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 patients switch from standard half-life products to damoctocog alfa pegol (Jivi)

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Compound Number:	BAY 94-9027/ Damoctocog alfa pegol; Human Pegylated rFVIII; Jivi
Brief Title:	Jivi interventional study to assess a new risk score approach
Study Phase:	Phase 4
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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Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 3	4.0	02 OCT 2023	
Amendment 2	3.0	19 AUG 2022	
Amendment 1	2.0	17 SEP 2021	
Clinical Study Protocol	1.0	28 JUN 2021	Original version (internal use only)

Amendment 3 (02 OCT 2023)

Overall Rationale for the Amendment:

It was planned to enroll a maximum of 70 participants such that approximately 60 evaluable participants would complete the study. Due to the observed rate of recruitment, it will not be feasible to enroll 70 participants within the planned recruitment period. Given the actual recruitment (as of August 2023), it is assumed that only 20-25 participants will be enrolled by the end of 2023. The protocol was updated to describe the anticipated reduced sample size and the impact on the precision of estimates.

Furthermore, the inclusion criteria were adjusted to reduce restrictions to enrollment.

Although the change in inclusion criteria has the potential to introduce bias in comparisons to patients enrolled prior to the amendment, the risk is thought to be minimal given the 2 possible extreme scenarios below:

- 1 – interruptions in treatment (eg, insurance, migration): a maximum period of 6 months (assuming untreated during that time) is not expected to dramatically change patients' disease phenotype such that it would reflect during Jivi prophylaxis while on study
- 2 – patients treated with an extended half-life (EHL) prior to study entry: the reason for switching to an EHL following stable SHL prophylaxis could be due to external conditions unrelated to patients' bleeding phenotype (eg, formulary changes, insurance requirements, patient preference, etc.). Nevertheless, if the change to an EHL treatment was due to a patient's bleeding phenotype and/or any structural differences compared to any patients enrolled before amendment 3, the risk of bias is thought to be low, since any data from the time of EHL treatment are excluded from the risk score calculation for those patients remaining to be enrolled.

Due to the decision to no longer pursue enrolling participants from Colombia, the protocol is amended back to a single country United States study.

The changes incorporated in this amendment are described in the table below. Edits to update amendment number and dates in the current version, and minor editorial changes for style have been made, but are not documented in the table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall Design 1.1 Synopsis, Number of Participants	Changed number of participants approximately assigned to study intervention from 70 to 20-25	Due to feasibility reasons, specifically the observed rate of recruitment
	Added definition for determination of pre-study annualized bleed (ABR), treatment frequency, and stable standard half-life (SHL) prophylaxis.	Clarification of terms used in protocol, and removal of reference to multi-country study design

	Removed “multi-country”	
Section 1.2 Figure 1-1: Dosing Regimen Schema	Updated N and clarified trough level timepoint at Month 3	Updated due to reduction of study sample size and for clarification
Section 1.3 Schedule of Activities (SoA)	Human coagulation factor VIII (FVIII) levels line item: added note describing required washout period for patients whose previous product was an SHL or extended half-life (EHL). Added a conditional measurement timepoint in Visit 5 and Visit 6 columns and new footnote g in Visit 2, Visit 5, and Visit 6 columns	Clarification of washout period and addition of a conditional measurement timepoint
	Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) analysis line item: added note describing use of FVIII levels from Visit 2 and Visit 5, and a reference to footnote h	Clarification of which FVIII levels to use in WAPPS-Hemo
	FVIII trough levels line item: added a note clarifying that Visit 5 level will be first of 2 trough levels for those on a 2x/week regimen	Clarification; text moved from footnote to table
	Created new footnote g; subsequent footnotes renumbered	Creation of footnote describing conditional timepoint for repeating FVIII levels
	Updated footnote h to clarify timepoints for WAPPS-Hemo data entry	Clarification
	Clarified footnote j regarding timing of trough level measurements	Clarification
Section 2.1 Study Rationale; Section 4.1 Overall Design;	Added definition for determination of pre--study ABR, treatment frequency, and stable SHL prophylaxis	Clarification of terms used throughout protocol The rationale to continue with the current baseline definition is that a comparison between SHL and score-based Jivi prophylaxis is intended, and inclusion of another period (untreated or different treatment) would bias this comparison.
Section 4.1 Overall Design; Section 9.4.1 General Considerations; Section 9.4.5.1 Disposition of Participants	Removed text identifying the study as a multi-country design, text stating that primary endpoint tables will be stratified by country to consider a potential country effect, and text stating that disposition will be presented by country	Due to decision to no longer pursue enrolling participants from Colombia
Section 4.1 Overall Design	Added Screening schematic to clarify screening process (Figure 4-1); updated subsequent figure numbering	Clarification
	Text describing possible interim analysis removed due to reduction in study sample size	Due to reduction in sample size
	Text describing rationale for the baseline definition, and statement regarding feasibility of drawing conclusions with reduced sample size added	Clarification
	Cross-reference to Section 9.4.2	Clarification and improvement of

	added for full definition of pre-study ABR, treatment frequency, and stable SHL prophylaxis	document navigation
Section 4.1, Table 4-1: Parameters for determining participant risk scores	Participant Variables were clarified. New footnotes a and b were added and subsequent footnotes renumbered accordingly	Clarification
Section 4.1.1 Screening	Text clarified to read that during the screening period, participants will continue treatment with their current FVIII treatment	Clarification
Section 5 Study Population	Text added to allow that adolescent/adult participants must be previously treated, and on continuous prophylaxis with an SHL FVIII product for at least 6 consecutive months within the previous 12 months prior to the screening visit	Adjustment of requirements for participants
Section 5.1 Inclusion Criteria; Inclusion Criterion #3	Text added 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	Adjustment to reduce restrictions to enrollment
Section 5.1 Inclusion Criteria; Inclusion Criterion #4	Text added to clarify requirements and to clarify that window for evaluating documented bleeding rate (ABR) occurs prior to screening	Clarification
Section 5.1 Inclusion Criteria; Inclusion Criterion #5	Text added to modify conditions under which a participant can be enrolled if they had past evidence of a positive inhibitor titer	To relax restrictions to enrollment due to lack of evidence of past FVIII inhibitors presenting an issue in patients with subsequent negative titers for inhibitors
Section 5.2 Exclusion Criteria; Exclusion Criterion #3	Reduced evidence of inhibitor to FVIII from 3 years to 1 year	Alignment with Inclusion Criterion #5
Section 5.2 Exclusion Criteria; Exclusion Criterion #6	Added cross-reference to Inclusion Criterion #4 and Section 9.4.2	Clarification and cross-reference to full definition for improved document navigation
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Text added to describe potential for introduction of bias due to pre-study window of bleed frequency data collection	Transparency about possible introduction of bias due to change in data collection time period
Section 8.1.1 Demographics	Removed country from demographic characteristics to be recorded at screening	Due to decision to no longer pursue enrolling participants from Colombia
Section 8.1.3 Disease History	Clarification of information on history of hemophilia to be recorded at screening	Clarification
Section 8.2 Effectiveness Assessment	Note added with cross-references to the sections of the protocol with full definitions of pre-study ABR, treatment frequency, and stable SHL prophylaxis	Clarification and improvement of document navigation
Section 8.2.1 Treatment Logs/Bleeding Verification	Corrected that participants and their parent or legal guardian will be trained on the use of eDiary at the Baseline Visit rather than the screening visit	Corrected to align with SoA
Section 8.2.3 Joint status assessment	Corrected that joint status assessment will occur at baseline	Correction

	rather than at screening	
Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Text added to clarify that bleeds that occur during the screening period should be recorded in the participant's medical record	Clarification
Section 9.2 Sample Size Determination	Anticipated sample size changed from 70 to 20-25. Precision of estimates for the primary outcome updated accordingly. Statement regarding low expected precision added Table 9-1 replaced with table presenting updated estimates appropriate for reduction in sample size Statement regarding feasibility of drawing conclusions with reduced sample size added	Due to feasibility reasons. To be transparent about estimate precision for reduced study size
Section 9.4.2 Primary Endpoints	Text added to comprehensively define the basis for establishing pre-study ABR and treatment frequency, and stable SHL prophylaxis	Clarification
	Removed text stating that outcome on risk score-selected prophylaxis regimen will be presented by country	Due to decision to no longer pursue enrolling participants from Colombia
Section 9.4.3 Secondary Endpoints	Added cross-reference to Section 9.4.2 for definition of pre-study values	Clarification of terms and improvement of document navigation
Section 9.5 Interim Analysis	Text was changed to Not applicable, as due to reduction in sample size for the study, no interim analysis will be performed	Due to change in study sample size
Appendix 7 Section 11.7.4 Visit 5 – (Month 3) and Section 11.7.5 Visit 6 – (Month 6, End of Study/Early Withdrawal)	Text added regarding a conditional measurement timepoint, to align with new footnote g in Visit 5 and Visit 6 columns of the SoA	Consistency and addition of a conditional measurement timepoint
Appendix 10, Section 11.10 Definitions (Common Terms)	Added definitions for Pre-study ABR, Pre-study Treatment Frequency, and Stable SHL prophylaxis	Clarification of common terms used throughout the protocol
Section 11.3 Appendix 3, Clinical Laboratory Tests	Referenced table number corrected from 10-1 to 11-1	Correction
Section 11.7.1 Visit 1-Sceening (Up to 30 Days Prior to Baseline)	Corrected table number referenced for blood sample information from 10-1 to 11-1	Correction

Protocol Date: 02 OCT 2023

Name: PPD PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the Trial Master File (TMF) and available on request.

Medical Monitor (Study Medical Expert) name and contact information can be found in the TMF.

Table of Contents

Table of Tables

Table of Figures

1. Protocol Summary

1.1 Synopsis

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 patients switch from standard half-life products to damoctocog alfa pegol (Jivi)

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

Rationale: This study 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.

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); 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

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 pharmacokinetic (PK) parameters derived from Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) and assess an 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	

Overall Design:

This is a multicenter, open-label, single arm, prospective study of previously-treated adolescent/adult (≥12 years) patients (PTPs) with congenital hemophilia A treated with a SHL FVIII product for regular prophylaxis who are willing to switch to the extended half-life (EHL) product, Jivi (throughout this document, the symbol ® indicating a proprietary name is not displayed for Jivi. However, the omission of the symbol does not imply that this name is not protected). The study will be conducted to assess the effect of using a new risk score approach to select the most appropriate prophylaxis regimen for reaching a favorable outcome. Favorable outcome is defined for this study as: no dosing regimen change from the risk score-assigned regimen during the study period along with an improved annualized bleeding rate (ABR) from pre-study ABR and decreased or similar dosing frequency compared to the previous treatment, or no dosing regimen change compared to risk score-assigned regimen with a similar ABR and a decreased dosing frequency compared to the previous treatment. All participants will have received prophylaxis with any licensed SHL FVIII product with a stable dosing regimen. Pre-study ABR and treatment frequency is based on data from a minimum of 6 continuous months (up to a maximum of 12 months) of stable SHL prophylaxis at any given time within the 12 months prior to the screening visit. Stable SHL prophylaxis is defined as a minimum of 18 weeks of treatment in a 6 (consecutive) calendar month period in the 12 months prior to the screening visit.

At baseline, participants' total risk scores will be determined based on 5 individually weighted variables: pre-study bleeding phenotype, number of active target joints, von Willebrand factor (vWF) antigen levels, previous treatment frequency, and physical activity. All parameters are determined at screening. If the physical activity variable is missing, then zero will be assigned. When other variables are missing, the participant score cannot be determined and participant data cannot be analyzed. The total risk score is used to assign participants to 1 of 3 prophylaxis regimens according to their score. The effect of participants' risk scores on determining the most appropriate prophylaxis regimen will be evaluated by the proportion of participants with a favorable outcome.

Along with regimen details and ABR, data collected will include PRO measurements (Haemophilia Quality of Life Questionnaire [Haem-A-QoL or Haemo-QoL], Patient's Global Impression of Change [PGI-C], EuroQoL 5 Dimensions [EQ-5D-5L], Treatment Satisfaction Questionnaire for Medication [TSQM], and Work Productivity and Activity Impairment [WPAI] questionnaires), joint status outcomes, human recombinant factor VIII (rFVIII) incremental recovery and trough levels, and safety including treatment-emergent adverse events (AEs). Additional data will include documentation of blood type and BMI, and a Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) pharmacokinetic (PK) analysis to determine whether these would have contributed to another risk score assignment for the prophylaxis regimen.

Intervention Model: Single group

Primary Purpose: Assess the effect of using a new risk score approach to select the most appropriate prophylaxis regimen

Number of Arms: One treatment arm with 3 different regimens

Masking: No masking

Brief Summary:

The purpose of this study is to assess the effect of a new risk score approach based on participant's phenotypic and biologic variables to determine the most appropriate prophylaxis regimen for adolescent/adult (≥ 12 years) PTPs with congenital hemophilia A who switch from a SHL FVIII prophylaxis to an EHL product (Jivi).

Study Duration: Approximately 7.5 months

Treatment Duration: 6 months

Number of Participants: Approximately 20 – 25 participants will be assigned to study intervention.

Intervention Groups and Duration:

All eligible participants will be assigned a risk score at baseline and will start treatment 2x/week (40 IU/kg/dose) with Jivi for 4 weeks. Treatment will then continue based on their assignment to 1 of the 3 following prophylaxis regimens:

- Participants with a high risk score (> 4) continue on prophylaxis 2x/week (40 IU/kg/dose)
- Participants with a medium risk score (2 to 4) will switch after 4 weeks to prophylaxis Q5D (50 IU/kg/dose)
- Participants with a low risk score (< 2) will switch after 4 weeks to prophylaxis Q5D (50 IU/kg/dose) and then after 4 weeks to a less frequent (e.g. Q7D) regimen (60 IU/kg/dose)

Prophylaxis regimens will not be altered during the study period unless a participant experiences ≥ 2 muscle or joint bleeds (without evident trauma) during any given 8-week period during the 6-month study. These participants will be assigned to the next highest dosing frequency. In line with the Jivi prescribing information, the treating investigator reserves the right to change a participant's regimen at any time if the investigator determines the score-determined regimen is not well-suited for the participant.

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.

The details regarding duration and risk score assigned prophylaxis regimen are as follows:

Dosing Regimen:

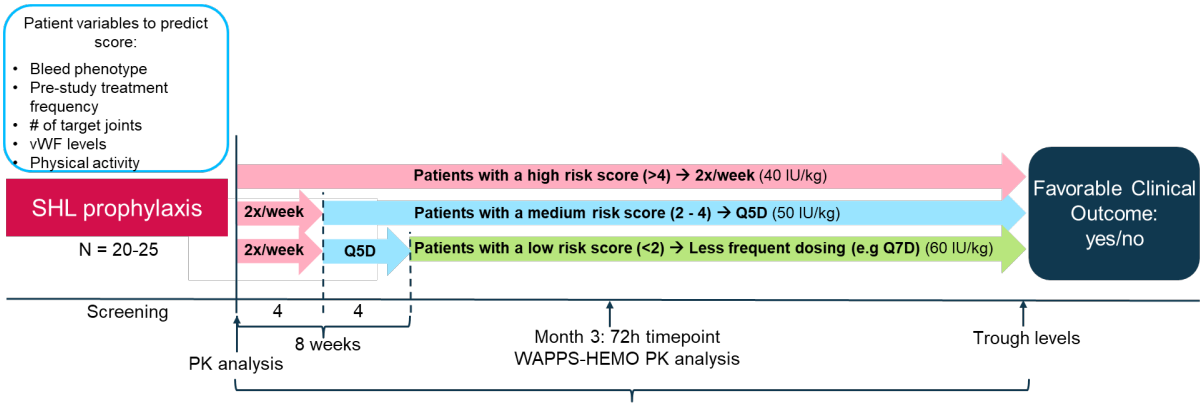
Procedure	Duration	Dose regimen	
Screening	Up to 30 days prior to Baseline	Continuation of previous treatment	
Treatment Phase	Weeks 1-4	Starting dose 40 IU/kg/dose 2x/week	
	Weeks 5-8	Low Risk	Switch to 50 IU/kg/dose Q5D until Week 8
		Medium Risk	Switch to 50 IU/kg/dose Q5D until end of study
		High Risk	Continue 40 IU/kg/dose 2x/week until end of study
	Week 9	Low Risk	Switch to less frequent dosing 60 IU/kg/dose (e.g. Q7D)[a] until end of study

Abbreviations: Q5D = every 5 days; Q7D = every 7 days.
[a] As determined by the investigator.
Note: If ≥ 2 muscle or joint bleeds (without evident trauma) occur within any given 8 week period during the 6 month study, then participant will be assigned to next highest frequency regimen. Per protocol, the treating investigator reserves the right to change a participant's regimen at any time if the treating investigator determines the score-determined regimen is not well-suited for the participant.

Data Monitoring/Other Committee: No

1.2 Schema for Dosing Regimen Assignment

Figure 1–1: 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.

1.3 Schedule of Activities (SoA)

Procedure		Intervention Period Months						Notes
	Visit 1 (Screening)	Visit 2[a] (Baseline)	Visit 3	Visit 4	Visit 5[a]	Visit 6[a] (EOS/Early Withdrawal)[b]	Visit 7 (Safety Follow-up)	
	Up to 30 days before Day 1	Day 1	Month 1 (±7 days)	Month 2 (±7 days)	Month 3 (±7 days)	Month 6 (+14 days)	7 to 14 days after last dose	
Contact	**Visit**	**Visit**	**Phone**	**Phone**	**Visit**	**Visit**	**Phone**	
Informed consent/assent	X							
Inclusion and exclusion criteria	X	X						Recheck clinical status before first dose of study medication.
Demography	X							
Weight	X				X			
Physical examination including height, weight		X				X		
Joint status (defined by ISTH)		X				X		
Highly sensitive serum pregnancy test (WOCBP only)	X	X[c]			X	X		
Physical activity level (contact/no contact/sedentary)		X[d]			X	X		
History of hemophilia	X							
Previous hemophilia treatment	X							
Other past and current medical conditions and surgical history (includes substance usage)	X							Substances: drugs
Total risk score calculation		X						
PROs[e]		X			X[f]	X		
FVIII levels: pre-dose, 15-30 minutes post-infusion, and at a minimum of 4 hours post-infusion		X[g]			X[g]	X[g]		A 3- or 5-day wash-out period is required for those patients whose previous product was an SHL or EHL, respectively
WAPPS-Hemo analysis					X[h]	X[g, h]		FVIII levels to be used from Visit 2 (if felt to be accurate levels) and Visit 5 (72-hour post-infusion level). See footnote h

Procedure		Intervention Period Months						Notes
	Visit 1 (Screening)	Visit 2[a] (Baseline)	Visit 3	Visit 4	Visit 5[a]	Visit 6[a] (EOS/Early Withdrawal)[b]	Visit 7 (Safety Follow-up)	
	Up to 30 days before Day 1	Day 1	Month 1 (±7 days)	Month 2 (±7 days)	Month 3 (±7 days)	Month 6 (+14 days)	7 to 14 days after last dose	
Laboratory assessments (hematology: CBC)	X							
Immunogenicity (FVIII inhibitor)	X							If suspect inhibitor to follow local clinical guidance for inhibitor testing
History of previous FVIII inhibitor	X							Please refer to eligibility criteria (Section 5.1 and 5.2) for participants with a history of inhibitors. Recovery and half-life data for the SHL product should be extracted from medical records when available.
von Willebrand factor antigen (if not available in medical records)	X[i]							Please review Section 8.3.4 when drawing blood for von Willebrand factor antigen.
FVIII trough levels with study intervention					X[j]	X		Visit 5 72-hour level will also serve as the first of 2 trough levels for those on a 2x/week regimen
AE/SAE review	X[k]	←==========				==========→	X	
Concomitant medication review	←==========					==========→	X	
Dispense study intervention		X			X			
Administration of study intervention[l,m]		←==========				==========→		
Return used vials					X	X		
Training on use of eDiary		X						
eDiary (bleed and study intervention) review		←==========				==========→		

Abbreviations: AE = adverse event; CBC = complete blood count; EHL = extended half-life; EOS = End of Study visit; EQ-5D-5L = EuroQoL 5 Dimensions questionnaire; FVIII = human coagulation factor VIII; Haem-A-QoL = Haemophilia Quality of Life Questionnaire; ISTH = International Society on Thrombosis and Haemostasis; PGI-C = Patient's Global Impression of Change questionnaire; PRO = Patient Reported Outcome; SAE = serious adverse event; SHL = standard half-life; TSQM = Treatment Satisfaction Questionnaire for Medication; WOCBP = women of childbearing potential; WPAI = Work Productivity and Activity Impairment questionnaire.

[a] Visit 2 (Baseline) should occur 72 hours after the prior prophylaxis infusion. Visit 5 should occur 72 hours after the last Jivi infusion. Visit 6 should occur on the following days of the assigned prophylaxis regimen (i.e. as close as possible to the next infusion): on Day 4 for those on the 2x/week regimen, on Day 5 for those on the Q5D regimen, and on Day 7 for those

on less frequent dosing regimens.

[b] In case of withdrawal of consent, these activities will occur at the time of the return of the unused vials.

[c] If > 14 days since last menstrual period or from screening (Visit 1).

[d] Refers to the participant's usual physical activity level, based on the last 12 months. Level of activity will be defined as Sedentary, Low, or Medium/High. 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.

[e] Haem-A-QoL or Haemo-QoL, EQ-5D-5L, WPAI, TSQM. At Visit 6 (Month 6), PGI-C will also be collected.

[f] EQ-5D-5L only.

[g] If the investigator feels the baseline peak FVIII level at 15-30 minutes or 4-8 hours post-infusion at Visit 2 does not seem to be appropriate for the dose infused, then, if possible, the levels should be repeated at Visit 5 and the results also uploaded to WAPPS-Hemo. For those patients who do not have appropriate FVIII levels at either Visit 2 or Visit 5, the levels should be repeated at Visit 6.

[h] WAPPS-Hemo data entry should include FVIII levels measured pre-dose, post-infusion, hour 4-8 at Baseline (Day 1) and Month 3 (Visit 5; 72 hours after the last Jivi infusion).

[i] von Willebrand factor levels should be recorded within 12 months of screening. Please refer to Section 8.3.4 for timing of von Willebrand factor blood draw.

[j] At Month 3 (72 hours after the previous infusion for all subjects). Post-infusion FVIII levels will be measured for all participants and included in the WAPPS-Hemo analysis.

[k] 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.

[l] The first Jivi dose will be administered at the clinic at Baseline (Day 1) and may be administered at the clinic at Month 3 (Visit 5) and Month 6 (EOS/Early withdrawal; as long as the infusion does not occur before blood sampling). All other doses will be self-administered at home.

[m] In case of any infusion-related AE at a site visit, vital signs will be collected.

2. Introduction

2.1 Study Rationale

Hemophilia A is an X-linked, inherited, genetic bleeding disorder characterized by deficiency of human coagulation factor VIII (FVIII) (Srivastava et al., 2013; NHF, 2021). Hemophilia A patients are treated by intravenous (IV) administration of FVIII on-demand or as a prophylactic therapy administered 2 to 4 times a week with FVIII products. The need for frequent IV infusion creates barriers to patient compliance and makes adherence to prophylaxis difficult. According to the World Federation of Hemophilia (WFH), it is estimated that only between 25% and 30% of hemophilia patients globally are adequately diagnosed and managed (WFH, 2021).

Prophylactic regimens lead to favorable outcomes by reducing the amount of spontaneous bleeds. The hemophilia A treatment landscape is evolving from using standard half-life (SHL) recombinant coagulation FVIII (rFVIII) products for routine prophylaxis to extended half-life (EHL) products. Switching patients from a SHL to an EHL factor product allows for the maintenance of efficacy with less frequent dosing, leading to significant benefit in long-term outcomes and quality of life (QoL) improvement for patients with hemophilia.

The EHL products, which provide treatment options with dosing intervals of 3 to 5 days for prophylactic treatment (such as Esperoct®, Eloctate®, Adynovate®, Jivi), have been approved recently in several countries worldwide. Any other FVIII products are considered SHL. Jivi was developed as an EHL FVIII for prophylaxis, peri-operative management, and treatment of acute bleeding events. Site-specific PEGylation was used to increase the FVIII half-life, resulting in a longer duration of the effect by raising plasma levels for a longer duration, thereby allowing for less frequent dosing when used in a prophylaxis setting. Efficacy and safety of Jivi were demonstrated in the pivotal trials (Reding et al., 2017; Coyle et al., 2014).

There is still no agreement on what constitutes an optimal prophylactic treatment regimen in adults with hemophilia. Consequently, the dose and frequency of infusions are often determined according to local established practice and left to clinicians' judgment. In general, the current strategies used for prophylaxis can be divided into those that aim to maintain FVIII activity > 1 IU/dL and those that are guided by the clinical bleeding patterns of individual patients. Currently, if Health Care Professionals (HCPs) do not rely on traditional pharmacokinetic (PK) or population PK analysis of rFVIII decay curves to determine an optimal treatment regimen when patients are switching to EHL products, the most common approach is to rely on assumptions that are informed by patients' characteristics and clinical history. This "trial and error" approach could lead to suboptimal protection of the patient and cause harmful, potentially avoidable bleeds or, on the other hand, an excessive use of rFVIII products that will have an economic impact and might not ease the burden of frequent infusions (Yu et al., 2019). The difficulty in determining the most optimal prophylaxis regimen for a patient lies with the disease variability among patients; it is comprised of a series of phenotypic and biologic parameters that render every patient unique in his/her treatment needs and begs for an individualized tailored approach.

The challenge, then, is to optimize hemophilia therapy by individualizing prophylactic regimens to the needs of each patient, while reducing the burdens associated with IV infusion. Thus, the clinical community has several unanswered questions regarding the most appropriate treatment regimen for a patient switching products and the best approach to

achieve an optimal therapeutic and economic regimen with the first attempt. Clinicians rely on their own clinical judgment, using criteria that potentially have an impact on predicting the right dosing regimen. However, these criteria have neither been studied prospectively to select the optimal treatment regimen nor were they studied for their combinatorial usefulness.

In this proposed clinical study, the effect of using a new risk score approach, based on the best known predictive phenotypic and biologic variables, to select the most appropriate prophylaxis regimen for reaching a favorable outcome will be assessed for participants switching from SHL to Jivi. The scoring approach in this study has not yet been validated and is different from classical risk-based models in that the score allocation and the dosing regimen itself has an influence on the outcome of interest. Due to the nature of the study, the inclusion of sub-populations such as mild/moderate hemophilia patients, women, and patients with past FVIII inhibitors should not prevent them from participating.

The scoring approach will be composed of 5 individually weighted variables: pre-study bleeding phenotype, previous treatment frequency, number of active target joints, von Willebrand factor (vWF) antigen levels, and physical activity. These variables were selected on the basis of the existing data regarding their established or potential role in determining the most appropriate EHL regimen.

The relevance of pre-study bleeding patterns and prior treatment frequency in tailoring an appropriate prophylaxis regimen is supported by the results of the Jivi PROTECT VIII study. In the main study, significant improvements in ABR were demonstrated for patients in 3 prophylaxis regimens selected on the basis of prior bleeding pattern (Reding et al., 2017). Importantly, ABR and total bleeds were further reduced after on-study dosing adjustments (e.g. changes from Q7D to Q5D dosing) were made based on treatment response and individual patient preference (Lalezari et al., 2019). Clinical outcomes have also been correlated with baseline disease burden as measured by the presence or absence of target joints. Substantially lower health-related QoL scores were observed in hemophilia patients with 2 or more target joints affected, and score decreases were likewise recorded in patients with only one active joint (Carroll et al., 2019). Variability at the cellular level should also be accounted for when assessing the value of different prophylaxis regimens. The pharmacokinetics of FVIII is regulated by the clearance of vWF from plasma (Swystun et al., 2019). Therefore, individual differences in vWF levels and the genetic determinants that impact FVIII-vWF binding will influence the response to EHL FVIII prophylaxis regimens. The final variable in the scoring approach weighs the link between physical activity and bleed risk. Data regarding the bleeding risk associated with various levels of physical activity is inconclusive due to variations in frequency, intensity, and the age of the patient. However, risk has been associated with high levels of physical activity and, in one study, this risk was mitigated by typical prophylactic regimens (Broderick et al., 2012). Dose and frequency modifications in alignment with the activity level of the patient may improve clinical response.

Each of the variables will have an assigned maximum and minimum value for a given participant that are summed into a personalized risk score for each participant. With defined value thresholds, this total risk score is expected to predict the most appropriate Jivi regimen (2x/week, Q5D, or less frequent dosing [e.g. Q7D]) leading to a favorable outcome for at least 70% of the participants enrolled in this study.

A favorable outcome is defined as:

- no change of the risk score-assigned dosing regimen during the study, with one of the following:

- improved 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 vs. pre-study frequency.
- decreased frequency of administration versus pre-study frequency and similar ABR versus pre-study ABR.

Pre-study ABR and treatment frequency is based on data from a minimum of 6 continuous months (up to a maximum of 12 months) of stable SHL prophylaxis at any given time within the 12 months prior to the screening visit. Stable SHL prophylaxis is defined as a minimum of 18 weeks of treatment in a 6 (consecutive) calendar month period in the 12 months prior to the screening visit. Pre-study ABR will be determined by treatment infusion history or by a participant's bleed diary, if one is available. This cannot be controlled or mitigated in the study design (refer to Section 6.3 for additional details).

2.2 Background

Hemophilia A comprises approximately 80% of all hemophilia cases, with an annual incidence of approximately 1 in 5,000 live male births (NHF, 2021). All races and economic groups are affected equally. Prevalence estimates vary by country, ranging between 5 and 21 cases per 100,000 male inhabitants. Individuals with severe hemophilia A experience frequent and recurrent bleeding into the soft tissue and joints, resulting in joint damage and debility, as well as significant negative effects on their QoL, psychosocial well-being, education, and financial condition. Factor replacement therapy is used to treat bleeding events when they occur; however, such "on-demand" therapy is insufficient for the prevention of arthropathy (Petrini et al., 1991; Aledort et al., 1994). International treatment guidelines recommend that all individuals with severe hemophilia should be treated with some form of prophylactic therapy. The current accepted standard regimen for prophylaxis consists of regularly scheduled infusion of FVIII as often as every other day. The efficacy of standard regimens has been confirmed in multiple observational and interventional studies (Löfqvist et al., 1997; Ljung, 1998; Nilsson et al., 1992) and the value of prophylaxis starting early in childhood was recently confirmed to prevent joint damage (Manco-Johnson et al., 2017).

Jivi is a recombinant B-domain deleted human coagulation FVIII variant site specifically conjugated with a 60 kDa, branched (30 kDa each) polyethylene glycol (PEG). Jivi was developed as an EHL rFVIII product through PEGylation resulting in a reduced clearance from plasma while retaining the normal activity of the FVIII molecule. Pharmacokinetic studies with Jivi demonstrated a prolonged half-life and improved area under the curve (AUC) compared to Kogenate® (antihemophilic factor [recombinant]) (Coyle et al., 2014). Clinical efficacy and safety for treatment of bleeds and prophylaxis with 2x/week, Q5D, and Q7D have been evaluated in the clinical development program including 232 patients between the ages of 2 and 65 years. Jivi has received market authorization approval for treatment and prophylaxis of bleeding in previously-treated patients (PTPs) ≥ 12 years of age with hemophilia A (congenital FVIII deficiency). For prophylaxis, the recommended initial dosing regimen is 30 to 40 IU/kg/dose twice weekly, which may be adjusted to 45 to 60 IU/kg/dose every 5 days based on a patient's bleeding episodes. Further adjustments can be made for less or more frequent dosing, and the total recommended maximum dose per infusion is 6000 IU.

2.3 Benefit/Risk Assessment

Jivi has received marketing authorization by the Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Health Canada and other regions of the world for the treatment and prevention of bleeds in patients ≥12 years of age.

Jivi has demonstrated the potential for dosing Q5D or Q7D in a majority of participants in clinical studies, offering the option of a prophylaxis treatment with less frequent dosing for hemophilia A patients ≥ 12 years of age. For patients with increased bleeding tendency, 2x/week treatment with Jivi provided an efficacious treatment option.

The potential benefits to participants are less frequent dosing and less reliance on central venous catheters, which may reduce physical and emotional burden for the participant, leading to better adherence. This, in turn, may translate into improved FVIII activity, good activity coverage, and good prophylactic coverage from bleeds.

As with all FVIII replacement therapies, the most serious expected adverse event (AE) is the development of inhibitory antibodies against FVIII rendering FVIII treatments ineffective. No new or confirmed inhibitors have been observed during the clinical studies. Other known risks for the class of FVIII replacement products are allergic type of hypersensitivity reactions which may progress to anaphylaxis (including shock), cardiovascular events, and possible catheter-related complications. Data from more than 200 patients aged 2 to 62 years demonstrated that these risks are not different for Jivi administered to PTPs. No cases of anaphylaxis were reported, and no serious cardiovascular event was observed.

A clinical immune response associated with anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect has been observed within the first 4 exposure days (EDs) primarily in children < 6 years of age (Study 15912 – PROTECT VIII Kids). Low post-infusion FVIII levels in the absence of detectable FVIII inhibitors indicate that loss of drug effect is likely due to anti-PEG IgM antibodies; in such cases Jivi should be discontinued and patients switched to a previously effective FVIII product.

More detailed information about the known risks and reasonably expected AEs of Jivi may be found in the approved prescribing information.

There is a risk of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for study participants as long as the coronavirus disease 2019 (COVID-19) pandemic situation is ongoing. To minimize their infection risk during study participation, the investigators/sites will follow all recommendations issued by local authorities and guidelines aiming to reduce the risk of disease spreading. Details on the measures are specified by the site and agreed with the sponsor.

As part of the study procedures, participants will be closely monitored (including for signs of COVID-19) during the entire study duration. A pre-visit call before each in-person study visit is recommended to confirm the study participant does not have any symptoms suspicious for a SARS-CoV-2 infection.

Measures which prioritize participant safety and data validity are implemented. In case these 2 objectives conflict, participant safety always prevails.

During a pandemic situation, further measures according to recommendations and requirements from local health authorities may become necessary. These will be followed within the context of this study as far as applicable.

2.3.1 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with Jivi are justified by the anticipated benefits that may be afforded to participants with hemophilia A.

3. 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 QoL and physical activity, as measured by Patient Reported Outcomes (PROs)	Change in Haemophilia Quality of Life Questionnaire (Haem-A-QoL or Haemo-QoL); 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

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 pharmacokinetic (PK) parameters derived from Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) and assess an 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	

4. Study Design

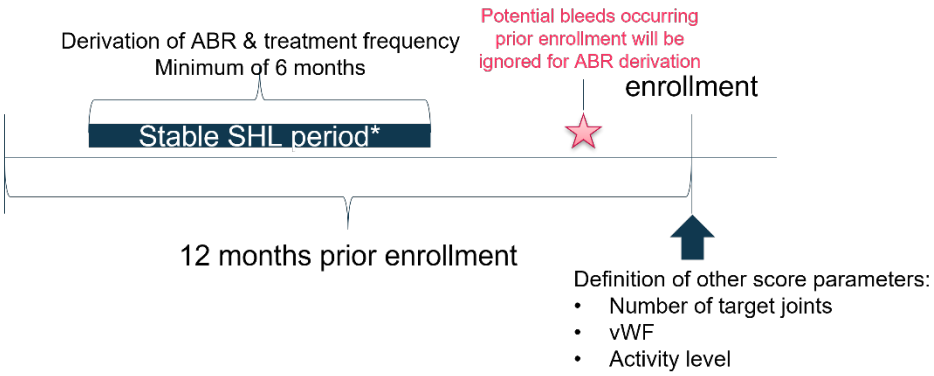
4.1 Overall Design

This is a 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.

At baseline, participants' total risk scores will be determined based on 5 individually weighted variables: pre-study bleeding phenotype, previous treatment frequency, number of active target joints, vWF levels, and physical activity (Table 4–1). If the physical activity variable is missing, then 0 will be assigned. When other variables are missing, the participant total risk score cannot be determined and participant data cannot be analyzed. The rationale for the baseline definition is that a comparison between SHL and score-based Jivi prophylaxis is intended and inclusion of another period (untreated or different treatment) would bias this comparison.

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.

Figure 4–1: Pre-study Timeline



**stable SHL period is defined as at least 18 weeks with minimum one injection per week within a period of 6 consecutive months in the 12 months prior enrollment*

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

Table 4–1: 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.

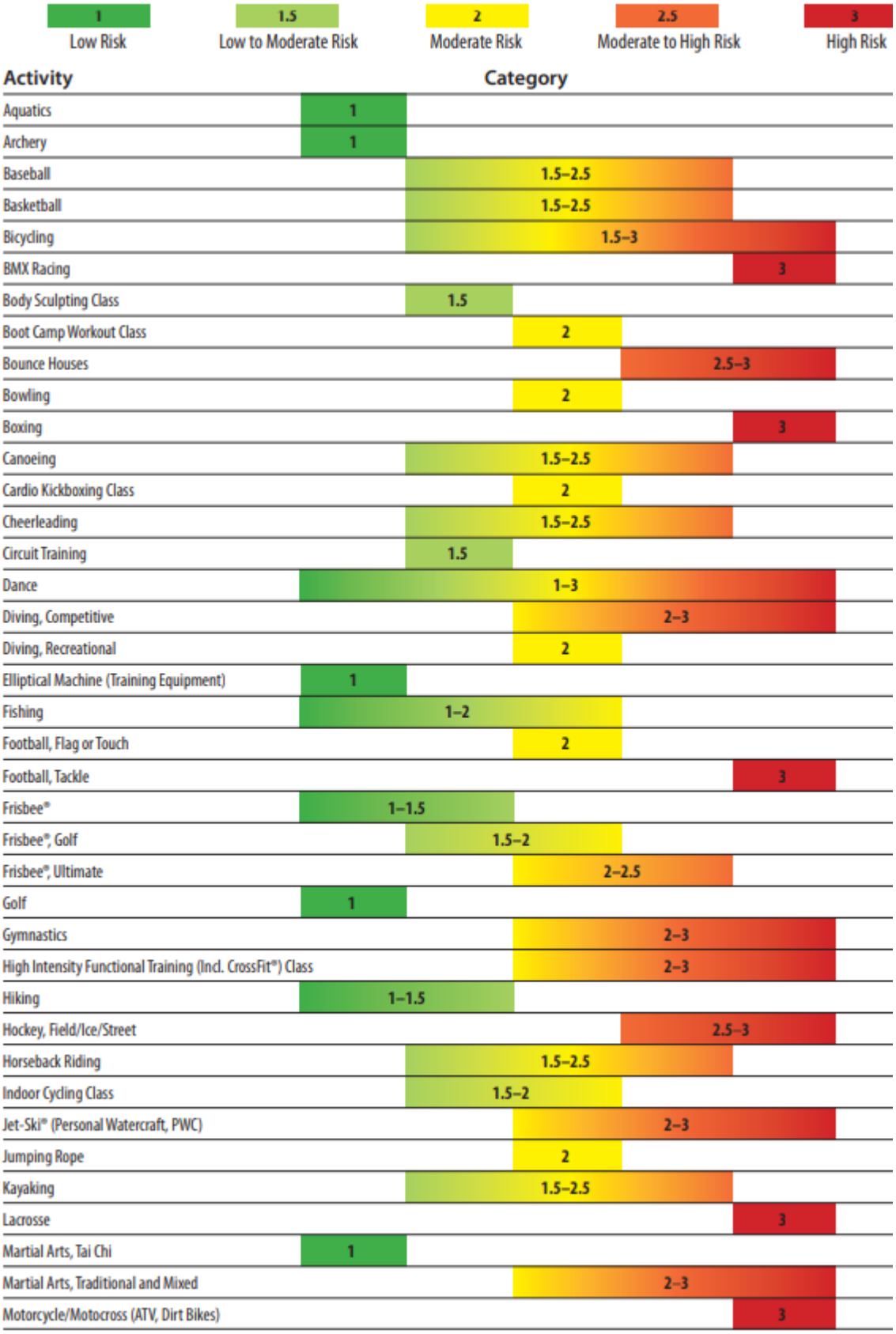
[c] Refers to a participant's usual physical activity level, based on the last 12 months. If a significant change in activity level is expected in the next 6 months, the criteria for the physical activity variable should be based on that anticipated level.

[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 (please refer to 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 (please refer to 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 (please refer to Figure 4–2 [scores ≥1.5]).

Figure 4–2: National Hemophilia Foundation Activity Rankings



Activity	Category
Mountain Biking	2.5
Pilates	1.5–2
Power Lifting	3
Racquetball	2.5
River Rafting	2
Rock Climbing, Indoor or Challenge/Ropes Course	1.5–2
Rock Climbing, Outdoor	2–3
Rodeo	3
Rowing	1.5
Rowing Machine (Training Equipment)	1.5
Rugby	3
Running/Jogging	2
Scooters, Motorized	2–2.5
Scooters, Nonmotorized	1.5–2.5
Scuba Diving	2–2.5
Skateboarding	1.5–2.5
Skating, Ice	1.5–2.5
Skating, Inline and Roller	1.5–2.5
Skiing, Cross-Country	2
Skiing, Downhill	2.5
Skiing, Water	2–2.5
Ski Machine (Training Equipment)	1.5
Snorkeling	1
Snowboarding	2.5
Snowmobiling	3
Soccer	2–3
Softball	1.5–2.5
Stationary Bike (Training Equipment)	1
Stepper (Training Equipment)	1–1.5
Strength Training/ Resistance Training/ Weight Lifting	1.5
Surfing	2–2.5
Swimming	1
Tee-Ball	1.5
Tennis	2
Track and Field	2–2.5
Trampoline	2.5–3
Treadmill (Training Equipment)	1.5
Volleyball	2–2.5
Walking	1
Water Polo	2.5
Wrestling	3
Yoga	1.5–2
Zumba® Class	1.5–2

Source: https://stepsforliving.hemophilia.org/resources/physical-activity/playing-it-safe-activity-ratings-chart?page=1

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 4–2.

Table 4–2: 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.

The effect of using participant's baseline risk score to determine the most appropriate prophylaxis regimen will be evaluated by the proportion of participants with a favorable outcome defined as:

- no change of the risk score-assigned dosing regimen during the study, with one of the following:
  - improved 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.

See Section 9.4.2 for complete definitions of pre-study ABR, treatment frequency, and stable SHL prophylaxis.

Along with regimen details and ABR, prospective data will include PRO measurements (Haemophilia Quality of Life [Haem-A-QoL or Haemo-QoL], Patient's Global Impression of Change [PGI-C], EuroQoL 5 Dimensions [EQ-5D-5L], Treatment Satisfaction Questionnaire for Medication [TSQM], and Work Productivity and Activity Impairment [WPAI] questionnaires), joint status outcomes, and safety. Additional data will include Jivi trough level measurements and documentation of blood type, BMI, and Web-accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) PK measurements to determine whether these would have contributed to another risk score assignment for the prophylaxis regimen.

The participants' planned study duration, including a screening (up to 30 days), treatment (6 months), and safety follow-up period (7 to 14 days after the last dose), will be approximately 7.5 months.

4.1.1 Screening

Screening examinations will only be performed after the participant (and parent[s] or legal guardian) has signed the informed consent form (ICF) and assent form (if necessary).

Participants will be screened for eligibility for up to 30 days prior to the treatment period. During this period, the inclusion and exclusion criteria will be evaluated and all screening procedures will be performed, including the risk score calculation based on the variables presented in Table 4–1. Participants will be assigned a patient identification (PID) code via the Interactive Voice/Web Response System (IxRS) at the screening visit for use by the site only. All screening evaluations must be completed and reviewed prior to treatment allocation. Results of all screening evaluations must be reviewed by the investigator or his/her designee prior to enrollment of each participant into the study to ensure that all inclusion and exclusion criteria are met. During the screening period, participants will continue treatment with their current FVIII treatment.

4.1.2 Treatment

All participants will receive treatment for a total of 6 months, dispensed using the study IxRS. The total duration of the study will be approximately 7.5 months (including screening, treatment, and safety follow-up period). During the study, all participants will receive treatment with Jivi as prophylaxis and for treatment of bleeds, if they occur. All participants will start with a Jivi dosing regimen of 2x/week (40 IU/kg/dose) for 1 month. Participants will then continue in 1 of 3 treatment regimens assigned according to pre-calculated baseline risk score.

The details about duration and recommended dose regimen of study participation are presented in Table 4-3.

Table 4–3: Dosing Regimens

Procedure	Duration	Dose regimen	
Screening	Up to 30 days prior to Baseline	Continuation of previous treatment	
Treatment Phase	Week 1-4	Starting dose 40 IU/kg/dose 2x/week	
	Week 5-8	Low Risk	Switch to 50 IU/kg/dose Q5D until Week 8
		Medium Risk	Switch to 50 IU/kg/dose Q5D until end of study
		High Risk	Continue 40 IU/kg/dose 2x/week until end of study
	Week 9	Low Risk	Switch to less frequent dosing 60 IU/kg/dose (e.g. Q7D)[a] until end of study

Abbreviations: CRF = case report form; Q5D = every 5 days; Q7D = every 7 days.
[a] As determined by the investigator.
Note: For twice weekly dosing regimens, dosing must be administered at 3- and 4-day intervals. If a dose is missed, it will be documented in the CRF and the next dose will be administered as soon as possible before resuming the regular schedule.
Note: If ≥ 2 muscle or joint bleeds (without evident trauma) occur within any given 8week- period during the 6-month study, then the participant will be assigned to next highest frequency regimen. Per protocol, the treating investigator reserves the right to change a participant's regimen at any time if the treating investigator determines the score-determined regimen is not well-suited for the participant.

Participants are allowed to change the dose frequency at any time during the study in case of increase in bleeding frequency as per investigator judgment. The recommended maximum total dose per infusion should not be higher than 6000 IU.

Participants who have an unplanned major surgery will be treated at the discretion of the investigator per their standard of care. Treatment with other FVIII products after unplanned major surgery is also acceptable according to local practice at the discretion of investigators. Participants will resume their prophylaxis regimen with Jivi as per protocol after recovery.

4.2 Scientific Rationale for Study Design

This is a Phase 4, open-label, prospective study aiming to assess the effect of using a new scoring approach based on known phenotypic variables to select the most appropriate prophylaxis regimen for a favorable outcome in adolescent/adult (≥ 12 years) PTPs with congenital hemophilia A switching from SHL products to Jivi. Participants will receive prophylaxis with Jivi at authorized doses in regimens of 2x/week, Q5D, and less frequently (e.g. Q7D, as determined by the investigator). Observations with the currently available FVIII products suggest that prevention of bleeds with extended interval treatment regimens is possible in many patients treated with individualized approaches who are selected on the basis of bleeding frequency and disease severity.

Prophylaxis regimens will be determined according to bleeding risk scores calculated at baseline using the variables in Table 4–1. Participants with high risk for bleeding will be treated with a twice weekly regimen throughout the study. Participants with a medium or low

risk for bleeding are assigned to an extended interval after a treatment period of 4 weeks with the twice weekly dosing. As no formal statistical comparisons between treatment regimens are planned, balanced treatment allocation to each of the 3 groups is not required as part of the study design (Section 9.1).

The new scoring approach uses the best known predictive phenotypic and biologic variables to provide a more comprehensive measurement of the clinical severity of the disease and individual requirements and to determine a tailored dosing regimen. The following variables have been documented in the literature as having high predictive potential that may aid in determining the most appropriate prophylaxis regimen for a patient which results in the most favorable treatment outcome.

- Bleeding frequency (ABR): This is the most logical identifier for the clinical identification of phenotype. One study in patients receiving prophylactic Jivi dosing regimens (including dosing intervals of up to every 7 days) showed that those randomized based on baseline bleeding phenotype achieved bleeding control that was better than or comparable to their pre-study levels, highlighting the value of individualized phenotype-based dosing with Jivi (Reding et al., 2017 [PROTECT VIII]). In the run-in period of this study, the vast majority of patients were identified as having low bleeding risk (≤1 bleed). Most of these patients were randomized to receive higher prophylaxis dosing regimens (e.g. Q5D or Q7D) and achieved good bleed control in the remaining study period (Lalezari et al., 2019). The substantial benefit in ABR experienced by this more common low-risk patient population supports a non-linear score characterization for this variable in the baseline risk calculation, with considerably more risk assigned to patients with a pre-study ABR > 4.
- Treatment frequency: Variations in treatment requirements may reflect variations in the underlying bleeding tendency. In a retrospective analysis of patients with hemophilia A, median infusion intervals of 2.6 days and 11.1 days were recorded in those receiving prophylaxis and on-demand therapy, respectively, while patients who switched from on-demand to prophylaxis regimens had a 3.8 day infusion interval (Ay et al., 2020). As expected, ABR was lowest in the prophylaxis group, with substantial differences appearing within 1 week of observation. Notable decreases in ABR were also observed in patients who switched from on-demand to prophylaxis regimens, and this variability should be accounted for in any phenotype-guided dosing scheme.
- Joint status: A strong correlation has been shown between the presence of 2 or more target joints and decreases in health-related QoL measures for patients with hemophilia A (Carroll et al., 2019). In a recent assessment of bleeding patterns and treatment frequency, a 5-fold decrease of ABR at target joints was observed in patients on prophylaxis compared to those receiving on-demand therapy (Ay et al., 2020). Moreover, in patients who switched from on-demand to prophylactic FVIII regimens, decreases were observed in both the number of target joints and ABR at active joints. Individual variations in the number and location of active target joints with frequent bleeding are an important factor in the determination of prophylaxis dosing frequency.
- Endogenous vWF levels: This is another important parameter when considering individualized dosing due to correlation with the PK of rFVIII. A previous study has shown that higher vWF levels are associated with decreased rFVIII clearance,

increased rFVIII AUC, and longer half-lives resulting in a significant correlation with ABR (Lalezari et al., 2014). A recent integrated regression analysis of 6 clinical studies showed a consistent vWF and PK relationship amongst 5 modified and unmodified FVIII products (including Jivi), further supporting the usefulness of vWF antigen levels in dose regimen selection (Iorio et al., 2019).

- Physical activity: Physical activity involved with various contact sports is associated with increased risk of bleeding; however, moderate physical activity may also decrease the risk of bleeding episodes. In children and adolescents, the bleeding risk associated with vigorous physical activity was moderate and could be mitigated by typical prophylactic regimens (Broderick et al., 2012). Determining the degree of bleeding risk connected to variations in types of physical activity and the age of the patient is important in determining the most appropriate prophylaxis regimen.

The study will be open-label. A controlled comparator arm is not necessary for this study.

4.3 Justification for Dose

The dose is based on the approved United States label (United States Prescribing Information).

Prophylactic treatment regimens should be guided by clinical judgment based on individual patient characteristics and treatment response.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA. The end of study (EOS) is defined as the date of the clean database.

Primary completion

The primary completion is defined as the date when all participants have completed the last visit for the primary endpoint (i.e. measurement of favorable outcomes based on changes in ABR and frequency of administration).

5. Study Population

Previously-treated adolescent/adult (≥ 12 years) patients with congenital hemophilia A on continuous prophylaxis with an SHL FVIII product for at least 6 consecutive months within the previous 12 months prior to the screening visit will be included. Medical records or a detailed participant documentation (i.e. diary, etc.) covering the last year is required to confirm the participant's prophylaxis treatment modality.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be ≥ 12 years of age inclusive, at the time of signing the informed consent/assent.

Types of Participants and Disease Characteristics

2. Previously-treated patients (≥ 150 EDs) with congenital hemophilia A.

3. Prophylaxis with any SHL FVIII product with a stable frequency for at least 6 consecutive months within the last 12 months prior to screening, before entering the study and documented in medical records.
    - Stable frequency is defined as a minimum of 18 weeks of treatment in a 6 (consecutive) calendar month period in the 12 months prior to screening.
    - Patients can be on any non-Jivi EHL between the 6 -month stable SHL prophylaxis period and start of study treatment.
4. Documented bleeding rate (ABR) while on stable frequency prophylaxis for at least 6 consecutive months within the last 12 months prior to screening.
5. No current evidence (≥ 0.6 BU/mL) of FVIII inhibitors.
    - If a participant has had a positive inhibitor titer in the past (≥ 0.6 BU/mL on 2 occasions) but has been tolerized for at least 1 year since the last positive titer with at least 1 negative inhibitor assay test during that period, they can be enrolled.
    - If a participant has had a positive inhibitor titer in the past (≥ 0.6 BU/mL) but did not require tolerization and has had at least 1 negative inhibitor assay test during a minimum period of at least 1 year since the last positive titer, they can be enrolled.
6. If they are human immunodeficiency virus (HIV) positive, cluster of differentiation 4 (CD4)+ lymphocyte count should be > 200/mm^3 within 1 year before entering the study and documented in medical records.
7. Participants who are willing to complete an electronic diary (eDiary).

Sex and Contraceptive/Barrier Requirements

8. Male or female participants

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Male participants: It has been shown that there is no target-related specific transport mechanism for Jivi into semen or from semen into the conceptus. Following administration to a male participant, Jivi would not be bioavailable via seminal delivery to the developing conceptus of an untreated partner. Therefore, no method of contraception for male participants is needed.
- Female participants of childbearing potential (see Section 11.6) can only be included in the study if a pregnancy test is negative at the screening visit and if they agree to use adequate contraception during the study and until 8 weeks (inclusive) after last dose of study intervention. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least 1 is a physical barrier (e.g. condoms with hormonal contraception or implants or combined oral contraceptives, certain intrauterine devices).
    - For adolescent (nulliparous) participants, long-acting reversible contraception (LARC) methods are considered first-line options.
- Postmenopausal females (no menses for 12 months without an alternative medical cause; see Section 11.6) are not required to use contraception. A high follicle-

stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Females of non-childbearing potential (premenarchal, documented hysterectomy, documented bilateral salpingectomy, documented bilateral oophorectomy) are not required to use contraception.
  - If the childbearing potential changes after start of the study (e.g. a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g. a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception (e.g. LARC) or a male participant must use a condom. If reproductive status is questionable, additional evaluation should be considered.
- For females with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis or androgen insensitivity), investigator discretion should be applied to determining study entry.

Informed Consent

9. Participant and/or parent(s)/legal guardian is capable of giving signed informed consent (and informed assent, as required) as described in Section 11.1.3 of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.

Other

10. For adolescent participants (≥ 12 to < 18 years), a legal guardian must be available to help the study site personnel ensure follow-up; accompany the participant to the study site on each assessment day according to the SoA (e.g. able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures); consistently and consecutively be available to provide information on the participant using the PROs during the scheduled study visits; accurately and reliably dispense study intervention as directed.
11. For adolescent participants, a legal guardian must be able to accurately maintain the child's take-home record, including items of general health.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any other inherited or acquired bleeding disorder in addition to hemophilia A. Note: von Willebrand disease should be diagnosed per local clinical practice. Participants with a diagnosis of von Willebrand disease in medical records or diagnosed at the time of screening will be excluded.

2. Platelet count < 100,000/mm^3.
3. Evidence of inhibitor to FVIII (≥ 0.6 BU/mL) within the last 1 year (refer to Inclusion Criterion #5).

Prior/Concurrent Clinical Study Experience

4. The participant is currently participating in another investigational drug study or has participated in a clinical study involving an investigational drug or device within 30 days of signing informed consent.

Other Exclusions

5. The participant has a planned major surgery.

   Note: Major surgery is defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk may be excessive, would require a general anesthetic in an individual without a bleeding disorder, penetrates or exposes a major body cavity, could result in substantial impairment of physical or physiological functions, or requires special anatomic knowledge or manipulative skill (e.g. tonsillectomy, laparotomy, thoracotomy, joint replacement).
6. Documentation for any of the following risk score parameters is missing/unknown: ABR, pre-study treatment frequency (refer to Inclusion Criterion #4 and Section 9.4.2), number of target joints affected, and vWF levels.
7. Known hypersensitivity to the drug substance, excipients, or mouse or hamster protein.
8. Any other significant medical condition that the investigator feels would be a risk to the participant or would impede the study.
9. Close affiliation with the investigational site (e.g. a close relative of the investigator) or dependent person (e.g. employee or student of the investigational site).
10. Otherwise vulnerable participants (e.g. participants who are in custody by order of an authority).
11. Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures (i.e. eDiary completion), restrictions, and requirements.

5.3 Lifestyle Considerations

No specific restrictions from the participants are required in the study.

5.4 Screen Failures

Screen failures are defined as participants who consent (or assent) to participate in the clinical study but are not subsequently entered in the treatment phase of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5 Criteria for Temporarily Delaying Study Intervention Administration

The following conditions may allow a participant to be started on study intervention once the conditions have resolved and the participant is otherwise eligible:

- Unexpected or life-threatening SAE
- Current febrile illness (temperature of 38.0°C [100.4°F]) or other acute illness, including reaction after COVID-19 vaccination, within 48 hours before the first study intervention administration at baseline. If such an intercurrent acute event occurs, the screening period can be prolonged without a need to repeat the screening assessment.

6. Study Intervention and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention Administered

Treatment decisions for identifying appropriate prophylaxis regimens should be guided by treatment regimens as defined by the protocol, clinical judgment, and individual participant characteristics (Table 6-1). Refer to Section 9.4.2 for details regarding statistical analysis of participants who switch from the protocol-assigned regimen.

Table 6–1: Study Intervention

Treatment	2x/week	Every 5 days	Less Frequent (e.g. every 7 days)
Intervention Name	Jivi		
Type	Biologic		
Dose formulation	Ampule		
Duration of intervention	6 months using study IxRS		
Unit dose strengths	500 or 2000 IU/vial		
Dosage Levels	40 IU/kg/dose Two times per week	50 IU/kg/dose Every 5 days The total recommended maximum dose/infusion is 6000 IU.	60 IU/kg/dose Less frequent dosing (e.g. every 7 days)[a] The total recommended maximum dose/infusion is 6000 IU.
Route of Administration	IV infusion		
IMP	IMP (Jivi)		
Sourcing	Provided by the sponsor		
Packaging and Labeling	Jivi will be provided in glass vials with a prefilled syringe. Each glass vial will be labeled per local requirements.		
Current Name / Former Name	Commercial name: Jivi / BAY 94-9027		

Abbreviations: IMP = Investigational medicinal product; IV = intravenous; IxRS = Interactive Voice/Web Response System.
[a] As determined by the investigator.

Treatment of bleeds

All bleeding events that occur in participants receiving prophylactic infusion after the start of treatment (Visit 2) will be treated with Jivi as outlined in the approved prescribing information. If a bleed occurs on a day of the planned infusion, the participant should treat the bleed instead of receiving the scheduled prophylactic infusion.

All bleeding events that occur after the start of treatment will be treated with Jivi in accordance with the bleeding location and severity of the bleed, and treatment will be repeated as needed. The dose to be used for treating the bleed will depend on the severity of the bleed, the participant's prior experience with treatment of bleeding events, and the treating physician's recommendations. The recommended maximum dose is 60 IU/kg (with maximum 6000 IU). Additional follow-up treatments can be administered as needed, and the dose may be tailored to a participant's individual response.

The appropriate treatment of bleeding events is left to the discretion of the treating physician, local clinical practice, and may be extrapolated from published guidelines (e.g. WHO/ WFH/ISTH/EMA).

If the bleed occurs on a non-scheduled prophylactic infusion day, then the prophylactic schedule with Jivi is not affected by the additional treatment of bleeds (e.g. if a participant treats a bleed on Sunday and is due to infuse his/her prophylactic dose on Monday, he/she will still receive the scheduled infusion). If a repeated treatment for the bleed is required and falls on a day of a scheduled prophylactic infusion, the dose administered on the scheduled infusion day may be modified to ensure the participant receives appropriate treatment.

6.1.1 Medical Devices

The Jivi vials will be supplied with the necessary medical devices to facilitate the preparation and infusion of the study intervention. The medical devices that are used in this study are the same as those marketed with Jivi (approved for use in PTPs ≥ 12 years), as well as Kovaltry, a rFVIII product manufactured by the sponsor and indicated for use in patients with congenital hemophilia A, including patients < 12 years.

The medical devices provided by the sponsor for use in the study are:

- Vial adapter
- Prefilled syringe contain sterile water for injection
- Administration set

If device deficiencies occur (including malfunction, use error, and inadequate labeling), they shall be documented and reported by the investigator to the sponsor throughout the clinical investigation (see Section 8.4.8) and appropriately managed by the sponsor.

6.2 Preparation/Handling/Storage/Accountability

The current approved prescribing information for use of Jivi are relevant for this study and will be provided to the participants and caregivers.

Jivi is supplied as a lyophilized powder in glass vials. Study vials may contain 500 IU or 2000 IU. The vials of Jivi will be packaged together with a needle-less reconstitution system, which contains the following: a vial adapter with built-in 15-micrometer filter and a 2.5-mL diluent in a 5-mL syringe 25-gauge butterfly needle.

Instructions for the preparation of study interventions can be found in the leaflet for using Jivi. Jivi must be stored under refrigeration (2°C to 8°C) for up to 24 months from the date of manufacture. Within this period, the unopened product carton may be stored for up to 6 months at room temperature, but should not be returned to the refrigerator. The reconstituted product should be used within 3 hours of reconstitution at room temperature.

All study intervention will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor or its affiliates.

Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study intervention.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only eligible participants enrolled in the study (and parent[s] or legal guardian) will receive study intervention and only authorized site staff will supply study intervention. The responsible site personnel will instruct participants (or parent[s] and legal guardian) on requirements for proper home transport/storage of study drug. Study intervention will be administered by participants (or parent[s] or legal guardian). All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the

labeled storage conditions with access limited to the investigator and authorized site staff.

3. The personnel will use the study intervention only within the framework of this clinical study and in accordance with this protocol.
4. The authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance. Receipt, distribution, return, and destruction (if any) of the study intervention must be properly documented using the study IxRS, according to the sponsor's agreed and specified procedures.

The investigator maintains responsibility and control for dispensing via IxRS. Participants can obtain study intervention at the site. At selected sites, site-to-patient distribution of study intervention can occur and the sponsor may contract a distribution provider to facilitate distribution including the delegation of storage and handling as needed until handover to the participant.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single treatment arm study, and no randomization or masking will be performed. All participants will receive study intervention and will be allocated to a prophylaxis regimen based on the total risk score determined at baseline. The retrospective data collection on bleed frequency before trial for comparison may be biased towards lower bleed rates due to incomplete documentation and collection from any given 6-month period within 12 months of study screening, as it is assumed that the time a subject is not on stable prophylaxis (up to 6 months prior to enrollment) does not have an influence on the occurrence of bleeds during the study period. This would affect the outcome negatively, because the data collection during the study is prospective. Nevertheless, the pre-study bleed rate has been documented in all clinical studies based on participant diaries as per local standard of care and has been seen to provide a good estimate of the participant's bleed rate.

Participants will be identified by a unique participant number with 9 digits once the ICFs (and assent forms) are signed. The first 5 digits will identify the country and study site; the last 4 digits are assigned to the participant of the specific site in increasing order.

6.4 Study Intervention Compliance

Study intervention will be self-administered by the participant or by a parent or legal guardian. Study personnel should review dose administration requirements with the participant, as appropriate, and with the delegated legal guardian(s) or parent(s) before administration and throughout the study as necessary.

Participant compliance with study intervention will be assessed at each visit.

Used vials of study medication will be returned to the site at every visit for accounting. Any discrepancies between actual and expected amount of returned vials must be discussed with the participant (and his/her parent[s] or legal guardian) at the time of the visit, and any explanation must be documented in the source records.

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.

The eDiary will be reviewed at visits and at regular contacts with the participant during the study.

6.5 Dose Modification

If a participant treated with an extended interval regimen experiences ≥ 2 muscle or joint bleeds (without evident trauma) within any given 8-week period during the study, then he/she will be assigned to next highest frequency regimen. In line with the Jivi prescribing information, the treating investigator reserves the right to change a participant's regimen at any time if he/she determines the score-determined regimen is not well-suited for the participant.

Further dose adaptations according to participant needs and at the investigator's discretion are allowed within the approved dose range and rounding up to full vials which may result in slightly higher dosages.

6.6 Continued Access to Study Intervention After the End of the Study

After completion of the study, treatment with study intervention will end. Subsequent treatment will be mutually agreed upon by the participants and the investigator.

6.7 Treatment of Overdose

The recommended maximum dose as per the approved prescribing information is approximately 6000 IU (rounded to vial size). The sponsor does not recommend specific treatment for an overdose. Any intervention is left to the discretion of the treating physician, local clinical practice, and may be extrapolated from published guidelines (e.g. WHO/WFH/ISTH/EMA). No symptoms of overdose have been reported during the pivotal clinical trials. The next dose after the discovery of a dose above the maximum recommended one should be corrected and not delayed.

In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Medical Monitor (Study Medical Expert) should be contacted if there are any questions regarding concomitant or prior therapy.

Bleeds which occur during the screening period (screening visit until Visit 2) will be treated with the participant's previous FVIII product.

All medications and blood products required by the participant after the ICF (and assent form) is signed, including FVIII products other than study intervention, will be listed in the appropriate case report form (CRF). All concurrent prescription and nonprescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements), antibiotics, and pain medications being administered starting at least 3 months prior to screening will be recorded in the CRF and throughout the treatment and safety follow-up periods.

All planned vaccinations should be completed at least 2 weeks prior to start of study intervention. If a vaccination (including the COVID-19 vaccine) is to occur during the study, the vaccination should occur no more than 2 days after a Jivi infusion to prevent any potential bleeding at the injection site.

The participant should not be taking any other investigational drug while receiving treatment with Jivi, and all SHL prophylactics will have been stopped at least 3 days prior to the start of Jivi administration. All bleeding events that occur in participants receiving prophylactic infusion after the start of treatment (Visit 2) will be treated with Jivi as outlined in the approved prescribing information. After treatment of bleeding, the prophylactic Jivi regimen will be resumed according to assigned dosing schedule.

Medications which cause a bleeding diathesis (for example, Aspirin® or any acetylsalicylic acid) should be avoided in individuals with hemophilia, except as specifically prescribed by a treating physician. Low dose Aspirin should not be discontinued in participants who have been identified to be at risk for cardiovascular events. The decision to prescribe non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or brief courses of corticosteroids to treat pain or acute synovitis is at the discretion of the treating physician.

Inhaled or topical steroid medications (as required for the treatment of asthma or eczema) are allowed. Brief courses of prednisone/methylprednisolone (< 14 days) for treatment of disorders such as synovitis, asthma, etc. are at the discretion of the treating physician. For any participant requiring longer courses of corticosteroids or use of other immunomodulatory treatment, the investigator should notify the sponsor.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

All participants who enter the study should complete all applicable study periods. Participants can be withdrawn from any study period at any time. Withdrawal from the treatment period alone does not constitute withdrawal from the study.

Participants who withdraw from the treatment period for any reason are to be encouraged to remain on the study for follow-up of primary, secondary and other objectives. Participants are expected to participate in follow-up unless they explicitly object. Withdrawal of consent to the treatment period should be documented in the participant's medical record. If the participant does not wish to be followed up further, this additional consent withdrawal for follow-up must also be documented.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study and an EOS visit will be performed.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Inhibitor Development

Any inhibitor development (≥ 0.6 BU/mL, confirmed; see Section 9.4.4.1) is considered a SAE. Discontinuation of study intervention due to a high titer inhibitor development (titer > 5 BU/mL) should be considered if the investigator believes that it is in the best interest of the participant and/or if bypassing agents are needed to treat bleeds. Participants who discontinue study intervention due to inhibitor development cannot continue in the study and will be withdrawn.

7.1.2 Planned Major Surgery During the Study

Planned major surgeries are exclusionary for this study (see Section 5.2, Exclusion Criterion #5).

If the participant has an unplanned emergency surgery during the study, the investigator and sponsor will determine if the participant can continue in the study and if any change in participant management is needed.

7.1.3 Temporary Discontinuation from Study Intervention

Participants who have an elective unplanned major surgery during the study will be treated outside of the clinical study. The participant may be treated according to local practice at the discretion of investigators. Participants will resume their treatment assignment of Jivi as per this protocol after surgical recovery.

Participants with a concurrent illness requiring study intervention interruption may be discontinued, at the discretion of the investigator, as explained in Section 7.2. In the event of a trial-continuity issue (e.g. caused by a pandemic), the sponsor may provide additional guidance in study-specific communication.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant (and his/her parent[s] or legal guardian) has the right to withdraw permission at any time during the study. If the study staff identify any reluctance in the legal guardian or pediatric participant (e.g. signs of verbal or physical dissent) about continued participation in the study, the pediatric participant's continuation in the study should be reevaluated. The same principles that govern permission/assent/consent also govern his/her withdrawal.
- The participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A participant must be withdrawn from the study if the development of an inhibitory antibody to Jivi (i.e. FVIII antibody or antibody to PEG) that neutralizes activity sufficiently to interfere with effective treatment or requires use of a bypassing agent to treat bleeds occurs.
- A participant must be withdrawn from the study if he/she fails to comply with scheduled appointments for the study-related evaluations and with eDiary data entry to an extent that compromises collection of critical data.
- A participant must be withdrawn from the study if significant concurrent illness or deterioration occurs in the participant's condition, including laboratory values that the investigator deems to be incompatible with the participant's continued safe participation in the study.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant (and his/her parent[s] or legal guardian[s]) and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (and his/her parent[s] or legal guardian[s]) where possible (3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3) and visit description in Appendix 7. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- If deemed necessary for an individual participant, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. Unscheduled visits will be documented in the electronic CRF.
- In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The study consists of a screening period of up to 30 days prior to Day 1, a 6-month treatment period, and a Safety Follow-up Visit 7 to 14 days after the last dose of study intervention. After laboratory visits at screening and Baseline (Day 1), 5 visits are scheduled, including telephone-only visits at Months 1 and 2 and Safety Follow-up, and site visits at Months 3 and 6 (EOS/Early withdrawal). The telephone visits between the participant and personnel at the study site are required to check documentation compliance, adherence and response to treatment, AEs, concomitant medications, and other medical problems that may occur between study visits. Contacts should be documented in the medical record.

The maximum time interval between screening and Baseline (Day 1) visits is up to 30 days. There is no minimal interval between screening and Baseline visits, except for the amount of time required to confirm eligibility criteria.

8.1 Population Characteristics

8.1.1 Demographics

Demographic characteristics to be recorded at screening will include age, sex, race and ethnicity, and blood type. Employment will also be recorded at Baseline (Day 1).

8.1.2 Medical and Surgical History

Medical history findings (i.e. previous diagnoses, diseases, surgeries, and substance usage) meeting all criteria listed below will be collected at screening:

- Not pertaining to study indication
- Start before signing of informed consent
- Considered relevant to the study
- Include any information on cardiovascular risk, hepatic disease, renal impairment, prior use of PEGylated medications (e.g. PEG- interferon, PEG-anti-TNF), and concomitant medications

8.1.3 Disease History

Specific information on history of hemophilia to be recorded at screening will include date of diagnosis, start of therapy, start of prophylaxis, for all prior and current FVIII products within 12 months, estimated number of EDs, type of FVIII gene mutation (from history, if available), family history, FVIII level and type of assay, family and personal history of past inhibitor formation (including date of inhibitor testing, whether immune tolerance induction was performed, and recovery and half-life data, if available; Section 1.3), previous or current SHL treatment product and regimen, used for score calculation, within 12 months of Baseline Visit, and number and type of bleeds derived from the before-mentioned SHL time period of a minimum of 6 months within the last 12 months of study screening . If available, data on prior PK with the participants' previous SHL FVIII product (used for score calculation) will be collected (concentration timepoints, and half-life).

Blood samples will be collected at screening to determine the participant's vWF antigen levels, if not already available in the medical records. If available in the medical records, vWF antigen testing should have been performed within 12 months prior to enrollment.

8.1.4 Other

At screening, blood type will be recorded and BMI will be calculated.

Physical activity levels (medium/high [contact sports]; low [non-contact sports]; and sedentary) will be recorded at Baseline (Day 1).

8.2 Effectiveness Assessments

This is an exploratory study of the effect of using a risk score approach to select the most appropriate prophylaxis regimen for favorable clinical outcomes and reduced treatment burden. Planned time points for all effectiveness assessments are provided in the SoA (Section 1.3). Effectiveness variables to be evaluated are listed below (further details will be provided in the Statistical Analysis Plan [SAP]).

- ABR (total, joint, spontaneous)
- Jivi treatment frequency, expressed as total number of infusions per month

- Occurrence of participants with 0 and ≤ 1 spontaneous bleeds
- Quality of life, as measured by Haem-A-QoL or Haemo-QoL, PGI-C, EQ-5D-5L, TSQM, and WPAI
- Number and location of affected target joints, defined per ISTH

The primary effectiveness variables used in the determination of favorable outcome will be change in total ABR and FVIII treatment frequency (infusions/month). The primary endpoint is the occurrence of favorable outcome (see Section 9.4.2 for additional details), defined as:

- no change of the risk score-assigned dosing regimen during the study, with one of the following:
    - improved 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.

NOTE: The full definitions of pre-study ABR, treatment frequency, and stable SHL prophylaxis are provided in Section 9.4.2 and Section 11.10.

8.2.1 Treatment Logs/Bleeding Verification

Treatment logs are commonly used for hemophilia participants for documentation of their home treatment. Home treatment and bleeding information are the key variables for evaluation of effectiveness. Study-specific treatment logs will be provided in the national language. The system for this study will be an eDiary since this allows for an interactive, record-stamp date and time of fulfillment and facilitates the clarification of data with the site as well as the data cleaning process. Participants will be provided access to the eDiary for the entire study. At the Baseline Visit, participants (and their parent[s] or legal guardian) will be trained in the use of the eDiary. These logs will be used to document the treatment data and bleeding episodes by the participants, and the data will be verified for accuracy and completion by the investigator or delegate during regularly scheduled interactions with the participant. Thus, the eDiary will be considered the source for these data. In the event a participant does not have internet access, alternative means of diary completion will be provided.

For each infusion of Jivi, information must be recorded in the diary as follows:

Each infusion of Jivi:

a. Date and time
b. Infusion record
c. Individual vial/batch number (bar code scan from vial label or manual entry) and units administered
d. Reason for treatment
    - Prophylaxis
    - Spontaneous bleed first treatment

- Trauma bleed first treatment
- Follow-up treatment
- Unscheduled Prophylaxis due to surgery
- Unscheduled Prophylaxis due to injury
- Unscheduled Prophylaxis due to activity
- Other (as specified by participant or legally authorized representative)

Infusions of Jivi as part of protocol-mandated visits and procedures will be recorded on the respective CRF pages.

All bleeding episodes (regardless if treated or not, or treated at home or under medical supervision) as well as any potential treatment with other hemophilia drugs will be recorded in the diary:

Bleeding episode (onset)

a. Date and time of onset
b. Type of bleed (spontaneous, trauma; joint, muscle, skin/mucosal, internal, other)
c. Location
d. Intensity (mild, moderate, severe)
e. Treated [YES/NO]; If YES, the following is to be recorded:
   - Date and time
   - Number of infusions
   - Dose/infusion

8.2.2 Patient Reported Outcomes

The PRO data on QoL and health status, work and school productivity, pain, and treatment satisfaction will be collected. The objective of PRO data is to collect the participant's perspectives and opinions on the impact and effectiveness of Jivi in the treatment of hemophilia. Questionnaires will be filled out by the participant in the treatment center at Baseline (Day 1; Haem-A-QoL or Haemo-QoL, PGI-C, EQ-5D-5L, TSQM, and WPAI), Month 3 (EQ-5D-5L only), and Month 6 (EOS; Haem-A-QoL or Haemo-QoL, PGI-C, EQ-5D-5L, TSQM, and WPAI). Appendix 2 provides representative examples of the PROs to be used in the study.

The following PROs assessments will be obtained:

- **Haemophilia specific quality of life (Haem-A-QoL and Haemo-QoL) questionnaires:**

  The questionnaire will be used to capture the full impact of Jivi and the treatment modalities on the participants' hemophilia-specific QoL during the previous 4 weeks. The Haem-A-QoL is a hemophilia-specific QoL questionnaire for adults aged 18 years and above. The questionnaire has 41-items covering 6 domains: Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact, and Treatment Concerns. For participants 17 years and younger, the Haemo-QoL Short Form Questionnaire for children and adolescents will be used. The Haemo-QoL

Short Form contains 35 questions covering 9 domains: Physical Health, View of Yourself, Family, Friends, Others, Sports, Dealing, and Treatment.

The respondent burden for both questionnaires is approximately 15 minutes.

- **Patient's Global Impression of Change (PGI-C)**

  The self-report measure PGI-C reflects a participant's belief about the efficacy of treatment. The PGI-C consists of a 7-point scale depicting a participant's rating of overall improvement. Participants rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

  The respondent burden for the questionnaire is approximately 5 minutes.

- **Five-Level European Quality of Life Five Dimension (EQ-5D-5L)**

  The EQ-5D-5L is a standardized health-related QoL questionnaire that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has 3 levels: no problems, some problems, or severe problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

  The respondent burden for the questionnaire is approximately 5 minutes.

- **Treatment Satisfaction Questionnaire for Medication (TSQM)**

  The TSQM comprises 9 items across 3 domains focusing on effectiveness (3 items), convenience (3 items), and global satisfaction (3 items) of the medication over the previous 2 to 3 weeks, or since last use. All items have 5 or 7 responses, scored from one (least satisfied) to 5 or 7 (most satisfied). Item scores are summed to give 3 domain scores, which are in turn transformed to a scale of 0-100.

  The respondent burden for the questionnaire is approximately 5 minutes.

- **Work Productivity and Activity Impairment (WPAI) questionnaire:**

  The WPAI is a validated instrument to assess the effect of hemophilia on ability to work, attend classes, and perform regular daily activities in ages 12 and above. The WPAI will also contain classroom impairment questions. The questionnaire is self-administered and comprises 9 questions that elicit information on work, classroom, and daily activity impairment during the previous 7 days. Scores are expressed as percentages of impairment/productivity loss, with higher scores indicating greater impairment.

  The respondent burden for this questionnaire is approximately 10 minutes.

8.2.3 Joint Status Assessment

A joint status assessment (including target joints) will be recorded at baseline and EOS using the ISTH criteria. A target joint is defined as one having 3 or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤ 2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint (Blanchette et al., 2014).

8.3 Safety Assessments

Safety will be assessed by monitoring and recording all AEs, AEs of special interest (AESIs), and SAEs, and any abnormal findings observed during the performance of physical examinations.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Measurements of Immunogenicity

All participants will be tested for inhibitors to FVIII according to the Bethesda assay as per local clinical practice. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU/mL. Repeat testing should be obtained within 1 to 2 weeks of initial identification of a positive result. Only after confirmation of a second positive result does the inhibitor have to be reported as a SAE.

A low post-infusion FVIII level in the absence of detectable FVIII inhibitors indicates that loss of drug effect is likely due to anti-PEG antibodies. Jivi should be discontinued and participants switched to a previously effective FVIII product (refer to Section 8.4.7 as this qualifies for an AESI-Loss of Efficacy [LoE]).

8.3.2 Physical Examinations

- Physical examinations will be performed at Baseline (Day 1) and EOS/Early Withdrawal Visit.
- A physical examination will include, at a minimum, assessments of the general health status, and review of systems. Height and weight will also be measured using a calibrated stadiometer (appropriate for the participant's age) and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Any abnormal finding should be documented.

8.3.3 Clinical Safety Laboratory Assessments

- See Section 11.3 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

8.3.4 von Willebrand Factor (vWF) Antigen

The investigator must ensure absence of the following conditions or other factors which may influence the levels of vWF before drawing blood for the vWF test.

A number of transient clinical conditions can raise the vWF levels of individuals with congenital deficiency into the normal range. The vWF is an acute phase reactant and levels can increase due to stress, inflammation, acute infection, physical exercise, and following surgery. Levels can also increase with estrogen administration for contraception or hormone replacement (Adcock et al., 2006). Furthermore, two- to three-fold increases in the second and third trimesters of pregnancy have been observed (Brandt, 2002; Rick, 2002). In addition,

vWF levels may increase during menstruation and should not be measured during active menstruation (Brown et al., 2019).

Note: Individuals with blood type O tend to have approximately 30% lower vWF levels than those with other blood types.

8.3.5 Pregnancy Testing

A negative serum pregnancy test during screening and at Visit 5 (Month 3) and Visit 6 (Month 6) is required for women of childbearing potential (WOCBP) (see Section 1.3). If Visit 2 (baseline) occurs > 14 days after a female participant's last menstrual period, an additional pregnancy test is required. Premenarchal women, postmenopausal women with no menses for at least 1 year, or surgically sterilized women will not be required to undergo a pregnancy test. Confirmation of childbearing status should be documented in the medical history page of the CRF.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of an AE or SAE can be found in Section 11.4.

The AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or HCP not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI, or SAE. They remain responsible for following up on SAEs or AEs considered related to the study intervention or study procedures, or those events that caused the participant to discontinue the study.

Events of Special Interest have to be followed up regardless of causality or relationship to study intervention (see Section 8.4.7).

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs, AESIs, and SAEs will be collected from Baseline until the end of the Safety Follow-up Visit at the time points specified in the SoA (Section 1.3).

(S)AEs which are related to protocol-required study procedures (e.g. [S]AEs related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF until the start of study intervention. Medical occurrences that begin before the start of study intervention but after obtaining informed consent (and assent) but are diagnosed at screening or during the screening period (e.g. abnormal lab values) will be recorded on the Medical History/Current Medical Conditions section of the electronic CRF not the AE section, with the exception of bleeds occurring during the screening period which should be recorded in the patient's medical record.

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately; under no circumstances should this exceed 24 hours, as indicated in Section 11.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of the data being available.

Investigators are not obligated to actively seek information regarding AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers

the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Clinical Presentation of Adverse Events in Pediatric Population

Study site staff should instruct the legal guardian(s) on how to report signs and symptoms (e.g. pain) in the individual pediatric participant. The legal guardian(s) will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.7) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE or AESI is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.4.5 Pregnancy

- 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.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- 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.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study after completing the early withdrawal visit.

8.4.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related event is common in participants with hemophilia A and can be serious/life-threatening:

- Bleeding event

Any bleeding event, regardless if treated or not, occurring during the study will not be documented as an AE, because this is captured in the assessment of effectiveness.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of AEs. These events will be recorded in the participant diary.

NOTE: However, if the bleed fulfills the criterion for an SAE (e.g. results in hospitalization), then the event should be recorded and reported as an SAE (see Section 11.4.2).

8.4.7 Events of Special Interest

Hypersensitivity reactions, including severe allergic reactions (which can progress to anaphylaxis), chest or throat tightness, dizziness, mild hypotension, and nausea, are known and listed adverse drug reactions for FVIII products and have been reported with use of Jivi. Loss of efficacy of the drug product has also been reported in children < 6 years of age and may be associated with the development of antibodies to PEG. Loss of efficacy can present as bleeding and must be confirmed by low recovery or post-infusion FVIII level, and a negative FVIII inhibitor test. A low recovery or no detectable FVIII post-infusion in a participant with a hypersensitivity reaction in the presence of PEG IgM antibodies is considered LoE even in the absence of a bleeding event. All such reported events (hypersensitivity and LoE) occurred early in treatment (within the first 4 EDs).

Hypersensitivity reactions and LoE are defined in this study as AESIs and must be reported within 24 hours of the investigator's awareness. The LoE must be confirmed by an abnormal low recovery after the infusion of Jivi.

In the event of reported LoE of the study intervention, the following is to be done:

1. Schedule a visit within 4 days of the reported event.
2. Obtain 2 pre-infusion blood/plasma samples for FVIII levels and FVIII inhibitor (for local laboratory).
3. Administer BAY 94-9027 (use current prophylaxis dose [IU/kg]).
4. Obtain one post-infusion blood/plasma samples (for local laboratory) for FVIII levels (15-30 minutes post-infusion).

Non-serious hypersensitivity events should not automatically be upgraded by the reporting investigator to serious.

If hypersensitivity reactions occur, immediately discontinue study intervention administration and initiate appropriate treatment. Please refer to the approved prescribing information.

8.4.8 Medical Device Deficiencies

Medical devices approved for use with Jivi are being provided for use in this study to facilitate the preparation and infusion of the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 11.5.3.

Device deficiencies only should be reported to the sponsor, by completing the Product Technical Complaint form and submitting it to the sponsor via the email address (ptc-imp@bayer.com) given to the site.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 11.5.5 of the protocol.

8.5 Pharmacokinetics

8.5.1 Incremental Recovery and Trough Levels of Jivi

Blood samples for Jivi incremental recovery, FVIII levels, and FVIII trough levels will be collected in all participants. Incremental recovery will be determined at Baseline (Day 1) by collecting a sample for FVIII level before the scheduled infusion and a second sample collected 15 to 30 minutes after end of the infusion. A third sample collected at a minimum of 4 hours after the end of the infusion to assess FVIII levels. The measurements should only be performed when the participant is not actively bleeding. If a participant is actively bleeding, the samples for incremental recovery will be postponed until the sample can be done after a prophylactic dose.

The exact sampling times before and after infusion and the dose administered will be documented in the CRF. Incremental recovery of Jivi is determined by measuring FVIII activity with a validated assay for FVIII.

Infusions given at study visits will be recorded in the site participant records, which will be the source documents and will be used to enter this information in the CRF.

All samples will be processed in the investigator's local laboratory. Plasma concentrations of FVIII will be measured using a validated FVIII activity assay.

Recoveries should be performed using the participants assigned treatment dose, rounded to full vial size.

At Month 3 (72 hours after the previous infusion), FVIII levels will be measured for all participants for the WAPPS-Hemo PK analysis. For participants on the twice weekly regimen, this will also serve as 1 of 2 trough level measurements (i.e. Day 3 of 2x/week regimen). At Month 6 [EOS]), samples for trough levels will be collected just prior to the scheduled infusion for all participants in alignment with the prophylaxis regimen (i.e. at Day 4 for 2x/week regimen, at Day 5 for Q5D regimen, and at Day 7 for less frequent regimens).

8.5.2 Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) Analysis

The WAPPS-Hemo database will be used to assess sources of variability between participants' PK data and clinical risk scores. WAPPS-Hemo is a centralized, dedicated, actively moderated database run by the Health Information Research Unit at McMaster University that allows participating hemophilia treatment sites to input FVIII data from sparse samples and receive individual PK estimates. These estimates are generated by an automated proprietary population PK engine and are then manually validated.

The WAPPS-Hemo analysis will be performed at the end of Visit 5 (Month 3). Each study site investigator will register in WAPPS-Hemo database (https://www.wapps-hemo.org/UserRegistration.aspx), if not already registered. Once a site is registered, the investigator will enter the required participant details (gender, date of birth, baseline factor level, blood group, and positive history of inhibitors). The investigator will then enter infusion data at least 3 time points post-infusion (with or without pre-infusion levels), as specified in the SoA (Section 1.3). The investigator will be required to input the following data for each infusion: weight, height, dose and type of factor administered (as total and IU/kg), and infusion duration. If available, hematocrit, hemoglobin, serum creatinine, vWF measurements, and laboratory methods used to measure FVIII will also be entered.

Data entered will be cleaned by WAPPS-Hemo PK experts. Duplicate submissions will be removed, and all original data that was duplicated from merged infusions will be deleted. Any data not valid for modelling, such as user input errors, insufficient data, or conditions that exclude use of participant data will be removed and excluded from analysis. The dataset will be analyzed to search for outliers. Input errors missed at the source will be corrected where the incorrect measurement has been used (i.e. weight, height).

The investigator will then request extraction of the following from the database: 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/mL (with their credibility intervals), FVIII trough level (2 measures for participants with 2x/week regimen), AUC, clearance, and predicted peak factor value. Once extracted, the data will be stored in the participant's medical record and entered into the electronic CRF.

8.6 Pharmacodynamics

Pharmacodynamics parameters are not evaluated in this study.

8.7 Genetics

Genetics parameters are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Other Investigations

Investigations related to the mode of action or the safety of Jivi and similar drugs may be performed. The same applies to further investigations deemed relevant to hematologic diseases and associated health problems. Examples of these investigations include diagnostic, safety, pharmacodynamics, monitoring, or potentially predictive biomarkers.

Results from any additional investigations may be reported separately.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics data, associated with medical encounters, will be collected by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [e.g. intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

9. Statistical Considerations

9.1 Statistical Hypotheses

The study is not designed to test any predefined hypothesis. All analyses will be descriptive or exploratory.

9.2 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 9-1.

Table 9–1: 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

Abbreviation: 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.

9.3 Analysis Set

For the purposes of analysis, the following analysis sets are defined in Table 9–2:

Table 9–2: 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.

9.4 Statistical Analyses

The SAP will be finalized prior to before first participant first visit (FPFV) and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Statistical analyses will be performed using SAS release 9.2 or higher (SAS Institute Inc., Cary, North Carolina, United States [US]). The version used will be specified in the SAP.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation [SD], minimum, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All endpoints will be analyzed according to the modified intention-to-treat (mITT). The entire study period will be analyzed regardless of the regimen.

Some tables will be stratified by the risk score-selected dosing regimen. Additionally, 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.

In general, missing clinical outcomes 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.

Baseline is defined as time point of enrollment into study. The participant total risk score will be calculated at baseline and the resulting prophylaxis regimen will be assigned as describe in Section 4.1.

9.4.2 Primary Endpoint

The analysis of the primary endpoint will be performed on the mITT population. The entire study treatment period will be analyzed regardless of the dosing regimen.

The proportion and 95% 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.

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.

Definitions

- No regimen change during study: participant is treated according to the score-assigned regimen and does not deviate or switch frequency.
- Improved ABR: Reduction from pre-study ABR is ≥ 1.
- Similar ABR: Absolute change from pre-study ABR is < 1.

- Worse ABR: Increase from pre-study ABR is ≥ 1.
- Decreased frequency of administration: Reduction from pre-study in number of infusions per month is ≥ 2.
- Similar frequency of administration: Absolute change from pre-study in number of infusions per month < 2.
- Worse frequency of administration: Increase from pre-study in number of infusions per month is ≥ 2.

Pre-study ABR and treatment frequency is based on data from a minimum of 6 continuous months (up to a maximum of 12 months) of stable SHL prophylaxis at any given time within the 12 months prior to screening. Stable SHL prophylaxis is defined as a minimum of 18 weeks of treatment in a 6 (consecutive) calendar month period in the 12 months prior to the screening visit.

A switch to a higher frequency regimen due to a bleed during study is considered as non-favorable outcome, whereas participants who switch due to other reasons (e.g. personal decision, study compliance issues, or changes in physical activity level) will be censored at time of switch.

The number (frequency) of participants switching the risk score-selected dosing regimen will be summarized.

As sensitivity analyses, the proportion of participants with favorable outcome on the risk score-selected prophylaxis regimen will be presented by inhibitor history.

9.4.3 Secondary Endpoints

The components of the primary endpoint, ABR (total, joint, spontaneous) and frequency of administration (infusions/month), will be presented via summary statistics and will be presented overall only. Values for the study period and intra-individual change from pre-study value will be presented for total ABR and frequency of administration (see Section 9.4.2 for full definition). In addition, the proportion and 95% CIs of participants with improved/similar/worse value of total ABR and frequency of administration will be provided.

The other secondary objectives will be demonstrated by the following endpoints:

- Proportion of participants with 0 and ≤ 1 spontaneous bleeds
  - Frequency tables will be provided for the proportion and 95% CIs of participants with 0, ≤ 1, and > 1 spontaneous bleeds.
- PROs
  - PRO data will be summarized by presenting descriptive statistics during the study and as change from baseline to EOS. The questionnaires are summarized in Section 8.2.2.
- Joint status assessment
  - The number and location of affected target joints (per ISTH; see Section 8.1.3) at baseline and at EOS will be summarized descriptively. The change from baseline in the number of affected joints will be evaluated at EOS.

Other pre-specified exploratory endpoints will be described in the SAP finalized before FPFV.

9.4.4 Safety Analyses

All safety analyses will be performed on the Safety Population and will be presented overall and stratified by FVIII inhibitor history.

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

Individual listings of AEs will be provided which will include any information on history of FVIII inhibitors.

9.4.4.1 Immunogenicity

Inhibitor development will be summarized by time point and presented in participant listings. The purpose of the listing is to delineate the clinical factors which may be positively associated with development of the inhibitor. Confirmation of positive inhibitor titers (Bethesda assay, as per local clinical practice, ≥ 0.6 BU/mL) will require repeat measurement. If the repeated inhibitor result is < 0.6 BU without intervention, the inhibitor is not confirmed and should not be reported as an SAE. Inhibitors will be classified as being either low titer (≥ 0.6 BU/mL and ≤ 5 BU/mL) or high titer based upon persistence of an inhibitor > 5 BU.

9.4.4.2 Pharmacokinetics

PK parameters will be analyzed via descriptive statistics (e.g. mean, standard deviation, minimum, median, and maximum) and will be presented overall as well as by FVIII inhibitor history. Details will be provided within the SAP.

9.4.5 Other Analyses

9.4.5.1 Disposition of participants

The number and percentage of participants screened, assigned to treatment, and treated will be presented by score-assigned prophylaxis regimen and overall. The reasons for participants discontinuing from treatment will be summarized by score-assigned prophylaxis regimen. In addition, the number of participants screened and included in each analysis population will be displayed overall and by investigator.

9.4.5.2 Demographics and other baseline characteristics

Summary statistics (arithmetic mean, SD, median, minimum, and maximum) will be presented for quantitative variables by score-assigned prophylaxis regimen. Frequency tables for qualitative data will be provided. The summaries will be provided for both mITT and Safety analysis set.

Medical history findings will be summarized using the latest version of MedDRA terms by prophylaxis dosing regimen for the mITT analysis set.

9.5 Interim Analysis

Not applicable.

10. Tokenization (United States Participants Only)

Participation in tokenization is optional and those who decline to participate in tokenization will still be able to join the clinical study.

Data linkage with real-world data

Data linkage using de-identified data provides the opportunity to connect clinical trial data to real-world data (e.g. claims, electronic health records, laboratory results, pharmacy, etc.) at the participant level without compromising the privacy of trial participants. Dedicated software will be used to encrypt the original participant identification information into a new de-identified key (i.e. a "token") that is unique to each participant (Appendix 8, Figure A). Third -party entities will create the encrypted tokens and verify privacy compliance.

No additional compensation will be provided to participants for participating in tokenization and linking of their data. Participants would still receive compensation for their participation in the clinical study.

Benefits

Participants' de-identified data could be linked to and/or combined with real-world datasets for research purposes within the scope of this clinical study or subsequent future medical research uses (e.g. retrospective analyses, long-term follow-up, or healthcare resource utilization studies) (Appendix 8, Figures B and C).

This may decrease the need for follow-up studies and also expedite future results. Ultimately, the accelerated time will benefit patients awaiting the development of treatments and ensure sponsors can more readily investigate benefits and risks.

Additionally, by linking tokenized clinical trial data with real-world data, a more comprehensive picture of a participant's medical history will be available to researchers, further improving future patient experience.

Risks

The encryption process for tokenization will be performed by sites and will occur without the sponsor's involvement. Furthermore, the sponsor has no access to participant identifiable information. A third-party will verify that de-identified data cannot be traced back to the original participant identifiable information. Therefore, the tokenization process will not increase loss of confidentiality risk. The sponsor will handle de-identified participant protected health information in a confidential manner with reasonable security measures, as required by key data protection regulation and in accordance with national/local data protection laws. However, as with any de-identified study, there exists a minimal potential loss of confidentiality risk.

Informed consent process

At the time a participant is screened for enrollment into the clinical study, he or she can opt-in via the additional consent language for tokenization for the linking of their clinical trial data. No additional study procedures beyond what is outlined in the clinical study protocol would be completed as result of his or her participation in the trial. Participation in tokenization is optional and participants who decline to participate in tokenization will still be able to join the clinical study. Non-participation in tokenization will not affect the study or the clinical care of the participants (Appendix 8, Figure D). A participant's tokenized data will be available for linking to other future data indefinitely or until they withdraw their consent for future data linking. If a participant chooses to withdraw their tokenized data from future data linking, he or she can access the trial tokenization portal or contact the study site at the phone number (provided in the ICF). A participant can locate his or her PID information (found on the cover page of the ICF), and state that they would like to withdraw

their consent for future use of their clinical trial data (i.e. future linking). Note that any of the participant's data that has been linked prior to the withdrawal of their consent for re-use will remain linked. Once the participant withdraws consent for the re-use of their data, no further data links will be created.

11. Supporting Documentation and Operational Considerations

11.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1 Regulatory and Ethical Considerations

- The protocol, protocol amendments, ICF, informed assent form, approved prescribing information, and other relevant documents (e.g. advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) 50, International Council for Harmonisation (ICH) guidelines, the IRB, and all other applicable local regulations
  - Reporting cases of suspected child abuse and/or neglect according to local regulations including local medical association (e.g. American Academy of Pediatrics, European Union [EU] Academy of Pediatrics), or Health Department guidelines.

11.1.2 Financial Disclosure

Investigators and sub-investigators directly involved in the treatment or evaluation of study participants will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3 Informed Consent and Pediatric Participant Assent Process

- The investigator or his/her representative will explain the nature of the study to the participants (and parent[s] or legal guardian) and answer all questions regarding the study, based on the patient informed consent. The patient informed consent and assent forms will contain all relevant information on the study.
- The investigator, or a person designated by the investigator, will provide the participant and/or legal guardian (refer to Appendix 9: Abbreviations and Definitions) with the written ICF and the pediatric participant with the assent if applicable. They must be informed that participation is voluntary. The participant and/or legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act

(HIPAA) requirements, where applicable, and the IRB or study center after the nature of the study has been fully explained and before performance of any study-related activity.

- Assent requirements for pediatric participants may vary across regions; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent (and written informed assent for pediatric participants) was obtained before the participant was enrolled in the study and the date the written consent (and assent) was obtained. The authorized person obtaining the informed consent (and assent) must also sign the ICF.
- Participants (and parent[s] or legal guardian) must be reconsented to the most current version of the ICF(s) during their participation in the study.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- Minor participants must be reconsented if they reach the age of majority during the course of the study to continue participating.
- As appropriate, pediatric participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- A copy of the consent forms and assent forms must be provided to the participant (and parent[s] or legal guardian).

11.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

  The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

11.1.5 Committees Structure

A Data Monitoring Committee will not be used.

11.1.6 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3, and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug

studies will be provided on the publicly funded website www.ClinicalTrials.gov in line with the applicable regulations.

Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical study data, study-level clinical study data, and protocols from clinical studies in patients for medicines and indications approved in the US and EU on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical studies are considered for publication in the scientific literature irrespective of whether the results of the clinical studies are positive or negative.

11.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk -Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a source document checklist.

11.1.9 Study and Site Start and Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

11.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

11.2 Appendix 2: Patient Reported Outcomes

11.2.1 Haemophilia specific quality of life questionnaires (Haem-A-QoL and Haemo-QoL)

Trial ID:	Page 1/7
VISIT X Centre ID/No.:	
Subject No.:	
Visit Date:	D D M M M Y Y Y Y

HAEM-A- QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please answer the following questions in this questionnaire, which was designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- Please read each question carefully.
- Think about how things have been for you over the past weeks.
- Put an "X" in the box corresponding to the answer that fits you best.
- Only mark one box for each question.
- There are no right or wrong answers.
- It's what you think that matters.
- There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: __ / __ / __ (month/ day/ year)

Trial ID: Page 2/7

VISIT X

Subject No.: □

1. Here we would like to find out about hemophilia and your PHYSICAL HEALTH

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. ... my swellings hurt	☐	☐	☐	☐	☐
2. ... I had pain in my joints	☐	☐	☐	☐	☐
3. ... it was painful for me to move	☐	☐	☐	☐	☐
4. ... I had difficulty walking as far as I wanted to	☐	☐	☐	☐	☐
5. ... I needed more time to get ready because of my condition	☐	☐	☐	☐	☐

2. and now about how you have been FEELING because of your hemophilia

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. ... my hemophilia was a burden for me	☐	☐	☐	☐	☐
2. ... my hemophilia made me angry	☐	☐	☐	☐	☐
3. ... I was worried because of my hemophilia	☐	☐	☐	☐	☐
4. ... I felt excluded	☐	☐	☐	☐	☐

Trial ID: Page 3/7

VISIT X

Subject No.: □

3. How does hemophilia affect your VIEW OF YOURSELF?

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. ... I envied healthy people my age	□	□	□	□	□
2. ... I felt comfortable with my body	□	□	□	□	□
3. ... hemophilia made my life more difficult	□	□	□	□	□
4. ... I felt different from others because of my hemophilia	□	□	□	□	□
5. … I was able not to think all the time about my hemophilia	□	□	□	□	□

4. These questions are about SPORTS AND LEISURE

In the past 4 weeks...	never	rarely	some-times	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	□	□	□	□	□	□
2. ... I had to avoid sports like football	□	□	□	□	□	□
3. … I played sports just as much as others	□	□	□	□	□	□
4. … I didn't have the freedom to travel where I wanted	□	□	□	□	□	□
5. … it was necessary for me to plan everything in advance	□	□	□	□	□	□

Trial ID: Page 4/7

VISIT X

Subject No.: □

5. These questions are about WORK AND SCHOOL

In the past 4 weeks...	never	rarely	some-times	often	all the time	not applicable
1. ... I was able to go to work/school regularly in spite of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I was able to work/study like healthy colleagues	☐	☐	☐	☐	☐	☐
3. ... my everyday work/school activities were jeopardized by my hemophilia	☐	☐	☐	☐	☐	☐
4. ... I found it difficult to pay attention at work/school because I was in pain	☐	☐	☐	☐	☐	☐

6. The next questions are about DEALING WITH HEMOPHILIA

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2. ... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
3. ... I was able to control my bleeds	☐	☐	☐	☐	☐

Trial ID: Page 5/7

VISIT X

Subject No.: □

7. and what about your TREATMENT?

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. … I was dependent on the factor concentrate because of my hemophilia	□	□	□	□	□
2. … I was dependent on physicians for the treatment of my hemophilia	□	□	□	□	□
3. ... I was annoyed about the amount of time spent having the injections	□	□	□	□	□
4. ... I felt the injections interrupted my daily activities	□	□	□	□	□
5. … I was afraid of complications	□	□	□	□	□
6. … I had problems with how my treatment was administered	□	□	□	□	□
7. … I was afraid that in case of emergency, other doctors wouldn't know how to treat hemophilia	□	□	□	□	□
8. … I was satisfied with the hemophilia center	□	□	□	□	□

Trial ID: Page 6/7

VISIT X

Subject No.: □

8. What do you think about the FUTURE?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been thinking that it will be difficult for me to lead a normal life	□	□	□	□	□
2. ... I have been expecting that things will get better in the future	□	□	□	□	□
3. ... I have been worrying that my condition is worsening	□	□	□	□	□
4. ... my life plans have been influenced by my hemophilia	□	□	□	□	□
5. ... I have been afraid that I will need a wheelchair	□	□	□	□	□

9. The next questions are about hemophilia and your FAMILY PLANNING

Recently...	never	rarely	some-times	often	all of the time	not applicable
1. ... I have had difficulties having children	□	□	□	□	□	□
2. ... I have been afraid that I cannot have children	□	□	□	□	□	□
3. ... I have been afraid that I will not be able to take care of my children	□	□	□	□	□	□
4. ... I worry about not being able to raise a family	□	□	□	□	□	□

Trial ID: Page 7/7

VISIT X

Subject No.: □

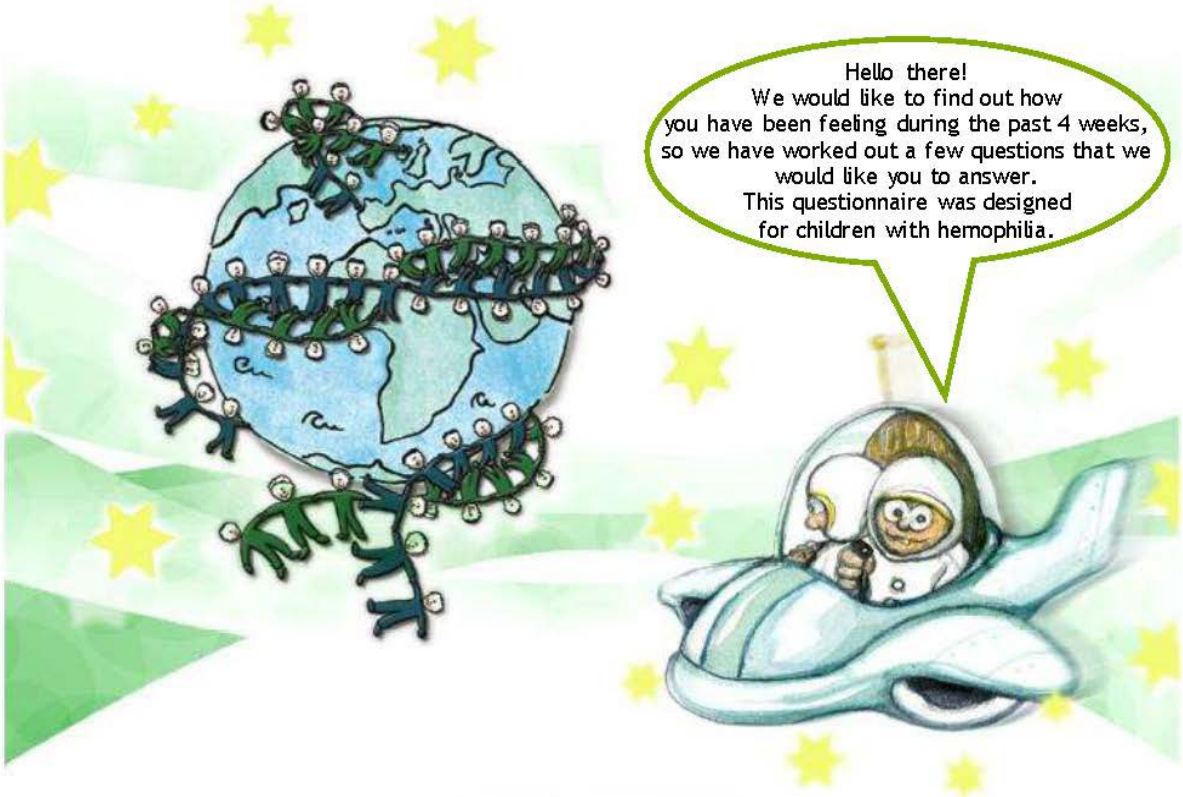
10. What about PARTNERSHIP AND SEXUALITY?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been finding it difficult to date because of my hemophilia	☐	☐	☐	☐	☐
2 ... I have been insecure in my intimate relationships because of my hemophilia	☐	☐	☐	☐	☐
3. … I haven't been able to have a normal relationship because of my hemophilia	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

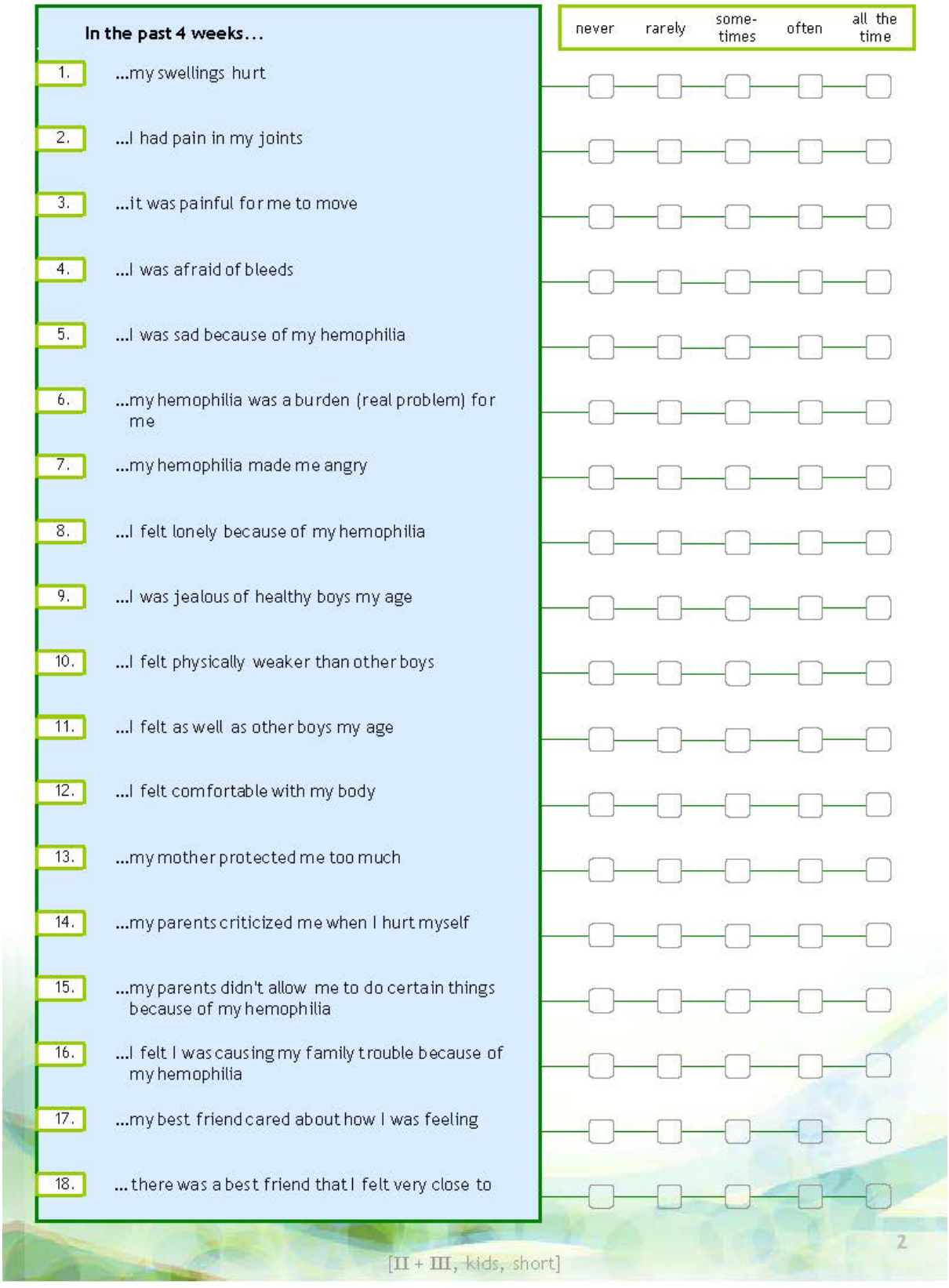
HAEMO-QoL

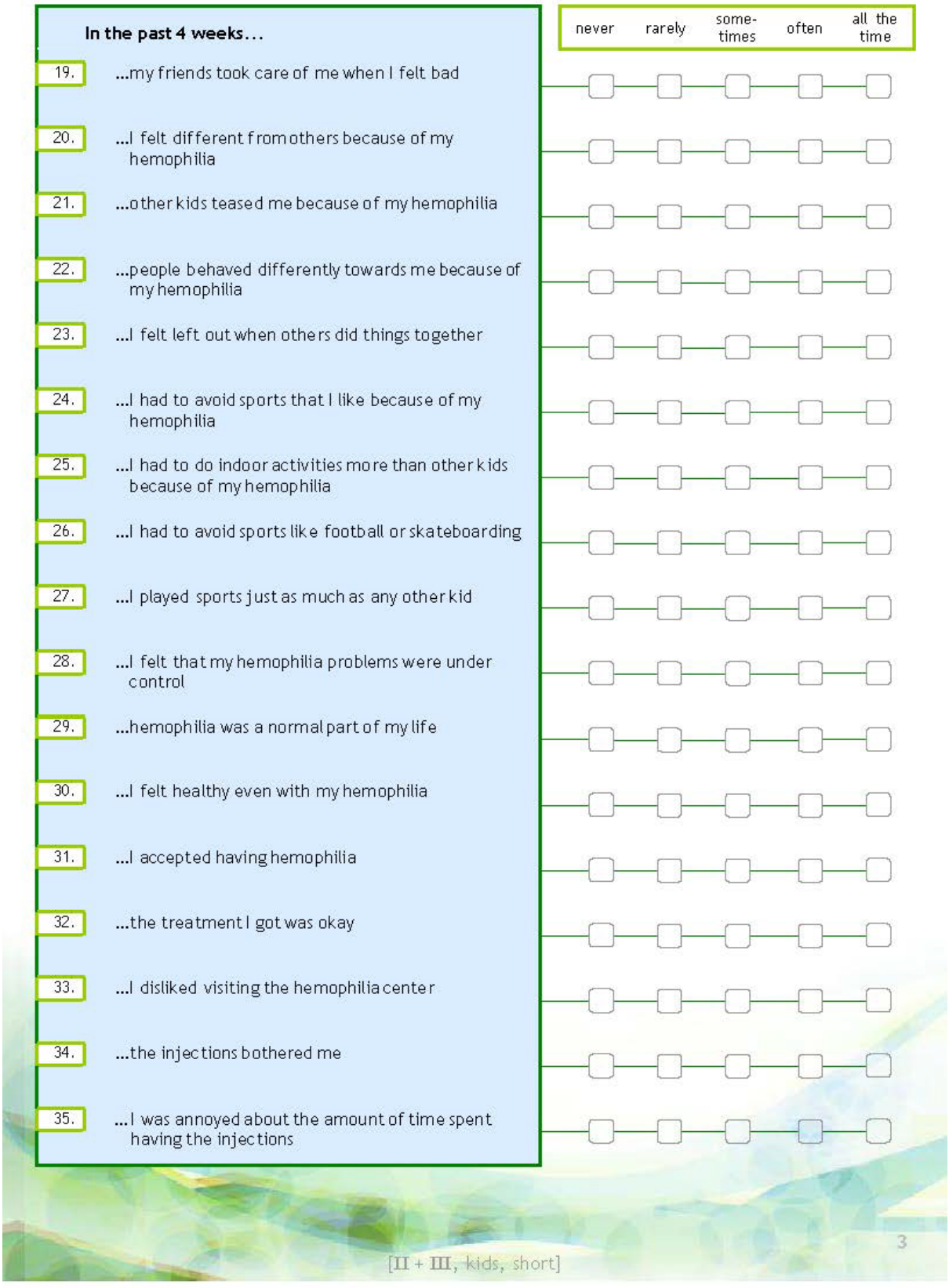
Questionnaire for Children and Teenagers | Kids' short version | age: 8-16



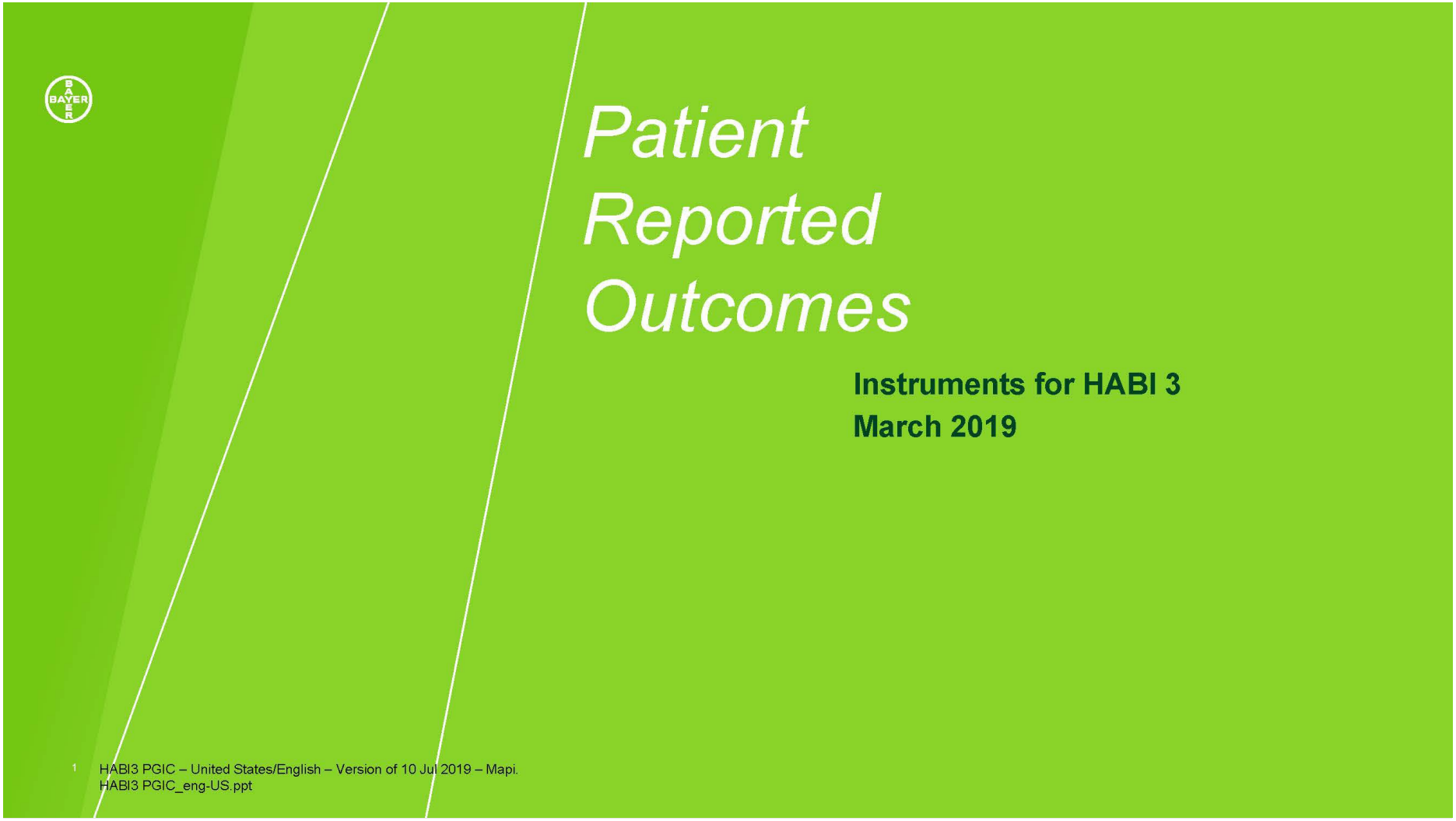
Date of completion: |_|_|_|_|_|_| (month/ day/ year)

Country: |_|_| Center: |_|_| ID no.: |_|_|_|_|


In the past 4 weeks...
never
rarely
some-times
often
all the time
1. ...my swellings hurt
2. ...I had pain in my joints
3. ...it was painful for me to move
4. ...I was afraid of bleeds
5. ...I was sad because of my hemophilia
6. ...my hemophilia was a burden (real problem) for me
7. ...my hemophilia made me angry
8. ...I felt lonely because of my hemophilia
9. ...I was jealous of healthy boys my age
10. ...I felt physically weaker than other boys
11. ...I felt as well as other boys my age
12. ...I felt comfortable with my body
13. ...my mother protected me too much
14. ...my parents criticized me when I hurt myself
15. ...my parents didn't allow me to do certain things because of my hemophilia
16. ...I felt I was causing my family trouble because of my hemophilia
17. ...my best friend cared about how I was feeling
18. ...there was a best friend that I felt very close to
2
[II + III, kids, short]


In the past 4 weeks...
never
rarely
some-times
often
all the time
19. ...my friends took care of me when I felt bad
20. ...I felt different from others because of my hemophilia
21. ...other kids teased me because of my hemophilia
22. ...people behaved differently towards me because of my hemophilia
23. ...I felt left out when others did things together
24. ...I had to avoid sports that I like because of my hemophilia
25. ...I had to do indoor activities more than other kids because of my hemophilia
26. ...I had to avoid sports like football or skateboarding
27. ...I played sports just as much as any other kid
28. ...I felt that my hemophilia problems were under control
29. ...hemophilia was a normal part of my life
30. ...I felt healthy even with my hemophilia
31. ...I accepted having hemophilia
32. ...the treatment I got was okay
33. ...I disliked visiting the hemophilia center
34. ...the injections bothered me
35. ...I was annoyed about the amount of time spent having the injections
3
[II + III, kids, short]

11.2.2 Patient's Global Impression of Change (PGI-C)


Patient Reported Outcomes
Instruments for HABI 3
March 2019
1
HABI3 PGIC – United States/English – Version of 10 Jul 2019 – Mapi.
HABI3 PGIC_eng-US.ppt

Patient Global Impression of Change

// Since the start of the study, my overall status is (one box only):

- ❑ Very much improved
- ❑ Much improved
- ❑ Minimally improved
- ❑ No change
- ❑ Minimally worse
- ❑ Much worse
- ❑ Very much worse

11.2.3 Five-Level European Quality of Life Five Dimension (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

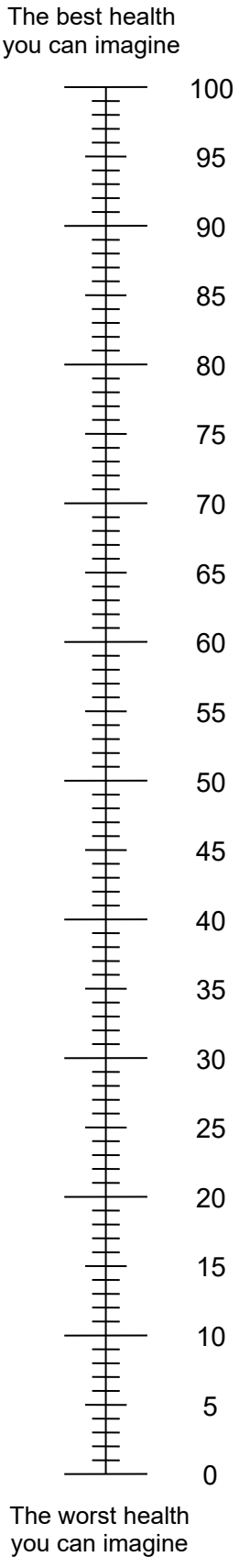
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



11.2.4 Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please select the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11.2.5 Work Productivity and Activity Impairment (WPAI) Questionnaire

Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS)

The following questions ask about the effect of your hemophilia on your ability to work, attend classes, and perform regular daily activities. When you think about the past seven days, do not include today. Please check the line or fill in the blank as indicated.

1) Are you currently employed (working for pay)?
___NO ___YES
(If NO, check "NO" and skip to question 5.)

2) In general, how many hours per week do you usually work?
_____HOURS

3) During the past seven days, how many hours did you miss from work because of problems associated with your hemophilia? Include hours you missed because you were sick, times you went in late, left early, etc. because you were experiencing problems with your hemophilia. *(Do not include time you missed to participate in this study.)*
_____ HOURS

4) During the past seven days, how much did hemophilia affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If hemophilia affected your work only a little, choose a low number. Choose a high number if hemophilia affected your work a great deal.*

Hemophilia had no effect on my work 0 1 2 3 4 5 6 7 8 9 10 Hemophilia completely prevented me from working

CIRCLE A NUMBER

5) Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)?

___NO ___YES
(If NO, check "NO" and skip to question 9.)

6) In general, how many hours per week do you usually attend classes?
_____HOURS

7) During the past seven days, how many hours did you miss from class or school because of problems associated with your hemophilia? *(Do not include time you missed to participate in this study.)*
_____ HOURS

8) During the past seven days, how much did hemophilia affect your productivity while in school or attending classes in an academic setting? *Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as*

effectively as usual. If hemophilia affected your productivity at school or in classes only a little, choose a low number. Choose a high number if hemophilia affected your productivity a great deal.

Hemophilia had no effect on my class work	0	1	2	3	4	5	6	7	8	9	10	Hemophilia completely prevented me from doing my class work

CIRCLE A NUMBER

9) During the past seven days, how much did your hemophilia affect your ability to do your regular daily activities, other than work at a job or attend classes? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If hemophilia affected your activities only a little, choose a low number. Choose a high number if hemophilia affected your activities a great deal.*

Hemophilia had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Hemophilia completely prevented me from doing my daily activities

CIRCLE A NUMBER

11.3 Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 11-1 will be performed by the local laboratory.
- All laboratory analyses will be performed at local laboratories according to local standards.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations locally or centrally as needed.

Table 11–1: Protocol-required Laboratory Tests

Laboratory Assessments	Parameters
Hematology	von Willebrand Factor antigen Complete blood count (platelets)
Other Laboratory Tests	Pregnancy: Highly sensitive serum pregnancy test (as needed for WOCBP) Serology: HIV antibody for screening purpose only, if not available in medical records CD4+ lymphocyte count: For HIV positive participants only, if not available in medical records FVIII inhibitor by Bethesda assay as per local clinical practice FVIII level by validated one-stage or chromogenic assay

Abbreviations: CD4+ = cluster of differentiation 4; FVIII = human coagulation factor VIII; HIV = human immunodeficiency virus; WOCBP = women of childbearing potential
Note: All routine study-required laboratory assessments will be performed by the local laboratory.

Investigators must document their review of each laboratory safety report.

11.4 Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.4.1 Definition of AE

Adverse Event (AE) Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology) or other safety assessments (e.g. vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
  - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/serious AE (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
  - The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Any bleeding event occurring during the study will not be documented as an AE, because this is captured in the assessment of effectiveness. However, if the bleed fulfills the criterion for an SAE (e.g. results in hospitalization), then the event should be recorded and reported as an SAE.

11.4.2 Definition of SAE

An SAE is defined as any AE that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

11.4.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Study Monitor/Medical Monitor (Study Medical Expert) in lieu of completion of the AE/SAE CRF/required form.
  - There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
  - The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

    An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

11.4.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor's Medical Monitor (Study Medical Expert) by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor's Medical Monitor (Study Medical Expert).
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

11.5 Appendix 5: Medical Device AEs, SAEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

11.5.1 Definition of Medical Device AE

Medical Device AE

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device provided by the study sponsor. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the medical device. This definition includes events related to the investigational medical device and events related to the procedures involved.

11.5.2 Definition of Medical Device SAE

A medical device SAE is any SAE that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:
   - A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
   - A permanent impairment of a body structure or a body function.
   - Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is **not** considered an SAE.
   - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
   - Chronic disease (EU Medical Device Regulation 2017/745).

c. Led to fetal distress, fetal death or a congenital abnormality or birth defect

11.5.3 Definition of Device Deficiency

Device Deficiency Definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

11.5.4 Recording and Follow-up of Medical Device AEs/SAEs/Device Deficiencies

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

The investigator will provide a preliminary assessment of the relationship between the event and the medical devices listed in Section 6.1.1.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

11.5.5 Reporting of AEs/SAEs Related to the Device

- For any SAE that was assessed as device-related: the investigator should manually complete the Medical Device Incident form and electronically complete the complementary SAE page in RAVE. The Medical Device Incident form will be sent to the sponsor via email at PV.caseprocessing@bayer.com within 24 hours.
- For any AE that was assessed as device-related: the investigator should manually complete the Medical Device Incident form and electronically complete the complementary AE page in RAVE. The Medical Device Incident form will be sent to the sponsor via email at PV.caseprocessing@bayer.com within 24 hours.

- If the device deficiencies could potentially lead to the death or serious deterioration of health (serious injury) of the study pa or others (e.g. staff), manually complete the Medical Device Incident form only and send it to the sponsor via email at PV.caseprocessing@bayer.com within 24 hours.

  For any AE or SAE that occurred in a person other than the study participant, the investigator should manually complete the Medical Device Incident form only and send it to the sponsor via email at PV.caseprocessing@bayer.com within 24 hours.

11.6 Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determine study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

WOCBP can only be included in the study if a pregnancy test is negative at the screening visit and if they agree to use adequate contraception during the study period until 8 weeks after last study intervention. Adequate contraception is defined as any combination of at least 2 effective methods of birth control, of which at least 1 is a physical barrier (e.g. condoms with hormonal contraception or implants or combined oral contraceptives, certain intrauterine devices).

For nulliparous adolescent participants, LARC methods are considered first-line options.

Collection of pregnancy information for female participants who become pregnant:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or serious AE (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks' gestational age) or still birth (occurring at > 22 weeks' gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study after completing early withdrawal visit.

11.7 Appendix 7: Visit Description

11.7.1 Visit 1 – Screening (Up to 30 Days Prior to Baseline)

Screening may take place over multiple site visits. At the screening visit, the following procedures and assessments will be performed:

- Obtain signed informed consent (and assent) from participant and parent(s) or legal guardian(s), as necessary.
  Note: No screening procedures should be performed unless written informed consent (and assent) has been obtained.
- Allocation of a unique participant number.
- Review of eligibility requirements; no participant should receive study intervention unless all inclusion and no exclusion criteria are met as listed in Section 5.1 and 5.2. Confirmation of selection criteria may be based on medical records for some conditions, but laboratory test results must be available for the listed items to confirm eligibility.
- Collect demographic data (age, sex, race, ethnicity) as well as blood type and weight.
- Collect information on previous hemophilia treatment.
- Obtain a complete medical and surgical history (general, disease, family history of hemophilia, and history of inhibitor development).
  - Specific information on history of hemophilia (date of diagnosis, start of prophylaxis, prior and current FVIII products, estimated number of ED, type of human coagulation FVIII gene mutation (from history), family history, FVIII level and type of assay, family and personal history of past inhibitor formation (including date of inhibitor testing, whether immune tolerance induction was performed, and recovery and half-life data, if available; Section 1.3), current treatment product and regimen, number and type of bleeds in the last 12 months, and presence and location of target joints). If available, data on prior pharmacokinetics with the participants' previous FVIII product will be collected (e.g. concentration timepoints and half-life).
- Collect information on previous medication (medication history, including substance usage).
- Concomitant medication review.
- AE/SAE review
  Note: Only events which are related to protocol-required study procedures will be recorded from the signing of the ICF.
- Blood samples for the following (see details in Table 11-1):
  - Pregnancy test (female participants)
  - Laboratory evaluation (platelets and von Willebrand factor (vWF): antigen).
    Note: If available in the medical records, vWF antigen testing should have been performed within 12 months prior to enrollment
  - HIV screening, if not available in medical records

- CD 4+ cell count (only if participant is HIV positive and if not available in medical records)
- Immunogenicity testing (human recombinant factor VIII [rFVIII] inhibitor)

- Training on use of eDiary and confirm participant access to eDiary

11.7.2 Visit 2 – Baseline (Day 1)

This visit will serve as the Baseline Visit; it will include the first administration of study intervention. The Baseline Visit should take place within 30 days after the screening visit.

This visit should start with the following assessments:

- Confirmation of eligibility including check of laboratory test results
  Note: Participants must have negative results from the local laboratory for inhibitory antibodies against FVIII (< 0.6 BU/mL determined with the Bethesda assay as per local clinical practice)

Thereafter, the following procedures and assessments will be performed and data recorded:

- Physical examination including height and weight
- Collect information on physical activity level (medium/high [contact sports]; low [non-contact sports]; sedentary). Please see Table 4–1 and Figure 4–1.
- Assessment of joint status
- Concomitant medication review
- AE/SAE/AESI review
- Administration and completion of PRO questionnaires (Haemophilia Quality of Life [Haem-A-QoL or Haemo-QoL], EuroQoL 5 Dimensions [EQ-5D-5L], Treatment Satisfaction Questionnaire for Medication [TSQM], and Work Productivity and Activity Impairment [WPAI] questionnaires)
- Blood sample collection **before** administration of study intervention for incremental recovery of Jivi (FVIII levels)
- Infusion of Jivi at study site
- Procedures and sample collection **after** administration of study intervention for incremental recovery of Jivi (15 to 30 minutes after end of infusion and at a minimum of 4 hours after end of infusion to assess FVIII levels; see Section 8.5.1)
  - In case of any infusion-related AE, vital signs will be collected.
- Pregnancy test for female participants if visit occurs >14 days after last menstrual period
- Bleeding risk score calculation and prophylaxis regimen selection
- Dispense study intervention for home infusions
- Instruction on the treatment regimen to be administered to the participant
- Check of eDiary entries and bleeding history

Begin regular monthly contact between participant and the site to check eDiary documentation and review AEs and concomitant medication use until the EOS/Early Withdrawal.

11.7.3 Visit 3, 4 – (Months 1, 2)

This visit should take place via telephone.

- Dose regimen adjustment according to score. At Visit 3 for medium risk participants and Visits 3 and 4 for low risk participants
- At home infusion of Jivi
- Concomitant medication review
- AE/SAE/AESI review
- Check of eDiary entries and bleeding history

11.7.4 Visit 5 – (Month 3)

This in-person visit should take place 72 hours after the last infusion of Jivi.

- Collect information on physical activity level (medium/high [contact sports]; low [non-contact sports]; sedentary)
- Measurement of weight
- Blood sample collection 3 days after previous dose for all participants: FVIII (Jivi) levels for all participants for Web-accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) PK analysis. For participants on the 2x/week regimen, collected samples will also serve as a trough level measurement.
- If the PI feels the baseline peak FVIII level at 15-30 minutes or 4-8 hours post-infusion at Visit 2 does not seem to be appropriate for the dose infused, then the levels should be repeated at Visit 5 and the results also uploaded to WAPPS-Hemo. For those patients who do not have appropriate FVIII levels at either Visit 2 or Visit 5, the levels should be repeated at Visit 6.
- Pregnancy test (female participants)
- Infusion of Jivi at study site (not mandatory)
- Concomitant medication review
- AE/SAE review
- Administration and completion of PRO questionnaire (EQ-5D-5L only)
- Return used vials, and dispense remainder of study intervention
- Check of eDiary entries and bleeding history

11.7.5 Visit 6 – (Month 6, End of Study/Early Withdrawal)

This in-person visit should take place in alignment with the weekly prophylaxis regimen (i.e. as close as possible to the participant's next infusion) as follows: on Day 4 for participants on the 2x/week regimen, on Day 5 for participants on the Q5D regimen, and on Day 7 for participants on less frequent regimens (e.g. Q7D).

The following procedures and assessments will be performed in participants at the EOS visit or at the time of premature termination:

- Concomitant medication review
- AE/SAE/AESI review
- Physical examination including height and weight
- Assessment of joint status
- Collect information on physical activity level (medium/high [contact sports]; low [non-contact sports]; sedentary)
- Blood sample collection **before** administration of study intervention: FVIII (Jivi) trough levels
    - Sample collection on Day 4 for participants on the 2x/week regimen, on Day 5 for participants on the Q5D regimen, and on Day 7 for participants on less frequent regimens (e.g. Q7D)
- Pregnancy test (female participants)
- In-hospital infusion of Jivi
- If the PI feels the baseline peak FVIII level at 15-30 minutes or 4-8 hours post-infusion at Visit 2 does not seem to be appropriate for the dose infused, then the levels should be repeated at Visit 5 and the results also uploaded to WAPPS-Hemo. For those patients who do not have appropriate FVIII levels at either Visit 2 or Visit 5, the levels should be repeated at Visit 6.
- Administration and completion of PROs (Haem-A-QoL or Haemo-QoL, EQ-5D-5L, TSQM, WPAI, and Patient's Global Impression of Change [PGI-C])
- Return used and unused vials
- Check of eDiary entries and bleeding history

11.7.6 Visit 7 – (Safety Follow-up; 7 to 14 days after last dose of study intervention)

This visit should take place 7 to 14 days after the last dose of study intervention visit via telephone.

The following procedures and assessments will be performed:

- Concomitant medication review
- AE/SAE/AESI review

11.8 Appendix 8: Tokenization

Figure A: What is Tokenization

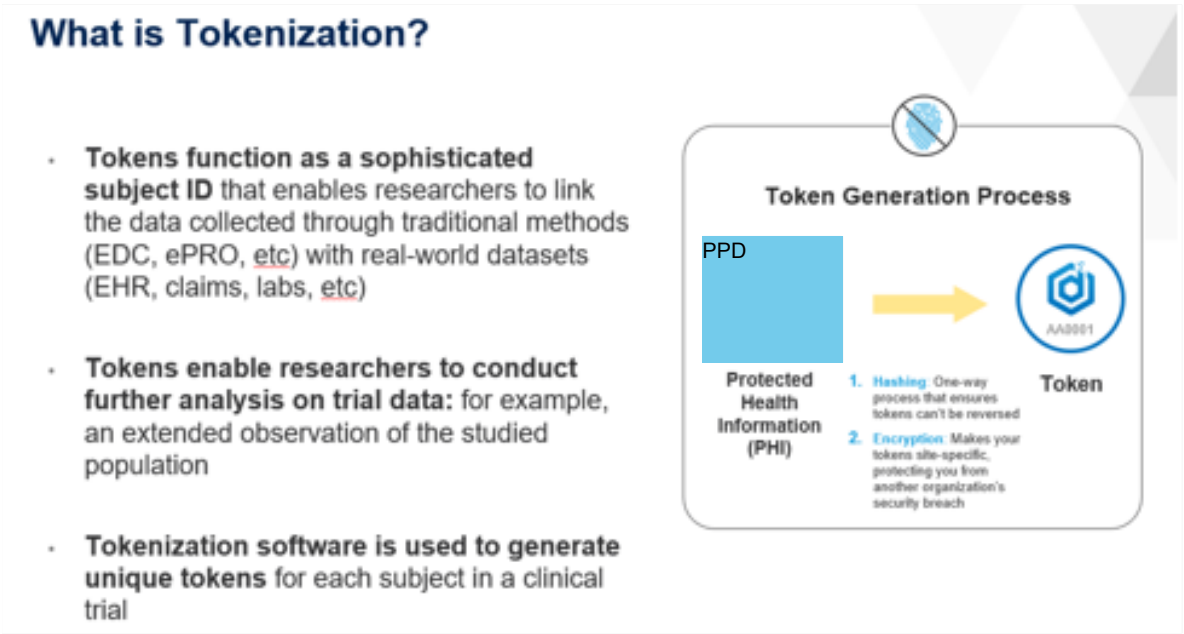


Figure B: Use of De-identified Data in Retrospective and Future Outcomes Analyses

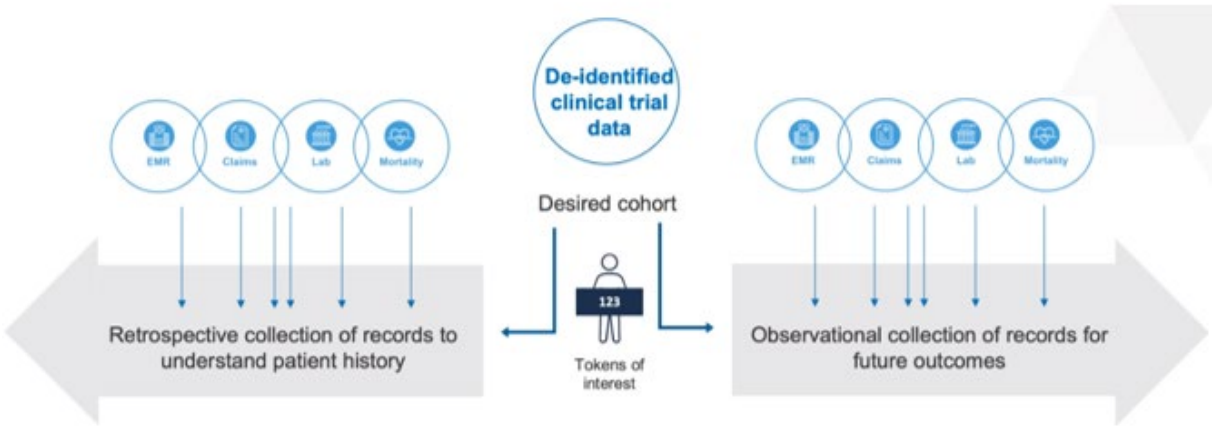


Figure C: Linking of De-identified Clinical Trial Data

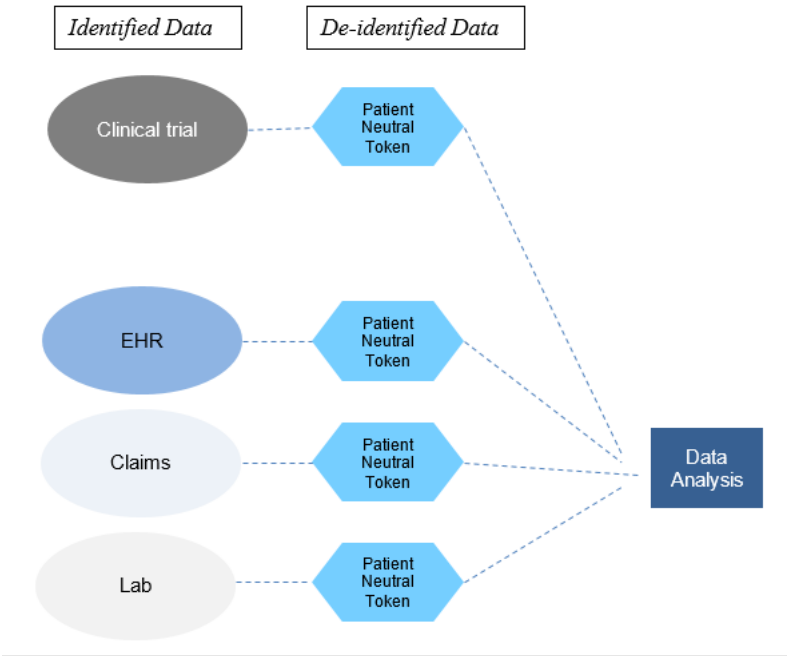
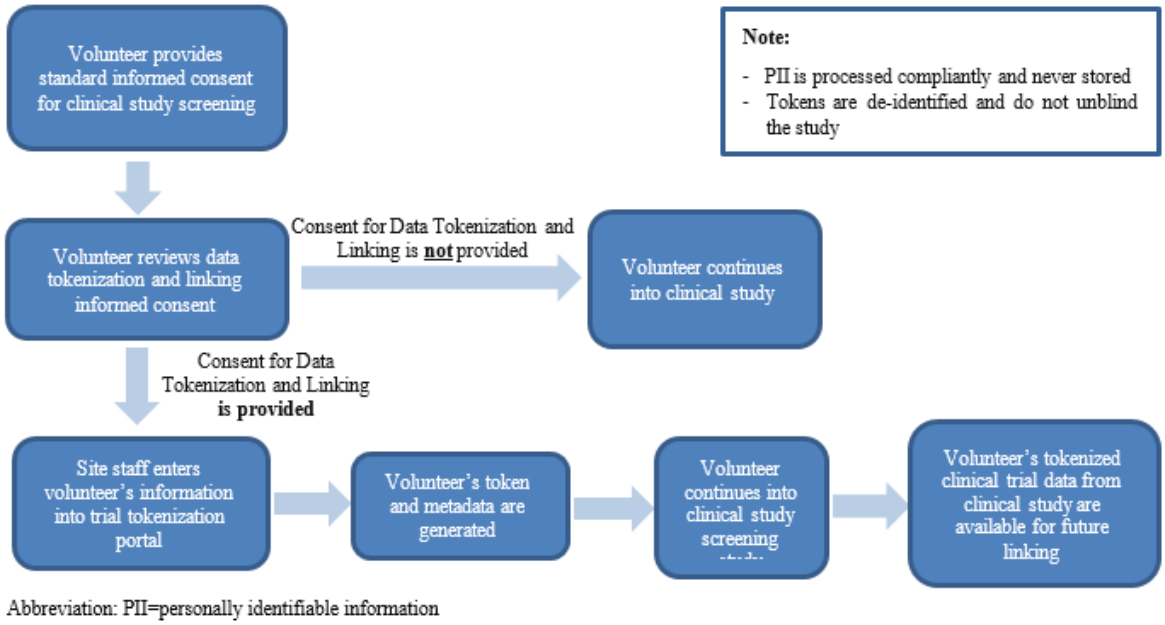


Figure D: Methodology for Initiating Tokenization

The flow chart below presents the steps a participant will undertake after deciding whether to consent to tokenization.



Abbreviation: PII=personally identifiable information

Tokenization Frequently Asked Questions

For conversations between health care providers and potential study participants

1) **What is Tokenization?**

   Tokenization is the process of transforming sensitive personal data, such as participant identifiable information, into non-sensitive data (tokens) whereby information cannot be connected back to the participant. Each participant record is converted into a token, which is like a secret code that retains these records (e.g., gender, birth year, disease state, etc.) without revealing any information about the participant's identity.

2) **What is the purpose of Tokenization?**

   Every time a participant is in contact with a healthcare entity, some information on that participant is retained by healthcare systems. Each healthcare entity (including insurance companies) is using different ways of storing this data. Tokenization will help to bundle all the different pieces of information, without identifying the participant.

   As a result, researchers who use datasets from different sources have no common way to connect participant level data from these sources together to understand the full participant healthcare journey. Tokenization will allow us to connect the fragmented data without identifying the participant.

3) **What are the benefits of Tokenization?**

   Tokenization allows investigators to connect participant data from the multiple studies in which they may have participated. This means that the information is not just reflecting a snapshot in time but rather over time.

4) **How is participant privacy maintained?**

   Each token or participant code is encrypted (coded to prevent hacking) which helps retain essential information (e.g. gender, birth year, disease state, etc.) but does not contain traceable information about the participant. This allows for participant information to be connected from different sources while maintaining the participant's privacy.

5) **How does HIPAA impact Tokenization?**

   In the US, the HIPAA Privacy Rule establishes national standards to protect individuals' medical records and other individually identifiable health information (collectively defined as "protected health information") This is covered under federal regulation known as Code of Federal Regulations (CFR). Tokenization is also under the same CFR and as such all information used in tokenization is protected. If there is no way health information can identify an individual participant, then the Privacy Rule does not restrict the use or disclosure of the de-identified health information by covered health entities

6) **In which Countries is Tokenization used?**

   Currently, tokenization is only used in the US, and conducted by select health information technology companies (vendors) such as Datavant, HealthVerity, and Synoma.

7) How is a Token created?

The few authorized vendors use a special software which is installed, at the study site. The participant information is then transformed into tokens/codes that are unique to each participant but common across different health entities with information about the same participant. A third-party technology company not associated with Bayer or other healthcare providers, verifies, and ensures that these tokens cannot be reversed to reveal the identity of the participant.

8) Will I be declined to participate in this study if I do not consent to this?

A patient's participation in a study is not dependent on their consent to tokenization. A participant who declines to take part in the tokenization but who is otherwise qualified for the study, is still allowed to take part in the study. Therefore, the format of this consent is specifically an opt-in consent that is included in the main ICF. This is similar to a consent you might receive from a biobank to store tissue (e.g., tumor tissue) for potential future research use.

9) Do I get paid to participate in Tokenization?

You will not be paid to participate in tokenization.

10) If I participate in multiple studies will my data be tracked?

Every time you participate in a new study, a new tokenization consent form will be used. Data across studies cannot lead back to you as a person.

11) Will my health data be supplied to insurance companies or Federal agencies?

Data privacy is maintained at all times. Your data does not lead back to you as a person. However, combined de-identified data can be part of submission packages to regulatory (Federal) agencies.

12) Can I be denied insurance or claims if I participate in Tokenization?

Tokenization contains de-identified participant-specific data, which cannot be connected to the participant and therefore, there is no ability for an insurance company to deny a claim based on tokenized data.

13) What happens if I withdraw consent?

Participants are allowed to withdraw their consent for tokenization at any point in the study. When withdrawal happens, this will prevent further connecting of their information to the study but maintains previously collected data.

Also, withdrawing consent for tokenization does not prevent you from continuing in the PREDICT study.

14) Will my data still be used if I withdraw consent half-way through the study?

The participants' data tracking will be stopped. The data entered up until the date of your withdrawal will remain in the system.

15) What are some of the data you are able to link?

This is a new concept which is being used for the first time by Bayer. Tokenization might allow researchers to access data across various sources such as clinical studies, insurance claims (open and closed), electronic health records, Specialty Pharmacy aggregators, labs, participant-reported outcomes, etc. in the US.

11.9 Appendix 9: Protocol Amendment History

Amendment 1 (17 SEP 2021)

Overall Rationale for the Amendment:

This amendment was prepared prior to the initial IRB submission to clarify the protocol language. Additional updates were made to reflect the latest sponsor standards related to safety reporting/assessments.

Amendment 2 (19 AUG 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment was to accommodate the inclusion of additional countries in the study. This and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, and changes for consistency across the clinical program have been made; as these changes were minor, they are not listed in detail in the table.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added National Clinical Trial number.	To align with regulatory requirements.
Section 1.1 Synopsis, Section 4.1 Overall Design	Added modification that this is a multi-country study, and removed statement that the study will be conducted in the United States (US) only.	To accommodate the inclusion of additional countries.
Section 1.1 Synopsis, Section 1.2 Schema for Dosing (Figure 1-1, Footnote “a”), Section 2.3 Benefit/Risk Assessment, Section 4.1.2 Treatment, Section 6.1 Study Intervention Administered, Section 6.2 Preparation/Handling/ Storage/Accountability, Section 6.7 Treatment of Overdose, Section 6.8 Concomitant Therapy, Section 8.4.7 Events of Special Interest, Appendix 1 Regulatory, Ethical, and Study Oversight Considerations	Removed reference to US prescribing information (USPI) and, as applicable, referenced the protocol instructions or approved prescribing information.	To accommodate the inclusion of additional countries.
Section 1.2 Schema for Dosing Regimen Assignment, Section 9.4.1 General Considerations	Removed text referring to “run-in“ period.	To align with currently preferred study terminology.
Section 1.3 Schedule of Activities	Revised note for inhibitor testing to follow local clinical guidance if human coagulation factor VIII (FVIII) inhibition is suspected upon screening, and added row/note regarding collection of data for patients with a history of inhibitors.	To accommodate inclusion of additional countries and align with modified eligibility criteria regarding participants with a history of FVIII inhibitors.
Section 2.1 Study Rationale	Added statement regarding inclusion of sub-populations.	For alignment with revised eligibility criteria.
Section 4.3 Justification for Dose	Added modification that dosing has been chosen based on the USPI.	To avoid ambiguity.
Section 5.1 Inclusion Criteria	Removed eligibility requirement that participants have no history of FVIII inhibitors and added	To clarify participant eligibility criteria related to FVIII inhibitor medical history.

	specifications for participants with past positive inhibitor titers.	
Section 5.2 Exclusion Criteria	Added clarification in Exclusion Criterion #1 that participants with a diagnosis of von Willebrand disease are not eligible to participate in the study.	To align with standard clinical practice and clarify that local diagnosis guidelines should be followed.
Section 5.2 Exclusion Criteria	Added criterion regarding participants with evidence of FVIII inhibitors within the last 3 years and referenced revised Inclusion Criterion #5.	To clarify participant eligibility criteria related to current and historical used of FVIII inhibitors.
Section 6.1 Study Intervention Administered	Modified statement detailing how investigators should identify appropriate prophylaxis regimen.	To highlight for investigators that, while choice of prophylaxis regimen should ultimately be guided by protocol, clinical and individual participant factors should be considered in the decision-making process.
	Added reference to statistical analysis section for details regarding participants who switch from the protocol-assigned regimen.	To avoid ambiguity.
Section 6.2 Preparation/Handling/ Storage/Accountability	Modified statement regarding dispensation of study intervention to allow participants to obtain study intervention on site.	To allow flexibility for study participants and sites.
Section 8.1.1 Demographics	Added country to list of demographic characteristics to be recorded at screening.	To align with expansion of study.
Section 8.1.3 Disease History, Appendix 7 Visit Description	Included additional details to be collected with regard to past FVIII inhibitor formation.	For alignment with new eligibility criteria regarding participants with previous FVIII inhibitor use.
	Added statement that von Willebrand factor (vWF) antigen levels extracted from the Medical Record should have been performed within 12 months prior to screening.	For alignment with current best safety practices.
Section 8.3.1 Measurements of Immunogenicity, Section 9.4.4.1 Immunogenicity, Appendix 3 Clinical Laboratory Tests, Appendix 7 Visit Description	Deleted reference to Nijmegen modified Bethesda assay and revised to include Bethesda assay per local clinical practice.	To allow flexibility in assay used based on local clinical practice.
Section 8.4.5 Pregnancy, Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information	Removed section regarding collection of pregnancy information for female partners of male participants.	For alignment with current Jivi safety information.
Section 9.4.1 General considerations	Added statement that primary endpoint table and table for number of participants enrolled will be presented in total and by country.	To align with expansion of study.
	Added statement that select statistical tables will be presented by subgroup of participants with FVIII inhibitor history.	To assess the impact of previous FVIII inhibitor use on frequency of prophylaxis administration and other factors.
Section 9.4.2 Primary Endpoint	Added statement that data for participants with favorable outcome will be presented by FVIII inhibitor history and by country.	To assess the impact of previous FVIII inhibitor use and country-specific differences in those participants with favorable outcomes.
Section 9.4.4 Safety Analyses	Added clarification that safety	To assess the impact of previous

	analyses will be stratified by FVIII inhibitor history and AE listings will include data related to previous FVIII inhibitors.	FVIII inhibitor use on safety.
Section 9.4.4.2 Pharmacokinetics	Added clarification that pharmacokinetic (PK) parameters will be presented overall and by FVIII inhibitor history.	To assess the impact of FVIII inhibitor use on PK parameters.
Section 9.4.5.1 Disposition of participants	Revised analyses of participant disposition to include by country assessments.	To align with expansion of study.
Section 10 Tokenization	Added clarification that tokenization is an option for US participants only.	To avoid ambiguity.
Appendix 8 Tokenization	Added Frequently Asked Questions related to tokenization.	To support the physician/investigator and participant interaction.
Administrative change: Sponsor's medically responsible person	Sponsor's medical expert role was changed from Clinical Development Leader to Medical Director.	Clarification of sponsor personnel.

11.10 Appendix 10: Abbreviations

ABR	Annualized bleed rate
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BMI	Body mass index
CD4	Cluster of differentiation 4 (CD4 receptor)
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form (either paper or electronic)
EHL	Extended half-life
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FPFV	First participant first visit
FSH	Follicle-stimulating hormone
FVIII	Human coagulation factor VIII
GCP	Good Clinical Practice
HCP	Health Care Professional
HIV	Human immunodeficiency virus
HRT	Hormonal-replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IU	International units
IV	Intravenous
IxRS	Interactive Voice/Web Response System
kg	Kilogram
LARC	Long-acting reversible contraception
LoE	Loss of efficacy
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	Modified intention-to-treat
PEG	Polyethylene glycol
PGI-C	Patient's Global Impression of Change
PID	Patient Identification Code
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient Reported Outcome
PTP	Previously-treated patients
QoL	Quality of Life
rFVIII	Human recombinant factor VIII
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SD	Standard deviation

SHL	Standard half-life
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
vWF	von Willebrand factor
WAPPS-Hemo	Web-Accessible Population Pharmacokinetic Service-Hemophilia
WFH	World Federation of Hemophilia
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI	Work Productivity and Activity Impairment

DEFINITIONS (Common Terms)

Term	Definition
Legal guardian	parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or legally acceptable representative(s), as defined by national and local laws and regulations, who consent(s) on behalf of the minor. For the purposes of this study, all references to informed consent and assent refer to the pediatric participant (child) and his or her legal guardian who have provided consent (and assent as applicable) according to the Informed Consent Process and Assent Form described in Section 11.1.3.
Pre-study ABR	Pre-study ABR is based on data from a minimum of 6 continuous months (up to a maximum of 12 months) of stable SHL prophylaxis at any given time within the 12 months prior to the screening visit (refer to Section 9.4.2).
Pre-study treatment frequency	Pre-study treatment frequency is based on data from a minimum of 6 continuous months (up to a maximum of 12 months) of stable SHL prophylaxis at any given time within the 12 months prior to the screening visit (refer to Section 9.4.2).
Stable SHL prophylaxis	Stable SHL prophylaxis is defined as a minimum of 18 weeks of treatment in a 6 (consecutive) calendar month period in the 12 months prior to the screening visit (refer to Section 9.4.2).

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