Title Page

Protocol Title:

A multicenter, prospective, open-label, clinical study to assess the effect of using a new risk score approach to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when hemophilia A participants switch from standard half-life products to damoctocog alfa pegol (Jivi)

Protocol Number: 21924

Compound Number: BAY 94-9027/ Damoctocog alfa pegol; Human Pegylated rFVIII; Jivi

Short Title: Jivi interventional study to assess a new risk score approach

Acronym: PREDICT (**PR**ediction factors for optimal **E**fficacy and **D**osing regimen when sw**I**t**C**hing from SHL **T**o EHL)

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

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Version History

This Statistical Analysis Plan (SAP) for Study 21924 is based on the protocol Version 3.0 dated 19AUG2022.

SAP Version	*Date*	*Change*	*Rationale*
3	*09JAN2024*	*Based on adjusted inclusion criteria, include definitions for determination of pre-study annualized bleed (ABR), treatment frequency, and stable standard half-life (SHL) prophylaxis.* *Reduce number of participants, remove summaries by country, present separate summaries of participants with a history of FVIII inhibitors only if n ≥ 5.* *Interim analysis removed*	*To align with amended protocol v4.0, 02 Oct 2023 considering the modified eligibility criteria (reduced restriction to enrollment), amendment back to a single country US study, and reduced sample size.* *Inclusion criteria were adjusted to reduce restrictions on enrollment as follows:* • *to modify requirements and window for prophylaxis with SHL FVIII with a stable frequency prior to start of study intervention,* • *to define stable frequency, and* • *to permit non-Jivi EHL between the 6-month stable SHL prophylaxis period and start of study treatment*
3	*09JAN2024*	*Details on transformation of HAEM-A-QoL, HAEMO-QoL KIDS, and WPAI scores added*	*For clarity*
2	*06Oct2022*	*Removed statements that the study is planned to be conducted in the US only and added analyses of country and FVIII inhibitor sub-populations*	*To align with amended protocol v3.0, 19 Aug 2022, considering the potential country effect after allowing enrollment not limited to the US and modified eligibility criteria regarding participants with a history of FVIII inhibitors.*
1	*10 Dec 2021*	*Not applicable*	*Original version (based on protocol version 2.0, 17 Sep 2021)*

1. Introduction

Study 21924 (PREDICT) is a multicenter, open-label, single arm, prospective study that aims to assess a new risk score approach utilizing the best known phenotypic and biologic variables to select the most appropriate prophylaxis regimen for reaching a favorable outcome when switching from standard half-life (SHL) human coagulation factor VIII (FVIII) treatment to Jivi. Participants will be ≥ 12 years of age with congenital hemophilia A who have a documented history of at least 150 EDs with any FVIII product. All participants will have received prophylaxis with any licensed SHL FVIII product with a stable dosing regimen.

This SAP does not address pharmacokinetic (PK) calculations of parameters derived using the Web-Accessible Population Pharmacokinetic Service Hemophilia (WAPPS-Hemo) system nor medical resource utilization and health economics outcomes that may be collected by data linkage using de-identified data of participants who consent to participate in tokenization.

The SAP describes the final analysis of the study. Table, figure and listing specifications including table mock shells are contained in a separate document.

There are no changes to the analyses described in the protocol.

1.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of using a baseline risk score, based on a participant's phenotypic and biologic variables, to select the most appropriate prophylaxis regimen for reaching a favorable outcome, when switching from a SHL product to Jivi	Occurrence of favorable outcome on the score selected dosing regimen
Secondary	
To assess the effectiveness of Jivi compared to a previous SHL treatment	ABR (total, joint, spontaneous) and change in total ABR from pre-study
To assess the frequency of Jivi administration	Change in the frequency of pre-study SHL treatment to the frequency of Jivi administration (infusions/month)
To assess the proportion of participants with 0 and ≤ 1 spontaneous bleeds	Occurrence of participants with 0 and ≤ 1 spontaneous bleeds
To assess participant quality of life (QoL) and physical activity, as measured by Patient Reported Outcomes (PROs)	Change in Haemophilia Quality of Life Questionnaire (Haem-A-QoL or Haemo-QoL KIDS, depending on age of participant); Patient's Global Impression of Change (PGI-C); EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire; Treatment Satisfaction Questionnaire for Medication (TSQM); Work Productivity and Activity Impairment (WPAI) questionnaire scores
To assess target joint status, per International Society on Thrombosis and Haemostasis (ISTH) guidelines	Number of target joints and change in target joint status from baseline

Objectives	Endpoints
Other, Pre-specified	
To assess whether blood type and body mass index (BMI) would have led to a different score allocation	Participant score considering ABO type and BMI
To describe PK parameters derived from WAPPS-Hemo and assess any association with clinical risk score	PK parameters derived from WAPPS-Hemo
To determine participant Jivi trough levels while on a specific regimen	Trough measurement of Jivi levels
To determine the percentage of participants who can maintain > 1%, > 3 %, and > 5% FVIII trough levels while on a specific prophylaxis regimen	Occurrence of trough levels above 1%, 3% and 5%, stratified by prophylaxis regimen
Abbreviations: ABR = annualized bleeding rate; EQ-5D-5L = EuroQoL 5 dimensions; FVIII = human coagulation factor VIII; SHL = standard half-life	

1.2 Study Design

This is a Phase 4, multicenter, open-label, single arm, prospective study to assess the effect of using a new risk score approach to select the most appropriate prophylaxis regimen for reaching favorable outcomes when PTPs with congenital hemophilia A switch from a SHL FVIII product for regular prophylaxis to the EHL FVIII product, Jivi. Participants will be ≥ 12 years of age with congenital hemophilia A who have a documented history of at least 150 EDs with any FVIII product. All participants will have received prophylaxis with any licensed SHL FVIII product with a stable dosing regimen for at least 6 consecutive months within the previous 12 months prior to the screening visit.

A controlled comparator arm is not necessary for this study. The primary endpoint (i.e. measurement of favorable outcomes based on changes in ABR and frequency of administration) will be reported for the combined sample, pooled across risk groups and by assigned prophylaxis regimen. End of study (EOS) assessments and intra-individual change from pre-study will be reported for other endpoints.

1.2.1 Total Risk Score at Baseline

Participants' total risk scores will be determined at baseline based on 5 individually weighted variables: pre-study bleeding phenotype, previous treatment frequency, number of active target joints, vWF levels, and physical activity (Table 1).

Table 1: Parameters for Determining Participant Risk Scores

Participant Variables	Score Assignment
Bleed phenotype (total bleeds, occurring during the stable SHL period[a])	
ABR ≤ 1	-2
1 < ABR ≤ 4	+2
ABR > 4	+3
Treatment frequency derived from the stable SHL period[a]	
< 3x/week	-1
3x/week	0
> 3x/week	+1
Number of active target joints[b]	
0	-1
1	0
2	+1
> 2	+2
vWF antigen levels (within previous 12 months)	
vWF ≥ 150%	-1
100% ≤ vWF < 150%	0
vWF < 100%	+2
Physical activity[c]	
Low[d] (non-contact sports)	-1
Sedentary[e]	0
Medium/high[f] (contact sports)	+1

Abbreviations: ABR = annualized bleeding rate; SHL = standard half-life; vWF = von Willebrand Factor.

[a] Stable SHL period: Stable SHL prophylaxis for at least 6 months within the 12 months prior to the screening visit.

[b] Derived at baseline from the patients most current status.

[c] Refers to a participant's usual physical activity level, based on the last 12 months. If a significant change in activity level is expected in the next 6 months, the criteria for the physical activity variable should be based on that anticipated level.

[d] Low intensity activities are those that involve gentle and fluid motions, and may include non-contact sports such as swimming, elliptical training, or archery (Protocol Figure 4–2 [scores <1.5]).

[e] Sedentary behavior refers to time spent sitting or lying down (except when sleeping), with very little energy expenditure (Protocol Figure 4–2).

[f] Medium/High activities are those that require some effort or lead to harder breathing or puffing and panting (depending on your fitness) including contact sports (Protocol Figure 4–2 [scores ≥1.5]).

- Participants will be scored on a range of -6 (low risk) to +9 (high risk).
- If the physical activity variable is missing, then 0 will be assigned.
- Participant missing any variable other than physical activity level is not eligible to be enrolled.

1.2.2 Assignment to Dosing Regimen

Participants will be scored on a range of -6 (low risk) to +9 (high risk) and will be allocated to the prophylaxis regimens presented in Table 2.

Table 2: Risk Score Treatment Assignment

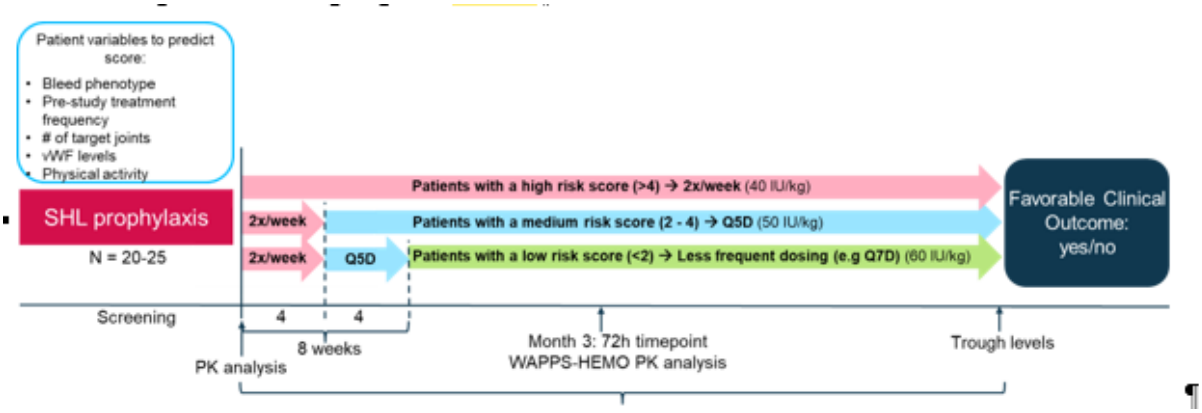
Total Risk Score (Baseline)	Assignment	Dosing Regimen
High (> 4)	2x/week	2x/week infusions at 40 IU/kg/dose for 6 months
Medium (2-4)	Q5D	2x/week at 40 IU/kg/dose for 1 month + Q5D infusions at 50 IU/kg/dose for 5 months
Low (< 2)	Less frequent dosing (e.g. Q7D)	2x/week at 40 IU/kg/dose for 1 month + Q5D infusions at 50 IU/kg/dose for 1 month + less frequent infusions (e.g. Q7D)[a] at 60 IU/kg/dose for 4 months.

Abbreviations: Q5D = every 5 days; Q7D = every 7 days
[a] As determined by the investigator.

1.2.3 Study Intervention Period

The participants' planned study duration, including a screening (up to 30 days), treatment (6 months), and safety follow-up period (14 days after last dose), will be approximately 7.5 months (Figure 1).

Figure 1: Dosing Regimen Schema



Abbreviations: PK = pharmacokinetics; Q5D = every 5 days; Q7D = every 7 days; SHL = standard half-life; vWF = von Willebrand factor.

[a] Score exception: if ≥2 muscle or joint bleeds (without evident trauma) occur within any given 8-week period during the 6-month study, then the protocol recommends assigning the participant to the next highest frequency regimen. Per protocol, the treating investigator reserves the right to change a participant's regimen at any time if they perceive the risk score-determined regimen is not well-suited for the participant.

The participant eDiary will be used to assess the participant's compliance with the treatment schedule/dose, and to reconcile study medication inventory. The eDiary will be used to record date and time of self-administration of study intervention for prophylaxis as well as every bleeding episode with details of the bleeding and administered intervention.

1.2.4 Favorable Outcome

The primary endpoint is the occurrence of favorable outcome on the score selected dosing regimen, which will be described via the proportion of participants with a favorable outcome. Favorable outcome is defined for this study as:

- no change of the risk score-assigned dosing regimen during the study, with one of the following:
  - improved annualized bleed rate (ABR) versus pre-study ABR and decreased frequency of administration versus pre-study frequency.
  - improved ABR versus pre-study ABR with similar frequency of administration versus pre-study frequency.
  - decreased frequency of administration versus pre-study frequency and similar ABR versus pre-study ABR.

2. Statistical Hypotheses

The study is not designed to test any predefined hypothesis. All analyses will be descriptive or exploratory. Confidence intervals, 95%, two-sided, will be reported for the primary endpoint and for selected secondary endpoints, assessed as occurrence rates, mean scores or counts, and change from baseline.

2.1 Multiplicity Adjustment

Confidence intervals reported for primary, secondary and pre-specified exploratory endpoints will not be adjusted for multiple endpoints assessed.

3. Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Table 3: Analysis Sets

Participant Analysis Set	Description
Enrolled	All participants who signed the ICF
Modified intention-to-treat (mITT) set	All enrolled participants who had received at least 1 dose of study intervention, who have infusions/bleeding data from the diary and CRF available, and who have been followed for a minimum of 4 months.
Safety analysis set	All participants who had received at least 1 dose of study intervention.

Abbreviations: CRF = case report form; ICF = informed consent form.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

4. Statistical Analyses

4.1 General Considerations

Statistical analyses will be performed using SAS release 9.4 or higher (SAS Institute Inc., Cary, North Carolina, US).

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and metric (or continuous) variables by sample statistics (i.e. mean, standard deviation [SD], minimum, median, quartiles, and maximum). The number of data available and missing data will be calculated

for metric data. Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All data will be presented in the participant data listing as they are recorded on the electronic case report form (eCRF), eDiary and Interactive Voice/Web Response System (IxRS), i.e. partially missing data will appear as such.

The primary analysis will be performed after the database lock after Last Participant Last Visit.

The mITT set will be used to analyze endpoints related to the effectiveness objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety. Data will be pooled across study sites for all reporting of participant characteristics, primary, secondary, and safety endpoints.

Analysis will be presented overall for the combined risk score groups. Some tables will be stratified by the risk score-selected dosing regimen. Analysis of risk score-selected dosing regimen will include the entire treatment period. The first 8 weeks on study will not be presented separately. Safety listings will include assigned dosing regimen, based on risk score, and actual current dosing regimen at start of AE or time of assessment. Safety summaries will be presented only overall, for the combined risk score groups.

Subgroup analysis of study endpoints and safety events by history of FVIII inhibitors will be presented only if the mITT set includes at least 5 participants in each category, with and without history of FVIII inhibitors.

In general, missing clinical outcomes as well as missing assessments of PRO summary scores collected in this study will not be imputed. Missing exposure and AE/concomitant medication start/end date will be imputed based on a worst case scenario. For calculation of intra-individual change from pre-study value or baseline: No missing baseline ABR or frequency of administration is expected among participants who meet study enrollment criteria, as these are required to calculate total risk score.

Visit 2 is considered baseline, when the participants risk score and resulting regimen scheme will be determined (refer to section 1.2.2).

4.1.1 Data Rules

4.1.1.1 Annualized bleed rate (ABR)

Pre-study ABR is reported in History of Hemophilia eCRF as ‘ABR during period of stable SHL treatment’.

The ABR response is calculated over the entire intervention period:

- Intervention period (days) = (1 + Visit 6/EOS date – Visit 2 date)

The ABR is calculated using the number of bleed events reported to the eDiary. Types of bleed event and counting of bleeds are described in the section below.

The ABR for each type of bleed will be calculated as:

- ABR = 365.25 × # of bleed events / Intervention period (days)
  - ABR will be rounded to 2 decimal places

Improved, similar, or worsening ABR will be assessed by comparison to pre-study ABR:

$$ABR_{post} - ABR_{pre} = \begin{cases} \geq 1 & worsening \\ (-1, 1) & similar \\ \leq -1 & improved \end{cases}$$

4.1.1.2 Counting of Bleeds

- 'Treated bleeds' will include all treated bleeds (=all treated spontaneous and treated trauma bleeds).
- 'All bleeds' will include all bleeds, regardless of treated or untreated.
- A bleed will be counted as treated bleed if either the flag variable from the diary indicates that the bleed was treated or there is a matching infusion for this bleed.

24-hour rule:

All bleeds that occur during the same calendar day will be considered as one bleed. As a bleed event may be in more than one category, priority will be determined according to the following order:

- spontaneous bleed
- joint bleed
- treated bleed
- earliest bleed

The analyzed bleed will be the one with the highest priority. It will be classified by the following derived characteristics:

- combination of all types and locations
- highest treated status (i.e. treated if at least one bleed on that day is treated)

All other bleeds on the same calendar day will not be considered for analysis but only listed in section 16.

72-hour rule:

A spontaneous joint or spontaneous muscle bleed will not be counted if it occurs within 72 hours of a bleed (or infusion for that bleed) at the same site. For a spontaneous bleed to be affected by this rule, all sites listed for the bleed must also be specified in the previous bleeds during a 72-hour time frame. Infusions for such bleeds will be considered to be follow-up infusions. If the current and previous bleeds are both skin/mucosa bleeds, this rule does not apply. The rule operates with date/time and bleed locations adjusted by 24-hour rule. Bleeds eliminated by 24-hour rule are not considered.

4.1.1.3 Joint Bleeds and Target Joints

Target joints will be identified at baseline in the eCRF. Participants will identify the affected joint (site) of any joint bleed during the study in the eDiary. The record of bleed events at each site of each participant will be tracked. The count of joint bleed events for a participant will include all sites and each event at each site that is at least 72 hours after any previous bleed at that site or at least 72 hours after a treatment for a previous bleed at that site.

Target joints (modified ISTH definition[i]):

A **pre-existing** target joint is a joint that was reported to be a target joint at start of the study.

A **new** target joint is defined as a joint that was not reported as pre-existing target joint but showed at least 3 spontaneous bleeds during the study (6-month treatment period).

A **resolved** target joint is a previous target joint with <= 1 spontaneous bleeds during the last 6 months. Due to study design, this definition differs and is pro-rated from the current ISTH definition for resolution of target joints, where 12 months are considered to count for <=2 spontaneous bleeds in a joint.

Number of target joints at end of study:
Pre-existing target joints + new target joints – resolved target joints

4.1.1.4 Frequency of Administration

Baseline frequency of administration is reported in Previous Hemophilia Treatment for the past 6 months eCRF as 'Previous Hemophilia Treatment during the stable SHL period' and is converted to frequency per month.

The frequency of administration response is calculated over the entire intervention period:

- Intervention period (days) = (1 + Visit 6/EOS date – Visit 2 date)

The frequency of administration (/month) will be assessed using the record of prescribed dose regimen in the eCRF. These following are example calculations of the risk group planned dose frequency:

Example 1: Participant in high risk score group was prescribed 2x/week on Day 1 and remained in study until Day 182 (26 weeks) with no prescribed dose change. The total prescribed number of dose administrations is 26 weeks x 2/week. The frequency (/month) of prescribed Jivi prophylaxis is 30.4375 x total prescribed number of dose administrations/ dose interval (days) = [30.4375 (days/month) x 52]/ 182 (days) = 8.6964/ month.

Example 2: Participant in low risk score group was prescribed 2x/week on Day 1, Q5D on Day 29, and Q7D on Day 57. The participant remained in study until Day 182 with no other prescribed dose change. The frequency of prescribed Jivi prophylaxis is 30.4375 (days/month) x 32 total doses/182 (dose interval days) = 5.3516/month.

- Frequency of administration (/month) = 30.4375 × total doses over intervention period of prescribed Jivi prophylaxis / Intervention period (days)
  - Frequency of administration will be rounded to 2 decimal digits.

Improved, similar, or worsening frequency of administration will be assessed by comparison of prescribed prophylaxis to the baseline frequency of administration (each expressed as infusions per month):

$$Infusions_{post} - Infusions_{pre} = \begin{cases} \geq 2 & worsening \\ (-2, 2) & similar \\ \leq -2 & improved \end{cases}$$

4.1.1.5 Incremental Recovery

FVIII levels measured by a validated assay will be analyzed. Planned time points for assessment of incremental recovery are prior to start of infusion and 15 to 30 minutes after end of infusion.

Incremental recovery is calculated as shown below:

Incremental recovery =
(post-infusion FVIII level – pre-infusion FVIII level) * weight (in kg)/ dose (in IU)

The most recent weight measurement will be used for calculation.

If a pre-infusion FVIII level value is below the lower limit of quantification (LLOQ), a data point with the value of one-half the LLOQ will be substituted.

A validity flag for incremental recovery values will be created. All incremental recoveries will be considered valid except when the following conditions apply:

- Pre-infusion FVIII >37.5% after 3 days, >23.1% after 4 days, >21.5 after 5 and 6 days, or >8.1% after 7 or more days
- Post-infusion FVIII value is below the LLOQ
- Post-infusion FVIII value is below Pre-infusion FVIII value

If an incremental recovery is flagged as not valid, then the corresponding pre-infusion, post-infusion and incremental recovery value will not be considered in tables displaying summary statistics of incremental recovery values and FVIII levels. FVIII levels that are not valid for calculation of incremental recovery will be listed.

4.1.1.6 FVIII Trough Levels

Trough levels = FVIII levels measured at Visit 6 (month 6) for all participants and for participants on 2x/week regimen at Visit 5 (month 3, 3-day trough).

Trough levels depend on the time since previous prophylactic infusion. All trough levels will be assigned to one of the following time intervals. Measurements outside of these intervals will be excluded from the analysis (outside of +/- 12 hours of target time point).

- 3 days: trough level measurement took place >=60 - <84 h after previous infusion
- 4 days: trough level measurement took place >=84 - <108 h after previous infusion
- 5 days: trough level measurement took place >=108 - <132 h after previous infusion
- 6 days: trough level measurement took place >=132 - <156 h after previous infusion
- 7 days: trough level measurement took place >=156 - <180 h after previous infusion
- 8 days: trough level measurement took place >=180 - <204 h after previous infusion
- 9 days: trough level measurement took place >=204 - <228 h after previous infusion
- 10 days: trough level measurement took place >=228 - <252 h after previous infusion

Validity rule for trough levels:

The following trough levels will be considered invalid: >37.5% after 3 days, >23.1% after 4 days, >21.5 after 5 and 6 days, >8.1% after 7 or more days.

Treatment administration:

Documented infusions with other FVIII products or with a dose of 0 IU will be excluded. Infusions with a missing dose will be counted for number of infusions and exposure days but will be excluded from other treatment administration analyses.

4.2 Primary Endpoint Analysis

The proportion and 95% exact (Clopper-Pearson) CI of participants with favorable outcome on the risk score-selected prophylaxis regimen will be described. The proportion will be provided overall, as well as by assigned prophylaxis regimen and by subgroup of history of FVIII inhibitors.

4.2.1 Definition of Endpoint

Occurrence of favorable outcome is the primary endpoint which is assessed by ABR and frequency of prophylaxis Jivi administration (/month) evaluated from Visit 2 (baseline) through Visit 6 (Month 6, EOS/ early withdrawal) among participants in the mITT.

Favorable outcome is defined as no change of the score-assigned dosing regimen with one of the following intra-individual measures:

- improved ABR and decreased frequency of administration.
- improved ABR with similar frequency of administration.
- decreased frequency of administration and similar ABR.

Change of the score-assigned dosing regimen is addressed in section 0 below.

Definition for improved/similar ABR:

$$ABR_{post} - ABR_{pre} = \begin{cases} \geq 1 & worsening \\ (-1, 1) & similar \\ \leq -1 & improved \end{cases}$$

Definition for decreased/similar frequency of administration (/month):

$$Infusions_{post} - Infusions_{pre} = \begin{cases} \geq 2 & worsening \\ (-2, 2) & similar \\ \leq -2 & improved \end{cases}$$

Therefore, a favorable outcome is achieved when either:

$$ABR_{post} - ABR_{pre} \leq -1 \quad and \quad Infusion_{post} - Infusion_{pre} < 2$$

or:

$$ABR_{post} - ABR_{pre} < 1 \quad and \quad Infusion_{post} - Infusion_{pre} \leq -2$$

4.2.2 Main Analytical Approach

The analysis of the primary endpoint will be performed on the mITT population.

The entire study intervention period will be analyzed regardless of the score assigned dosing regimen (i.e. during the first 8 weeks on the study).

The strategy for primary endpoint analysis, including how to deal with participants who switch regimen frequency is listed below:

- A switch to a higher frequency regimen than the one assigned by the score, due to a bleed during study, is considered as non-favorable outcome
- Participants who switch due to other reasons than bleeding events (e.g. personal decision, study compliance issues, or changes in physical activity level) will be censored at the time of regimen change
  - switch after 4 months (> 122 days): participant data will be analyzed until censoring
  - switch prior to 4 months (≤ 122 days): participant data will not be used for analysis, as it is assumed that a shorter duration will not be sufficient to correctly estimate the ABR and would bias the results.

Note: a decrease in regimen per score assignment (during the first 8 weeks) is not considered a switch as discussed above.

Favorable outcome assessed by total ABR and frequency of administration (/month) is evaluated after considering regimen switch events.

4.2.3 Sensitivity Analysis

The following analysis will be performed if numbers of participants in the mITT population with and without history of FVIII inhibitors are each ≥5: As sensitivity analyses, the proportion of participants with favorable outcome on the risk score-selected prophylaxis regimen will be presented by inhibitor history.

The following analysis will be performed if > 3 participants in the safety analysis set are excluded from the mITT: The proportion of participants with favorable outcome will be reported for the safety analysis set, assigning non-favorable outcome to participants who discontinued or switched regimen prior to 4 months.

A further sensitivity will be conducted, assigning non-favorable outcome to all participants who discontinued or switched regimen at any time during study.

4.2.4 Supplementary Analyses

Not applicable.

4.3 Secondary Endpoints Analysis

4.3.1 Key Secondary Endpoints

The components of the primary endpoint, ABR (total, joint, spontaneous) and frequency of administration (infusions/month), will be presented via summary statistics. Values for the study period and intra-individual change from pre-study value will be presented for total ABR and frequency of administration. In addition, the proportion and 95% exact (Clopper-Pearson) CIs of participants with improved/similar/worse value of total ABR and frequency of administration will be provided. These tables will be presented overall.

Frequency tables will be provided for the proportion of participants with 0, >0 and <=1, and >1 spontaneous bleeds. Corresponding 95% CIs will be reported for the proportions with 0 or with 0 to <=1 spontaneous bleeds.

4.3.1.1 Definition of Endpoints

Refer to section 4.1 and section 4.2.1.

4.3.1.2 Main Analytical Approach

Refer to section 0.

4.3.1.3 Sensitivity Analysis

In addition to the analysis of treated bleeds ABR, all bleed ABR will be presented via summary statistics for all bleed ABR, the annualized rate of all bleeds (regardless of treated or untreated) and the intra-individual difference between all bleed and treated bleed ABR.

4.3.2 Supportive Secondary Endpoints

The analyses of supportive secondary endpoints will be performed on the mITT population. The entire study intervention period will be analyzed regardless of the dosing regimen (i.e. entire period includes the first 8 weeks).

4.3.2.1 Patient Reported Outcomes

PRO data will be collected in an eDiary form made available for Baseline (HAEM-A-QoL or HAEM-QoL [adult or kids], EQ-5D-5L, WPAI+CIQ:HS, TSQM-9 [baseline]), Month 3 (EQ-5D-5L only), and EOS (HAEM-A-QoL or HAEM-QoL, PGI-C, EQ-5D-5L, WPAI+CIQ:HS, TSQM-9) visits. Frequency summaries will be presented by visit and continuous variables will be described by absolute value and as change from baseline. Missing data will not be imputed.

- Haemophilia Quality of Life Questionnaire transformed scale scores (%) will be presented separately for participants ages ≥17 years and for those age 12-16.
  - *HAEM-A-QoL (adult)* has 46 questions in 10 groups
  - *HAEMO-QoL KIDS (ages below 16)* short form has 35 questions

  Steps to calculate total score[ii]:
  - Assorting: Assign the numbers to each question response
  - Recoding (HAEM-A-QoL): Numeric scores will be assigned to each item so that highest score is most impaired: 1= never, 2=seldom, 3=sometimes, 4=often, 5=all the time for negatively worded items or 1=all the time, 2=often, 3=sometimes, 4=seldom, 5= never for positively worded items.
    1. Physical Health, 5 questions, no recoding is needed
    2. Feeling, 4 questions, no recoding is needed
    3. View of yourself, 5 questions, #2 and #5 must be recoded
    4. Sports and Leisure, 5 questions, #3 must be recoded
    5. Work and School, 4 questions, #1 and #2 must be recoded
    6. Dealing with Hemophilia, 3 questions, #1, #2, #3 must be recoded
    7. Treatment, 8 questions, #8 must be recoded
    8. Future, 5 questions, #2 must be recoded
    9. Family Planning, no recoding is needed
    10. Partnership and Sexuality, 3 questions, no recoding is needed
  - Recoding (HAEMO-QoL KIDS):

    Total Score, 35 questions, #11, #12, #17, #18, #19, #27, #28, #29, #30, #31, #32 must be recoded

- Summing up the total score for each HAEM-A-QoL sub-scale and for the HAEM-A-QoL and HAEMO-QoL KIDS total scores
- Transferring a raw score to a transformed scale score between 0 and 100. The raw score 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. Missing items will be omitted from the raw score and also from the n used to calculate range.

- Patient's Global Impression of Change (PGI-C);
  - Scores will be presented as a frequency table and median response where 3 = very much improved, 0 = no change, and -3 = very much worse. The proportion and 95% CI of participants with any improved score at EOS will be presented.
- EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire
  - Scores in 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) each will be presented as a frequency table and median response at baseline, 3 months, and EOS, where 1 = least impaired and 5 = most impaired. Since EQ-5D-5L is a descriptive system based on five independent dimensions, a missing answer or ambiguous answer (i.e. marking of more than one level on scale) will lead to complete rejection of the questionnaire, but the visual analog scale (VAS) score will be retained if available.
  - Overall health assessment VAS will be summarized at baseline, 3 months, and EOS. Intra-individual overall health assessment change from baseline at 3 months and EOS will be summarized.
- Work Productivity and Activity Impairment (WPAI) questionnaire scores for hemophilia effect over the last 7 days on productivity or ability at work, at school, and in regular daily activities[iii]
  - WPAI employment (Q1 = Yes)
    - Percent work time missed due to problems associated with your hemophilia: 100×Q2/(Q2 + Q4)
      where Q2 = hours missed due to problems associated with your hemophilia and Q4 = hours actually worked.
    - Percent impairment while working due to health: 10×Q5
      where Q5 = how much did your hemophilia affect your productivity while you were working (scale is 0 to 10).
  - WPAI academic (Q5 = Yes)
    - Percent class time missed due to health: 100×Q7/Q8
      where Q7 = hours missed due to problems associated with your hemophilia and Q8 = hours actually attended.
    - Percent impairment while attending classes due to health: 10×Q9
  - WPAI regular daily activities
    - Percent impairment of daily activities due to health: 10×Q10
      where Q10 = how much your hemophilia affected your ability to do

your regular daily activities, other than work at a job or attending classes (scale is 0 to 10)

- WPAI average impairment score is the mean of employment, academic and regular daily activities impairment scores
- Percentage scores for work time, impairment while working, class time, impairment while attending classes, impairment of daily activities, and WPAI average will be presented. The actual mean scores at baseline and EOS will be presented and intra-individual change from baseline to EOS.

- Treatment Satisfaction Questionnaire for Medication (TSQM);
  - Frequency summaries will be presented of individual items together with median satisfaction scale scores. Scores range from 1=Extremely Dissatisfied to 7=Extremely Satisfied for Questions 1-3 and 9, from 1=Extremely Difficult to 7=Extremely Easy for Questions 4-5, from 1=Extremely Inconvenient to 7=Extremely Convenient for Question 6, from 1=Not at All Confident to 5=Extremely Confident for Question 7, and from 1=Not at All Certain to 5=Extremely Certain for Question 8. The sum of scores for each participant will be summarized at baseline and EOS and the intra-individual sum of scores change from baseline will be summarized at EOS.

4.3.2.2 Joint Status Assessment

The frequencies of pre-existing, new, resolved, EOS and change from baseline number of target joints per participant will be summarized as well as the median counts per participant. The change from baseline to EOS in the number of target joints will be summarized in a shift table.

4.4 Other Endpoints Analysis

4.4.1 Participant Score Considering ABO Type and BMI

To assess whether blood type and body mass index (BMI) would have led to a different score allocation, the participants' risk scores will be determined considering the two parameters (separately as well as combined) in addition to the original score calculation (refer to Table 1 in section 1.2.1).

The algorithms for all scores (score in study as well as theoretical scores) are as follows:

- In-study score (range from -6 to +9):

$$ABR\begin{cases}-2 & \leq 1\\ +2\ ABR\ in\ (1;4] & \\ +3 & > 4\end{cases}+\begin{cases}-1 & < 3\\ 0\ freq=\frac{3x}{week} & \\ +1 & > 3\end{cases}+\begin{cases}-1 & =0\\ 0\ t\ joints & =1\\ +1 & =2\\ +2 & >2\end{cases}+\begin{cases}-1 & \geq 150\\ 0\ vWF\ in\ [100;150) & \\ +2 & <100\end{cases}+\begin{cases}-1 & activity=low\\ 0 & activity=Sedentary\\ +1 & activity=Medium/High\end{cases}$$

- Theoretical Score Alternative 1 (range from -6 to 10):

$$In-study\ score+\begin{cases}0\ \ 20\leq\ BMI\leq 30\ \text{kg/m2}\\ 1\ BMI<20\ or\ BMI>30\ \text{kg/m2}\end{cases}$$

- Theoretical Score Alternative 2: (range from -7 to +9)

$$In-study\ score+\begin{cases}-1 & Blood\ type\ O\\ 0 & Other\ blood\ type\end{cases}$$

- Theoretical Score Alternative 3 (range from -7 to +10):

$$In-study\ score + \begin{cases} 0 & BMI < 30\ \text{kg/m2} \\ 1 & BMI \geq 30\ \text{kg/m2} \end{cases} + \begin{cases} -1 & Blood\ Type\ O \\ 0 & Other\ blood\ type \end{cases}$$

Summary statistics of the theoretical scores will be presented in total as well as by in-study risk score categories (i.e. low [< 2], medium [2-4], and high [>4]). Line plots will be presented showing individual score changes from in-study score through score alternative 1 to score alternative 3 and from in-study score through score alternative 2 to score alternative 3. Risk score groups will be represented by different plot symbols.

In addition, summary statistics of the original patient score as well as frequencies for score categories will be presented by BMI group and ABO type.

4.4.2 PK Parameters Derived from WAPPS-Hemo

The following WAPPS parameters will be summarized by risk score group and subgroup of history of FVIII inhibitors:

- Predicted post-infusion measurement of plasma factor activity level on Day 0 (Day of Infusion) up to Day 8,
- estimated terminal half-life, and
- time to 0.01, 0.02, 0.05, 0.1, and 0.2 IU/dL (with their credibility intervals),
- FVIII trough level (2 measures for participants with 2x/week regimen),
- area under the curve,
- clearance, and
- predicted peak factor value.

4.4.3 Incremental Recovery and Trough Measurements of Jivi Levels

Actual sampling times before and after infusion and the dose administered will be presented in listings of FVIII levels. Incremental recovery FVIII levels will be presented with the corresponding participant weight value.

A summary of incremental recovery will be presented by risk group and also the frequency of samples failing validity criteria.

A summary of quantitative trough levels will be presented by risk group and also the frequency of trough levels above 1%, 3% and 5%.

4.5 Safety Analyses

All safety analyses will be performed on the safety analysis set. Summary tables will be presented overall and stratified by subgroup of history of FVIII inhibitors.

4.5.1 Extent of Exposure

Intervention period as defined in section 4.1.1.1, and total dose (in IU/kg) summarized across eDiary entries will be summarized for the safety analysis set by risk group and overall. Total dose will also be presented for the intervals of month 1, month 2, and ≥ 3 months from Day 1 (Day 1 through Day 30, Day 31 through Day 61, Day 62 until censoring, and Day 62 until EOS.

4.5.2 Adverse Events

Adverse events will be reported using the latest version of the Medical Dictionary for Regulatory Affairs (MedDRA).

All AEs, SAEs, and AESIs will be collected from Baseline until the end of the Safety Follow-up Visit at the time points specified in the protocol schedule of activities (SoA). Only (S)AEs which are related to protocol-required study procedures will be recorded from the signing of the consent form until the start of study intervention. Adverse events or SAEs will be considered to be treatment-emergent (TEAEs or TE SAEs) if they have started or worsened after first administration of study intervention and not later than 7 days after the last infusion of Jivi.

The AE assessments recorded on the eCRF include SAE (yes/no) and SAE criteria, AESI (yes/no), reasonable causal relationship to Jivi (yes/no). reasonable causal relationship to protocol-required procedure (yes/no), medical device AE or deficiency (yes/no), intensity (mild/ moderate/ severe), action taken with the study intervention (drug withdrawn/ drug interrupted/ dose reduced/ dose not changed/ dose increased/ not applicable/ unknown), remedial drug therapy (yes/no), other actions or treatments of AE, and outcome. The AESIs are hypersensitivity and loss of efficacy (LoE).

An overall summary table of TEAEs will be presented to include all participants and stratified by subgroup of history of FVIII inhibitors. The Overall summary will include number and percentage of participants experiencing AEs in the following categories:

- Any TEAE
- Any TEAE by maximum intensity
- Any study intervention-related TEAE
- Any study procedure-related TEAE
- Any medical device-related TEAE
- Any medical device deficiency
- Any TEAE leading to discontinuation of the study intervention
- Any TEAE of Special Interest (TE AESI), including SAE/AE
- Any study intervention-related TE AESI, including SAE/AE
- Any TE SAE
- Any study intervention-related TE SAE
- Any study procedure-related TE SAE
- Any medical device-related SAE
- Any TE SAE leading to discontinuation of study intervention
- Any TEAE with outcome death

An overall summary of pre-treatment AEs will include number and percentage of participants experiencing pre-treatment AEs in the following categories:

- Any AE with causal relationship to protocol-required study procedures
- Any SAE with causal relationship to protocol-required study procedures
- Any AE with causal relationship to protocol-required study procedures with outcome death

If post-treatment AEs occur (i.e., those occurring >7 days after the last infusion of Jivi), these will be presented in an overall summary table and in a summary by primary SOC and PT.

In all AE summary tables, multiple AEs within same category of primary system organ class (SOC) or preferred term (PT) for a participant will be counted only once in that category. In summaries of events with causal relationship a participant with related and unrelated events in any category will be counted for event with causal relationship experienced in that category.

The following summaries of TEAEs will be presented

- TEAEs by primary SOC and PT overall and stratified by FVIII inhibitor history

The following summaries of TEAEs will be presented overall

- Study intervention-related TEAEs by primary SOC and PT
- Study intervention-related TE AESIs (including SAE/AESI) by primary SOC and PT
- Study procedure-related TE AESIs (including SAE/AESI) by primary SOC and PT
- Medical device-related TE AE by primary SOC and PT
- Medical device deficiency
- TEAEs leading to discontinuation of the study intervention by primary SOC and PT
- TE non-serious AEs by primary SOC and PT

The following summaries of TE SAEs will be presented

- TE SAEs by primary SOC and PT
- Study intervention-related TE SAEs by primary SOC and PT
- Study procedure-related TE SAE AESIs by primary SOC and PT
- Medical device-related TE SAE by primary SOC and PT

Individual listings of AEs, SAEs, and AEs leading to discontinuation will be provided with a flag to identify TE status. The individual listings will include any information on history of FVIII inhibitors.

If any death occurs, then summaries and listings of fatal AEs and deaths will be provided.

4.5.3 Additional Safety Assessments

- The record of pregnancy test performed will be summarized by visit.

  Details of all pregnancies in female participants will be collected after the start of study intervention and until 8 weeks after last dose of study intervention.

  While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Number and percentage of participants with confirmed positive FVIII inhibitor titer classified low (≥ 0.6 BU/mL and ≤ 5 BU/mL) or high (based upon persistence of an inhibitor > 5 BU) will be presented for the safety analysis set.
- Screening hematology assessments will be presented for the safety analysis set. In case of multiple assessments were performed for one participant, the summary will include the latest assessment prior to Day 1. A grouped summary of platelet count will be presented: Platelet count < 100,000/mm3 and ≥ 100,000/mm3.

- Number and percentage of participants with abnormal hematology during the study intervention period will be presented for the safety analysis set.
- Vital signs at baseline and Visit 6/ EOS will be presented for safety analysis set. In case of repeat baseline assessments performed for one participant, the summary will include the latest assessment prior to Day 1.

4.6 Other Analyses

4.6.1 Disposition

- Number of participants enrolled with enrollment dates and assigned risk score frequencies will be presented for enrolled participants, overall and grouped by investigator. The summary will also be presented grouped to history of history of FVIII inhibitors if each group includes at least 5 participants.
- Protocol deviations will be classified per study PD plan and important deviations will be presented overall for the safety analysis set.
- Analysis sets and validity findings will be presented for enrolled participants, overall and by assigned risk score.
- Visit and assessments not done and reasons will be presented overall for the safety analysis set.
- Disposition through the study phases (Screening Period, Study Intervention Period, Follow-up Period) with reasons discontinued will be presented for enrolled participants, overall and by assigned risk score. The summary will also be presented grouped to history of history of FVIII inhibitors if each group includes at least 5 participants.

4.6.2 Demographics and Other Baseline Characteristics

- Demographic characteristics: Age, sex, race and ethnicity, blood group (ABO, from disease history), height, weight, and BMI at screening, and employment will be presented overall for the safety analysis set and by risk score group.
- Disease history: Type of hemophilia, years since diagnosis, previous treatment with Factor VIII, history of FVIII inhibitors (yes/no), age (years) at first treatment, treatment regimen type(s), treatment regimen changed (from first treatment), type of first treatment, FVIII level at time of diagnosis, type of Factor VIII gene mutation, history of inhibitor, history of target joints, at least one target joint at time of screening, and family history of hemophilia, will be presented overall for the safety analysis set and by risk score group.
- Details of previous or current SHL treatment product and regimen, used for score calculation, within 12 months of Baseline Visit: Start and end period (months prior to date of informed consent), number of bleeding events in the assessment period, bleeding events standardized to last 12 months (ABR, quantitative), number of joint bleeds in the assessment period and standardized to the last 12 months,
- Risk score assessment: Bleed phenotype (ABR category), pre-study treatment frequency, number of active target joints, vWF antigen levels, physical activity level (low, sedentary, medium/high), total risk score, and risk score group will be presented overall for the mITT set and by risk score group.

- Medical history excluding study indication: Medical history will be coded using the latest version of MedDRA. Medical history SOC and PT frequencies will be summarized for the safety analysis set overall.
- Prior/concomitant medications: Medications will be classified using the latest version of WHODRUG. Prior medications and concomitant will be summarized separately by ATC class (Level 1 - Anatomical Main Group) and subclass (Level 2 - Therapeutic Subgroup) for the safety analysis set overall. Separate summaries will be presented of all prior medications, prior medications ongoing at study intervention start date, all concomitant medications and concomitant medications started during the study intervention period.
- Previous hemophilia treatment for the past 6 months: Treatment details of the most recently discontinued treatment including treatment modified reported name, treatment start months previous to study enrollment, treatment ended days previous to study intervention start date, type of treatment schedule and dosing frequency for prophylaxis will be presented overall for the mITT set and by risk score group.

4.6.3 Record of Infusions

The following analyses will be presented in total and, if applicable, by subgroup of history of FVIII inhibitors:

- Intervention period in days, months and grouped (< 4 months, ≥ 4 months).
- Frequency of infusions: treatments/month over the intervention period, treatments/month change from baseline, and grouped change from baseline, will be presented overall for the mITT set and by risk score group.
- Total infusions on study, total dose (IU/kg) received on study and through the first 1, 2, and 3 months will be presented overall for the mITT set and by risk score group.
- Prophylaxis treatment: Number of infusions for prophylaxis on study, total dose (IU/kg) received on study and dose per infusion will be presented overall for the mITT set and by risk score group.
- Treatment for bleeds: Number of infusions, total dose (IU/kg), and dose per infusion for bleeds will be presented overall for the mITT set and by risk score group.
- The reason for all infusions and percentages calculated relative to total infusions in the study will be presented overall for the mITT set and by risk score group.
- The record of all dose regimen switches including total count and reasons will be presented in a shift table overall for the mITT set and by risk score group.

4.6.4 Subgroup Analyses

Some selected tables (including the primary endpoint, safety events, study intervention administration, prophylaxis regimen, and PK parameters) will be presented in total and by subgroup of history of FVIII inhibitors for sensitivity purposes. This analysis will be performed only if each subgroup has at least 5 subjects evaluated for the primary endpoint.

4.7 Changes to Protocol-planned Analyses

Not applicable.

5. Sample Size Determination

The primary endpoint is the occurrence of favorable outcome on the score selected dosing regimen, which will be described via the proportion of participants with a favorable outcome.

The target sample size for this study is based on feasibility. It is expected that a minimum of 20-25 participants will be enrolled. The precisions, in terms of the width of the 95% confidence intervals (CIs), for different sample sizes and proportions of participants with a favorable outcome are shown in Table 4.

Table 4: Expected Precision of Estimates by Sample Size and Assumed Proportion of Participants with Favorable Outcome

N	Assumed true proportion of participants with favorable outcome	Expected observed proportion of participants with favorable outcome	95% CI, %	Width of CI, %
15	65%	9/15 = 60%	[32.3; 83.7]	51.4
	70%	10/15 = 67%	[38.4; 88.2]	49.8
	75%	11/15 = 73%	[44.9; 92.2]	47.3
	80%	12/15 = 80%	[51.9; 95.7]	43.8
	85%	12/15 = 80%	[51.9; 95.7]	43.8
	90%	13/15 = 87%	[59.5; 98.3]	38.8
20	65%	13/20 = 65%	[40.8; 84.6]	43.8
	70%	14/20 = 70%	[45.7; 88.1]	42.4
	75%	15/20 = 75%	[50.9; 91.3]	40.4
	80%	16/20 = 80%	[56.3; 94.3]	37.9
	85%	17/20 =85%	[62.1; 96.8]	34.7
	90%	18/20 = 90%	[68.3; 98.8]	30.5
25	65%	16/25 = 64%	[42.5; 82.0]	39.5
	70%	17/25 = 68%	[46.5; 85.1]	38.6
	75%	18/25 = 72%	[50.6; 87.9]	37.3
	80%	20/25 = 80%	[59.3; 93.2]	33.9
	85%	21/25 = 84%	[63.9; 95.5]	31.5
	90%	22/25 = 88%	[68.8; 97.5]	28.7
30	65%	19/30 = 63%	[43.9; 80.1]	36.2
	70%	21/30 = 70%	[50.6; 85.3]	34.7
	75%	22/30 = 73%	[54.1; 87.7]	33.6
	80%	24/30 = 80%	[61.4; 92.3]	30.9
	85%	25/30 = 83%	[65.3; 94.4]	29.1
	90%	27/30 = 90%	[73.5; 97.9]	24.4

Abbreviations: CI = confidence interval.
Exact Clopper-Pearson 95% CIs were calculated

When 70% of participants with favorable outcome are observed, a sample size of 20 participants will produce a two-sided 95% CI with a width of 42.4% (95% CI = 45.7% to 88.1%). It is acknowledged that the precision of estimates will be low for the anticipated sample size range. This will be considered in the interpretation of results. While it may not be possible to draw any conclusions based on the reduced sample size, the study may provide first hints whether the score could be useful in clinical practice.

6. Supporting Documentation

6.1 Appendix 1: List of Abbreviations

Abbreviation	*Definition*
ABR	*Annualized bleed rate*
AE	*Adverse event*
BMI	*Body mass index*
CI	*Confidence interval*
CRF	*case report form (either paper or electronic)*
eCRF	*electronic case report form*
eDiary	*electronic diary*
EHL	*Extended half-life*
FVIII	*Human coagulation factor VIII*
ICF	*Informed consent form*
ICH	*International Council for Harmonization*
ISTH	*International Society on Thrombosis and Haemostasis*
IU	*International units*
IXRS	*Interactive Voice/Web Response System*
Kg	*Kilogram*
LoE	*Loss of efficacy*
MedDRA	*Medical Dictionary for Regulatory Affairs*
mITT	*Modified intention-to-treat*
PGI-C	*Patient's Global Impression of Change*
PK	*Pharmacokinetic(s)*
PRO	*Patient Reported Outcome*
PT	*Preferred term*
PTP	*Previously-treated participants*
QoL	*Quality of Life*
rFVIII	*Human recombinant factor VIII*
SAE	*Serious adverse event*
SAP	*Statistical analysis plan*
SD	*Standard deviation*
SHL	*Standard half-life*
SoA	*Schedule of activities*
SOC	*System organ class*
TEAE	*Treatment-emergent adverse event*
TSQM	*Treatment Satisfaction Questionnaire for Medication*
US	*United States*
vWF	*von Willebrand factor*
WAPPS-Hemo	*Web-Accessible Population Pharmacokinetic Service-Hemophilia*
WHO	*World Health Organization*
WPAI	*Work Productivity and Activity Impairment*

7. References

[i] 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 Nov;12(11):1935-9.

[ii] HAEM-A-QoL scoring guide: https://haemoqol.de/scoring/manual/

[iii] http://www.reillyassociates.net/WPAI_Scoring.html