Document Type:	Statistical Analysis Plan
Official Title:	A phase 3, single group treatment, open-label, study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe hemophilia A
NCT Number:	NCT05147662
Document Date:	19-Dec-2023

Title Page
Protocol Title:
A phase 3, single group treatment, open-label, study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe hemophilia A

Protocol Number:	21824
Compound Number:	Damoctocog alfa pegol (Jivi®), BAY 94-9027
Short Title:	A Phase 3 safety study of BAY 94-9027 in children 7 to <12 years of age with severe hemophilia A
Acronym:	Alfa-PROTECT
Sponsor Name:	Bayer Consumer Care AG.,
Legal Registered Address:	Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland

Regulatory Agency Identifier Number(s):

Registry	**ID**
EudraCT	2021-004858-30

Date: 19 DEC 2023
Version: 3.0

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

Table of Contents

Table of Tables

Version History

This Statistical Analysis Plan (SAP) for study 21824 is based on the protocol Version 3.0 dated 06 APR 2023.

SAP Version	Date	Change	Rationale
1.0	17 FEB 2022	Not Applicable	Original version
2.0	30 JUN 2023	1.1 Objectives, Endpoints, and Estimands - Other objectives revised to include investigation of long-term safety and associated endpoints. - Other objectives revised to clarify that Patient Reported Outcomes questionnaires are used to assess health-related quality of life, not biomarkers. - Time period for endpoint of secondary estimand revised. - Changed in duration for the extension study (Part B) from 6 to 18 months.	 - Revised to reflect prolongation of study duration and addition of long-term safety-related measurements. - In the original protocol, patient reported outcomes were incorrectly grouped as an endpoint for the biomarkers' objective. - Revised to reflect prolongation of study duration and added the time point for 18 months in Part B. - Due to change in treatment duration in the protocol amendment.
		1.2 Study Design - Changed in duration for the extension study (Part B) from 6 to 18 months. - Added a paragraph regarding the first analysis of Part B	 - Due to change in treatment duration in the protocol amendment. - Reflect the change in the protocol amendments 1 and 2.
		3. Analysis Sets - Revised modified safety analysis set definition - Added Intent-to-treat analysis set (ITT Part A) - Added treatment duration to mITT Part A - Revised modified intent-to-treat analysis set - Added intent-to-treat analysis set	 - Change the wording to help avoiding the misinterpretation. - The analysis set is needed for the analysis of PROs. - Minimum treatment duration required for the ABR calculation - Add minimum of treatment requirement for participants to be included in the analysis set. - This analysis set is required for PROs analysis.
		- Removed safety analysis set	- No longer needed for this study since Parts A and B of the study will be analyzed separately.
		4.1 General Considerations - Planned analysis for Part B was revised to reflect	 - Change reflects treatment prolongation, due to the increase in

SAP Version	Date	Change	Rationale
		the increase in duration. Analysis of Part B to be conducted at Month 6 in addition to the analysis at the end of the study.	Part B duration from 6 months to 18 months
		- The first analysis of Part B data was added to the protocol	- Change reflects the change in the protocol, protocol amendments 1 and 2.
		- Add clarification for the data to be included Part B analysis	- To ensure that only Part B data will be included in the analysis of Part B.
		4.2.2 Main Analytical Approach - Changed the word “combined” or “pooled” to “utilized”	- Avoid the confusion since the data from PROTECT-KIDS only to be used in the analysis of primary endpoint.
		4.3.1.2 Main Analytical Approach - Removed SAF and mITT analysis sets from the lists of analysis sets to be used in analyses in this section	- The analysis of Part B data will not include data from Part A.
		4.3.2 Supportive Secondary Endpoints - Added the analysis for Part B to be performed by dosing frequency - Remove the mITT from the list of analysis sets	- Change to address to present the efficacy data by dosing frequency - Change to reflect that the analysis of Part B data will not include data from Part A.
		4.4.2 Tertiary/Exploratory Endpoints - Added the analysis for Part B to be performed by dosing frequency	- Change to address to present the efficacy data by dosing frequency
		4.5 Safety Analysis - Remove the mITT from the list of analysis sets - Additional endpoints based on exposure data have been added - Revise the lists of adverse events to be summarize by using the	- Change to reflect the way PROTECT Kids study presenting the results. - Change to reflect the way PROTECT Kids study presenting the exposure data. - Change to reflect the global standard naming convention for adverse event tables.

SAP Version	Date	Change	Rationale
		global standard table naming convention	
		4.6.1 Patient-reported Outcomes - Added the time points EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation to the summaries and analyses.	- Revised to reflect the changes in the protocol amendment 1.
		4.7 Interim Analysis - Planned analysis for Part B was revised to reflect the increase in duration. Analysis of Part B to be conducted at Month 6 in addition to the analysis at the end of the study.	- Change reflects treatment prolongation, due to the increase in Part B duration from 6 months to 18 months, the plan to evaluate efficacy and safety of the 5-day regimen during the first 6 months of Part B has not been changed; therefore, the Month 6 analysis has been added in addition to the analysis at the end of the study.
		6.9.7 Dosing Frequency - Added definition for dosing frequency to be used when analyzing Part B data	- Clearly define dosing regimens administer.
		6.9.8 Compliance and Exposure - Added details calculations for each variable to be displayed in the tables	- Clearly define how each variable to be derived.
		6.10 Appendix 11 Schedule of Activities - Change in the Schedule of Assessment for Parts A and B	- Revised to reflect the changes in the protocol amendment 1.
3.0	19 DEC 2023	4.3.2.2.2 BAY 94-9027 consumption - Removed one of the duplication of bullet point: Total dose per bleed (IU)	- Removed the duplication
		4.4.1.2 FVIII Recovery - Added “from central laboratory” in the second sentence.	- Added such wording to identify which FVIII levels to be used in the summary and analysis
		4.5.2 Adverse Events - Added “(Part B only) for the bullet points for post-treatment adverse events	- Summaries for post-treatment adverse events are not applicable for Part A.

SAP Version	Date	Change	Rationale
		- Added “leading to discontinuation” for one of the bullet points for treatment-emergent adverse events of special interest - Added treatment-emergent adverse events related to procedures required by protocol.	- The phrase was inadvertently left out. - This summary was inadvertent left out in previous version of the SAP.
		6.2 Appendix 2: Participant Dispositions - Added the number and percent of participants valid for ITT Part A to the list.	- This summary was inadvertently left out in previous version of the SAP.
		6.3 Appendix 3: Baseline Characteristics and Demographics - Added the ITT Part A analysis set to the list	- The summary for ITT analysis set needed to be included but inadvertently left out.
		6.3 Appendix 6: Concomitant Medication - Summary for new concomitant medications was added to the list - Added the ITT Part A analysis set to the list	- The summary needed to be included but inadvertently left out. - The summary for ITT analysis set needed to be included but inadvertently left out.
		6.9.1 Baseline and Change from Baseline - Definition of baseline was revised	- To address, for certain parameters, that measurements obtained on the same day of first dose could be used as baselines.
		6.9.4 FVIII Recovery - Validity criteria were revised	- To appropriately address which values need to be included in the analysis.
		6.9.9 LLOQ - This subsection was added to describe how to derive the LLOQ value when provided as characters values	- Provided the rules for conversion of the LLOQ as character to numerical values so that these values could be in the summaries and analyses.

1. Introduction

BAY 94-9027 is a recombinant FVIII (rFVIII) with extended half-life through reduced clearance from plasma by PEGylation while retaining the normal activity of the FVIII molecule. It has received marketing authorization for treatment and prophylaxis of bleeding (including perioperative management) in previously treated patients (PTPs) ≥ 12 years of age with hemophilia A (congenital FVIII deficiency) (USPI and EU SmPC).

The indication for the study intervention was restricted to previously treated patients 12 years and older, partly, because of the observation of an immune response to polyethylene glycol (PEG) in some children 2-5 years, manifested as hypersensitivity and/or loss of efficacy (LoE). A significant decrease in the risk of an immune response to PEG was observed with an increase in age. Amongst the 25 patients, aged 7 to <12 years, in the pivotal study in pediatric patients <12 years of age, no such cases were observed. However, due to the small sample size, as a safety margin, this age group (7 to <12 years) was excluded in the initial BLA/MAA.

This study will address the uncertainty as to the risk of potential hypersensitivity and lack of drug effect associated with anti- polyethylene glycol (PEG) antibodies during the first 4 exposures to BAY 94-9027 in previously treated children 7 to <12 years of age with severe hemophilia A and will provide supportive data for efficacy of prophylaxis treatment and long-term safety data.

The SAP describes the analyses of Part A, the first 6 months of Part B, and final analyses which contain only data from Part B of the study. Table, figure and listing specifications are contained in a separate document.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objectives and Endpoints

Objectives	Endpoints
Primary objective main study	
Safety	
To assess safety and tolerability of BAY 94-9027 replacement therapy in previously treated patients 7- <12 years of age with severe hemophilia A	**Primary endpoint** • AESI (hypersensitivity and LoE*) associated with the first 4 EDs leading to discontinuation **Secondary endpoints** • Adverse drug reactions (ADRs) • Anti-drug antibody (ADA) development • Inhibitor development
Secondary objective (main study and extension study)	
To describe clinical efficacy of BAY 94-9027	**Secondary endpoints** • Annualized bleeding rate (ABR) • BAY 94-9027 consumption • Number of infusions/month and year (Annualized Infusion Rate)
Other	
To further investigate long-term safety	• Quantitative PEG measurement • Renal safety related urine and serum biomarkers • Liver enzymes • Neurological assessment
To assess the impact of BAY 94-9027 in Health related QoL	• Patient-reported outcomes (PROs) questionnaires
To further investigate the study intervention and similar drugs (e.g. mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to hemophilia and associated health problems	• Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

AESI = adverse events of special interest, ED = exposure day
* As defined in Section 8.3.8 of the protocol

1.1.2 Estimands

1.1.2.1 Primary estimand

The primary clinical question of interest for the primary objective is:

What is the proportion of individuals with AESIs (hypersensitivity and LoE) associated with the first 4 EDs of BAY 94-9027 treatment and leading to discontinuation of BAY 94-9027 treatment in previously treated males, 7 to <12 years of age with severe hemophilia A, and without inhibitors to FVIII, who do not discontinue study for other reason than an AESI before the fourth exposure day with or without emergency use of other FVIII medication?

The estimand is described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals 7 to <12 years of age with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	AESI (i.e. hypersensitivity or LoE, as defined in Section 8.3.8 of the protocol) associated with the first 4 EDs of BAY 94-9027 treatment leading to discontinuation.
Treatment condition	2x/week BAY 94-9027 prophylactic treatment at a dosage of 40 IU/kg up to 60 IU/kg with or without emergency use of other FVIII products (treatment policy strategy).
Intercurrent events and strategies how to address them	• Individuals with the intercurrent event 'treatment discontinuation for any reason other than AESI before the fourth ED' will not be included in the assessment of the primary endpoint (principal stratum strategy) because at least 4 EDs are needed for event-free individuals to evaluate the primary endpoint. • The intercurrent event 'emergency use of other FVIII products' is addressed by the treatment condition attribute following the treatment policy strategy. • Other relevant intercurrent events are not anticipated at this point in time.
Population level summary	Proportion of individuals who experience a primary endpoint AESI.

* Treatment policy strategy, and principal stratum strategy refer to the strategies for addressing intercurrent events as described in the ICH E9 (R1) guideline.

Rationale for estimand:

In the pivotal Phase 3 studies PROTECT VIII and PROTECT Kids, an immune response associated with anti-PEG IgM antibodies was observed primarily in children 2-5 years of age. The immune response manifested as symptoms of hypersensitivity and/or LoE. All events occurred during the first 4 EDs of BAY 94-9027 and all led to study discontinuation. The primary estimand has been chosen to estimate the unknown risk of such events in previously treated children 7 to <12 years of age with severe hemophilia A. Since these events might occur up to the fourth ED, event-free children discontinuing before the fourth ED is reached do not provide sufficient information and will be excluded from the population of interest. Use of other FVIII products is not expected but might happen in emergency cases. Exposure to another FVIII medication is not considered an ED in terms of the primary endpoint. Four EDs with BAY 94-9027 are needed for the assessment. All AESIs associated with the first 4 BAY 94-9027 treatments will be counted regardless of other FVIII exposure.

1.1.2.2 Secondary estimands

The key clinical question of interest on the secondary endpoints for the primary objective is:

In previously treated males 7 to <12 years of age with severe hemophilia A without inhibitors to FVIII, or neutralizing ADA who are on a continuous prophylaxis treatment with BAY 94-9027, what are the proportions of ADRs, ADA development, and inhibitor development?

Secondary estimands for primary objective are described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals 7 to <12 years of age with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	• Adverse drug reactions (ADRs) • Anti-drug antibody (ADA) development • Inhibitor development
Treatment condition	2x/week prophylactic treatment with BAY 94-9027 at a dosage of 40 IU/kg up to 60 IU/kg with option to change to every 5 days prophylactic treatment with BAY 94-9027 at a dosage of 60 IU/kg IV after at least 50 EDs (with start of Part B) with or without emergency use of other FVIII medication (treatment policy strategy*).
Intercurrent events and strategies how to address them	• The intercurrent event 'emergency use of other FVIII products' is addressed by the treatment condition attribute following the treatment policy strategy. Other relevant intercurrent events are not anticipated at this point in time.
Population level summary	Proportion of individuals with ADRs, Proportion of individuals with ADA, and Proportion of individuals with inhibitor development.

Estimands for the secondary objective:

The key clinical question of interest for the secondary objective is:

What is the ABR of previously treated males 7 to <12 years of age with severe hemophilia A without inhibitors to FVIII, or neutralizing ADA who are on a continuous prophylaxis treatment with BAY 94-9027 for at least 3 months up to time when at least 50 EDs are reached (approximately 6 months) of Part A, during the first 6 months of Part B, during total duration of Part B, and across treatment regimens without major surgery and regardless of emergency use of other FVIII medication?

The estimand is described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals 7 to <12 years of age with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	Number of bleeds per individual observation period of continuous prophylactic treatment (overall and per treatment regimen) of at least 3 months up to time when at least 50 EDs are reached (approximately 6 months, Part A) and for further 6/18 months of Part B of BAY 94-9027 treatment.
Treatment condition	2x/week prophylactic treatment with BAY 94-9027 at a dosage of 40 IU/kg up to 60 IU/kg with option to change to every 5 days prophylactic treatment with BAY 94-9027 at a dosage of 60 IU/kg IV after at least 50 EDs (with start of Part B) with or without emergency use of other FVIII medication (treatment policy strategy*).
Intercurrent events and strategies how to address them	• The intercurrent events 'treatment discontinuation for any reason before month 3' and 'development of an inhibitory antibody to FVIII or ADA that neutralizes activity sufficiently to interfere with effective treatment' will be addressed by the endpoint attribute following the principal stratum strategy*. • The intercurrent events 'treatment discontinuation for any reason after month 3' and 'emergency use of other FVIII medication' will be addressed by the treatment policy strategy*. • The intercurrent event 'emergency major surgery' is addressed by the endpoint attribute following the hypothetical strategy*. The time of the surgery will not be considered for the observation period and bleeds during the time of the surgery (i.e., bleeds related to the surgery procedure) will not be counted. An individual with this intercurrent event will be analyzed as if the surgery had not happened. Other relevant intercurrent events are not anticipated at this point in time.
Population level summary	Mean and 95% confidence interval for ABR estimated by a negative binomial regression.

* Treatment policy strategy, and principal stratum strategy refer to the strategies for addressing intercurrent events as described in the ICH E9 (R1) guideline.

Rationale for estimand:

Efficacy is assessed by the number of bleeds per year. The ABR during continuous prophylaxis treatment with BAY 94-9027 is of clinical interest in this study. An observation period shorter than 3 months does not constitute a stable prophylaxis treatment and does not allow a reliable evaluation of annualized bleeding rates. Individuals who develop a FVIII inhibitor or an ADA that neutralizes activity of BAY 94-9027 sufficiently to interfere with effective treatment require other treatment modalities and are therefore excluded from the population of interest. An emergent or an urgent major surgery is a short-term event that requires specific treatment and leads to surgery-specific bleeding episodes. While the surgery period does not contribute to the ABR of prophylaxis treatment, the non-surgery related bleeds and treatment period can and will be evaluated. Bleeds treated with another FVIII product in an emergency case will be counted for the ABR as they occurred during prophylaxis treatment with BAY 94-9027.

Additional secondary estimands for secondary objective are described by the following attributes:

Population	Previously treated (≥50 EDs) male individuals 7 to <12 years of age with severe hemophilia A (FVIII:C <1%) without inhibitors to FVIII (<0.6 BU/mL).
Endpoint	• BAY 94-9027 consumption • Number of infusions/month and year (Annualized Infusion Rate)
Treatment condition	2x/week prophylactic treatment with BAY 94-9027 at a dosage of 40 IU/kg up to 60 IU/kg with option to change to every 5 days prophylactic treatment with BAY 94-9027 at a dosage of 60 IU/kg IV after at least 50 EDs (with start of Part B) with or without emergency use of other FVIII medication (treatment policy strategy*).
Intercurrent events and strategies how to address them	• Discontinuation of BAY 94-9027 treatment due to AESI in the first 4 EDs or any reason during 12 weeks of study period. <u>Principal stratum strategy:</u> Subjects without intercurrent event will be summarized.
	• The intercurrent event 'emergency major surgery' is addressed by the endpoint attribute following the hypothetical strategy*. The time of the surgery will not be considered for the observation period. BAY 94-9027 consumption and infusions during the time of the surgery will not be counted. An individual with this intercurrent event will be analyzed as if the surgery had not happened.
Population level summary	Summary statistics including mean, median, standard deviation, range, Q1, Q3

1.2 Study Design

This is an open-label, single-group, uncontrolled, prospective, multicenter study in male participants aged 7 to <12 years with severe hemophilia A. The study will comprise of the main study (Part A) and the extension study (Part B). Part A will last for 6 months and at least 50 exposure days (EDs). Extension study (Part B) will last 18 months.

The study intervention for Part A will be 40 IU/kg (up to 60 IU/kg at the investigator's discretion), two times per week (2x/week) with the first 4 infusions under medical supervision. Thereafter, participants will continue their treatment as home treatment. Dose may be increased up to 60 IU/kg if needed at any time during the study at the investigator's discretion.

For Part B, adjustments to prophylaxis dose / dose frequency can be made at the investigator's discretion (based on the bleeding events and individual needs). Dose may be increased to 60 IU/kg. Dose frequency may be decreased to every 5 days (prophylaxis dose: 60 IU/kg).

Bleeds will be treated with BAY 94-9027 as per the investigator's instruction.

Analysis of Part A will be conducted after the last participant completes Part A (Visit 11).

A first analysis of Part B data will be conducted after all participants, who do not early discontinue Part B, complete at least 6 months of Part B , only 6-months data from Part B will

be included. A final analysis, contained only data from Part B, will be conducted after the last participant completes Part B.

2. Statistical Hypotheses

Hypothesis testing is not planned for this study. Based on a Bayesian analysis for the primary endpoint, the posterior probability that the true incidence for an AESI is <5% will be estimated.

2.1 Multiplicity Adjustment

Multiplicity adjustment is not applicable since hypothesis testing is not planned for this study.

3. Analysis Sets

Participant Analysis Set	Description
Safety analysis set (SAF Part A)	A participant will be included in the SAF part A if he is enrolled into the part A of the study and has taken at least 1 dose of the study intervention.
Modified safety analysis set (mSAF Part A)	A participant will be included in the modified safety population in part A if he is enrolled into the study and did not discontinue treatment prior to the fourth planned study intervention for any reason other than an AESI.
Intent-to-treat analysis set (ITT Part A)	A participant will be included in the ITT Part A if he is enrolled in Part A of the study, has taken at least 1 dose of study intervention, and has subsequent data for infusions and/or bleeds documented in the EPD.
Modified Intent-to-treat analysis set (mITT Part A)	A participant will be included in the mITT Part A if he is enrolled into Part A of the study, has taken at least 1 dose of study intervention, and has subsequent data for infusions and/or bleeds documented in the EPD for at least 3 months.
Safety analysis set (SAF Part B)	A participant will be included in the SAF part B if he is enrolled into the part B of the study and has taken at least 1 dose of the study intervention in Part B.
Intent-to-treat analysis set (ITT Part B)	A participant will be included in the ITT Part B if he is enrolled into Part B of the study, has taken at least 1 dose of study intervention in Part B, and has subsequent data for infusions/bleeds documented in the EPD.
Modified intent-to-treat analysis set (mITT Part B)	A participant will be included in the mITT Part B if he is enrolled into Part B of the study, has taken at least 1 dose of study intervention in Part B, and has subsequent data for infusions/bleeds documented in the EPD for at least 3 months of Part B treatment duration.

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

4. Statistical Analyses

4.1 General Considerations

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA) and ValidR (version 3.5.2 or higher; Mango Solutions

Ltd., UK). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

The statistical analysis will be performed on cleaned and locked database at the following timepoints:

- Analysis of Part A will be conducted after the last participant completes Part A (completes Visit 11).
- A first analysis of Part B data will be conducted after all participants, who do not early discontinue Part B, complete at least 6 months of treatment in Part B, only 6-month data from Part B will be included.
- Final analysis, contained only data from Part B, will be conducted after the last participant completes Part B (completes Extension Visit 18).

Specifications for tables, listings, and figures are provided in separate documents, namely, TLF Specifications for Part A, and TLF Specifications for Part B.

4.2 Primary Endpoint(s) Analysis

4.2.1 Definition of Endpoint(s)

The primary endpoint for this study is defined as the occurrence of AESI (i.e., hypersensitivity or LoE, as defined in Section 8.3.8 of the protocol) associated with the first 4 EDs of BAY 94-9027 treatment leading to discontinuation.

4.2.2 Main Analytical Approach

See Section 1.1.2.1 for a description of the primary endpoint and estimand.

The mSAF for part A analysis set will be used in this analysis, see Section 3 for the definition of mSAF. As described in Section 1.1.2.1, the primary estimand targets the stratum of participants who do not discontinue treatment with BAY 94-9027 for other reason than an AESI before the fourth exposure day regardless of emergency use of other FVIII medication.

Due to the expected low incidence of AESIs (Santagostino et al., 2020), a Bayesian approach will be used for analysis of the primary endpoint.

The 25 participants from age group 7 to <12 years of PROTECT KIDS study (Study 15912) with 0 AESIs will be utilized along with the n participants and AESIs from this study for the analysis of the probability of an AESI (p), with a total observed sample size of 25 + n = N. The Bayesian model for the analysis is then specified as follows:

r_i ~ Bernoulli (p): occurrence of an AESI in participant $i, i = 1, \ldots, \mathrm{N}$;

p ~ Beta(1/4, 1/4); prior for the probability of an AESI.

The choice of the neutral prior Beta (1/4, 1/4) is to avoid over influence of the prior and limit the degree of polarization of the prior toward 0 and 1. The posterior distribution based on the utilized data will then be Beta(x+1/4, N-x+1/4), where x is the number of participants in the utilized data who experience an AESI.

To note, the above analysis by utilizing the 25 participants from PROTECT KIDS prior to the Bayesian analysis is equivalent to treating the 25 participants with 0 AESIs as historical data

and updating the initial prior Beta (1/4, 1/4) to be Beta (0+1/4, 25+1/4) as the updated prior for the analysis of participants from this study alone.

The safety of BAY 94-9027 will be characterized by the resulting posterior distribution for the probability of AESI, including its mean, median, mode, and 90% two-sided credible intervals. The posterior probability that the incidence of AESI is <5% will be derived.

4.2.3 Sensitivity Analyses

Not applicable.

4.2.4 Supplementary Analyses

Not applicable.

4.3 Secondary Endpoints Analysis

4.3.1 Key/Confirmatory Secondary Endpoints

Secondary endpoints for addressing the primary objective (to assess safety and tolerability of BAY 94-9027 replacement therapy in previously treated patients 7- <12 years of age with severe hemophilia A) which are as follows:

- Adverse drug reactions (ADRs)
- Anti-drug antibody (ADA) development
- Inhibitor development

4.3.1.1 Definition of Endpoints

Definition of secondary endpoints for addressing the primary objective:

- **Adverse Drug Reactions**
  Adverse drug reactions are defined as any adverse events where a causal relationship of at least possibly related with the use of BAY 94-9027 has been ascribed by investigator. In this study, treatment emergent study drug-related adverse events will be used in defining ADRs.
- **Anti-drug antibody development**
  All participants will be tested for the development of anti-drug antibodies (ADAs) (anti- PEG and anti-PEG IgM). Any participants with positive results for ADAs will be flagged.
- **Inhibitor development**
  A positive FVIII inhibitor test is defined with a threshold of ≥ 0.6 BU/mL at the central laboratory. The first positive measurement will be confirmed by a second different sample. After confirmation by the second positive result, such participants will be flagged.

4.3.1.2 Main Analytical Approach

Analysis of secondary endpoints for the primary objective will be based on the SAF part A, and SAF part B analysis sets.

- **Adverse drug reactions**
  The number and proportion of participants with any ADRs (treatment emergent study drug-related AEs), and by system organ class and preferred term will be presented.
- **Anti-drug antibody development**
  The number and proportion of participants with anti-drug antibodies will be presented by baseline anti-PEG status along with by-participant listings for anti-drug antibody development.
- **Inhibitor development**
  The number and proportion of participants with confirmed FVIII inhibitors will be presented by titer (low titer: $\leq$ 5 BU/mL, high titer: $>$ 5 BU/mL) along with by-participant listings for all measurements of FVIII inhibitors. Note that only inhibitors confirmed by a second positive measurement will be considered positive in the analysis, see Section 8.3.9 of the protocol. The listing will show all results.

4.3.1.3 Sensitivity Analyses

Not applicable.

4.3.1.4 Supplementary Analyses

Not applicable.

4.3.2 Supportive Secondary Endpoints

Secondary endpoints for addressing the secondary objective (to describe clinical efficacy of BAY 94-9027) which are as follows:

- Annualized bleeding rate (ABR)
- BAY 94-9027 consumption
- Number of infusions/month and year (Annualized Infusion Rate)

4.3.2.1 Definition of Endpoints

Definition of secondary endpoints for addressing the secondary objective:

4.3.2.1.1 Annualized bleeding rate (ABR)

As described in Section 1.1.2.2, the estimand targets the stratum of participants who receive continuous prophylaxis treatment with BAY 94-9027 for at least 3 months without development of an inhibitory antibody to FVIII or ADA that neutralizes activity sufficiently to interfere with effective treatment. The subsets of participants in the mITT Part A, and mITT Part B analysis sets fulfilling this condition will be used for estimation.

For each participant, the number of bleeds will be related to the individual observation period to assess bleeding rates. For descriptive analyses, bleeding rates will be annualized at the individual participant level using the formula:
ABR = (number of bleeds × 365.25 × 24 × 60)/(*Period*).

Period is defined as the number of minutes calculated from the date and time of the beginning of the treatment period and the date and time of the end of the treatment period of interest. Details in determination of the start and end of treatment period of interest, used in the calculation of ABR, will be provided in ADS specifications as mentioned in 6.9.2.

ABR for the following bleeding types will be examined:

- Total bleeds (spontaneous bleeds + trauma bleeds)
- Spontaneous bleeds
- Trauma bleeds
- Joint bleeds

Determination of bleeding count is described in detail in Section 6.9.3.

4.3.2.1.2 BAY 94-9027 consumption

For each participant, the following endpoints for BAY 94-9027 consumption will be defined using the following formula:

- Total dose (IU) = total dose (IU) received during study period.
- Total dose per infusion (IU) = total dose (IU) received during study period/number of infusions during study period.
- Total dose per kg per infusion (IU) = total dose per kg (IU/kg/infusion) received during study period/number of infusions during study period.
- IU/kg/infusion for prophylaxis
- Total dose per kg (IU/kg) = total dose per kg (IU/kg) received during study period.
- Total dose per year (IU) = (total dose (IU) * 365.25) / (the available period in the study in days).
- Total dose per kg per year (IU/kg/year) = (total dose per kg (IU/kg) * 365.25) / (the available period in the study in days).
- Total dose per bleed (IU) = The number of total dose (IU) used to treat a bleed is defined as the total dose for the first injection to treat the bleed and all the follow-up doses (IU) to treat the same bleed if there is any.
- IU/kg/infusion for treatment of bleeds

4.3.2.1.3 Number of infusions/month and year (Annualized Infusion Rate)

For each participant, the following endpoints for number of infusions will be calculated:

- Total number of infusions during study period
- Number of infusions per year = (total number of infusions during study period * 356.25) / (the available period in the study in days) and by prophylaxis regimen
- Number of infusions per month = (total number of infusions during study period * 30) / (the available period in the study in days) and by prophylaxis regimen
- Compliance based on number of infusions which comprises of number of expected infusions, actual number of infusions, percent compliance based on prophylaxis infusion counts, and percent compliance based on total infusion counts. Additional details for the calculation can be found in Section 6.9.8.

4.3.2.2 Main Analytical Approach

Analysis of secondary endpoints for the secondary objective will be based on the modified ITT analysis sets for Part A, and Part B.

4.3.2.2.1 Bleeding rates

Descriptive statistics (N, mean, median, standard deviation, range, Q1, and Q3) will be used to summarize the number of bleedings (total, treated, spontaneous, trauma, and joints bleedings) along with their corresponding annualized bleeding rates. For mITT Part B analysis set, the descriptive statistics will also be presented by dosing frequency, see Section 6.9.7 for definition of dosing frequency.

In addition, model-based estimates for the bleeding rates will be derived using a Negative Binomial model, where y_i denotes the number of bleeding episodes occurring during the time period t_i (possibly differing time periods of follow-up) for participant $i, i = 1, \dots, n$. Assume that Y_i follows a Negative Binomial distribution with mean μ_i and a common dispersion parameter α. Then μ_i can be modelled as

$$\log \mu_i = \log t_i + \beta_0 ,$$

We thus have

$$\log \mu_i = \log t_i + \beta_0 \Leftrightarrow \frac{\mu_i}{t_i} = \exp(\beta_0).$$

With an estimate for the parameter β_0 the mean rates of events per time unit can be estimated via $\exp(\beta_0)$. This estimate will be provided with its 95% confidence interval.

4.3.2.2.2 BAY 94-9027 consumption

Summary statistics (N, mean, median, standard deviation, range, Q1, and Q3) will be used in summarizing BAY 94-9027 consumption for prophylaxis treatment, for treatment of bleeds, and overall. For mITT Part B analysis set, the descriptive statistics will also be presented by dosing frequency.

Total BAY94-9027 consumption and consumption per infusion will be summarized for mITT Part A, mITT Part B, SAF Part A, and SAF Part B analysis sets for the following:

- Total dose (IU)
- Total dose per infusion (IU/infusion)
- Total dose per kg per infusion (IU/kg/infusion)
- IU/kg/infusion for prophylaxis
- Total dose per kg (IU/kg)
- Total dose per bleed (IU)
- Total dose per kg per year (IU/kg/year)
- IU/kg/infusion for treatment of bleeds

Annualized consumption will be analyzed based on participants in mITT Part A, and mITT Part B analysis sets who are included in the ABR calculation for the following:

- Total dose per year (IU/year)
- Total dose per kg per year (IU/kg/year)

4.3.2.2.3 Number of infusions/month and year (Annualized Infusion Rate)

Descriptive statistics (N, mean, median, standard deviation, range, Q1, and Q3) will be used in summarizing infusion endpoints. For mITT Part B analysis set, the descriptive statistics will also be presented by dosing frequency, as deemed applicable.

For total number of infusions will be presented, based on mITT Part A, and mITT Part B analysis sets.

For number of infusions per month and per year will be presented, based on participants in mITT Part A analysis set who are included in the ABR calculation.

4.4 Tertiary/Exploratory Endpoint(s) Analysis

Exploratory endpoints to be summarized are as follow:

- Bleeding characteristics
- FVIII recovery value (excluding values flagged as invalid) by visit and overall

4.4.1 Definition of Endpoints

4.4.1.1 Bleeding Characteristics

In addition to ABR as described in Section 4.3.2, the following bleeding characteristics will be presented:

- Participants with total bleeds and joint bleeds during treatment, treated bleeds
- Bleeding type, site, location, and severity
- Reason for bleeding treatment
- Bleeding response to BAY 94-9027

4.4.1.2 FVIII Recovery

The terms recovery and incremental recovery are synonymous and are used interchangeably in this context. FVIII levels measured by the chromogenic assay from central laboratory will be analyzed.

Recovery is calculated as shown below:

Recovery = (post-infusion FVIII activity – pre-infusion FVIII activity) * weight / dose (in IU)

The most recent weight measurement at the time of recovery will be used for calculation.

Derivation for FVIII recovery data is described in Section 6.9.4. Also note that if a recovery is flagged as not valid, then the corresponding pre-infusion, post-infusion and recovery value will not be included.

4.4.2 Main Analytical Approach

4.4.2.1 Bleeding Characteristics

Frequency and percentage will be used in summarizing bleeding characteristics endpoints. The analyses will be performed on the modified ITT analysis sets for Part A and Part B of the study, respectively. For mITT Part B analysis set, the summary statistics will also be presented by dosing frequency, as deemed applicable.

4.4.2.2 FVIII Recovery

Descriptive statistics (arithmetic mean, median, arithmetic SD, arithmetic CV, geometric mean, geometric SD, geometric CV, minimum, Q1, median, Q3, and maximum) will be presented for incremental recovery at each scheduled visit and overall, as described in SoA, Section 6.10.

4.5 Safety Analyses

Safety analyses will be performed for SAF Part A, and SAF Part B. All participants receiving any amount of study intervention will be included in the safety analysis.

Laboratory findings, adverse events, concomitant medications, vital signs, and medical history data will be provided in subject listings.

4.5.1 Extent of Exposure

Treatment duration (defined as number of days in study, calculated based on the start and stop date of receiving study intervention), number of EDs will be summarized using descriptive statistics (N, mean, standard deviation, minimum, Q1, median, Q3, maximum, and sum) for SAF Part A, mSAF Part A, mITT Part A, SAF Part B, and mITT Part B analysis sets.

In addition, the following exposure data will be presented:

- Number of prophylaxis infusions
- Total of prophylaxis dose (IU/kg)
- Total number of infusions (EDs)
- Total dose (IU/kg)
- Average dose per infusion (IU/kg/infusion)

Details for calculation for these variables are defined in Section 6.9.8.

4.5.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA terminology. The version number of MedDRA used for the analyses will be stored in the clinical database. A listing will be provided linking the original investigator terms and the coded terms.

Pre-treatment, treatment-emergent, and post-treatment AEs are defined in Section 6.9.5.

The following summaries of AEs will be generated for SAF Part A, and SAF Part B:

- Adverse events: overall summary of number of participants
- Pre-treatment adverse events: overall summary of number of participants
- Post-treatment adverse events: overall summary of number of participants (Part B only)
- Post-treatment adverse events: number of participants by primary system organ class and preferred term (Part B only)
- Treatment-emergent adverse events: overall summary of number of participants
- Treatment-emergent adverse events: number of participants by primary system organ class and preferred term

- Treatment-emergent adverse events by maximum intensity: number of participants by primary system organ class and preferred term
- Treatment-emergent adverse events of special interest: number of participants by primary system organ class and preferred term (also see Section 4.5.3)
- Treatment-emergent adverse events of special interest leading to discontinuation: number of participants by primary system organ class and preferred term
- Treatment-emergent serious adverse events: number of participants by primary system organ class and preferred term
- Treatment-emergent non-serious adverse events (excluding treatment-emergent serious adverse events): number of participants by primary system organ class and preferred term
- Treatment-emergent study drug-related adverse events: number of participants by primary system organ class and preferred term
- Treatment-emergent study drug-related adverse events by maximum intensity: number of participants by primary system organ class and preferred term
- Treatment-emergent adverse events related to procedures required by the protocol: number of subjects by primary system organ class and preferred term
- Treatment-emergent adverse events resulting in discontinuation of study drug: number of participants by primary system organ class and preferred term
- Treatment-emergent serious adverse events resulting in discontinuation of study drug: number of participants by primary system organ class and preferred term
- Deaths: number of participants with treatment-emergent adverse event with fatal outcome by primary system organ class and preferred term
- Deaths: number of participants with treatment-emergent serious adverse event with fatal outcome by primary system organ class and preferred term
- Listings will be provided for participants with SAEs, TEAEs leading to discontinuation for each phase of the study, i.e., pre-treatment, during treatment, and post-treatment for Part A, and Part B.

4.5.3 Adverse Events of Special Interest

Adverse events of special interest (AESI) in this study are:

- Hypersensitivity
- Loss of efficacy associated with anti-PEG antibodies

Details of analysis of AESI as a primary endpoint can be found in Section 4.2.

In addition, number of participants who experience AESI during the study will also be presented based on mSAF Part A, and SAF Part B, along with listings of participants with AESI, as applicable.

4.5.4 Additional Safety Assessments

The following safety variables will be included for safety and tolerability assessment:

- Vital signs (pulse, blood pressure, temperature)
- Physical examination (height, weight, BMI)
- Standard laboratory assessment (hematology, and chemistry)
- Antibodies to BAY 94-9027, PEG and/or FVIII
- Quantitative PEG measurement
- Renal safety related urine and serum biomarkers
- Liver enzymes
- Neurological assessment

Summary of safety variables mentioned above will be summarized using descriptive statistics at baseline, end of Part A and Part B visits, and change from baseline (before first infusion in Part A) for corresponding visits.

Incidence of shift in high or low abnormal values at screening to values below the lower limit of normal or to values above upper limit of normal at the end of the Part A, at the end of Part B, will be presented for laboratory parameters of interest.

By-subject listings of all safety-related laboratory data and a by-subject listing of all abnormal values will be provided.

4.6 Other Analyses

4.6.1 Patient-reported Outcomes

Patient-reported outcomes (PROs) questionnaires used in this study are:

- Haemo-QoL Short Form Questionnaire for children 8-16 years old
  The Haemo-QoL Short Form contains 35 questions covering 9 domains: Physical Health, View of Yourself, Family, Friends, Others, Sports, Dealing, and Treatment.
- Patient/Caregiver Global Impression of Severity and Change
  These 4 instruments are made of one single-item measure. They will explore patient-perceived and caregiver-perceived overall severity and change in health status since the start of study intervention. These instruments will be used to anchor the scores of Haemo-QoL. The participant/parent/legal guardian will complete the questionnaire and the data will be entered in eCRF by the investigator or study site staff.

The summary and analysis are as follows:

- Haemo-QoL: Descriptive statistics for each domain will be presented as follows:
  - For Part A analysis: at baseline, and visits V11 (Month 6) /Early Discontinuation along with corresponding change from baseline
  - For the first analysis of Part B: at baseline, and EV6 (Month 12) /Early Discontinuation along with corresponding change from baseline

  - For the final analysis of Part B: at baseline, EV6 (Month 12), EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation along with corresponding change from baseline.

- Patient Global Impression of Severity (PGIS), Caregiver Global Impression of Severity (CGIS): Frequencies and percentages of participants in the different PGIS, CGIS categories will be presented as follows:
  - For Part A analysis: at baseline, visits V11 (Month 6)/Early Discontinuation
  - For the first analysis of Part B: at baseline, and EV6 (Month 12) /Early Discontinuation
  - For the final analysis of Part B: at baseline, EV6 (Month 12), EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation.
  - Frequencies and percentages of participants for change categories in PGIS, and CGIS from baseline (e.g., unchanged, improved by x categories (where x = 0, 1, 2, 3, and 4), deteriorated by x categories, etc.) will be presented as follows:
    For Part A analysis: visits V11 (Month 6)/Early Discontinuation
    For the first analysis of Part B: EV6 (Month 12)/Early Discontinuation
    For the final analysis of Part B: EV6 (Month 12), EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation.
- Patient Global Impression of Change (PGIC), Caregiver Global Impression of Change (CGIC): Frequencies and percentages of participants in the different PGIC, CGIC categories will be presented as follows:
  - For Part A analysis: at visits V11 (Month 6)/Early Discontinuation
  - For the first analysis of Part B: EV6 (Month 12) /Early Discontinuation
  - For the final analysis of Part B: EV6 (Month 12), EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation.
- Patient/Caregiver Global Impression of Severity and Change will be used to anchor the scores of Haemo-QoL and/or change from baseline for each post-baseline visit with available data. The summary will be presented as follows:
  - For Part A analysis: at baseline, visits V11 (Month 6)
  - For the first analysis of Part B: at baseline, and EV6 (Month 12)
  - For the final analysis of Part B: at baseline, EV6 (Month 12), EV12 (Month 18), and EV18 (Month 24)/Early Discontinuation.

4.6.2 Subgroup Analyses

Subgroup analyses will not be performed for this study.

4.7 Interim Analyses

An interim analysis within a group sequential or adaptive design is not planned for this study.

Analysis of Part A will be conducted after the last participant completes Part A.

A first analysis of Part B data will be conducted after all participants, who do not early discontinue Part B, complete at least 6 months of Part B, only 6-month data from Part B will be included.

A final analysis, contained only data from Part B, will be conducted after the last participant completes Part B.

4.8 Changes to Protocol-planned Analyses

Not applicable.

5. Sample Size Determination

The selection of the sample size of 30 is based on the assumption that less than 5% of participant out of 30 will experience an AESI and that the data will be pooled with 25 participants from the age group of 7 to <12 years of study 15192 (PROTECT KIDS) for analysis of the incidence of AESIs. Additional participants may be enrolled in the event of treatment discontinuation during the first 4 EDs of Part A for reasons other than AESI.
A Bayesian beta-binomial model with each participant having an AESI as a Bernoulli response and a neutral prior probability distribution Beta (1/4,1/4) is used. The choice of the neutral prior Beta (1/4,1/4) is to avoid over influence of the prior and limit the degree of polarization of the prior toward 0 and 1.
Under these assumptions, the posterior probability that the true incidence for an AESI is <5% will be > 90%.
Details are described by the following scenarios:

- If none participant out of 30 from the new study experience an AESI, then with the Bayesian analysis mentioned above, it is calculated that the median of the posterior distribution of the true incidence of AESI is <0.1% and there is >99% posterior probability that the true incidence of AESI is <5%.
- If 1 participant out of 30 from the new study experience the AESI, it is calculated by a Bayesian beta-binomial inference with a prior of Beta (1/4,1/4) for the pooled 55 participants that the median of the posterior distribution of the true incidence of AESI is 1.7% and there is 91% posterior probability that the true incidence of AESI is <5%.
- If 2 participants out of 30 from the new study experience the AESI, then the median of the posterior distribution of the true incidence of AESI is 3.5%, and there is 71% posterior probability that the true incidence of AESI is <5%.
- If 3 participants out of 30 from the new study experience the AESI, then the median of the posterior distribution of the true incidence of AESI is 5.4%, and there is 46% posterior probability that the true incidence of AESI is <5%.

6. Supporting Documentation

6.1 Appendix 1: List of Abbreviations

Abbreviation	Definition
ABR	Annualized bleeding rate
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical

BMI	Body mass index
BU/mL	Biological units/milliliter
CGIC	Caregiver Global Impression of Change
CGIS	Caregiver Global Impression of Severity
CI	Confidence interval
DMC	data monitoring committee
ED	Exposure day
EMA	European Medicines Agency
FDA	US Food and Drug Administration
ICH	International Council on Harmonization
IgM	Immunoglobulin M
IU	International unit
kg	Kilogram
LloQ	Lower limit of quantification
LoE	Loss of efficacy
MedDRA	Medical dictionary for regulatory activities
ITT	Intent-to-treat
mITT	Modified intent-to-treat
mL	Milliliter
PEG	Polyethylene glycol
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	Patient-reported outcome
PTP	Previously treated patients
SAE	Serious adverse event
SAF	Safety analysis set
mSAF	Modified safety analysis set
SAP	Statistical Analysis Plan
SMQs	Standardized MedDRA queries
SMQ	Standard MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
TLF	Tables, listings, and figures
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

6.2 Appendix 2: Participant Dispositions

Participant dispositions will be summarized as follows:

- Screening:
  - Number of participants screened
  - Number and percent of participants did not complete screening along with primary reason for not completing screening period
- End of Part A study period:
  - Number of participants enrolled in the study
  - Number and percent of participants received study intervention
  - Number and percent of participants enrolled but never received study intervention

  - Number and percent of participants discontinued the study intervention within the first 4 EDs along with primary reason for discontinuation
  - Number and percent of participants completed Part A (completed Visit 11)
  - Number and percent of participants discontinued the study intervention during Part A study period along with primary reason for discontinuation
- First Analysis of Part B
  - Number and percent of participants received study intervention in Part B
  - Number and percent of participants discontinuing the study intervention in Part B with in the first 6 months along with primary reason for discontinuation
  - Number and percent of participants completed 6 months of Part B
- End of study (end of Part B)
  - Number and percent of participants complete study intervention
  - Number and percent of participants discontinuing the study intervention in Part B along with primary reason for discontinuation
  - Number and percent of participants who complete study intervention but not follow-up visit

In addition, the following will be summarized:

- For analysis of Part A:
  - Number and percent of participants valid for SAF Part A
  - Number and percent of participants valid for mSAF Part A
  - Number and percent of participants valid for ITT Part A
  - Number and percent of participants valid for mITT Part A
  - Number of participants by country and site
- First analysis of Part B
  - Number and percent of participants valid for SAF Part B
  - Number and percent of participants valid for mITT Part B
  - Number and percent of participants valid for ITT Part B
- For final analysis
  - Number and percent of participants valid for SAF Part B
  - Number and percent of participants valid for mITT Part B
  - Number and percent of participants valid for ITT Part B

6.3 Appendix 3: Baseline Characteristics and Demographics

Demographics and baseline characteristics will be summarized by using descriptive statistics (N, mean, median, standard deviation, range, Q1, and Q3) for metric variables and frequency tables will be presented for categorical variables. The summaries will be presented for SAF

Part A, mSAF Part A, ITT Part A, mITT Part A, ITT Part A, SAF Part B, and mITT Part B analysis sets.

Demography includes age, gender, race, ethnicity, body height, body weight, body mass index (BMI).

The following additional baseline disease characteristics will be analyzed: previous exposure to FVIII, joint status, and disease history.

6.4 Appendix 4: Protocol deviations

The number of patients with validity findings and important deviations will be presented overall and by investigator. The frequencies of each important deviation and other findings will also be presented.

6.5 Appendix 5: Medical history

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes. Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT), summarized using frequency counts. The summaries will be presented for SAF Part A, ITT Part A, mITT Part A, and SAF Part B analysis sets.

6.6 Appendix 6: Concomitant Medication

Prior, new, and concomitant medications will be coded by Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD) will be summarized using frequency counts. The summaries will be presented for SAF Part A, ITT Part A, mITT Part A, and SAF Part B analysis sets.

6.7 Appendix 7: Handling of Dropouts

A participant who discontinues study participation prematurely for any reason is defined as a dropout if the participant has already been administered at least one dose of study drug.

The reasons for withdrawal will be listed in a table. Dropouts will be included in all safety analyses. They will also be included in efficacy analyses if the treatment duration is >= 3 months. The ABR will be calculated for these participants. It is assumed that a shorter treatment duration will not be sufficient to correctly estimate the ABR and would bias the results. When calculating ABRs, the end of the measuring period for a dropout is defined as the later of last available infusion record from the electronic patient diary (ePD) or the last procedure in a scheduled visit, excluding the final visit.

6.8 Appendix 8: Handling of Missing Data

All missing or partial data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF) or EPD.

In general, as appropriate, the following imputation rules will be implemented so as not to exclude participants from statistical analyses due to missing or incomplete data:

- **Missing time of infusions or bleeds**
  If an in-hospital infusion has a missing time, the time of the pre-infusion FVIII level measurement plus 1 minute will be used. If this time is also missing, 10:00 will be substituted.

The EPD is designed to allow the collection of date and time for each infusion or bleed. If a bleed has a missing date or time, then the date of the associated infusion will be used as the bleed date or time. If the infusion for a bleed has a missing date or time, then the date and time of the bleed will be used to determine the infusion date or time.

- **Missing or incomplete adverse event (AE) start date**
  If there is no information regarding the AE start day, or there is partial information in comments that AE starts after treatment, the missing AE start day will be imputed as first day of dosing in the clinic at Visit 2. If there is information that the AE occurs before the first treatment, we will use the date of the day before the first treatment day to impute.
  If an AE start date has year and month but missing day, then the first day of the month will be used to impute the AE start date. However, if the month and year are the same month and year of the first dose date then the first dose date will be used. If an AE start date has year and day but missing month, then the first month of the year will be used to impute the AE start date given that the year is after the year of the first dose date.
  If an AE start date has year only, then the first day of the year will be used to impute the AE start date given that the year is after the year of the first dose date. However, if the year is the same as the year of the first dose date, then the start date of such AE will be the same as the first dose date.
  Missing end date for an AE will not be imputed and AE will be presumed to be ongoing.

- **Missing or incomplete concomitant medication start and end date**
  If a concomitant medication start date has year and month but missing day, then the first day of the month will be used to impute the concomitant medication start date. If a concomitant medication start date has year and day but missing month, then the first month of the year will be used to impute the concomitant medication start date. If an concomitant medication start date has year only, then the first day of the year will be used to impute the concomitant medication start date.
  Partially missing dates of medications categorized as ‘PRIOR FVIII THERAPY’ will not be imputed.

6.9 Appendix 9: Data Derivation Rules

6.9.1 Baseline and Change from Baseline

Baseline for both Parts, A and B, is defined as the last non-missing measurement prior to, or (in absence thereof) on the same day of, the first dose of the corresponding Parts A.

Change from baseline will be displayed as the difference to baseline defined as:

Change = Post baseline value – baseline value.

6.9.2 Determination of Start and End of Period or Treatment

Derivations for start of Part A, end of Part A, end of Part A treatment, start of Part B, end of Part B, end of Part B treatment, start of surgery interval, and end of surgery interval will be described in ADS specifications.

6.9.3 Bleeding Data

The following derivation rules will be applied to bleeding data in this study:

Counting of bleeds:

- 'All treated bleeds' will include all treated spontaneous and treated trauma bleeds
- 'All bleeds' will include all bleeds, regardless of treated or untreated (untreated bleeds will only be available from the study)

Annualized Bleeding Rate (ABR):

ABR will be calculated for those participants who have at least 3 months of infusion/bleeding EPD data. The following formula will be used in the calculation of ABR:

$$\text{Annualized Bleeding Rate} = \frac{\#\text{ of bleeds} \times 365.25 \times 24 \times 60}{\text{Period}}$$

Period is defined as the number of minutes calculated from the date and time of the beginning of the treatment period of interest and the date and time of the end of the treatment period of interest. Details in determination of the start and end of treatment period of interest, used in the calculation of ABR, will be provided in ADS specifications as mentioned in 6.9.2.

Evaluation periods for the study will be:

- Part A period
- Part B period

24-hour rule:

All bleeds that occur during the same calendar day will be considered as one bleed. Priority will be determined according to the following order:

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

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

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

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

72-hour rule:

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

apply. The rule operates with date/time and bleed locations adjusted by 24-hour rule. Bleeds eliminated by 24-hr rule are not considered.

Joint bleed:

Joint bleeds can occur in more than 1 joint site. When counting sites for the joint bleeds, all sites will be counted. Data reflecting joint site frequencies will include the frequencies over all sites.

6.9.4 FVIII Recovery

FVIII levels measured by the chromogenic assay will be analyzed.

Incremental recovery is calculated as shown below:

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

The most recent weight measurement will be used for calculation.

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

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

- If pre-infusion FVIII is equal to or greater than the 15-minute post-infusion FVIII value
- 15-minute post-infusion FVIII value is below the LLOQ
- Positive inhibitor result at time of measurement
- FVIII value > 300%

The presence of positive ADAs may affect the recovery results. To assess the impact of positive transient ADAs, FVIII level measurements at the time of a positive ADA will be kept included for the analysis of recovery by visit.

In addition, recovery results will be analyzed across visits. For this analysis, FVIII level measurements at the time of a positive ADA will not be considered. This will provide an estimate of recovery in the absence of antibodies.

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

6.9.5 Adverse Events

Pre-treatment Adverse Events

Any adverse events reported prior to the start of study intervention will be considered pre-treatment adverse events.

Treatment-emergent Adverse Events

For Part A study period, treatment-emergent AEs (TEAEs) are defined as follows:

- TEAEs start after the first dose of study intervention up to prior the start of the first dose for Part B.
- For any participant who prematurely discontinues from the study during Part A of the study, TEAEs occur within 7 days after the last dose of study intervention.

For Part B study period, TEAEs are defined as follows:

- TEAEs start after the first dose of study intervention of Part B up to 7 days of the last study intervention.

Post-treatment Adverse Events

Any AEs occur after 7 days of the last dose of study intervention or after the first dose of other FVIII will be classified as post-treatment AEs.

6.9.6 Haemo-QoL Scoring Manual

SCORING MANUAL

To correctly score the questionnaires, each version has to be identified and the appropriate scoring list has to be selected. Basically, high score represent low quality of life and scoring involves the following steps:

1. Assorting numbers to the response scale, which is for age group II and III
   1= never, 2=seldom, 3=sometimes, 4=often, 5=all the time
   Please note: for the age group I, scoring is 1=never, 2=sometimes, 3=very often
   For negatively worded items, the above classification can be applied in which higher values represent a lower quality of life. For positively worded items, the score has to be recoded (see below).
2. Recoding positively worded items
   Each item identified with a "R" has to be recoded so that numeric values assigned are reversed:
   1=all the time, 2=often, 3=sometimes, 4=seldom, 5= never (for age groups II and III)
   Note: for age group I, it is 1= very often, 2=sometimes, 3= never
   By recoding, high scores in positively worded items reflect not higher but lower quality of life. The then unidirectional values can subsequently be added to yield the summed scores according to the Scoring list for the respective questionnaire.
3. Using the Scoring List [https://haemoqol.de/scoring/scoring-list/] it is necessary to identify which items belong to a subscale. Items to be recoded (see step 2) are marked with an "R."
4. Summing up the items belonging to a subscale yields the raw score per subscale. Its range lies between the lowest possible (number of items (n) × 1) and highest possible (number of items(n) × 5 in the older; or × 3 for the youngest) value of the respective scale.
5. Comparing scores across subscales is possible. If this raw score is divided by the number of items in the scale, the resulting standardized scale score can have any (also decimal) value between 1 and 5 (or 3 for the youngest). A value of 1 represents the highest possible quality of life rating and a value of 5 (or three for the youngest) the lowest possible quality of life rating of the patient.

6. Transferring a raw score to a transformed scale score between 0 and 100 makes it possible to express the scale score in percent between the lowest (0) and the highest (100) possible value. To obtain the transformed scale score (TSS) the following transformation rule has to be applied:

$$TSS = \frac{100 \times (\text{raw score} - \text{minimal possible raw score (of the subscale)})}{\text{possible range of raw scores (of the subscale)}}$$

Example:

In age group II, a raw score of 20 on the "Physical Health" Scale is to be transformed:

Minimal possible raw score = 7

Possible range of raw scores = maximal possible raw score - minimal possible raw score = 35 – 7 = 28

$$TSS = \frac{100 \times (20 - 7)}{28} = 46.43$$

7. Producing the Total score of the specific Haemo-QoL age group version involves the addition of the subscale scores of a person using all items (instead of the subscale items only) of the questionnaire (again paying attention to the recoding procedure – see steps 1 and 2). Items may be added to form a total raw score (according to step 4, but using all items), a total standardized score (according to step 5, but using all items) or a total transformed score (according to step 6, but using all items)
8. Accumulating the values of more than one person – e.g., a patient group - may be done by summarizing the subscale and/or total scores of each individual in that group (on the level of raw, standardized or transformed scores) and dividing the respective result through the number of patients to produce the mean score of the group.

NOTE: The above-described scoring by hand may be made easier by using a scoring mask that can be easily produced from the scoring list (see step 3). In addition, the enclosed SPSS computer program routines can be used. To work with them, patient data have to be inputted into the computer and identified by variable names and labels, which are also suggested in the enclosed programs.

THE SCORING LIST

Scoring is easy since the items are already assorted within the subscales they belong to. Each subscale is identified by a title (heading) and items in each subscale are numbered starting with 1. To identify the item wording, the item number 4 (e.g.) in subscale Physical Health is the fourth item in that scale.

The scoring for each age group version applies both to the children and to the parent’s questionnaire of that age group.

The following information is given for each age group version, beginning with the version for Children I (8 subscales). This questionnaire is an exception because it is rather short (21 items), uses only 3 rather than 5 response choices and should be conducted as an interview.

The Children II long version contains 64 items, 5 response choices and 9 subscales. The Adolescent III version contains 77 items, 5 response choices and 11 subscales. For Children II and Adolescents III, it is possible to use a 35-item short version, which retains the scale structure and contains 9 subscales with identical items for both age groups. This version is

still experimental and needs to be tested psychometrically in upcoming studies. In addition, work in progress is ongoing with regard to the development and testing of an ultra-short 16-item version, identical for all 3 age groups, which will not yield scale scores but only a total score.

The following scoring list is applicable to children's and parents' long versions and will be described for each age group (I, II, III), followed by the 35-item short version for the age groups II and III.

INTERPRETATION OF HAEMO-QoL SCORES

Scale-based scoring: Haemo-QoL scale scores and total scores are available after scoring. Using standardized scores, each patient's subscale score can be compared across subscales and a total score can be identified with the anchors of the scale. Scores reaching 3 (for children age group I) or 5 (for age groups II and III) suggest high impairment in quality of life, while scores nearing 1 suggest low impairment and therefore a positive quality of life rating. Using transformed scales ranging from 0 to 100, the similarity with percent values is helpful for the interpretation; again, high scores (nearing 100) indicate a low quality of life rating. Raw scores are more difficult to interpret, because the range of the subscale –which differs from subscale to subscale depending on the number of items has to be included.

Reference groups-based scoring: In addition to an interpretation according to the location of the subscale score within the range of possible values, a comparison with reference scores is possible (e.g., as described in the Haemo-QoL final report. If questionnaire data are computer inputted and scored, this data bank can be used to statistically test differences in scores according to patient groups (e.g., according to treatment strategies) or over time (e.g., before and after change of treatment). Using variance analytical or correlational statistical procedures, the relationship between patient self-report and parent rating can be examined.

Evidence-based scoring: Since the Haemo-QoL database is still growing, clinical information is not yet sufficient to define cut-off scores for critical quality of life impairment. Also, the prognostic benefit of a subscale or total score remains to be researched in upcoming studies.

6.9.7 Dosing Frequency

Per Section 6.1, Table 6-1 of the protocol, those participants continue to Extension study (Part B), adjustments to dose frequency can be made at the investigator's discretion (based on the bleeding events and individual needs). Dosing frequency categories for Part B will be defined for the first analysis of Part B (see Section 4.7 for additional details) and the final analysis as follows:

For the first analysis of Part B (6 months data):

- Twice a week: No change in dosing frequency in Part B regardless of whether the prophylaxis dose has been changed. Additional preventative prophylaxis infusions may be given without changing the 2x/week regimen.
- Every 5 days: Dosing frequency decreased per investigator's discretion, must be done within the first 4 weeks of extension period (Part B), and participants remain in this dosing frequency throughout the first 6 months of Part B or until discontinuation if treatment duration was at least 3 months.

- Variable frequency: Those participants who switch back from every 5 days to twice a week during Part B or those participants who do not meet the criteria to be categorized into twice a week or every 5 days category.

For the final analysis of Part B only:

- Twice a week: Participants must receive twice a week regimen, regardless of prophylaxis dose change, for at least 80% of total duration in Part B which must be at least three months.
- Every 5 days: Dosing frequency decreased per investigator's discretion and participants must be treated with every 5 days regimen for at least 80% of total duration in Part B which must be at least three months.
- Variable frequency: Those participants who switch back from every 5 days to twice a week during Part B after receiving every 5 days for more than 4 weeks or those participants who were treated with either every 5 days or twice a week regimen for less than 80% of total Part B duration.

6.9.8 Compliance and Exposure

Compliance:

- Compliance (%) based on prophylaxis infusion count = (Actual prophylaxis infusions / Expected_ED) * 100%
- Compliance (%) based on total infusion count = (Actual_Total_infusions / Expected_ED) * 100%
- Compliance (%) based on prophylaxis dose (IU/kg) = (Actual_IU kg for prophylaxis / Expected_IU_kg) * 100%
- Compliance (%) based on dose (IU/kg) = (Actual_Total_IU_kg / Expected_IU_kg) * 100%

Exposure:

- Expected total number of infusions (EDs) = Sum of { interval_duration * interval_planned_frequency }
- Expected total dose (IU/kg) ED = Sum of { interval_duration * interval_planned_dose }
- Actual number of prophylaxis infusions (EDs) = Count of { prophylaxis_dates }
- Actual total of prophylaxis dose (IU/kg) = Sum of { prophylaxis_dose_per_weight }
- Actual total number of infusions (EDs) = Count of { infusion_dates }
- Actual total dose (IU/kg) = Sum of { infusion_dose_per_weight }
- Average actual dose per infusion (IU/kg/infusion) = Actual total dose (IU/kg) / Actual total number of infusions

6.9.9 LLOQ

For any LLOQ value of a laboratory parameter provided as characters, e.g. <x.xx, where x's are any numbers from 0 to 9, the value of x.xx/2 will be used in the analysis instead. For example, LLOQ value of <0.016, then 0.16/2 = 0.08 will be used instead.

6.10 Appendix 10: Schedule of Activities (SoA)

Table 6-1: Schedule of Activities - main study (Part A)

Period	**SCR**	**Treatment**									
Visit number **Exposure day (ED)**	**V1**	**V2** **ED1**	**V3** **ED2**	**V4** **ED3**	**V5** **ED4**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11** **ED 50 /E.Disc.**
In person (IP) or phone call	**IP**	**IP**	**IP**	**IP**	**IP**	**IP or ☎[a]**	**IP**	**IP**	**☎**	**IP**	**IP**
Relative time **W = week, D=day**	**Up to - 30 Days**	**D1 (BSL)**	**W1**	**W2**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W26 (Month 6)**
Allowed window		±1 days for all visits from V2 to V5, inclusive				±3 days for all visits from V6 to V11, inclusive					
Informed consent/assent	X										
Check inclusion/exclusion criteria	X	X									
Demography	X										
Physical examination (height and weight)	X							X			X
Neurological assessment		X [b]									X
Medical and surgical history	X										
Previous and concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X [c]	X [c]	X [c]	X [c]						X
Haemo-QoL questionnaire [d]		X									X
Patient/Caregiver Global Impression of Severity		X									X
Patient/Caregiver Global Impression of Change											X
Laboratory assessments (chemistry and hematology) [e]	X	X [f]									X
PEG quantification		X [b]									X
Urine / serum biomarkers for renal function		X [b]									X
Immunogenicity (FVIII inhibitor, ADA) – pre-infusion [g,h]	X	X	X	X	X		X				X
FVIII levels [g] if no prior result available (Section 5.1 of	X										

Table 6-1: Schedule of Activities - main study (Part A)

Period	**SCR**	**Treatment**									
Visit number **Exposure day (ED)**	**V1**	**V2** **ED1**	**V3** **ED2**	**V4** **ED3**	**V5** **ED4**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11** **ED 50 /E.Disc.**
In person (IP) or phone call	**IP**	**IP**	**IP**	**IP**	**IP**	**IP or ☎[a]**	**IP**	**IP**	**☎**	**IP**	**IP**
Relative time **W = week, D=day**	**Up to - 30 Days**	**D1 (BSL)**	**W1**	**W2**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W26 (Month 6)**
Allowed window		±1 days for all visits from V2 to V5, inclusive				±3 days for all visits from V6 to V11, inclusive					
the Protocol Amendment 2)											
Recovery (pre and 15-30 min post-infusion FVIII levels) [g,h,i]		X	X	X	X						X
In-hospital infusion of BAY 94-9027		X	X	X	X						X [j]
AE review	X [k]	X	X	X	X	X	X	X	X	X	X
Dispense study intervention [l]					X		X	X	X	X	(X) [m]
Return used /unused study intervention							X	X		X	X
Diary review [n]			X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies (anti-PEG, anti-PEG IgM in all treated study participants; IgE only in study participants who experience a hypersensitivity reaction) ED = exposure days, BSL = baseline, E.Disc. = early discontinuation, FVIII = factor VIII, IP = in-person visit, QoL = Quality of Life, SCR = screening, V = visit,

a: At the investigator's discretion based on participant's condition.
b: May be performed at a visit other than baseline if the participant is already enrolled at the time Amendment 1 is implemented, PEG quantification and urine/serum biomarkers must be performed before infusion at the scheduled visit.
c: Vital signs to be taken before and after infusion.
d: QoL questionnaire: Haemo-QoL Kids Short Form (8-16 years old version).
e: See Section 10.2 of the Protocol Amendment 2 for details on laboratory parameters.
f: Only chemistry collected at Visit 2
g: FVIII level and FVIII inhibitor tests must be done after a sufficient wash-out period depending on the participant's previous FVIII product – at least 48 hours or 72 hours for standard half-life (SHL) and extended half-life (EHL) FVIII products respectively (screening and baseline visits).
h: FVIII inhibitor tests and pre-infusion FVIII levels for recovery must be done after a wash-out period of at least 72 hours after previous dose of study intervention (V3, V4, V5, V7, and V11/E.Disc.). If a 72-hour wash-out period is not possible (e.g. participant received previous infusion within 48 hours), no restriction is needed during the first 4 EDs or at any visits for monitoring of ADA. In this scenario, recovery should also be measured without wash-out.
In case of early discontinuation, recovery is not required.
i: Local FVIII levels should be obtained to guide treatment for the next dose during the first 4 EDs.
j: In-hospital infusion will not be performed at early discontinuation visits for adverse events of special interest (hypersensitivity or loss of efficacy) or other reasons.
k: Only study procedure related AEs.
l: Unscheduled visits are permitted at any time at the discretion of the investigator. In addition, participants may visit the study center for study intervention and supplies.

Table 6-1: Schedule of Activities - main study (Part A)

Period	**SCR**	**Treatment**									
Visit number **Exposure day (ED)**	**V1**	**V2** **ED1**	**V3** **ED2**	**V4** **ED3**	**V5** **ED4**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11** **ED 50 /E.Disc.**
In person (IP) or phone call	**IP**	**IP**	**IP**	**IP**	**IP**	**IP or ☎[a]**	**IP**	**IP**	**☎**	**IP**	**IP**
Relative time **W = week, D=day**	**Up to - 30 Days**	**D1** **(BSL)**	**W1**	**W2**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W26** **(Month 6)**
Allowed window		±1 days for all visits from V2 to V5, inclusive				±3 days for all visits from V6 to V11, inclusive					

m: Drug dispensing for extension study (Part B).
n: Dispense diary at V2.

Table 6-2: Schedule of Activities – extension study (Part B)

Extension visit number	**EV1–EV2**	**EV3**	**EV4–EV5**	**EV6**	**EV 7–EV 11**	**EV 12**	**EV 13–EV 17**	**EV 18 / E. Disc.**	**Follow-up[a]**
In person (IP) or phone call	☎	IP	☎	IP	☎	IP	☎	IP	☎
Month and allowed window	**Months 7-8[b]** ± 1week	**Month 9** ± 1week	**Months 10-11[b]** ± 1week	**Month 12** ± 1week	**Months 13-17[b]** ± 1week	**Month 18** ± 1week	**Months 19-23[b]** ± 1week	**Month 24** ± 1week	**7 to 14 days after EV18 / E. Disc.**
Physical examination (height and weight)		X		X		X		X	
Neurological assessment								X	
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs				X		X		X	
Immunogenicity (FVIII inhibitor, ADA) [c]				X		X		X	
Recovery (pre and 15-30 min post-infusion FVIII levels) [c]				X		X		X	
In-hospital infusion of BAY 94-9027				X		X		X [d]	
AE review	X	X	X	X	X	X	X	X	X
Return used/ unused study intervention		X		X		X		X	
Dispense study intervention [e]	Intervention dispensed according to IxRS specification								
Diary review	X	X	X	X	X	X	X	X	
Haemo-QoL questionnaire [f]				X		X		X	
Patient/Caregiver questionnaires [g]				X		X		X	
Laboratory assessments (chemistry and hematology) [h]								X	
PEG quantification								X	
Urine/serum biomarkers for renal function								X	

ADA = anti-drug antibodies (anti-PEG, anti-PEG IgM in all treated study participants; IgE only in study participants who experience a hypersensitivity reaction), ED = exposure days, E.Disc. = early discontinuation, EV = extension visit, FVIII = factor VIII, IP = in-person visit

a: Follow-up call for early discontinuation in Part A and Part B.

b: One phone call per month for all months included in this window of time.

c: FVIII inhibitor tests and pre-infusion FVIII levels for recovery must be done after a wash-out period of at least 72 hours after previous dose of study intervention (EV6/E.Disc.).

Table 6-2: Schedule of Activities – extension study (Part B)

Extension visit number	**EV1–EV2**	**EV3**	**EV4–EV5**	**EV6**	**EV 7–EV 11**	**EV 12**	**EV 13–EV 17**	**EV 18 / E. Disc.**	**Follow-up[a]**
In person (IP) or phone call	☎	IP	☎	IP	☎	IP	☎	IP	☎
Month and allowed window	**Months 7-8[b]** ± 1week	**Month 9** ± 1week	**Months 10-11[b]** ± 1week	**Month 12** ± 1week	**Months 13-17[b]** ± 1week	**Month 18** ± 1week	**Months 19-23[b]** ± 1week	**Month 24** ± 1week	**7 to 14 days after EV18 / E. Disc.**

d: In-hospital infusion not performed at early discontinuation visits for adverse events of special interest (hypersensitivity or loss of efficacy) or other reasons.
e: Unscheduled visits are permitted at any time at the discretion of the investigator. In addition, participants may visit the study center for study intervention and supplies.
f: QoL questionnaire-: Haemo-QoL Kids Short Form (8-16 years old version).
g: Patient/Caregiver Global Impression of Severity and Patient/Caregiver Global Impression of Change.
h: See Section 10.2 of the protocol for details on laboratory parameters.

7. References

Not applicable.