be based on the FAS, unless otherwise specified.
Safety Analysis Set	The safety analysis is the same as the Full Analysis Set and will include all participants who receive at least one dose of study drug. All analyses of safety will be based on the Safety Analysis Set, unless otherwise specified.
Per Protocol Set	A subset of the Full Analysis Set including participants who do not have important protocol deviations potentially impacting efficacy. The Per Protocol Set will be utilized for sensitivity analysis of the efficacy endpoint of annualized bleeding rate.
PK Analysis Set (PKAS)	All participants who have completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist.
Surgery Subgroup	All participants who have undergone major surgery after the first dose of study drug.

4 STATISTICAL ANALYSES

All summaries and statistical analyses will be generated using SAS Version 9.0 or higher.

4.1 GENERAL CONSIDERATIONS

Unless otherwise specified, all data will be summarized for each age cohort (<6 years and 6 to <12 years) and overall.

The surgery subgroup will be included in baseline tables as well as the overall AE summary. When the surgery subgroup is included in a summary table, participants who participated in the surgery subgroup will be included in the columns for age cohort and the surgery subgroup but will only be counted once in the overall column.

Baseline

Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug, excluding measurements taken during a surgical/rehabilitation period. For HJHS, if there are no measurements taken prior to the first dose of the drug, and the first measurement is taken no more than 7 days after the first dosing, then this first measurement will be considered as baseline for HJHS.

Study Day

Study day is defined as the number of days relative to the date of the first dose of study drug. The first dose of study drug is Day 1. Study day will be calculated as (date of event – first dose date +1) if the date of event is on or after the first dose date or (date of event – first dose date) if the date of event is before the first dose date. If the date of event is missing or partial, the corresponding study day will be left blank.

Exposure Day

One exposure day (ED) is defined as a 24-hour period in which a participant receives 1 or more doses of study drug, with the time of the first injection of study drug defined as start of the ED.

4.1.1 Definition of study periods

This section defines the study periods used for different analyses, including treatment period, efficacy period, surgical/rehabilitation period, and safety period.

All analyses and summaries relating to bleeding and consumption will be based on the ***efficacy period*** (Section 4.1.1.2); data collected during the PK and surgical/rehabilitation periods (major and minor) will not be included.

All other efficacy analyses will be based on the ***treatment period*** (Section 4.1.1.1), excluding data that occurs during any major surgical/rehabilitation period to avoid confounding the treatment effect. Analysis of efficacy endpoints that are visit-based will not include visits that are coincidental with a major surgical/rehabilitation period.

Surgical evaluations will be based on the ***surgical/rehabilitation period*** (Section 4.1.1.3).

All safety analyses will be based on the ***safety period*** (Section 4.1.1.4). Unless otherwise specified, adverse events and laboratory evaluations occurred during major surgical/rehabilitation periods will not be included in the safety summaries.

4.1.1.1 Treatment period

The treatment period is defined as the actual treatment that the participant follows.

The start date and time of the treatment period is defined as the date and time of the first dose of study drug (or, if the time is not available, at 00:01 on the day of the first dose). The end date and time of the treatment period is defined as 23:59 on the day of the last dose of study drug.

The duration of treatment period is the time period from the start of the treatment period to the end of that treatment period. The total duration will be calculated in minutes and converted to days as the number of minutes divided by 1440.

4.1.1.2 Efficacy period

The efficacy period will be used for the evaluation of bleeding and consumption endpoints. For a participant to have an evaluable efficacy period over the duration of study, he/she must have at least 2 prophylactic dose of study drugs. The efficacy period is defined as the treatment period interrupted for PK periods, surgical/rehabilitation periods (major and minor) and large injection intervals as described below.

Adjustments Due to PK sampling period(s)

For participants undergoing PK sampling after their first dose of BIVV001, the efficacy period starts with the date and time of the first prophylactic dose following the completed PK sampling period (168 hours), and ends with the end of the treatment period as defined in Section 4.1.1.1. That is, if the initial PK sampling period is incomplete due to an aborted collection of blood samples following the PK injection (eg, because of a bleeding episode that required treatment), then the efficacy period will begin following a subsequent fully executed PK sampling period.

Adjustments Due to Surgical/Rehabilitation Periods

For analysis purposes, the efficacy period will be adjusted for all surgical/rehabilitation periods (major and minor). The start and end of the efficacy period are adjusted as follows:

- For all participants, the efficacy period continues up to 1 minute before the start of a surgical/rehabilitation period.
- For participants on a prophylactic regimen following the end of a surgical/rehabilitation period, the efficacy period for the prophylactic regimen re-starts at the first prophylactic dose following the end of the surgical/rehabilitation period.

Bleeding episodes that occur during the surgical/rehabilitation period will be attributed to the surgical/rehabilitation period and hence not counted towards the ABR.

Adjustments Due to Large Injection Intervals

For analysis purposes, the efficacy period will also be adjusted to account for large intervals between injections resulting from missing data. A large interval is defined as >28 days between any 2 adjacent BIVV001 injections within a prophylactic treatment regimen, and any such intervals will be removed from the efficacy period. The efficacy period prior to each such interval will end at the time of the last injection prior to the interval and restart at the time of the next prophylaxis injection. The efficacy period will be adjusted for each identified interval that is not within a surgical/rehabilitation period.

4.1.1.3 Surgical/rehabilitation period

The broadest span of time for the surgical/rehabilitation period is from the first dose of BIVV001 given for the surgery (ie, the pre-surgery dose) up to 1 minute before the first regular prophylactic dose after the last day of postoperative care/rehabilitation.

Since not all participants will have these events, specific considerations for the start and end of the surgical/rehabilitation period are as follows:

Start of the surgical/rehabilitation period:

- If there is more than one pre-surgical dose, then the first one should be selected (a pre-surgical dose can be administered on the day or the day before surgery).
- If there is no pre-surgical dose but there was a prophylactic dose, or a dose given for "OTHER" reason prior to the surgery on the day of or the day before surgery, then the last of these doses should be selected.
- If there is no pre-surgical dose or no prophylactic dose on the day before surgery, then select the start date/time of the surgery. If the time was not recorded, then select the date and impute 00:01 for the time.

End of the surgical/rehabilitation period:

- If the participant resumed the prophylactic regimen following the surgical/rehabilitation period, then the end of the surgical/rehabilitation period is 1 minute before the first regular prophylactic dose after the latest date and time among the following (impute 23:59 if time is not available): 1) discharge from the hospital, 2) end of perioperative period follow-up phone call, and 3) end of a two-week period (one-week for minor surgeries) after the resumption of weekly prophylaxis treatment.
- If the participant did not resume the prophylactic regimen following the surgical/rehabilitation period (eg, the participant received no further prophylactic doses), then the end of the surgical/rehabilitation period is imputed as 23:59 on the last date among the following: 1) discharge from the hospital, 2) end of perioperative period follow-up phone call, and 3) end of a two-week period (one-week for minor surgeries) after the last surgical dose.

- If the overall end of study is declared while the participant is still in the surgical/rehabilitation period, then select the date of the end-of-study visit and impute 23:59 for the time if a time is not provided.

Two exceptions are noted:

- If 2 (or more) major surgeries are performed without an intervening discharge from the hospital, then the first surgical/rehabilitation period will end 1 minute before the start of the next surgery and the second surgical/rehabilitation will end as described above. The same will also apply among overlapping minor surgeries.
- If minor surgery is performed during postoperative care or rehabilitation of a major surgery then the surgical/rehabilitation period for the minor surgery will start and end on the day of the minor surgery, at 00:01 and 23:59, respectively, if times are not otherwise provided or recorded as 00:00. The surgical/rehabilitation period for the major surgery will include the minor surgery (ie, the surgical/rehabilitation period for the major surgery does not stop and restart around the minor surgery) and will end as otherwise defined.

The surgical/rehabilitation period will be determined in the same manner for both major and minor surgeries.

4.1.1.4 Safety period

The safety period is defined as beginning at the first dose of study drug. For participants who enroll in the open-label extension study after completion of this study, the safety period ends at the end of their treatment period as defined in Section 4.1.1.1. For participants who do not enroll in the extension study, the safety period ends at the Safety Follow-up Call or Visit. If the Safety Follow-up Call or Visit is missing, then the safety period ends at the last ePD entry, the last study visit, or the last documented participant contact, whichever occurs latest.

4.2 PARTICIPANT DISPOSITIONS

Disposition of participants will be summarized using the All-Enrolled Analysis Set. The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized by age cohort and overall. The number of participants who completed the study and the number of participants who discontinued from the study early, including the primary reason for discontinuation, will be tabulated by age cohort and overall.

Separate summaries of enrollment by country/region and site and the number of participants attending each visit will be provided using the All-Enrolled Analysis Set by age cohort and overall. Disposition, including date of last visit and reason for early discontinuation, for participants who did not complete the study, will be provided in a listing by participant using the All-Enrolled Analysis Set.

Protocol deviations

The number of participants with major protocol deviations will be summarized by age cohort and overall for the FAS. Major protocol deviations that occurred during a major surgical/rehabilitation period will be presented separately in the summary.

Important protocol deviations impacting efficacy assessment will be identified by the study team from the following protocol deviation categories and will be finalized before the database lock:

- Entered the study even though entry criteria were not satisfied
- Developed withdrawal criteria during the study but were not withdrawn
- Received the wrong treatment or incorrect dose
- Received an excluded concomitant treatment
- Persistent misuse of the ePD device impacting interpretation of data based on medical review

Important protocol deviations will be summarized by age cohort and overall for the FAS. Participants who have at least one important protocol deviation will be excluded from the Per Protocol Set.

4.3 PRIMARY ENDPOINT ANALYSIS

4.3.1 Definition of endpoint

The primary endpoint for this study is the occurrence of inhibitor development, defined as an inhibitor result of $\geq$0.6 BU/mL that is 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 must be performed by the central laboratory using the Nijmegen-modified Bethesda assay. The date of inhibitor development is the date of the sample with the first positive test result which was subsequently confirmed by the second sample.

Results from blood samples collected during surgical/rehabilitation periods for the purpose of determining the presence of an inhibitor will be included in this analysis.

4.3.2 Main analytical approach

The overall incidence of positive inhibitor formation will be calculated as:

$$\frac{\text{Number of participants with an inhibitor}}{\text{Number of participants reaching ED milestone or who have an inhibitor}}$$

The primary analysis of inhibitor development is based on all participants who have reached at least 50 EDs and had at least one inhibitor test performed at or beyond this milestone. For the incidence calculation, any participant who develops an inhibitor following the initial BIVV001

administration will be included in the numerator, regardless of the number of EDs to BIVV001; the denominator will include participants who have an inhibitor as well as participants with a valid inhibitor test following at least 50 EDs to BIVV001.

The calculation will also be performed with a denominator that includes all participants with a valid inhibitor test following at least 25 EDs to BIVV001 and a denominator that includes all participants with a valid inhibitor test, regardless of how many days they were exposed to BIVV001.

The incidence of positive inhibitor formation will be summarized for each age cohort and overall; an exact 95% confidence interval (CI) will be calculated using the Clopper-Pearson method for each incidence.

4.3.3 Supplementary analyses

The incidence of inhibitor formation will also be analyzed by type of inhibitor.

- A positive low titer inhibitor is defined as an inhibitor test and confirmatory test, both with results of ≥0.60 and <5.00 BU/mL.
- A positive high titer inhibitor is defined as an inhibitor test and confirmatory test, both with results of ≥5.00 BU/mL.

Participants with discordant inhibitor test results (initial low titer result followed by high titer result or initial high titer result followed by low titer result) should have repeat inhibitor testing performed by the central laboratory from a third blood sample, collected 2 to 4 weeks following the previous sample.

- If 2 of 3 test results are <5.00 BU/mL, the inhibitor is considered low titer.
- If 2 of 3 test results are ≥5.00 BU/mL, the inhibitor is considered high titer.

In either case, the date of the inhibitor is the date of the sample with the first positive test result.

Summaries will be provided for participants with high-titer inhibitors and participants with low-titer inhibitors, separately, as defined above. Similar to the primary analysis, the supplementary analyses will be based on all participants who have reached at least 1, 25 and 50 EDs and had at least one inhibitor test performed at or beyond this milestone.

The incidence rates and the corresponding 95% CIs will be provided, for each age cohort and overall, using the same method as applied to the primary analysis.

4.4 SECONDARY ENDPOINT ANALYSIS

All secondary efficacy endpoints will be summarized descriptively based on the FAS and presented by age cohort and overall, unless otherwise specified.

All analyses of bleeding endpoints will be based on treated bleeding episodes, except for the summary of ABR for all bleeds which will include both treated and untreated bleeds.

Analysis of efficacy endpoints that are visit-based will include data from all study visits, whether or not in the efficacy period, unless a visit is coincidental with a surgical/rehabilitation period for a major surgery, in which case it would be excluded.

4.4.1 Annualized bleeding rate (ABR)

4.4.1.1 Definition of endpoint

Data for bleeding events will be collected by each participant via an ePD or, in the case of bleeds occurring and/or treated at the study site, on the eCRF and will include type of bleed, location of bleed, and treatment dates, if applicable. This information will be used to derive efficacy endpoints on bleeding.

During the course of the study, the Investigator is given the opportunity to disagree with the classification of bleeding episode as given by the caregiver, and the caregiver is subsequently given the opportunity to agree or disagree with the reclassification (spontaneous, traumatic, or not a bleed). If the caregiver agrees with the Investigator's assessment, then all analyses of bleeding will be based on the Investigator's determination of the bleeding type, whether or not the change was made to the participant's records.

Bleeding episodes of an unknown type will be included in the determination of the annualized bleeding rate and in summaries based on bleeding episodes but, unless specified otherwise, will not be included in summary tables where endpoints are summarized by type of bleed.

Definition of a bleeding episode (based on treated bleeds)

All primary analyses of bleeding endpoints will be based on treated bleeds consistent with ISTH criteria (1) using the following standardized definition:

In the analysis of treated bleeds, a bleeding episode starts from the first sign of bleeding and ends no more than 72 hours after the last injection to treat the bleed, within which any subsequent bleeding at the same location, injections ≤72 hours apart, are considered the same bleeding episode. Multiple bleeding locations treated with a single injection will also be considered a single bleeding episode. Any injection to treat the bleed, taken >72 hours after the preceding one, will be considered the first injection to treat a new bleeding episode in the same location. Any subsequent bleeding or injection at a different location will be considered a separate bleeding episode, regardless of the time from the last injection.

Annualized bleeding rate

The ABR for each individual participant is calculated using the following formula:

$$\text{ABR} = \frac{\text{Number of treated bleeding episodes during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

A bleeding episode is counted in the analysis if it was treated with BIVV001. All types of bleeding episodes (spontaneous, traumatic, and type unknown) will be included in determining the annualized number.

4.4.1.2 Main analytical approach

The mean and 95% CI of ABR will be estimated using a Negative-Binomial model. The model will include number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration. Individual ABR will also be calculated for each participant and summarized descriptively. The summaries will be presented by age cohort and overall for the FAS.

4.4.1.3 Sensitivity analyses

Sensitivity analysis of the ABR will also be performed using the Per Protocol Set, as well as using the FAS including participants with an efficacy period of at least 26 weeks.

4.4.1.4 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses of the ABR will be performed across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- By bleeding phenotype at Baseline (estimated bleeds in prior 12 months, 0, >0-5, >5-10, >10)
- By number of target joints (none present, ≤ median of number present, > median of number present)
- By dosing and dosing interval compliance (<80%, ≥80%)

The estimated mean ABR and the corresponding 95% CI will be provided, for each subgroup, using the same method as applied to the primary analysis. Forest plots will be provided.

4.4.2 ABR by type and location

ABR will be summarized descriptively by type and location for the following subsets of treated bleeds:

- Type of bleeding (spontaneous, traumatic, unknown)
- Location of bleeding (joint, muscle, internal, skin/mucosa)
- Location and type of bleeding (joint spontaneous, joint traumatic, muscle spontaneous, muscle traumatic, internal spontaneous, internal traumatic, skin/mucosa spontaneous, skin/mucosa traumatic)

The estimated mean ABR and the corresponding 95% CI will be provided, for each subset, using the same method as specified above. These tables will be presented by age cohort and overall for the FAS.

As a description of the raw data collected in this study, the unadjusted number of bleeding episodes per participant will be summarized using categorical (0, 1, 2, 3, 4, 5, and >5) and descriptive statistics overall and by bleed type (spontaneous, traumatic, unknown). The number

and percentage of participants experiencing a bleeding episode will be summarized categorically overall and by type of bleed (spontaneous, traumatic, unknown) as well as by bleed location (joint, muscle, internal, skin/mucosa, and unknown) for each bleed type; percentages will be based on the number of participants with an efficacy period. The total participant years followed during the efficacy period will be provided in order to put the un-annualized numbers in perspective.

4.4.3 ABR based on all bleeding episodes

ABR will be summarized for all bleeds (treated and untreated) by age cohort and overall. All types of bleeding episodes (spontaneous, traumatic, and unknown) will be included, regardless of whether treatment was used or not. The estimated mean ABR and the corresponding 95% CI will be provided, using the same method as described in Section 4.4.1.2.

Definition of a bleeding episode (based on all bleeds)

The definition of all bleeds will follow the ISTH criteria, accounting for both treated and untreated bleeds, based on the date and time of the bleed as follows:

In the analysis of all bleeds, a bleeding episode starts from the first sign of a bleed (treated and untreated) and ends no more than 72 hours after the last injection to treat the bleed or the last untreated bleed at the same location, within which any sign of bleeding (treated and untreated) at the same location, injections ≤72 hours apart, are considered the same bleeding episode.

Any injection or untreated bleed, occurring >72 hours after the preceding one, will be considered the start of a new bleeding episode. Any subsequent injection or untreated bleed at a different location will be considered a separate bleeding episode, regardless of the time from the last injection or bleed.

4.4.4 Percentage of participants who maintain FVIII activity levels

The number and percentage of participants achieving steady-state trough FVIII activity levels above 1%, 3%, 5%, 10%, 15%, and 20% will be summarized by age cohort and overall. In these summaries, FVIII activity level will be based on the average trough samples (ie, nominal 168-hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52) using the aPTT-based one-stage assay and chromogenic assay. Participants with trough samples that are outside 168 +/-5 hours from the previous dose will be excluded from this analysis.

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

The number of injections and total dose of BIVV001 (IU/kg) to treat a bleeding episode will be determined on both a per-bleeding episode and per-participant basis. A bleeding episode is considered resolved when treatment for the bleeding is no longer needed.

Per bleeding episode: The total number of injections will consider all injections, including initial and follow-up injections, in a bleeding episode. The total dose of BIVV001 will be the sum of these doses. The number of injections to treat a bleeding episode will be summarized across all

bleeding episodes both categorically (1, 2, 3, 4, >4; 1, >1; and ≤2, >2) and with descriptive statistics. The total dose of BIVV001 used to treat a bleeding episode will be summarized using descriptive statistics.

Per participant: The number of injections and total dose of BIVV001 to treat each bleeding episode, as determined for the per-bleeding episode summaries, will be averaged across all bleeding episodes for each participant. The average number of injections required for resolution of a bleeding episode will be summarized both categorically (1 to <2, 2 to <3, 3 to <4, and ≥4; and 1 to <2, ≥2) and with descriptive statistics. The averages for the per-participant total dose of BIVV001 used to treat a bleeding episode will be summarized using descriptive statistics.

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

The number and percentage of bleeding episodes treated with a single injection of BIV001 will be determined on a per-bleeding episode basis. The number and percentage of bleeding episodes treated with a single injection of BIVV001 will be summarized by age group and overall for the FAS.

4.4.7 Assessment of response to BIVV001 treatment of bleeding episodes

Participants will provide an assessment of response to each injection of BIVV001 for treating a bleed using a 4-point scale of excellent, good, moderate, and none, based on ISTH standardized definitions in hemophilia (1). Response categories of excellent and good will be presented combined as well as individually.

The assessment of response will be summarized first on a per injection basis. The number and percentage of injections in each response category will be tabulated based on all injections; percentages will be based on the total number of injections for treating a bleed for which a response was provided.

As a supplemental analysis, the assessment of response will also be summarized on a per bleeding episode basis by presenting the number and percentage of first injections to treat a bleeding episode for which the response to the treatment was categorized as excellent, good, moderate, or no response. Percentages will be based on the number of bleeding episodes for which a response was provided for the first injection.

The participant's assessment of response during the efficacy period will be summarized by age cohort as well as overall for the FAS.

4.4.8 Physician's global assessment of participant's response to BIVV001 treatment

The physician's global assessment of the participant's response to BIVV001 treatment will be summarized by age cohort and overall for each study visit as the number and percentage of participants classified as excellent, effective, partially effective, and ineffective. Percentages will be based on number of participants for whom an assessment was provided at the respective visit.

This table will also include a cumulative tabulation across all scheduled study visits; participants can be included in this tabulation once for each visit. Percentages for this collection of responses throughout the study will be based on the total number of assessments across all visits.

4.4.9 Annualized BIVV001 consumption

The consumption of BIVV001 will be annualized and summarized by age cohort and overall for the FAS. The total annualized BIVV001 consumption (IU/kg) will be calculated for each participant using the following formula:

$$\text{Annualized consumption} = \frac{\text{Total IU/kg of BIVV001 during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

The total amount of BIVV001 received will be the sum of the nominal IU/kg administered for each injection based on the units of BIVV001 as recorded from the participant's ePD and eCRF and the participant's most recent weight.

Total annualized BIVV001 consumption will be determined for the efficacy period, ie, excluding the PK assessments and surgery/rehabilitation periods (major or minor).

4.4.10 Annualized joint bleeding rate

The annualized joint bleeding rate (AJBR) will be summarized descriptively by age cohort and overall as described in Section 4.4.1.

4.4.11 Target joint resolution

Participants will be assessed for target joints at screening by the investigator. A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) into which ≥3 spontaneous bleeding episodes occurred in a consecutive 6-month period. Resolution is achieved when ≤2 bleeds occur into that joint during 12 months of continuous exposure (1).

The percentage of participants with resolution of at least 1 target joint and the percentage of total target joints that are resolved at 52 weeks will be summarized per age cohort and overall. Determination of resolution will be based on the number of spontaneous bleeding episodes into that joint as well as based on the number of total bleeding episodes into that joint (regardless of type). In this analysis, only participants who have at least 12 months of exposure (defined as duration of dosing ≥52 weeks) to BIVV001 will be included. Target joints on which surgery was performed on or before the end of the participant's 12 months of exposure will be censored.

4.4.12 Hemophilia Joint Health Score

Hemophilia Joint Health Score (HJHS) is a functional measure of joint health using ankle, knee and elbow (to access flexion, extension, range of movement, muscle strength, swelling, duration of swelling, crepitus, gait, pain, and muscle atrophy). The assessment is administered by a

healthcare professional trained in the use of anthropometric measures. Ideally HJHS should be performed and assessed by the same investigator or designee at each time point. The HJHS will be used in children aged ≥4 years at Baseline, Week 26 and Week 52. Details of the questionnaire are provided in protocol Appendix 6 (Section 10.7.3).

Table 4 - HJHS domains

Range	Left elbow	Right elbow	Left knee	Right knee	Left ankle	Right ankle	Domain total
Swelling	0-3	0-3	0-3	0-3	0-3	0-3	0-18
Duration	0-1	0-1	0-1	0-1	0-1	0-1	0-6
Muscle Atrophy	0-2	0-2	0-2	0-2	0-2	0-2	0-12
Crepitus on motion	0-2	0-2	0-2	0-2	0-2	0-2	0-12
Flexion loss	0-3	0-3	0-3	0-3	0-3	0-3	0-18
Extension loss	0-3	0-3	0-3	0-3	0-3	0-3	0-18
Joint pain	0-2	0-2	0-2	0-2	0-2	0-2	0-12
Strength	0-4	0-4	0-4	0-4	0-4	0-4	0-24
Joint Total	0-20	0-20	0-20	0-20	0-20	0-20	

The HJHS assessment includes the scoring of six joints (left ankle, right ankle, left elbow, right elbow, left knee, and right knee) on a scale from 0 to 20 according to the following criteria: swelling, duration of swelling, muscle atrophy, crepitus of motion, flexion loss, extension loss, joint pain, and strength (Table 4). Gait will be scored on a scale from 0 to 4 based on the number of skills that are not within the normal limits. The total score will be the sum of scores from all six joints plus the gait score (range from 0 to 124, with 0 being normal and 124 being the most severe disease).

The total joint score (ie, sum of scores from all six joints) will be defined and derived as follows:

- The total joint score will be set as missing if any one of the individual item score at any joint is missing;
- The total joint score will be set as missing if scores are evaluated within 2 weeks after a joint or muscle bleeding episode; and
- The total joint score will be re-derived if surgery is performed on a joint. The scores for that joint will be replaced with the scores of the same joint at the last visit prior to the surgery using the last observation carried forward (LOCF) technique. Then, the total joint score in the subsequent visits are re-derived using the abovementioned scores.

The individual domain score (ie, sum of scores from all six joints for each domain) will be calculated using the same rules as above for all domains.

The total joint score, gait scores, and total score (calculated as the sum of total joint score and gait score), as well as change from baseline will be summarized by age cohort and overall. In addition, individual domain scores and change from baseline will be summarized by age cohort and overall.

4.4.13 Haemo-QoL (≥4 years old)

Four HAEMO-QoL questionnaires are used in this study and administered at Baseline, Weeks 26 and 52. Details of the questionnaires are provided in protocol Appendix 6 (Section 10.7.5.2).

- Haemo-QoL kids short version (4-7 years)
- Haemo-QoL kids short version (8 to <12 years)
- Haemo-QoL parent proxy short version (for participants 4-7 years)
- Haemo-QoL parent proxy short version (for participants 8 to <12 years)

Each HAEMO-QoL questionnaire for 4-7 years will be summarized by calculating a total score, and each questionnaire for 8 to <12 years will be summarized in terms of subscale scores and a total score according to the recommendations of the questionnaire authors. As specified in Appendix 5.2 Haemo-Qol (Section 5.5.2), questions will either have been coded or will be re-coded to ensure that high scores represent a low quality of life and low scores represent a high quality of life. These scores are then transformed to produce a Transformed Scale Score (TSS). This score is scaled, as a percentage, from 0 to 100%, with higher TSS values representing a worse quality of life for each sub-score and total score summary measurement.

When missing data are presented, a subscale/total score can only be calculated if at least 50% of questions for that subscale/questionnaire are answered (non-missing and not "Not Applicable").

For each HAEMO-QoL questionnaire, the total score and individual subscale scores based on the TSS will be summarized descriptively for the actual value and change from baseline by visit for each age cohort and overall.

4.4.14 Surgery endpoints

An overall summary of surgeries will be provided which summarizes the number of major and minor surgeries and (%) of participants with at least one major surgery and (%) of participants with at least one minor surgery.

All major and minor surgeries in detail will be provided in the data listings.

4.4.14.1 Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment

The Investigators'/Surgeons' assessment of the participant's hemostatic response to BIVV001 treatment will be collected at 24 hours post-surgery based on the ISTH 4-point response scale and will be summarized categorically and using descriptive statistics for all major surgeries for participants in the surgery subgroup. Categorically, the number and percentage of surgeries given each rating will be tabulated. Percentages will be based on the number of surgeries for which a response was provided. Since the response is given as an ordered ordinal scale, the responses have also been given a numeric score (Excellent=1, Good=2, Fair=3, Poor/none=4). A lower average score indicates a better Investigators'/Surgeons' assessment of the participants' response to surgery with BIVV001 treatment. Descriptive statistics will be provided using the numeric value of the 4-point scale.

4.4.14.2 Number of injections and dose to maintain hemostasis for major surgery

The number of injections, mean dose per injection (IU/kg), and total dose (IU/kg) required to maintain hemostasis during surgery will be summarized for all major surgeries for participants in the surgery subgroup. The number of injections per surgery will be summarized categorically (0, 1, 2, 3, 4, >4) and with descriptive statistics. Percentages for the categorical summary will be based on the number of major surgeries. The mean dose per injection and total dose required to maintain hemostasis will be summarized using descriptive statistics. The mean dose per injection will be determined as the average dose across all injections per major surgery (including the loading dose); the total dose will be determined as the sum across all injections (including the loading dose) per major surgery.

4.4.14.3 Total BIVV001 consumption for major surgery

Total consumption (IU/kg) per major surgery on the day of surgery, for the first 2 weeks following surgery (Days 1-3, 4-14, and 1-14), and for the overall surgical/rehabilitation period will be summarized using descriptive statistics for all major surgeries for the surgery subgroup. The day of surgery refers to the calendar day of the surgery and includes the loading dose given for that surgery. The first 2 weeks following surgery begins the day after surgery and extends for 14 calendar days. The overall surgical/rehabilitation period is defined in Section 4.1.1.3. Total BIVV001 consumption will be determined as the sum of all doses administered during the referenced time periods.

4.4.14.4 Number and type of blood component transfusions for major surgery

The number of transfusions per surgery (regardless of the type of transfusion), the number of transfusions summed across all surgeries for each type of transfusion, and the number of surgeries requiring each type of transfusion will be summarized categorically for all major surgeries for the surgery subgroup. Percentages in the categorical summaries will be based on the number of major surgeries for which the respective data is available.

4.4.14.5 Estimated blood loss for major surgery

The estimated total blood loss during and post each major surgical procedure will be summarized using descriptive statistics for all major surgeries for the surgery subgroup.

4.5 EXPLORATORY ENDPOINTS ANALYSES

4.5.1 PROMIS instruments

Six PROMIS instruments are used in this study and administered at Baseline, Weeks 26 and 52. Details for each instrument are provided in protocol Appendix 6 (Section 10.7.5.1).

- PROMIS Pediatric NRS Pain Intensity (v1.0 Pain Intensity 1a; ≥8 years old)
- PROMIS Pediatric-SF Pain Interference (v2.0 Pain Interference 8a; ≥8 years old)
- PROMIS Pediatric-SF Physical Activity (v1.0 Physical Activity 8a; ≥8 years old)

- PROMIS Parent Proxy NRS Pain Intensity (v1.0 Pain Intensity 1a; 5 to <12 years old)
- PROMIS Parent Proxy-SF Pain Interference (v2.0 Pain Interference 8a; 5 to <12 years old)
- PROMIS Parent Proxy-SF Physical Activity (v1.0 Physical Activity 8a; 5 to <12 years old)

The two PROMIS instruments on pain intensity each uses an 11-point Numeric Rating Scale (NRS) ranging in value from 0 to 10, with 0 indicating no pain and 10 indicating worse pain. The NRS will be summarized descriptively for the actual value and change from baseline by visit for each age cohort and overall.

For each of the other four PROMIS instruments, each question has five response options ranging in value from one to five. To find the total raw score for an instrument with all questions answered, sum the values of the response to each question. All questions must be answered in order to produce a valid total score. The total raw score is then converted into a T-score for each participant using an instrument-specific *Conversion Table* (see APPENDIX 5.1 PROMIS instruments [Section 5.5.1]). The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person with a T-score of 40 is one SD below the mean.

A higher PROMIS T-score represents more of the concept being measured. For negatively-worded concepts like Pain Intensity and Pain Interference, a T-score of 60 is one SD worse than average. By contrast, for positively-worded concepts like Physical Function and Physical Activity, a T-score of 60 is one SD better than average.

T-scores for each of the four PROMIS instruments will be summarized descriptively for the actual value and change from baseline by visit for each age cohort and overall.

4.5.2 EuroQoL-Youth (EQ-5D-Y)

The EuroQol-5D-Youth (EQ-5D-Y) and its parent proxy version will be used for children aged 8 to <12 years and children aged 4-7 years, respectively, at Baseline, Weeks 26 and 52. Both instruments consist of 3 pages: the title page, the EQ-5D-Y descriptive system and the EQ visual analogue scale (VAS). A copy of the questionnaires is provided in protocol Appendix 6 (Section 10.7.5.3).

Both the EQ-5D-Y children and parent proxy versions will be analyzed according to the recommendations of the authors (see www.euroqol.org). The descriptive system contains 5 dimensions (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy), each with 3 response categories (no problems, some problems, and a lot of problems). The number and percentage of participants in each response category will be tabulated by age cohort and overall. Percentages are based on the number of participants for whom an assessment is provided at the respective visit.

The EQ visual analogue scale is a visual scale from 0-100 to record a respondent's overall self-rated health state. The respondent is asked to mark an "X" on the scale then record the corresponding number; 0 refers to the worst possible health state, 100 refers to the best possible

health state. The EQ VAS will be summarized for the observed response and change from baseline by visit for each age cohort and overall.

4.5.3 Caregiver interviews

The caregiver interviews data is not the scope of this SAP and will be analyzed in a separate report.

4.5.4 Healthcare resource utilization (HRU)

The number (0, 1-2, 3-4, >4) and percentage of healthcare visits by type (office visit, hospital ER visit, hospitalization, and ICU stay) will be summarized by-visit and age cohort and overall for the FAS.

4.6 MULTIPLICITY ISSUES

All analyses are descriptive in nature and therefore adjustments for multiplicity will not be applied.

4.7 SAFETY ANALYSES

The summary of safety results will be presented by age cohort as well as overall for the Safety Analysis Set. The analysis of the safety variables will be essentially descriptive, and no systematic testing is planned.

4.7.1 Extent of exposure

The extent of exposure and compliance will be assessed and summarized by age cohort and overall. In addition, study drug administered will be listed by participant including the reason for administration, date and time of administration, and dose. A listing of lot numbers and nominal potency of the lots will be provided by participant.

Except for PK doses, the unit body weight dose (IU/kg) for analysis of dosing will be calculated as the total IU (nominal dose) for each injection divided by the participant's most recent weight in kg prior to the dose of study drug.

PK doses are calculated using the actual potency of the vial (between 80% to 125% of nominal strength) and used partial vials where necessary. Therefore, PK doses in the analysis are similarly calculated using the exact number of complete and partial vials, the volume and actual potency of each vial and the participant's most recent weight:

$$\text{Dose (IU/kg)} = \frac{\left(\frac{\text{Total volume administered}}{\text{Volume of vial}}\right) \times \text{Actual Potency of Vial}}{\text{Weight (kg)}}$$

4.7.1.1 Overall exposure

The extent of investigational medicinal product (IMP) exposure will be assessed by the number of injections and exposure days to BIVV001 and duration of BIVV001 dosing based on the Safety Analysis Set.

Number of Injections and Exposure Days to BIVV001

For any participant, the total number of days of exposure to BIVV001 will be accumulated from the time of their first on-study injection of BIVV001. An ED is a 24-hour period in which one or more BIVV001 injections are given. The 24-hour window starts from the first injection on study and then for subsequent injections, it starts from an injection taken after/outside of a previously identified ED.

The total number of EDs on BIVV001 for each participant will be summarized categorically (<5, 5-<10, 10-<25, 25-<50 and ≥50; and ≥1, ≥5, ≥10, ≥25, ≥50) and with descriptive statistics for the Safety Analysis Set.

The total number of injections per participant will be summarized overall and by reason for injection (prophylactic regimen, spontaneous bleed, traumatic bleed, follow-up injection, surgical or other) using descriptive statistics for the Safety Analysis Set.

Duration of BIVV001 Dosing

The duration of BIVV001 dosing will be calculated from the start date time of the treatment dose to the end date time, as defined in Section 4.1.1.1. Any interruptions to dosing will not be accounted for when calculating this duration.

Duration of BIVV001 dosing (weeks) will be summarized using descriptive statistics for the Safety Analysis Set. Weeks will be represented in the descriptive statistics as if these were data collected with 1 decimal place. The number and percentage of participants whose duration of dosing was at least 13, 26, 39, and 52 weeks will be summarized.

4.7.1.2 Compliance

Compliance will be assessed during the efficacy period and will be summarized for the FAS by age cohort and overall. Except for doses administered in the clinic, study treatment may be administered by the participant or a caregiver. Data from the eCRF and ePD will be considered for the analysis of treatment received and participants' compliance with the study protocol.

Compliance of prophylaxis injections

The compliance rate of each participant during the efficacy period will be calculated in 2 ways: As dose compliance and as dosing interval compliance. Compliance will first be determined on a per-injection basis and then on a per-participant basis. That is, compliance for an individual dose or dosing interval will be determined and then the overall percentage of doses and dosing intervals that were in compliance will be determined for each participant.

For the purpose of evaluating compliance, the following will be considered per injection:

- The nominal dose taken compared to the study dose (50 IU/kg for prophylaxis treatment)
- The actual day of treatment compared to the study day of treatment (weekly for prophylaxis treatment)

An individual dose will be considered compliant if it is within 80%-125% of the study dose (50 IU/kg). An individual dosing interval will be considered compliant if the time between two prophylactic doses is within 36 hours of the study dosing interval (7 days).

The actual dosing intervals will be calculated as the length of time between consecutive prophylactic doses that are not separated by a bleeding episode or surgical/rehabilitation period (date / time of $dose_{x+1}$ – date / time of $dose_x$). The actual time between doses will be determined in minutes and converted to days as the number of minutes divided by 1440. The absolute value of the difference between the actual dosing interval and the study dosing interval of 7 days must be ≤1.5 day (+/-36 hours) in order to be compliant.

All prophylactic injections will be used to determine prophylactic dose compliance; only the prophylactic dosing intervals that are not separated by a bleeding episode or surgical/rehabilitation period will be used to evaluate prophylactic interval compliance. Large injection intervals as defined in Section 4.1.1.2 will be included in the interval compliance calculation. Dose and dosing interval compliance rates per participant will be determined as follows:

$$\text{Dose compliance rate} = \frac{\text{Number of doses taken within 80\%-125\% of study dose}}{\text{Total number of doses}} \times 100$$

where the percentage of a study dose is calculated as: (nominal dose taken / study dose) × 100.

$$\text{Dose interval compliance rate} = \frac{\text{Number of doses taken within +/-36 hours of study day/time}}{\text{Total number of intervals}} \times 100$$

Both participant dose and dosing interval compliance rates will be summarized as continuous variables using descriptive statistics as well as categorically (<80%, ≥80%) for the FAS.

A participant is considered “dose compliant” or “dosing interval compliant” if his respective rate is at least 80%. Based on this, participants will be further classified into the following mutually exclusive categories for overall compliance to their prophylactic treatment as:

- Both dose and interval compliant
- Dose compliant or interval compliant (but not both)
- Neither dose nor interval compliant

Compliance of ePD contemporaneous data entry

Injections (for prophylaxis or a bleed) and untreated bleeds must be entered into the ePD within 7 days from the date of the injection or the untreated bleed. Injections or untreated bleeds entered outside the 7-day window will be reported as protocol deviations. Descriptive statistics of the percentage of the participants with fewer than 80% of their total individual ePD records entered within this 7-day window and those with ≥80% of records meeting this criterion will be presented for the FAS as well as a summary of % compliance to this criterion by participant.

4.7.2 Adverse events

General common rules for adverse events

Summaries of adverse events will be presented by age cohort as well as overall for the Safety Analysis Set.

All adverse events will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock.

The primary focus of adverse event reporting will be on treatment-emergent adverse events (TEAEs). TEAEs are AEs that developed, worsened or became serious during the treatment-emergent period. Pretreatment adverse events will be listed separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment AE. Details on classification of adverse events with missing or partial onset dates are provided in Appendix 3 (Section 5.3).

TEAEs that occurred during major surgical/rehabilitation periods will be included in the overall (top-line) summary of TEAEs but not in any of the other TEAE tables. The exception to this rule is that TEAEs occurring during a major surgical/rehabilitation period with an onset date on the day the surgical/rehabilitation period starts or on the day of the surgery (whichever comes earlier) will be included in the TEAE summaries. Consideration is given to AEs with an onset date at the start of the surgical/rehabilitation period in the event the pre-surgical dose was administered the day before the surgery.

TEAE incidence tables will present by system organ class (SOC) and preferred term (PT).

Listings will be provided for all AEs, SAEs, AEs resulting in discontinuation of study treatment and/or from the study, and deaths. AEs that are emergent prior to the first BIVV001 treatment, AEs that are emergent during a major or minor surgical/rehabilitation period, and AEs that are emergent on the day the major surgical/rehabilitation period starts will be flagged.

Analysis of all adverse events

Overall summary of treatment-emergent adverse events

An overall (top-line) summary of TEAEs will be provided which summarizes number of TEAEs, treatment-emergent serious adverse events (TESAEs) and treatment emergent adverse events of special interest (TEAESI) and (%) of participants with any: TEAE, related TEAE, TESAE, related TESAE, TEAESI, related TEAESI**,** TEAE leading to death, and TEAE leading to treatment discontinuation.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- TEAEs by SOC and PT
- TEAEs by PT in descending order of incidence
- TEAEs by relationship, presented by SOC and PT. AEs with a missing relationship will be counted as "Related" in the summary table, as described in Appendix 3 (Section 5.3). A participant will be counted once for each SOC and PT based on the highest relationship within that SOC and PT, respectively.
- TEAEs by maximal severity, presented by SOC and PT. AEs with a missing severity will be counted as "Severe" in the summary table, as described in Appendix 3 (Section 5.3). A participant will be counted once for each SOC and PT based on the greatest severity within that SOC and PT, respectively.

Analysis of all treatment emergent serious adverse event(s)

- TESAEs by SOC and PT
- TESAEs by PT in descending order of incidence
- TESAEs by relationship and SOC and PT

Analysis of all treatment emergent adverse events of special interest

- TEAESIs by SOC and PT
- TEAESIs by relationship and SOC and PT

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- TEAEs leading to treatment discontinuation, by SOC and PT

Analysis of treatment-emergent adverse event(s) occurring during a major or minor surgical/rehabilitation period

- All TEAEs occurring during a major or minor surgical/rehabilitation period will be provided in a listing. The following categories will be flagged separately:
  - TEAEs occurring during a major surgical/rehabilitation period, excluding AEs with an onset date on the day the surgical/rehabilitation period starts

- TEAEs occurring during a major surgical/rehabilitation period with an onset date on the day the surgical/rehabilitation period starts
- TEAEs occurring during a minor surgical/rehabilitation period

Subgroup analysis

- All TEAEs will also be provided by demographic factors including: race (White, Black, Asian, Other), geographic location (Asia/Pacific, Europe, North America)

Analysis of deaths

A listing of AEs with an outcome of death will be provided.

Embolic and Thrombotic Events

The occurrence of embolic and thrombotic events will be described by age cohort and overall. The analysis will consist of a search of TEAE data using the Embolic and Thrombotic Events Standard MedDRA Query (SMQ). Medical adjudication of the search results will also be performed according to the following definition:

- Embolic and thrombotic events are defined as arterial or venous thrombosis, confirmed by imaging
- Coronary artery thrombosis/occlusion must be confirmed by coronary angiography to be included as part of medical adjudication
- Thrombosis involving the cerebral vasculature must be confirmed by imaging such as magnetic resonance imaging venogram (MRV), computed tomography venogram (CTV), magnetic resonance angiography (MRA), or computed tomography angiography (CTA) to be included as part of medical adjudication
- An indwelling central venous access device is a well-established risk factor for thrombosis (2) and thrombotic events associated with such devices will not be included as part of medical adjudication. Occlusion or malfunction of a central venous access device also will not be included as part of medical adjudication
- Infusion thrombophlebitis is a recognized complication of peripheral vein infusion (3) and will not be included as part of medical adjudication

4.7.3 Additional safety assessments

By-visit summaries of laboratory variables and vital signs will be presented by age cohort and overall for the Safety Analysis Set. Shifts and potentially clinically significant laboratory abnormality (PCSA) summaries will be presented by age cohort and overall for the Safety Analysis Set.

4.7.3.1 Laboratory variables

Blood samples for clinical laboratories will be taken at all scheduled visits. Clinical laboratory values will be analyzed after conversion into standard international units; international units will be used in all listings and tables. Data collected at local laboratories will be only included in the PCSA analysis and listing, and shift summary.

The laboratory parameters will be classified as follows:

- Hematology
  - Red blood cell (RBC) count
  - White blood cell (WBC) count and differential
  - Hemoglobin (Hgb)
  - Hematocrit (HCT)
  - Platelet count
- Clinical chemistry
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Alkaline phosphatase (ALP)
  - Gamma glutamyl transferase (GGT)
  - Bilirubin
  - Blood Urea Nitrogen (BUN)
  - Creatinine
  - Glucose
  - Total protein
  - Potassium
  - Sodium
  - Chloride
- von Willebrand Comprehensive panel
  - VWF ristocetin cofactor activity
  - VWF antigen

All laboratory evaluations will be summarized for the Safety Analysis Set. Laboratory evaluations taken during major surgical/rehabilitation periods will not be included in the summaries. In the event of retests or repeat assessments at the same time point, the last non-missing evaluable measurement will be used for the purpose of analysis. Laboratory values of the form "<x" (ie, below the lower limit of quantification [LLOQ]) or ">x" (ie, above the upper limit of quantification [ULOQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

Change from baseline

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit by age cohort and overall.

Shifts

Each participant's laboratory values will be classified according to whether the test result is "low" (below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (above the upper limit of normal [ULN]). Shift tables will be constructed based on both the minimum and maximum post baseline values for each participant. Data collected from unscheduled visits will be included in the determination of the per participant minimum and maximum values.

A separate table will be provided which summarizes the results of the shift tables in which the number and percentage of participants with a shift to low (from normal, high, or unknown) and the number of participants with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of participants at risk. The number at risk for a shift to low (high) is the number of participants whose baseline value was not low (high), including unknown, who had at least one post-baseline value. Only directions of change indicating a clinical concern will be included in this table summarizing the shifts. The direction of concern is provided in Table 5.

Table 5 - Direction of change indicating clinical concern for laboratory tests

Laboratory test	Direction	Laboratory test	Direction
Chemistry		Hematology	
Liver		White blood cells	Low and High
ALP	High	Lymphocytes	Low and High
ALT/SGPT	High	Neutrophils	Low and High
AST/SGOT	High	Monocytes	Low and High
Total bilirubin	High	Eosinophils	Low and High
GGT	High	Basophils	Low and High
Renal		Red blood cells	Low and High
Blood urea nitrogen	High	Hemoglobin	Low and High
Creatinine	High	Hematocrit	Low and High
Electrolytes		Platelets	Low and High
Sodium	Low and High		
Potassium	Low and High	Coagulation	
Chloride	Low and High	VWF antigen	Low
Other		VWF:RCo activity	Low
Glucose	Low and High		
Total protein	Low and High		

Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values will also be evaluated by determining the number and percentage of participants with at least one PCSA over the course of the study that also represents a worsening from baseline. The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (APPENDIX 4 [Section 5.4]).

Participants who have a post baseline laboratory value that meets the criteria for being potentially clinically significant but do not have a baseline value will be included in the numerator for determining the percentage of participants with an abnormality. Percentages will be based on the number of participants with at least one post baseline value for the given laboratory test. Data collected from unscheduled visits will be included in this analysis.

4.7.3.2 Vital signs and physical examination

Vital signs will be taken at Baseline, Weeks 4, 26 and 52. Vital signs include temperature, pulse rate, respiratory rate and blood pressure. All vital sign evaluations will be summarized for the Safety Analysis Set. Data from unscheduled visits and vital sign measurements taken during major surgical/rehabilitation periods will not be included in any summary but will be included in the listings and flagged.

Change from baseline

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital sign variables (and changes from baseline) will be calculated for each visit by age cohort and overall for the Safety Analysis Set. Evaluations taken during major surgical/rehabilitation periods will not be included in any summary.

Potentially Clinically Significant Vital Sign Abnormalities (PCSA)

Frequencies and percentages of participants with potentially clinically significant abnormalities will be summarized by age cohort and overall. Percentages will be based on the number of participants with a baseline and at least one post baseline value. Vital sign abnormality thresholds are defined in APPENDIX 4 (Section 5.4).

All physical examination findings are presented in a by-participant data listing.

4.8 OTHER ANALYSES

4.8.1 Pharmacokinetic analyses

All PK analyses will be performed based on the PK analysis set (PKAS).

If a repeat PK profile is required due to bleeding (or other reason) during the PK evaluations, then only the repeat profile will be used for the summary of the FVIII activity levels and in the analysis of PK summary parameters. Data from incomplete profiles will be included in data listings.

Actual sampling times, doses, and injection durations will be used for PK analysis. Nominal sampling times and doses will be used for the creation of tables, figures and listings.

FVIII activity values for each timepoint will be corrected for baseline activity at Day 1 using the residual decay function. The detailed methodology used to correct baseline activity will be provided either in the clinical study report or PK report. PK parameters will be computed using baseline corrected FVIII activity values.

PK parameters will be estimated using FVIII activity values measured by aPTT-baseline one-stage clotting assay, and values measured by chromogenic coagulation assay.

For participants undergo PK sampling at Day 1, for each participant using noncompartmental methods the following pharmacokinetic parameters will be included but not limited to: maximum FVIII activity (C_{max}), terminal half-life (t1/2), total clearance (CL), clearance at steady state (CL_{ss}), volume of distribution at steady state (Vss), area under the plasma FVIII activity-time curve from time zero to end of dosing period ($AUC_{0\text{-}tau}$), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}) and time to 1% FVIII activity level.

The detailed methodology for computing PK parameters using noncompartmental method will be described in the CSR or PK report. The detailed methodology for computing PK parameters using population PK method will be described in the population PK report.

The population PK analysis will be presented separately from the main CSR. Population PK analysis will be described fully in the population PK analysis plan and will be finalized before database lock.

For the PKAS the following analyses will be performed:

- For each assay type, a summary table of FVIII activity levels will be provided for BIVV001 at scheduled PK visits and time points for the PK subgroup (Baseline BIVV001). Summary descriptive statistics will include the number of non-missing values, mean, geometric mean, standard deviation, percent coefficient of variation, minimum, and maximum. In these summaries, values below the LLOQ will be imputed as zero.
- For each assay type, individual PK parameters will be listed for each participant and summarized descriptively for the PK subgroup (Baseline BIVV001). Any FVIII assessments flagged by the PK scientist as being implausible and excluded from computation of PK parameters will be excluded from summaries but included in listings. The listings will indicate which values, if any, were excluded from summaries. A separate listing of excluded values, together with the reason for exclusion will be provided.

In addition, for each assay type, the peak and trough concentrations will be summarized by visit for the FAS. The incremental recovery will also be summarized by visit for the FAS. Summary descriptive statistics will include the number of non-missing values, mean, geometric mean, median, Q1, Q3, standard deviation, percent coefficient of variation, minimum, and maximum. In these summaries, values below the LLOQ will be imputed as zero.

4.8.2 Additional Immunogenicity analysis

4.8.2.1 Anti-drug antibody

Participant's ADA status (see definitions below) will be summarized on the safety analysis set. A participant with at least one anti-drug antibody (ADA) result available in the database is considered evaluable.

Participant's ADA status

- Pre-existing ADA: participant with at least one ADA positive prior to receiving BIVV001.
  - Treatment-boosted ADA: participant with pre-existing ADA positive and the ADA titer level anytime post-baseline is significantly higher than that at baseline. The post-baseline titer value that is at least 4-fold of pre-existing ADA titer value is considered significant.
  - Unclassified ADA: participant with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s).
- Treatment-induced ADA: participant with all ADA negative (or missing) prior to receiving BIVV001 and at least one ADA positive at any time post-baseline.
- Treatment-emergent ADA: participant with treatment-induced or treatment boosted ADA.

ADA kinetics:

ADA response duration is defined as the date of last treatment-induced or treatment-boosted ADA sample minus date of first treatment-induced or treatment-boosted ADA sample +1. ADA response duration will be calculated only for participants with at least two treatment-induced or treatment-boosted ADA samples, irrespective of negative samples.

In case of participants with only one treatment-induced or treatment-boosted ADA, the ADA duration will be imputed to 0.

ADA response will be classified in the following categories for each participant:

- Persistent ADA response: an ADA response duration greater or equal than 16 weeks
- Transient ADA responses: an ADA response duration less than 16 weeks and the last sample in the study is not treatment-induced nor treatment-boosted.
- Indeterminate ADA response: ADA response that is neither persistent nor transient.

The number and percentage of participants with pre-existing ADA, treatment-boosted, unclassified, treatment-induced ADA, and treatment emergent ADA will be summarized by age cohort and overall for the Safety Analysis Set. The number and percentage of participants with different ADA kinetic status (ie, persistent, transient, indeterminate) will be summarized by age cohort and overall for the Safety Analysis Set. Median and $25^{th}/75^{th}$ quantiles, minimal and maximal of the ADA titer for pre-existing ADA, treatment-boosted, unclassified, treatment-induced ADA, and treatment emergent ADA will be provided.

A listing will be provided for confirmed positive anti-BIVV001 antibody information, including sample collection date and time, and ADA characterization testing. To evaluate the potential impact of ADAs and PK parameters, PK parameters for participants who have incidence of ADA positive (i.e., treatment-boosted or treatment-induced), along with the group mean of participants who are ADA negative at all times will be tabulated. As needed, FVIII activity level over time for participants who have incidence of ADA positive (ie, treatment-boosted or treatment-induced), along with the group mean of participants who are ADA negative at all times may be evaluated.

4.9 INTERIM ANALYSES

Interim PK analyses will take place for each of the individual age cohorts (<6 years and 6-12 years) once evaluable PK data are available for a minimum of 6 participants in each the cohort.

An interim safety, PK and efficacy analysis will be performed after 12 participants are enrolled in the older age cohort (6-12 years). The PK analysis will be conducted once each of the 12 participants from the older age cohort complete the first dose of BIVV001; the safety and efficacy analysis will be conducted once the12 participants from the older age cohort have reached 25 EDs to BIVV001.

In addition, for the purposes of regulatory submission, an interim analysis of key safety data, PK data and selected efficacy data for this study will be performed when the pivotal adult/adolescent study EFC16293 is completed.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ED: exposure day
SAP: statistical analysis plan

5.2 APPENDIX 2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographic characteristics

Demographic variables include sex, date of birth (year of birth only), height, weight, body mass index (BMI), race, ethnicity and geographic location.

Demographic characteristics will be summarized by age cohort, including the surgery subgroup, and overall for the FAS using descriptive statistics.

Hemophilia history

The following hemophilia history variables will be summarized by age cohort, including the surgery subgroup, and overall for the FAS using descriptive statistics:

- Age at diagnosis of severe hemophilia (years)
- Family inhibitor history (Yes, No)
- Blood type (A, B, AB, O)
- Rh factor (Positive, Negative)
- Lowest documented historical FVIII level (<1%, ≥1%)
- FVIII genotype (Intron 22 inversion, Intro 1 inversion, Frameshift, Missense, Nonsense, Other mutation, Unknown)
- HIV status (Positive, Negative, Unknown)
- Hepatitis B (HBV) status (Positive, Negative, Unknown)
- Hepatitis C (HCV) status (Positive, Negative, Unknown)
- Vaccination history in past 12 months (Yes, No, and if Yes, how many)
- Types of FVIII products previously administered (FVIII plasma derived, FVIII recombinant, FVIII cryoprecipitate, Non FVIII product)
- Age at start of first prophylaxis regimen
- Number of prior exposure days to FVIII (<50, 50-<100, 100-<150 and ≥150; <150, ≥150)

- Number of bleeds in the past 12 months
- Number of joint bleeds in the past 12 months
- Number of spontaneous joint bleeds in the past 12 months
- Number of traumatic joint bleeds in the past 12 months
- Number of target joint at baseline

Medical and surgical history

Medical (or surgical) history will be collected at screening and will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock.

The number and percentage of participants with any medical and surgical history will be summarized for each body system by age cohort, including the surgery subgroup, and overall using the Safety Analysis Set. A participant will be counted only once if the participant reported one or more occurrences of the same body system.

Prior or concomitant medications

All medications taken in the 30 days prior to the time the participant enrolls in the study and until the Safety Follow Up Call or Visit are to be reported on the eCRF.

Medications will be identified as being prior and/or concomitant based on the start and stop dates compared to the first dose of study drug. Prior medications are those taken before the first dose of study drug. Concomitant medications are those administered during or after the first dose of study drug. A medication that started prior to the first dose of study drug and was ongoing during and/or after the first dose of study drug will be classified as both prior and concomitant.

No imputation of medication start/end dates will be performed. If the start/end date is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify the medications as prior and/or concomitant as follows.

If a concomitant medication start day is missing then the medication will be assumed to be both a prior and a concomitant medication unless the start month and/or year or medication stop date can be used to determine if a medication is concomitant or prior, as follows:

- If the medication start day is missing, but the month and year precede the month and year of the first treatment and the medication stop date is before the date of first treatment, then the medication will be classified as prior only.
- If the medication start month is missing, but the year precedes the year of first treatment and the medication stop date is before the date of first treatment, then the medication will be classified as prior only.
- If the medication start day is missing and the month and/or year are on or after the month and year of the first treatment, then the medication will be classified as concomitant only.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at Sanofi at the time of database lock.

Separate summaries will be provided for prior and concomitant medications. Prior and concomitant medications will be presented by age cohort and overall for the Safety Analysis Set. Summaries will be based on the number and percentage of participants taking medications by WHO-DD standardized medication text. Within each WHO-DD standardized medication text a participant will be counted once even if he/she reported taking the medication more than once.

Concomitant medications taken for hemophilia-related pain

Concomitant medications taken for hemophilia-related pain will be summarized by age cohort and overall for the Safety Analysis Set. Summaries will be based on the number and percentage of participants taking pain medications by class (acetaminophen/paracetamol, NSAIDs, opioids, other).

In addition, the number of days pain medication was used for hemophilia-related pain in the past 2 weeks will be summarized categorically (0 [None], 1-3, 4-7, 8-14) for each study visit by age cohort and overall.

5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

Electronic Patient Diary (ePD) Data

Participant recorded diary data will be handled taking into consideration previous audit findings and industry standards to control changes to participant reported data. Only changes defined as not requiring participant confirmation and that are supported by site source documentation will be allowed.

The following programming algorithms are allowable to address record consolidation and true duplicate removal.

1) Record consolidation:

When a dose requires more than one vial and these vials are erroneously recorded in the ePD/eCRF as separate injections, albeit within a short time window, the change to consolidate these multiple records into one record is called single vial consolidation. The programming algorithm to identify and consolidate the records is as follows:

- Identify all injection records within 60 minutes of one another where the variables (injection date/times, lot numbers, number of vials, and vials strength in nominal IU) are not exactly the same on each record. There are four scenarios:
  - Date and time of injections are not exactly same, and lot numbers, number of vials, and vials strength in nominal IU are not the same.
  - Date and time of injections are not exactly same, but lot numbers, number of vials, and vials strength in nominal IU are the same.

- Date and time of injections are exactly same, but lot numbers, number of vials, and vials strength in nominal IU are not the same.
- Date and time of injections are exactly same, and lot numbers, number of vials, and vials strength in nominal IU are the same and these duplicates occurred for reasons which cannot be attributed to administrative issues as specified below

- Consolidate injections as follows:
  - Record with earliest injection date/time retained with corresponding contextual information
  - Combine/sum values related to the dose (eg, lot numbers, number of vials, volume injected, nominal and actual dose) into the single retained record

If injections identified with the above algorithm have distinctly different reasons (eg, one injection is recorded as bleeding or surgery and another is recorded as prophylaxis, or OTHER), then the records should NOT be consolidated. However, if one record has reason or bleed information missing, then consolidation can be performed.

2) True duplicates removal:

When injections are identified in the ePD with exactly the same date/times, bleed information if applicable (type, location, and sublocation), lot numbers, number of vials, and vials strength in nominal IU, these may have resulted due to administrative issues and are therefore true duplicates. There are three types of administrative issues as follows:

- Technical transmission issue
- Entry of same record into 2 different devices
- Records duplicated in ePD and eCRF which remain despite attempts to correct the data via the query process

The programming algorithm to identify and delete the duplicates is as follows:

- Identify all injections that have exactly the same date/times, reasons for injection, bleed information (if applicable), lot numbers, number of vials, and vials strength in nominal IU
- Remove the duplicates and keep a single record

As with single vial consolidation, if injections identified as duplicates have distinctly different reasons (eg, one injection is recorded as bleeding or surgery and another is recorded as prophylaxis or OTHER), then these cannot be considered duplicates and removed. However, if one reason is missing, then they can be considered duplicates and removed.

Algorithm for determining analysis visit windows for PRO and HJHS observations

A scheduled measurement will be used if it is available. Otherwise, the following analysis window will decide how the unscheduled and EOS/ET visits will be used in the analyses of PRO and HJHS variables.

A measurement (unscheduled or EOS/ET) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

Table 6 - Analyses window definition

Scheduled visit post baseline	Target study day	Derived Window in study days	
		Lower bound	Upper bound
Baseline	1	-INF	1(7 for HJHS)
Week 26	182	2 (8 for HJHS)	272
Week 52	364	273	-

Handling of adverse events with missing or partial date/time of onset

No imputation of adverse event onset/end dates will be performed. If the onset/end date is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify the adverse events as treatment-emergent or not as follows:

- If the onset day of an adverse event is missing and the onset month and year of the AE are either the same as or later than the month and year of the first treatment, the AE will be considered a TEAE.
- If the onset day of an adverse event is missing and the onset month and year of the AE precede the month and year of the first treatment, the AE will not be considered a TEAE.
- If the onset month of an adverse event is missing and the onset year of the AE is either the same as or later than the year of first treatment, the AE will be considered a TEAE.
- If the onset month of an adverse event is missing and the onset year of the AE precedes the year of first treatment, the AE will not be considered a TEAE.
- If the onset day, month, and year of an adverse event are missing, the AE will be considered a TEAE.
- If start date is partial but the stop date can be determined to be before the start of the first dose of study drug, then the AE will not be considered a TEAE.

Handling of adverse events with missing relationship to investigational product

If the assessment of relationship to study drug is missing, the event will be counted as “related” in the frequency tables of treatment-emergent adverse events by relationship to study drug.

Handling of adverse events with missing severity

If the assessment of severity is missing, the event will be counted as "severe" in the frequency tables of treatment-emergent adverse events by severity.

Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will not be included in the by-visit summaries but will be used for computation of baseline, maximum or minimum on-treatment values, and PCSAs.

5.4 APPENDIX 4 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

Table 7 - Threshold levels for potentially clinically significant hematology abnormalities

Parameter name	Age	Low	High
White Blood Cells	6 to <12 years old	<5.0 Giga/L or 5,000/mm^3	>17.0 Giga/L or 17 000/mm^3
	24 months/2 years to <6 years old	<3.0 Giga/L or 3,000/mm^3	>16.0 Giga/L or 16 000/mm^3
	28 days/1 month to 23 months old	<4.0 Giga/L or 4000/mm^3	>20.0 Giga/L or 20 000/mm^3
	Birth/0 to 27 days old	<4.0 Giga/L or 4000/mm^3	>25.0 Giga/L or 25 000/mm^3
Neutrophils	6 to <12 years old	<1.2 Giga/L or 1200/mm^3	>1 ULN
	24 months/2 years to <6 years old	<1.2 Giga/L or 1200/mm^3	>1 ULN
	28 days/1 month to 23 months old	<1.0 Giga/L or 1000/mm^3 (1-3 months) <1.2 Giga/L or 1200/mm^3 (3-24 months)	>1 ULN
	Birth/0 to 27 days old	<4.0 Giga/L or 4000/mm^3 (1 day old) <1.5 Giga/L or 1500/mm^3 (2-7 days old) <1.25 Giga/L or 1250/mm^3 (>7 day-1 month old)	>1 ULN
Lymphocytes	6 to <12 years old	<1.0 Giga/L or 1000/mm^3	>8.0 Giga/L or 8000/mm^3
	24 months/2 years to <6 years old	<1.0 Giga/L or 1000/mm^3	>9.5 Giga/L or 9500/mm^3
	28 days/1 month to 23 months old	<2.0 Giga/L or 2000/mm^3	>13.5 Giga/L or 13 500/mm^3
	Birth/0 to 27 days old	<1.2 Giga/L or 1200/mm^3	>17.0 Giga/L or 17 000/mm^3
Hemoglobin	24 months/2 years to <12 years old	<1.55 mmol/L or 10.0 g/dL or any decrease	$\geq$0.31 mmol/L or 2 g/dL
	28 days/1 month to 23 months old	<1.40 mmol/L or 9.0 g/dL or any decrease	$\geq$0.31 mmol/L or 2 g/dL

Parameter name	Age	Low	High
	Birth/0 to 27 days old	<8.6 mmol/L or 12.0 g/dL or any decrease	≥0.31 mmol/L or 2 g/dL
Hematocrit	24 months/2 years to <12 years old	<0.32 l/l or 32%	>0.47 l/l or 47%
	28 days/1 month to 23 months old	<0.29 l/l or 29%	>0.42 l/l or 42%
	Birth/0 to 27 days old	<0.39 l/l or 40%	>0.61 l/l or 47%
Platelet count	<12 years	<100 Giga/L or 100 000/mm^3	>700 Giga/L or 700 000/mm^3

N/A = not applicable

Table 8 - Threshold levels for potentially clinically significant chemistry abnormalities

Parameter name	Age	PCS low	PCS high
Sodium	<12 years	≤129 mmol/L or 129mEq/L	≥150 mmol/L or 150mEq/L
Potassium	24 months/2 years to <12 years old	≤3.5 mmol/L or 3.5 mEq/L	≥5.5 mmol/L or 5.5 mEq/L
	28 days/1 month to 23 months old	≤3.5 mmol/L or 3.5 mEq/L	≥6.0 mmol/L or 6.0 mEq/L
	Birth/0 to 27 days old	≤3.0 mmol/L or 3.0 mEq/L	≥7.0 mmol/L or 7.0 mEq/L
Chloride	<12 years	≤80 mmol/L or 80mEq/L	≥115 mmol/L or 115 mEq/L
ALT/SGPT	<12 years	N/A	≥3 x ULN
AST/SGOT	<12 years	N/A	≥3 x ULN
Alkaline phosphatase	<12 years	N/A	≥1.5 x ULN
Total Bilirubin	<12 years	N/A	≥1.3 x ULN
Creatinine	6 years to <12 years old	N/A	≥90 µmol/L or 1.1 mg/dL
	Birth/0 to <6 years old	N/A	≥53 µmol/L or 0.6 mg/dL
Creatinine Clearance	<12 years	50% of normal <60 mL/min/1.73m^2 (after 1 year old)	
Uric Acid	<12 years	≤2.0 mg/dL or 119 µmol/L	≥8.0 mg/dL or 476 µmol/L
Blood urea nitrogen (BUN)	28 days/1 month to 12 years old	N/A	≥6.4 mmol/L or 18 mg/dL
	Birth/0 to <27 days old	N/A	≥4.3 mmol/L or 12 mg/dL
Bicarbonate	<12 years	≤16 mmol/L or 16 mEq/L	≥30 mmol/L or 30 mEq/L
Glucose	<12 years	<2.7 mmol/L or 50 mg/dL (Hypoglycaemia)	≥7 mmol/L or 120 mg/dL (Hyperglycaemia and fasted after >12 hours of fast) ≥10.0 mmol/L or 180 mg/dL (unfasted)
Calcium total	<12 years	≤2.0 mmol/L or 8.0 mg/dL	≥2.9 mmol/L or 11.6 mg/dL
Calcium ionized	<12 years	≤1.0 mmol/L or 4.0 mg/dL	≥1.4 mmol/L or 5.6 mg/dL

Parameter name	Age	PCS low	PCS high
Total Cholesterol	<12 years	N/A	≥6.20 mmol/L or 240 mg/dL
Triglycerides	<12 years	N/A	≥4.0 mmol/L or 350 mg/dL
Lipasemia	<12 years	N/A	≥2 ULN
Amylasemia	<12 years	Hypoglycaemia <2.7 mmol/L or 50 mg/dL	Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); >10.0 mmol/L or 180 mg/dL (unfasted)
CRP	<12 years	N/A	>2 ULN or >10 mg/L (if ULN not provided)

N/A = not applicable, ULN = upper limit of normal

Table 9 - Threshold levels for potentially clinically significant coagulation abnormalities

Parameter name	Age	Low	High
VWF antigen	All	< LLN	N/A
VWF:RCo activity	All	< LLN	N/A

N/A = not applicable, ULN = upper limit of normal

Table 10 - Threshold levels for potentially clinically significant vital sign abnormalities

Variable	Age	Low	High
Systolic Blood Pressure	6 to <12 years old	≤80 mmHg and decrease from baseline ≥20 mmHg	≥108 mmHg and increase from baseline ≥20 mmHg
	24 months/2 years to <6 years old	≤70 mmHg and decrease from baseline ≥20 mmHg	≥101 mmHg and increase from baseline ≥20 mmHg
	28 days/1 month to 23 months old	≤70 mmHg and decrease from baseline ≥20 mmHg	≥98 mmHg and increase from baseline ≥20 mmHg
	Birth/0 to 27 days old	≤60 mmHg and decrease from baseline ≥20 mmHg	≥85 mmHg and increase from baseline ≥20 mmHg
Diastolic Blood Pressure	6 to <12 years old	≤48 mmHg and decrease from baseline ≥10 mmHg	≥72 mmHg and increase from baseline ≥10 mmHg
	24 months/2 years to <6 years old	≤34 mmHg and decrease from baseline ≥10 mmHg	≥59 mmHg and increase from baseline ≥10 mmHg
	28 days/1 month to 23 months old	≤34 mmHg and decrease from baseline ≥10 mmHg	≥54 mmHg and increase from baseline ≥10 mmHg
	Birth/0 to 27 days old	≤34 mmHg and decrease from baseline ≥10 mmHg	≥50 mmHg and increase from baseline ≥10 mmHg
Orthostatic hypotension	< 12 years	SBP : St - Su ≤-20 mmHg DBP : St - Su ≤-10 mmHg	N/A
Sa02	<12 years	≤95%	N/A
Weight	<12 years	N/A	≥5% weight loss from baseline
Heart Rate	6 to <12 years old	≤50 bpm and decrease from baseline ≥20 bpm	≥120 bpm and increase from baseline ≥20 bpm

Variable	Age	Low	High
	24 months/2 years to <6 years old	≤75 bpm and decrease from baseline ≥20 bpm	≥140 bpm and increase from baseline ≥20 bpm
	28 days/1 month to 23 months old	≤80 bpm and decrease from baseline ≥20 bpm	≥175 bpm and increase from baseline ≥20 bpm
	Birth/0 to 27 days old	≤90 bpm and decrease from baseline ≥20 bpm	≥190 bpm and increase from baseline ≥20 bpm
Temperature	<12 years	N/A	Ear/temporal artery: ≥100.4°F/38.0°C Oral: ≥99.5°F/37.5°C Axillary: ≥99°F/37.2°C
Respiration Rate	6 to <12 years old	<18 per minute	>30 per minute
	24 months/2 years to <6 years old	<22 per minute	>34 per minute
	28 days/1 month to 23 months old	<24 per minute	>40 per minute
	Birth/0 to 27 days old	<30 per minute	>60 per minute

5.5 APPENDIX 5 QUESTIONNAIRE SCORING

5.5.1 Appendix 5.1 PROMIS instruments

Six PROMIS instruments are used in this study:

a) PROMIS Pediatric NRS Pain Intensity (v1.0 Pain Intensity 1a; ≥8 years old)

b) PROMIS Parent Proxy NRS Pain Intensity (v1.0 Pain Intensity 6b; 5 to <12 years old)

c) PROMIS Pediatric-SF Pain Interference (v2.0 Pain Interference 8a; ≥8 years old)

d) PROMIS Parent Proxy-SF Pain Interference (v2.0 Pain Interference 8a; 5 to <12 years old)

e) PROMIS Pediatric-SF Physical Activity (v1.0 Physical Activity 8a; ≥8 years old)

f) PROMIS Parent Proxy-SF Physical Activity (v1.0 Physical Activity 8a; 5 to <12 years old)

For PROMIS instruments c) - f), within each instrument, each question has five response options ranging in value from one to five. To find the total raw score for an instrument with all questions answered, sum the values of the response to each question. All questions must be answered in order to produce a valid total score. For pain intensity forms, the items are not calibrated and do not produce a T-score. Instead, raw response scores (0 to 10) should be used for analyses. For other forms, total raw score is then converted into a T-score for each participant using an instrument-specific *Conversion Table* as provided in Table 11. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person with a T-score of 40 is one SD below the mean.

Table 11 - Conversion table for PROMIS instruments

(c) PROMIS Pediatric-SF Pain Interference (≥8 years)

Pain Interference 8a - Pediatric v2.0		
Short Form Conversion Table		
Raw Score	T-Score	SE*
8	34.0	5.6
9	38.7	4.4
10	40.6	4.2
11	42.7	3.8
12	44.3	3.7
13	45.8	3.4
14	47.1	3.3
15	48.4	3.2
16	49.5	3.2
17	50.6	3.1
18	51.7	3.1
19	52.7	3.1
20	53.7	3.0
21	54.7	3.0
22	55.7	3.0
23	56.6	3.0
24	57.6	3.0
25	58.5	3.0
26	59.5	3.0
27	60.4	3.0
28	61.4	3.0
29	62.4	3.0
30	63.4	3.0
31	64.4	3.0
32	65.4	3.1
33	66.5	3.1
34	67.6	3.2
35	68.8	3.2
36	70.1	3.3
37	71.5	3.4
38	73.2	3.7
39	75.0	3.8
40	78.0	4.3

*SE = Standard Error on T-Score

(d) PROMIS Pediatric-SF Physical Activity (≥8 years)

Physical Activity 8a - Pediatric v1.0		
Short Form Conversion Table		
Raw Score	T-Score	SE*
8	28.8	4.8
9	32.6	3.8
10	34.5	3.5
11	36.4	3.1
12	37.9	2.8
13	39.2	2.6
14	40.4	2.5
15	41.4	2.4
16	42.4	2.3
17	43.4	2.3
18	44.3	2.3
19	45.2	2.3
20	46.1	2.3
21	47.0	2.3
22	47.8	2.3
23	48.7	2.3
24	49.6	2.3
25	50.5	2.3
26	51.4	2.3
27	52.3	2.4
28	53.3	2.4
29	54.3	2.4
30	55.3	2.4
31	56.3	2.4
32	57.3	2.4
33	58.4	2.4
34	59.5	2.5
35	60.8	2.5
36	62.1	2.7
37	63.7	2.8
38	65.5	3.1
39	67.8	3.5
40	71.7	4.6

*SE = Standard Error on T-Score

(e) PROMIS-SF Pain Interference (5 to <12 years)

Pain Interference 8a - Parent Proxy v2.0		
Short Form Conversion Table		
Raw Score	T-Score	SE*
8	38.0	6.0
9	44.0	3.0
10	46.0	3.0
11	48.0	3.0
12	49.0	2.0
13	50.0	2.0
14	51.0	2.0
15	52.0	2.0
16	53.0	2.0
17	54.0	2.0
18	55.0	2.0
19	56.0	2.0
20	57.0	2.0
21	58.0	2.0
22	58.0	2.0
23	59.0	2.0
24	60.0	2.0
25	61.0	2.0
26	62.0	2.0
27	62.0	2.0
28	63.0	2.0
29	64.0	2.0
30	65.0	2.0
31	66.0	2.0
32	67.0	2.0
33	67.0	2.0
34	68.0	2.0
35	69.0	2.0
36	70.0	2.0
37	71.0	3.0
38	73.0	3.0
39	74.0	3.0
40	78.0	4.0

*SE = Standard Error on T-Score
bles based on default Parent Proxy

(f) PROMIS Parent Proxy-SF Physical Activity (5 to <12 years)

Physical Activity 8a - Parent Proxy v1.0 *Short Form Conversion Table*		
Raw Score	T-Score	SE*
8	28.4	4.9
9	31.9	4.0
10	33.5	3.7
11	35.5	3.3
12	37.0	3.0
13	38.4	2.8
14	39.6	2.7
15	40.7	2.6
16	41.8	2.5
17	42.8	2.5
18	43.8	2.5
19	44.7	2.5
20	45.7	2.5
21	46.6	2.5
22	47.6	2.6
23	48.6	2.6
24	49.6	2.6
25	50.6	2.6
26	51.6	2.6
27	52.6	2.6
28	53.7	2.6
29	54.8	2.6
30	55.9	2.6
31	57.1	2.6
32	58.3	2.7
33	59.5	2.7
34	60.9	2.7
35	62.3	2.8
36	63.8	2.9
37	65.5	3.0
38	67.5	3.3
39	70.0	3.7
40	73.7	4.6

*SE = Standard Error on T-Score

5.5.2 Appendix 5.2 Haemo-Qol

The Haemo-Qol questionnaires for children aged 4-7 years will be summarized in terms of a total score, and the questionnaires for children aged 8 to <12 years will be summarized in terms of subscale scores and a total score according to the recommendations of the questionnaire authors.

When missing data are presented, a subscale/total score can only be calculated if at least 50% of questions for that subscale/questionnaire are answered (non-missing and not "Not Applicable").

Haemo-QoL (age group I; 4-7 years old)

The Haemo-Qol questionnaire for participants with hemophilia who are 4-7 years of age consists of 16 items for past 4 weeks time period.

Haemo-QoL (age group II; 8 to <12 years old)

The Haemo-Qol questionnaire for participants with hemophilia who are 8-<12 years of age consists of 35 items pertaining to 9 subscales for past 4 weeks time period.

Time Period	Subscales for Haemo-QoL	No. of questions	No. of non-missing items required to calculate subscale
In the past 4 weeks	1. Physical health	4	2
	2. Feeling	4	2
	3. View of yourself	4	2
	4. Family	4	2
	5. Friends	3	2
	6. Other persons	4	2
	7. Sports and school	4	2
	8. Dealing with hemophilia	4	2
	9. Treatment	4	2
	Total Score	35	18

Haemo-QoL parent proxy (age group I; 4-7 years)

The Haemo-QoL questionnaire for parents of participants with hemophilia who are 4-7 years of age consists of 16 items for past 4 weeks time period.

Haemo-QoL parent proxy (age group II; 8 to <12 years)

The Haemo-QoL questionnaire for parents of participants with hemophilia who are 8 to <12 years of age consists of 35 items pertaining to 9 subscales for past 4 weeks time period.

Time Period	Subscales for Haem-A-QoL	No. of questions	No. of non-missing items required to calculate subscale
In the past 4 weeks	1. Physical health	4	2
	2. Feeling	4	2
	3. View of yourself	4	2
	4. Family	4	2
	5. Friends	3	2
	6. Other persons	4	2
	7. Sports and school	4	2
	8. Dealing with hemophilia	4	2
	9. Treatment	4	2
	Total Score	35	18

Scoring algorithm

Per the algorithm on http://www.haemoqol.de/manual.htm, to correctly score the questionnaires, each version has to be identified and the appropriate scoring list has to be selected. High score represent low quality of life and scoring involves the following steps:

1. Assigning numbers to the response scale

1= never, 2=seldom, 3=sometimes, 4=often, 5=always

For negatively worded items, the above classification can be applied in which higher values represent a lower quality of life. For positively worded items, the score has to be recoded (see below).

2. Recoding positively worded items

Positively worded items in table have to be recoded so that numeric values assigned are reversed:

1=always, 2=often, 3=sometimes, 4=seldom, 5= never

By recoding, high scores in positively worded items reflect not higher but lower quality of life. The then unidirectional values can subsequently be added to yield the summed scores according to the scoring list.

3. Producing the raw score

A raw subscale score is produced by summing up all items within a subscale. Its range lies between the lowest possible (number of items (n) x 1) and highest possible (number of items (n) x 5) value of the respective scale.

The raw total score is produced by the addition of all items (instead of the subscale items only) of the questionnaire (again paying attention to the recoding procedure - see Steps 1 and 2).

4. Transferring a raw score to a Transformed Scale Score (TSS) between 0 and 100

Creating a Transformed Scale Score (TSS) makes it possible to express the score as a percentage between the lowest (0) and the highest (100) possible value. To obtain the TSS the following transformation rule has to be applied:

TSS = 100 x ((raw score – minimal possible raw score) / possible range of raw scores) where:

- minimal possible raw score = number of questions answered × 1
- maximal possible raw score = number of questions answered × 5
- possible range of raw scores = maximum possible raw score - minimal possible raw score

Example: A raw score of 12 on the "Physical Health" scale is to be transformed:

- When all 4 questions were answered:
  - minimal possible score=4
  - maximal possible score=20
  - range of scores=16
  - TSS=(12-4)/16 = 50
- When 3 of the 4 questions were answered:
  - minimal possible score=3
  - maximal possible score=15
  - range of scores=12
  - TSS=(12-3)/12 = 75

Transformed scores can be produced from raw subscale and raw total scores.

The total and subscale scores based on TSS will be presented in outputs.

6 REFERENCES

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2014;12(11):1935-9.

2. Baskin JL, Pui CH, Reiss U, Wilimas JA, Metzger ML, Ribeiro RC, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet. 2009;374(9684):159-69.

3. Tagalakis V, Kahn SR, Libman M, Blostein M. The epidemiology of peripheral vein infusion thrombophlebitis: a critical review. Am J Med. 2002;113(2):146-51.

Signature Page for VV-CLIN-0611426 v1.0
efc16295-16-1-9-sap

Approve & eSign	[redacted]

Approve & eSign	[redacted]