Statistical Analysis Plan

NCT Number: NCT03370172

Title: A Global, Open-Label, Multicenter, Phase 1/2 Study of the Safety and Dose Escalation of BAX 888, an Adeno-Associated Virus Serotype 8 (AAV8) Vector Expressing B-Domain Deleted Factor VIII (BDD-FVIII) in Severe Hemophilia A Subjects Administered a Single Intravenous Infusion

Study Number: 201501

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STATISTICAL ANALYSIS PLAN

TAK-754 / BAX888
PHASE 1/2

STUDY TITLE: A Global, Open-Label, Multicenter, Phase 1/2 Study of the Safety and Dose Escalation of BAX 888, an Adeno-Associated Virus Serotype 8 (AAV8) Vector Expressing B-Domain Deleted Factor VIII (BDD-FVIII) in Severe Hemophilia A Subjects Administered a Single Intravenous Infusion

STUDY SHORT TITLE: Safety and Dose Escalation Study of an Adeno-Associated Viral Vector for Gene Transfer in Hemophilia A Subjects

PROTOCOL IDENTIFIER: 201501

Study Sponsor(s):
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Baxalta is now part of Takeda

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	23MAR2023	Based on Protocol Amendment 9
2.0	15Nov2023	Updated section 11.2 in SAP to indicate: "Reference start date is defined as the date of administration of BAX888 and will be referred to as Study Day 1." Instead of "Reference start date is defined as last non-missing date **prior to administration** the administration of BAX888 and will be referred to as Study Day 1". **Changed the "**$Study\ Day = (Date\ of\ Event - Reference\ Start\ Date)$" to "$Study\ Day = (Date\ of\ Event - Reference\ Start\ Date)$ +1 (if the date of the event is on or after the reference start date)".

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ABBREVIATIONS

ABR	Annualized Bleed Rate
AE	Adverse Event
BMI	Body Mass Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	EuroQol-5D
FVIII	Factor VIII
HaemoPREF	Patients' preference for hemophilia treatment questionnaire
Haemo-QoL-A	Hemophilia-Specific Quality of Life Index
IgG	Immunoglobulin G
ITT	Intention-To-Treat
IV	Intravenous
LFT	Liver Function Tests
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of The Mean
SF-36v2	36-item Short Form survey version 2
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analogue Scale
VERITAS-Pro	Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis
WHODD	World Health Organization (WHO) Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, efficacy, and pharmacodynamic (PD) data as described in the final study protocol 201501 dated 10 November 2021 incorporating most recent amendment 9. Specifications for tables, figures, and listings are contained in a separate document. There are no pharmacokinetic/pharmacodynamic and/or health economics and outcome research data collected that require separate analyses plans. All planned Analyses are included in this SAP.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives and Purpose

To evaluate the safety and determine the dose of BAX 888 required to achieve Factor VIII (FVIII) activity levels ≥20% of normal in severe hemophilia A subjects.

2.1.1 Primary Objective

To evaluate the safety of a single intravenous (IV) infusion of BAX 888 in 3 dose cohorts.

2.1.2 Secondary Objective(s)

1. To evaluate plasma FVIII levels pre- and post-BAX 888 infusion and investigate the relationship between FVIII activity and BAX 888 dose.

2. To determine the BAX 888 dose needed to achieve FVIII activity level of ≥20% of normal in ≥60% of the subjects.

3. To collect bleeding rate and consumption of exogenous FVIII after gene transfer.

4. To assess humoral and cellular immune responses to FVIII and the AAV8 viral capsid.

5. To determine the duration of BAX 888 genome presence in blood, saliva, semen, urine and stool.

2.2 Estimands

For the primary safety endpoints estimands are not formally defined.

For efficacy endpoints, descriptive summaries will be provided by following the "While on treatment strategy". The treatment period includes all time data collected after investigational product infusion.

2.3 Outcome Measures

2.3.1 Primary Endpoint

The primary endpoint is the incidence of BAX 888-related adverse events (AE) (serious or non-serious) that includes development of FVIII inhibitory antibodies, clinically significant changes in standard laboratory parameters, physical exam, and vital signs that are reported as AEs.

2.3.2 Secondary Outcome Measures

2.3.2.1 Efficacy

1. Circulating plasma FVIII activity and antigen levels.
2. Annualized bleed rates (ABR) in comparison to before gene transfer.
3. Consumption of exogenous FVIII in comparison to before gene transfer.

2.3.2.2 Safety

1. Development of inhibitory and total binding antibodies to FVIII.
2. Humoral and cell-mediated immune response to AAV8 and FVIII proteins.
3. Surveillance of AAV8 genome shedding in blood, saliva, semen, urine and stool.

2.3.3 Tertiary Outcome Measures

1. Hemophilia Joint Health Score at screening and Months 12, 24, 36, 48, and 60 post-gene transfer.
2. Changes in the following assessments:
    - Health-related quality of life (HRQoL) (post-gene transfer vs. baseline) measured by:

- Generic: 36-item Short Form survey version 2 (SF-36v2), EuroQol-5D (EQ-5D).
- Disease-specific: Hemophilia-Specific Quality of Life Index (Haemo-QoL-A).

- Patient Experience(baseline):
  - Adherence: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-Pro).
  - Disease-specific patient experience: Patients' preference for hemophilia treatment questionnaire (Haemo-PREF).

3. STUDY DESIGN

This is a global, Phase 1/2 multicenter, open-label, safety and dose escalation study of BAX 888 in adult subjects with severe hemophilia A. Up to 12 subjects may be administered BAX 888 in up to 3 dose cohorts.

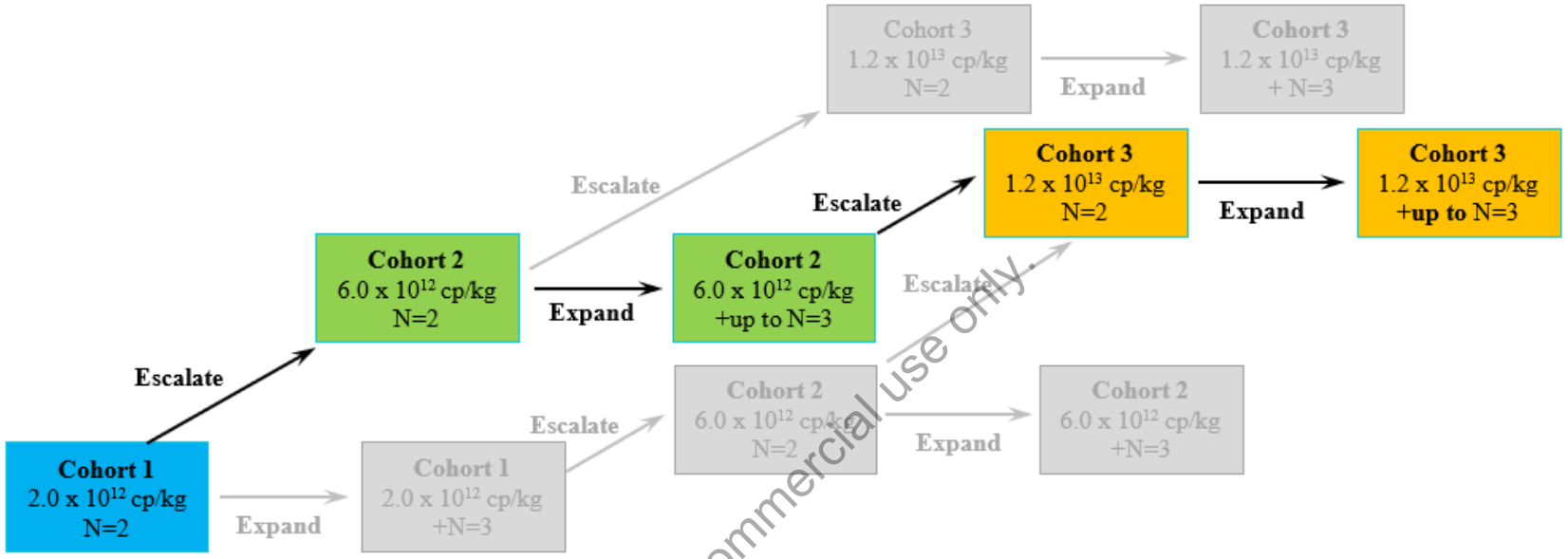
At study initiation, subjects will be assigned to a dose cohort, with a minimum of 24 hours between dosing of each subject. Initially, 2 subjects will be dosed in a cohort, with up to a total of 5 subjects if the cohort is expanded. The dose escalation schema is further presented in Figure 1. Safety and FVIII expression data from subjects dosed with BAX 888 will be utilized to make decisions on dose escalation and cohort expansion. Rules for cohort expansion and dose escalation are provided in the study protocol. However, if any subject in a given cohort achieves >50% FVIII activity levels at Week 14, the Data Monitoring Committee (DMC) will provide a recommendation on further dose escalations after review of all safety and FVIII activity data. If any subject in any cohort achieves ≥150% FVIII activity levels at any time while on the study, further dosing will be paused until DMC review. Baseline FVIII activity level is defined as the value obtained based on the central laboratory one-stage FVIII assay before study drug administration. Only central laboratory one-stage FVIII values will be considered for dose escalation decisions.

The three cohorts that will be included in presentations are:

- Cohort 1 (2.0×10^{12} cp/kg)
- Cohort 2 (6.0×10^{12} cp/kg)
- Cohort 3 (1.2×10^{13} cp/kg)

In addition to a safety data review by the DMC, further analyses on efficacy and safety data may be performed at study milestones (e.g., when the initial two subjects in the first cohort finishes the Week 18 visit), or otherwise up to 2 times every year for the duration of the study. Analyses due to different trigger points may be waived or combined for efficiency. No formal interim analysis is planned. Refer to Section 10 for more details.

Figure 1: Dose Escalation Schema for Baxalta Clinical Study 201501



Dose Escalation / Cohort Expansion Decision Based on <u>Week 4</u> data:

- If Week 4 FVIII levels ≈ baseline (i.e. <2%) in the first 2 subjects of any cohort, then escalate dose (DMC review not required).
- If Week 4 FVIII levels are > 2% baseline in at least 1 of the first 2 subjects in any cohort, then dose escalation / cohort expansion decision will be based on data through Week 14.

Dose Escalation / Cohort Expansion Decision Based on <u>Week 14</u> data:

- If sustained Week 14 FVIII activity level of ≥30%[v,viii] is not achieved
  - in the first 2 subjects of Cohort 1 or Cohort 2, then escalate or expand dose after DMC review of all available safety and FVIII activity level data.
  - in at least 3 subjects in Cohort 1 or in Cohort 2, then escalate dose after DMC review of all available safety and FVIII activity level data.
  - in both subjects in Cohorts 3, then dosing of additional subjects will be paused until further review of all available data.
- If sustained Week 14 FVIII activity level of ≥30%[v,viii] is achieved:
  - in at least 1 of the first 2 subjects of any cohort, then expand the cohort with dosing of 3 additional subjects for a total of 5 subjects in that cohort.
  - in at least 3 subjects of Cohort 1 or 1 subject in Cohort 2, then either:
    - Escalate to next dosing cohort

      OR
    - Complete study with no further dosing

OR

- Expand the cohort

If any subject in a given cohort achieves FVIII activity levels >50% at Week 14, DMC must review all safety and FVIII activity level data to provide a recommendation on further dose escalations.

3.1 Randomization

This is a non-randomized, open-label, active treatment, dose escalation clinical study.

3.2 Blinding

Not applicable.

3.3 Sample Size and Power Considerations

The sample size is expected to range from 2 to 12 evaluable subjects depending on the actual number of cohorts and the actual number of subjects in each cohort. This sample size was chosen to provide sufficient evidence of safety and exploration of signs of efficacy for this indication and is not based on formal statistical considerations. The sample size and escalation plan is designed to minimize the risk to subjects of experiencing significant toxicity or receiving a sub-therapeutic dose. If a given dose shows lack of efficacy, enrollment will be limited to 2 subjects in the cohort.

With the limited number of subjects per group and study enrollment terminated, statistical analyses will be conducted in a descriptive fashion.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent, including Screening Failures.

4.2 Enrolled Set

Enrolled Set consists of all subjects who have enrolled onto the study, this is signed informed consent, and passed inclusion/exclusion criteria. Analysis will be performed according to treatment regimen.

4.3 Safety Set

Classification into the Safety Analysis Set will be conducted prior to database lock. The Safety Set will consist of all subjects who receive any amount of investigational product (IP). All safety analyses (including the primary analysis) will be performed on the Safety Analysis Set.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Information on disposition of subjects will be obtained from the eCRF.

The number of subjects who were included in and excluded from each defined analysis set (i.e., Screened, Enrolled and Safety) will be summarized by cohort and overall, except for the Screened Set, which will be summarized only overall.

The number and percentage of subjects who completed and prematurely discontinued during the duration of the study evaluation phase, post infusion of BAX 888, will be presented for each cohort and overall, for Safety Set. Reasons for premature discontinuation from the duration of the study evaluation phase, post infusion of BAX 888, as recorded on the termination page of the eCRF will be summarized (number and percentage) by cohort and overall, for the Safety Set. All subjects who prematurely discontinued during the study evaluation phase, post infusion of BAX 888, will be listed by discontinuation reason for Safety Set.

The number of subjects screened, enrolled, that received investigational product and completed will be tabulated by site and country. In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

Subject disposition will also be listed. As well as an independent, listing of all Screen Failures (i.e., subjects who were screened but not dosed) will be presented along with reasons for screen fail. This is to be based on unique subject identifier.

Subjects that sign informed consent and fail screening under their first subject identifier, but continue to re-screen successfully under a second subject identifier will be handled as follows:

- For the summary of disposition, a unique subject (using last subject number) is to be identified and summarized as screened and separately under a differentiated screening failure counts category, but only counted once per category as appropriate.
- For listing of subject disposition, they will be listed as per their re-screened subject identifier.

- For listing of all Screen Failures, they will be listed as per their failed screening number.

5.2 Demographic and Other Baseline Characteristics

Demographic and screening characteristic information will be obtained from the eCRF.

Descriptive summaries of demographic and baseline characteristics will be presented by cohort (1:2.0 x 10^{12} cp/kg, 2:6.0 x 10^{12} cp/kg and 3:1.2 x 10^{13} cp/kg) and overall, for the Safety Set.

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, ethnicity, race. In addition, other baseline characteristics will be summarized to include: weight (kg), height (cm), BMI (kg/m^2), and FVIII:C.

BMI will be calculated as

$$\text{BMI } (kg/m^2) = (\text{Weight } [kg] / \text{Height } [m]^2)$$

Conversion of eCRF collected weight (lbs) to (kg) is divided by a factor of 2.205, height (in) to (m) is divided by a factor of 0.0254.

5.3 Medical History

Information on medical and surgical history will be obtained from the eCRF.

Medical history will be collected at the Screening Visit 1 or later. This will include all conditions that occurred during the 12 months prior to study enrollment and surgeries over entire lifetime. A listing will be provided using the Safety Set. The medical history will also be summarized by system category for each cohort and overall, for the Safety Set.

Similarly, congenital hemophilia A history/target joint identification will be collected at Screening Visit 1 or later. A subject's confirmation of diagnosis & severity, gene mutation, presence of any target joints and historical ABR, FVIII replacement therapies and other medications based on documented data within the last 12 months will be listed using the Safety Set. Summaries by severity, gene mutation type and annualized bleed rates, FVIII replacement therapies and other medications, based on the last 12 months, will be produced.

Hospitalizations that occurred during the 12 months prior to study enrollment, exposure to mutagenic agents, recent malignancy(ies), recent incidence or exacerbation of a pre-existing neurologic disorder, recent incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, recent incidence of hematologic disorder recorded from month 5 up to study completion/discontinuation will be summarized and listed.

Medical history is not coded for this study.

5.4 Prior Hemophilia Treatment

Information on Prior Hemophilia treatments will be obtained from the eCRF.

Prior Hemophilia treatments are defined as any FVIII replacement product with the start date prior to the date of BAX 888 infusion (Day 1~~0~~), used within the last 12 months prior to study enrollment.

Prior treatments will be coded using the World Health Organization (WHO) Drug Dictionary dated 01MAR 2020 or newer. Prior therapies and procedures will be coded using MedDRA Version MEDDRA 23.0_ or newer.

The prior treatments will be summarized by use of all and by prophylactic/ on-demand treatment as the number and proportion of subjects in each cohort and in overall subjects for the Safety Set. Multiple medication usage by a subject within a treatment type (prophylactic or on-demand) will be counted only once by summaries will include all administrations of exogenous FVIII.

All prior hemophilia Treatments, procedures and medication will be listed for the Safety Set.

5.5 Concomitant Therapies, Procedures and Medications (Excluding Prednisone/ Prednisolone and Exogenous FVIII administration)

Information on concomitant therapies, procedures and medications will be obtained from the eCRF.

Concomitant medications, therapies and procedures will be coded using the World Health Organization (WHO) Drug Dictionary and MedDRA respectively, as the versions stated in the data management plan.

Concomitant medication (therapy) is defined as any medication (therapy) with a start date prior to the date of BAX 888 infusion (Day 1~~0~~) that continue after the date of BAX 888 infusion (Day 1~~0~~), for permitted medications and non-drug therapies, as stated in the Protocol (Section 10.4), a start date occurring 4 weeks before providing informed consent or with a start date between the dates of the date of BAX 888 infusion (Day 1~~0~~) and study follow-up, inclusive. Concomitant procedure is also defined as any procedure with a start date between the dates of BAX 888 infusion (Day 1~~0~~) and study follow-up, inclusive.

Prednisone/ Prednisolone information reported on the *Concomitant Medications* eCRF will not be presented as part of prior and concomitant medications. Prednisone/ Prednisolone will be identified after coding with WHO-DD as all medications with a base name of PREDNISONE or PREDNISOLONE respectively.

The concomitant therapies, procedure and medication usage will be summarized by the number and proportion of subjects in each cohort receiving each medication and in overall subjects within each preferred term for the Safety Set. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures and medication will be listed for the Safety Set.

5.6 Glucocorticosteroid (Prednisone/ Prednisolone) Administration

Information on prednisone/ Prednisolone administration will be obtained from the Concomitant Medication and Administration of Prednisone/Prednisolone Treatment eCRF panels. Prednisone/ Prednisolone medications from the Concomitant Medications eCRF panel will be identified as detailed in Section 5.5.

Information on Prednisone/ Prednisolone administration will be listed for the Safety Set. Prednisone information will further be presented graphically overlaid on laboratory results as detailed in Section 7.5. No summaries on Prednisone/ Prednisolone administration will be presented.

5.7 Exposure to Investigational Product

Information on investigational product administration, including initial infusion, remaining infusion and any interruptions will be obtained from the eCRF. Lot specific details, such as lot number and expiry date information will be obtained from Clinical.

No summaries on investigational product administration will be presented.

A listing will be created by subject number giving the lot numbers and expiry date of investigational product will be presented. Likewise, a listing by subject number giving the date and time of dose administration details.

5.8 Measurements of Treatment Compliance

Treatment compliance will not be summarized or listed as it is not appropriate.

5.9 Protocol Deviations

Protocol deviations will be obtained from the IQVIA clinical trial management system (CTMS), as recorded by site. The CRO/Takeda will classify critical, major and minor protocol deviations per the agreed protocol deviation management plan. The Takeda study team will review the protocol deviations and their classification throughout the study and before database lock.

Decisions of the review will include:

- Accuracy of critical, major and minor protocol deviations categorization.

For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications.

Confirmed critical, major and minor protocol deviations will be documented in the Protocol Deviation tracker for the study. For reporting, critical and major deviations will be as major. Protocol deviations will be summarized by category and site for each cohort and overall, for the Safety Set. Major/minor protocol deviations will be listed for the Safety Set.

6. SAFETY AND EFFICACY PRIMARY AND SECONDARY ANALYSES

All efficacy and safety analyses will be based on the Safety Analysis Set unless stated otherwise.

All efficacy analyses will be conducted according to the cohort.

Unless otherwise described, for summaries, only data collected from scheduled visits be analyzed. When there are multiple results on a scheduled visit, the latest result for the visit will be used. For listings and graphical displays all data will be presented.

For subjects who are re-screened under a second subject ID, their prior screening data will be re-mapped for analysis to form part of their patient profile, to be included in reporting.

Except for Section 11.7 specified, other missing data will not be imputed.

6.1 Analyses of Primary Safety Endpoint

The primary outcome measure is the incidence of BAX 888-related AEs (serious or non-serious) that includes development of FVIII inhibitory antibodies, clinically significant changes in standard laboratory parameters, physical exam, and vital signs that are reported as AEs.

All safety analyses will be conducted according to the cohort.

Unless otherwise described, for summaries, only data collected from scheduled visits will be analyzed. When there are multiple results on a scheduled visit, the latest result for the visit will be used. For listings and graphical displays all data will be presented.

Information on AEs will be obtained from the eCRF.

AE summary and listing details are explained in Section 7.4.

6.2 Analyses of Secondary Efficacy Endpoints

6.2.1 Circulating plasma FVIII activity and antigen levels

The determination of circulating plasma FVIII activity and antigen levels will be assessed by FVIII genotyping, FVIII activity (Central Laboratory: one-stage clotting and chromogenic assays; Local Laboratory: one-stage clotting or chromogenic assay) and FVIII antigen results.

6.2.1.1 FVIII genotyping

FVIII genotyping information will be obtained centrally from vendor data.

Data collected for FVIII genotyping will be presented in a listing. No summaries will be produced.

6.2.1.2 FVIII activity and antigen

FVIII activity information will be obtained centrally and locally, antigen will only be obtained centrally. Both central and local results will come from vendor data.

Central laboratory FVIII activity testing results will be converted for consistency to a comparable unit to the local laboratory testing. Results of UL/mL will be converted to UL/dL by multiplying the SI unit (UL/mL) by a conversion factor of 100, i.e., {result [UL/mL]}*100. UL/dL is equal to %.

FVIII activity including changes from baseline will be summarized for results obtained centrally based on one-stage clotting testing. The proportion of subjects achieving FVIII activity levels of ≥20% of normal will also be summarized by visit for each cohort. FVIII Antigen results will not be summarized descriptively.

FVIII activity (both results obtained, centrally and locally) and FVIII antigen (obtained centrally) will be listed as part of the coagulation panel described in Section 7.5.

FVIII activity (One-stage and chromogenic) will be presented graphically overlaid with FVIII Antigen (if testing is performed), bleeding episodes and exogenous FVIII treatment for unique new and ongoing bleeding episodes. FVIII activity (One-stage and chromogenic) will also be graphically overlaid with ALT, AST and GGT. Unique bleeding episodes are as described in section 6.2.2.

6.2.2 Bleeding Episodes

Information on bleeding episodes will be obtained primarily from the eCRF for the purpose of analysis and reporting. Electronic diary capture of bleeding events was captured with the intent of discussion between patient and site investigator, corrections and updates were entered into the eCRF. Reporting of anatomical bleeding site, severity and causality will be pulled from the electronic diary as linked by bleeding reference ID in order to preserve additional patient reported details.

The following derivations will be performed based on results reported, prior to the result being presented:

- Timing of the bleeding episode relative to reference start date as defined in Section 11.2, will be determined and only bleeding episodes occurring post informed

consent and before, on or after the reference start date will be used in subsequent derivations.

- A bleed will be considered a joint bleed if the bleeding site is specified as JOINT in the anatomical bleed site response of the electronic diary.

- A bleed will be considered a non-joint bleed if the bleeding site is not specified as JOINT in the anatomical bleed site response of the electronic diary.

- A bleeding episode is considered a spontaneous/unknown bleed if the cause is specified as SPONTANEOUS or UNKNOWN in the anatomical bleed site response of the electronic diary.

- The overall number of bleeds, the number of joint bleeds, the number of non-joint bleeds, the number of spontaneous/unknown bleeds will be determined as the count of unique bleeds in each category during the study.

- The ABR for bleeds overall, joint bleeds, non-joint bleeds, spontaneous/unknown bleeds will be derived as

$$ABR = \frac{Number\ of\ unique\ bleeds}{Duration\ (years)}$$

where the number of unique bleeds applies to each category separately for which ABR is determined and the duration in years are as described in Section 6.2.3

  - ABR for bleeds overall, will also be considered by time-period. Each time-period will be based on study day as presented in Table 1.

ABR will be modified as:

$$ABR\ (time\ period) = \frac{Number\ of\ unique\ bleeds\ (within\ time\ period)}{TPDuration\ (years)}$$

TP duration in years is as described in Section 6.2.3

Information on bleeding episodes and ABR will be listed. ABR will also be summarized, by cohort and overall, at both pre-BAX 888 infusion, based on that reported by site on a subjects 12 months prior to gene transfer as well as derived ABR on study report bleeds. ABR as calculated from on study bleeds, will be summarized by all bleeds (further

categorized by overall, Year 1, Year 2, Year 3, Year 4 and Year 5), joint bleeds, non-joint bleeds and spontaneous/unknown, joint bleeds.

Bleeding episodes including treatment for bleeding episodes will be presented graphically overlaid on FVIII activity and FVIII antigen results.

6.2.3 Consumption of Exogenous FVIII

Information on exogenous FVIII consumption will be obtained from the eCRF for the purpose of analysis and reporting. Electronic diary capture of exogenous FVIII infusions was captured with the intent of discussion between patient and site investigator, corrections and updates were entered into the eCRF. Reporting of Product Used, Infusion Reason, Planned Total Dose in IUs, Total Dose Infused in IUs and occurrence of Infusion Interruptions, restart and completion will be pulled from the electronic diary as linked by infusion reference ID in order to preserve additional patient reported details.

The following derivations will be performed based on results reported on the eCRF, prior to the result being presented:

- Timing of the infusion relative to reference start date, as defined in Section 11.2, will be determined and only infusions occurring post informed consent but on or after the reference start date will be used in subsequent derivations.

- The duration (years) will be determined as

$$Duration(years) = \frac{([Date\ of\ Completion - Reference\ Start\ Date]+1)}{365.2425}$$

  where the date of completion is the date the subject completed or discontinued the study and reference start date as defined in Section 11.2.

- The time-period (TP) duration (years) will be determined as

$$TP\ Duration(years) = \frac{([Date\ of\ reference\ visit - TP\ Reference\ Start\ Date]+1)}{365.2425}$$

Date of reference visit and TP Reference Start Date can be referenced from Table 1 for each time period. Should a subject discontinue the study prematurely, they will substitute Date of reference visit with their date of discontinuation, within the appropriate time-period that they withdrew the study.

Table 1: Time-period Windows

Time-period	TP reference start date	Reference visit	Study Day	
			Lower bound	Upper bound
Year 1	BAX 888 infusion	Month 12	1	366
Year 2	Month 12 +1	Month 24	367	731
Year 3	Month 24 +1	Month 36	732	1096
Year 4	Month 36 +1	Month 48	1097	1461
Year 5	Month 48 +1	Month 60	1462	1826

- The duration (Months) will be determined as

$$Duration\ (Months) = Duration(Years)\ x\ 12$$

- The average number of infusions per month will be derived as

$$Average\ infusions\ per\ month = \frac{Total\ infusions\ in\ study\ (or\ time\ period)}{\text{Duration (Months)}}$$

Infusions of exogenous FVIII either prophylactically infused (for prevention) or those given for episodic management (on-demand to control clinical bleeding episodes) as collected in patient diaries and on the eCRF, will be summarized by the number and proportion of subjects in each cohort. Additionally, summaries of the number of infusions and total dose received and average infusions per month over the course of the study and annually by reason for treatment will be created.

All summaries are to be based on the Safety set.

All infusions will be listed to detail the Product Used, Infusion date, times of start and stop, reason for infusion, planned and total infused dose, as well as interruption, restart and completion confirmations.

Exogenous FVIII alongside bleeding episodes will also be presented graphically against selected central laboratory results (ALT, AST and GGT(One-stage and chromogenic)) over time.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set.

Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last non-missing value prior to IP administration will be used as baseline for all analyses of that safety variable.

Unless otherwise described, for summaries and graphical displays, only data collected from scheduled visits will be analyzed. For listings all data will be presented.

7.1 Development of inhibitory and total binding antibodies to FVIII

The presence of binding antibodies to FVIII (anti-FVIII antibodies) and FVIII transgene product, binding and neutralizing antibodies to AAV8 and AAV2, and cell-mediated immune (CMI) response to AAV8 and FVIII transgene products will be followed at scheduled timepoints.

The development of antibodies that inhibit FVIII activity (FVIII Inhibitors) will be measured at a central laboratory using a clot-based method following Nijmegen modification. Additionally, for subjects who received Hemlibra (Emicizumab) or other non-FVIII agents, FVIII inhibitors will be assessed using chromogenic-based method due to clot-based assay interference by Emicizumab.

Descriptive statistics for immunogenicity parameters at screening and at the scheduled post-transfusion assessments will be presented by cohort and overall.

All immunogenicity results will be listed.

7.2 Humoral and cell-mediated immune response to AAV8 and FVIII proteins

Both cellular immune response and humoral immune response data will be obtained centrally from vendor data.

Central laboratory results on cellular immune response (Individual AAV8 and FVIII pools) and humoral immune response (anti-AAV8 and anti-AAV2 IgG and neutralizing antibody responses [inverse titers]) will be summarized over time by cohort and overall, as the number and percentage of positive immune responders.

For AAV8 pooled and FVIII pooled mean results, a positive immune response for each peptide pool is defined as the presence of 3x above medium background, and higher than 60 Interferon-gamma (IFN-γ) spots per 1,000,000 cells plated per well (where background represents the production of secreted IFN-gamma cytokine molecules, by plated cells in the absence of an antigen). PHA is the positive control whereas Medium is the negative control.

For antibody responses, a positive response is thought to occur should there be an observed binding antibody titer of greater than or equal to 80, and neutralizing antibody (AAV8/AAV2) Titer greater or equal to 5.

Individual subject bar charts of cellular immune response (AAV8 and FVIII) will be presented graphically over time by pool. Likewise, individual subject line plots of humoral immune response (anti-AAV8 and anti-AAV2 IgG antibody response [inverse titers]) and line charts of humoral immune response (Neutralizing antibodies to AAV8 and AAV2 [inverse titers]) will be presented graphically over time.

All cellular immune response and humoral immune response data, including mean and specific/observed response results will further be listed.

7.3 Vector Genomes

Vector genome concentrations in blood, saliva, semen, stool and urine samples will be obtained from external vendor data. Samples will be available at scheduled visits until two consecutive negative results have been obtained.

The duration genomes are present will be determined for each sample as

$$Duration\ (Days) = [Date\ no\ Genomes\ Present - Relative\ Start\ Date] + 1$$

where the date no genomes are present anymore is the date of the first negative genome result of the two consecutive genome results and reference start date as defined in Section0.

Descriptive statistics for the presence of BAX 888 vector genomes for the lead-in period and at the scheduled post-transfusion assessments will be presented by cohort and overall.

BAX 888 vector genome concentrations will further be listed and presented graphically.

7.4 Adverse Events

Adverse events (AEs) will be coded using MedDRA Version MEDDRA23.0~~0~~_ or newer.

An AE (classified by preferred term) that occurs during the study evaluation phase will be considered a Treatment Emergent Adverse Event (TEAE) if it has a start date on or after the first exposure to IP or if it has a start date before the date of BAX 888 infusion (Day 1~~0~~) but increases in severity on or after the date of BAX 888 infusion (Day 1~~0~~). If more than 1 AE with the same preferred term is reported before the date of BAX 888 infusion (Day 1~~0~~) exposure to IP, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study evaluation phase under the preferred term. An AE that occurs after study completion/ discontinuation will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, Serious Adverse Events (SAEs), TEAEs related to BAX 888, TEAEs leading to study discontinuation, TEAEs related to Prednisone or Prednisolone, TEAEs leading to the withdrawal of Prednisone or Prednisolone and TEAEs leading to death.

The number and percentage of subjects reporting TEAEs and TESAEs, as well as the number of events, in each cohort and overall will be tabulated by system organ class (SOC) and preferred term. Summaries of this type will also be tabulated by maximum severity, as well as for both TEAEs and SAEs considered 'Possibly related' or 'Probably related' to investigational product and TEAEs considered related to Prednisone or Prednisolone. If more than 1 TEAE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product or Prednisone or Prednisolone. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence. This will include presentation by PT and sorted in descending order.

An exploratory, descriptive analysis will be performed for TEAEs categorized as development of inhibitory antibodies to FVIII and total binding antibodies to FVIII, severe allergic reactions, and thrombosis-associated events. These analyses will be independently summarized by SOC and preferred term as the number and proportion of subjects experiencing TEAEs considered 'Possibly related' or 'Probably related' to investigational product by cohort and overall.Hospitalizations will also be listed.

7.5 Clinical Laboratory Data

Centralized and local laboratory results will be obtained from external vendor, no results will be obtained from the eCRF.

For the purpose of summaries on numeric results and calculation of changes from baseline, results with qualifiers (“>” or “<”) will be handled as the numerical part without the qualifier. That is “>XX” or “<XX” will be used as XX in summaries and changes from baseline.

Descriptive statistics for both local and central clinical laboratory values (in SI units) and changes from baseline (where appropriate) at each assessment time point will be presented by cohort and overall for the following clinical laboratory variables:

Hematology Hemoglobin, hematocrit, erythrocytes [i.e., red blood cell {RBC} count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet counts, RBC distribution width (RDW), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCH/ MCHC).

Coagulation PT, activated partial thromboplastin time, FVIII antigen, FVIII activity (performed as one-stage assay and as chromogenic assay), FVIII Bethesda inhibitor, in addition chromogenic-based method for subjects on Hemlibra and non FVIII agents, international normalized ratio, thrombin time, D-dimer, and fibrinogen activity.

Clinical Chemistry Sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, albumin, total protein, creatine kinase (CK), bilirubin (total & direct), ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and lactate dehydrogenase (LDH).

As well, Esoteric tests on FibroSURE™ (Laboratory Corporation of America, Raritan, NJ, United States) as well as Markers of autoimmune-mediated hepatitis including ANA, total IgG, anti-smooth muscle antibody, and anti-LKM1 titers, serum cytokines and Local Laboratory Liver Function Tests (LFTs) including ALT, AST, and GGT will also be considered.

Viral serology testing will include HIV-1 and HIV-2 antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibody and HCV RNA. The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. Descriptive statistics for viral serology parameters for the screening period and at the scheduled post-transfusion assessments will be presented by cohort and overall.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria (lower and higher limits) listed in

Table 2: Criteria for Potentially Clinically Significant Laboratory Tests. PCS values will not be tabulated but a supportive listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline values.

Table 2: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	SI Unit	Lower Limit[a]	Higher Limit[a]	LLOQ	ULOQ
Hematology					
Hemoglobin	g/L	Age (18-65): 130 Age (>65): 130	175 177	<0	-
Hematocrit	V/V	Age (18-65): 0.40 Age (>65): 0.37	0.52 0.50	-	-
Erythrocytes [i.e., red blood cell {RBC} count]	x10E12/L	Age (18-65): 4.1 Age (>65): 4.0	5.9 5.8	<0	-
Leukocytes [i.e., white blood cell count])	x10E9/L	4.1	12.3	<0	-
Basophils Basophils Absolute	% x10E9/L	0.0 0.0	2.4 0.17	-	-
Eosinophils Eosinophils Absolute	% x10E9/L	0.0 0.00	6.0 0.56	-	-
Lymphocytes Lymphocytes Absolute	% x10E9/L	15.5 1.02	46.6 3.36	-	-
Monocytes Monocytes Absolute	% x10E9/L	3.1 0.18	12.5 0.90	-	-
Neutrophils Neutrophils Absolute	% x10E9/L	40.9 2.03	77.0 8.36	-	-
Platelet counts	x10E9/L	145	450	<0	-
RBC distribution width (RDW)	%	11.6	14.8	-	-
Mean corpuscular volume (MCV)	fL	79	97	<0	-

Mean corpuscular hemoglobin concentration MCH MCHC	pg/cell g/L	26 310	34 370	-	-
Coagulation					
Prothrombin time (PT)	Seconds	9.4	12.5	-	-
Activated partial thromboplastin time (aPTT)	Seconds	20.6	39.9	-	-
FVIII antigen	IU/mL	-	-	-	-
FVIII activity, performed as: one-stage assay [b] chromogenic assay [b]	 IU/mL IU/mL	 0.500 0.500	 1.500 1.700	-	-
FVIII Bethesda inhibitor	BU/mL	≥0.6	-	<0.4	-
International normalized ratio (INR)		0.8	1.20	-	-
Thrombin time	Seconds	13	19	-	-
D-dimer	ug/L D-DU	-	<=243	<150	-
Fibrinogen activity	g/L	1.84	4.80	-	-
Clinical Chemistry					
Sodium	mmol/L	135	147		-
Potassium	mmol/L	3.3	5.1		-
Chloride	mmol/L	97	110	<60	-
Carbon dioxide	mmol/L	19	29	-	-
Blood urea nitrogen (BUN)	mmol/L	Age (18-60): 2.14 Age (>60): 2.86	7.14 8.21	-	-
Creatinine	umol/L	59	103	<0.03	-
Glucose	mmol/L	Age (18-59): 4.1 Age (>59): 4.6	5.9 6.4	-	-
Calcium and Calcium (Albumin Corrected)	mmol/L	Age (<=65): 2.10 Age (>65): 2.20	2.58 2.55	-	-
Phosphate	mmol/L	0.81	1.45	-	-
Magnesium	mmol/L	0.65	1.05	-	-
Albumin	g/L	35	52	-	-
Total protein	g/L	60	80	-	-
Creatine kinase (CK)	IU/L	39	308	<7	-
Bilirubin Total Direct	 umol/L umol/L	 - 0	 <=21 5	-	-
ALT	U/L	-	<=41	-	-
AST	U/L	-	<=37	-	-
Alkaline phosphatase (ALP)	IU/L	40	129	-	-
Gamma-glutamyl transpeptidase (GGT)	U/L	8	61	-	-

Lactate dehydrogenase (LDH)	U/L	-	<=250	-	-
Markers of autoimmune-mediated hepatitis					
ANA	-		<1:80	-	-
Total IgG	g/L	Age (<=19): 5.49 Age (>19): 7.00	15.84 16.00	-	-
Anti-smooth muscle antibody	units	-	<20	-	-
Anti-LKM1 titers (Liver Kidney Microsome-1 Antibody IgG)	units	-	<=20	-	-
Serum Cytokines					
IL-6	ng/L	-	-	<1.62	>1486.00
TNF-a	ng/L	-	-	<0.68	>1280.00

LLOQ= Lower Limit of Quantification; ULOQ= Upper Limit of Quantification

[a] Lower and Higher limits are as provided by central laboratory as Reference Range - SI results.

[b] For analysis, central laboratory FVIII activity testing results will be converted for consistency to a comparable unit to the local laboratory testing. Results of UL/mL will be converted to UL/dL by multiplying the SI unit (UL/mL) by a conversion factor of 100, i.e {result [UL/mL]}*100. UL/dL is equal to %.

All laboratory data (central and local) will be listed.

7.6 Vital Signs

Descriptive statistics for vital signs (e.g., body temperature, respiratory rate, pulse rate systolic and diastolic blood pressure) for the duration of the study and their changes from baseline at each post-baseline visit and at the end of study will be presented by cohort and overall.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline criteria listed in Table 3: Criteria for Potentially Clinically Significant Vital Signs.

Table 3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15

[a] A post-baseline value is considered as a PCI value if it meets both criteria for observed value and change from baseline.

All vital signs data will be listed.

7.7 Electrocardiogram (ECG)

Electrocardiogram overall interpretation results will be obtained from the eCRF. Results will be listed for the safety set. No summaries will be presented for ECG.

7.8 Multiplicity Adjustment

Not applicable.

7.9 Subgroup Analyses

There are no subgroup analyses planned.

8. PHARMACODYNAMIC ANALYSIS

8.1 Pharmacodynamic Data

The pharmacodynamic activity of BAX 888 will be evaluated using the following assessments:

- FVIII activity (central laboratory one-stage and chromogenic clotting assays) and FVIII antigen (protein) levels in plasma.
- Antibodies to FVIII and FVIII transgene product.
- Neutralizing antibodies against AAV8 and AAV2.
- CMI response to AAV8 and FVIII transgene product.

8.1.1 Pharmacodynamic Variables and Analysis

All Pharmacodynamic analyses are described in Section 7.5.

9. TERTIARY OUTCOME ANALYSES

9.1 Hemophilia Joint Health Score

The Hemophilia Joint Health Score (HJHS) sum and score assessments (Sum of Joint Totals, Global Gait Score and Total Hemophilia Joint Health Scores) (Feldman et al., 2011) will be characterized descriptively by cohort and overall, for the screening period and at the scheduled post-transfusion assessment as well as changes in the following assessments (post-gene transfer vs. baseline) over time. These analyses will be assessed using descriptive summaries appropriate for the measure (e.g., number and percent for categorical measures and mean, SD, median, minimum, and maximum for continuous measures).

Individual joint component scores as well as sum and score results will be listed.

9.2 Health-related Quality of Life Analyses

The HRQoL assessments will be characterized descriptively on the safety set by cohort and overall . These analyses will be assessed using descriptive summaries appropriate for the measure (e.g., number and percent for categorical measures and mean, SD, median, minimum, and maximum for continuous measures).

All HRQoL data will be included in listings.

9.2.1 36-item Short Form survey (SF-36v2)

The SF-36v2 is a self-administered, validated questionnaire designed to measure generic HRQoL. This 36-item questionnaire measures 8 domains, including:

- physical functioning
- role limitations due to physical health
- bodily pain
- general health
- vitality
- social functioning
- role limitations due to emotional problems
- mental health

Two summary scores will be calculated, the Physical Component Score and the Mental Component Score; additionally, scores can be calculated for each of the 8 domains. Higher scores indicate better health status.

Each of the 36 questions will be assigned to a specific scale and score based on the answers provided as set out in Table 6: SF-36 Scoring for Individual Questions.

After scores have been assigned for each individual question, scores for scales will be calculated as set out in Table 4: SF-36 Scoring for Scales.

Table 4: SF-36 Scoring for Scales

Scale	Items to Sum (scores as assigned in Table 6: SF-36 Scoring for Individual Questions)	Lowest and Highest Possible Score	Possible Raw Score Range
Physical Functioning (PF)	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
Role Physical (RP)	4a + 4b + 4c + 4d	4, 20	16
Bodily Pain (BP)	7 + 8	2, 12	10
General Health (GH)	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality (VT)	9a + 9e + 9g + 9i	4, 20	16
Social Functioning (SF)	6 + 10	2, 10	8
Role-Emotional (RE)	5a + 5b + 5c	3, 15	12
Mental Health (MH)	9b + 9c + 9d+ 9f + 9h	5, 25	20

The score for each scale will then be transformed to a 0 – 100 range using the following formula:

$$Transformed\ Scale = \frac{[(Actual\ Raw\ Score - Lowest\ Possible\ Raw\ Score)]}{Possible\ Raw\ Score\ Range} \times 100$$

A z-score standardization of the SF36 transformed scale scores will be determined as follows:

- $PF_z = \frac{PF - 83.29094}{23.75883}$
- $RP_z = \frac{RP - 82.50964}{25.52028}$
- $BP_z = \frac{BP - 71.32527}{23.66224}$
- $GH_z = \frac{GH - 70.84570}{20.97821}$
- $VT_z = \frac{VT - 58.31411}{20.01923}$
- $SF_z = \frac{SF - 84.30250}{22.91921}$
- $RE_z = \frac{RE - 87.39733}{21.43778}$
- $MH_z = \frac{MH - 74.98685}{17.75604}$

After the z-scores have been determined the z-scores will be used to determine norm-based scores that will be presented in listings and summaries. The norm-based score will be determined as:

$$XX_N = 50 + (XX_z \times 10)$$

where XX represents the different scales (PF, RP, BP, GH, VT, SF, RE and MH).

The raw aggregate summary scores for the physical and mental components will be determined as follows:

- $AGG_{Phys} = (PF_z \times 0.42402) + (RP_z \times 0.35119) + (BP_z \times 0.31754) + (GH_z \times 0.24954) + (VT_z \times 0.02877) + \big(SF_z \times (-0.00753)\big) + \big(RE_z \times (-0.19206)\big) + \big(MH_z \times (-0.22069)\big)$
- $AGG_{Ment} = \big(PF_z \times (-0.22999)\big) + \big(RP_z \times (-0.12329)\big) + \big(BP_z \times (-0.09731)\big) + \big(GH_z \times (-0.01571)\big) + (VT_z \times 0.23534) + (SF_z \times 0.26876) + (RE_z \times 0.43407) + (MH_z \times 0.48581)$

The normalized aggregate scores that will be presented in listings and summaries will be determined as:

$$YY_N = 50 + (AGG_{YY} * 10)$$

where YY is either the physical component score or mental component score.

Any scale with less than half of the questions answered will have no score calculated. For scales with any questions not answered, but with more than half of the questions answered, the raw scale will be adjusted in terms of the lowest and highest possible score, including the possible raw range. All other scores will be affected by this change in raw score. As an example, say question 3a is not answered, then the lowest score for physical functioning will change from 10 to 9, the highest score will change from 30 to 27 and the possible raw range from 20 to 18. The new values will be used in determining the raw score for physical functioning.

Descriptive statistics for each of the transformed scale scores (e.g. physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health) as well as the normalized aggregate scores for physical and mental components for the duration of the study and their changes from baseline at each post-baseline visit and at the end of study

will be presented by cohort and overall. The appropriate measure for this response is mean, range and SD.

All individual components, scale scoring and aggregate scores for physical and mental components will be listed.

9.2.2 EuroQol-5D (EQ-5D)

The EuroQol-5D (EQ-5D) is a self-administered, standardized measure of health status that provides a generic measure of health for clinical and economic appraisal consisting of the following 5 dimensions, each with 5 levels:

- mobility
- self-care
- usual activities
- pain/discomfort
- anxiety/depression

For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems) and will be assigned to a specific scale and score based on the answers provided as set out in Table 7: EQ-5D Scoring for Individual dimension. Overall EQ-5D total scores will be calculated at baseline, each post-baseline visit and changes from baseline, at each post-baseline visit by cohort and overall.

It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as an ordinal score.

In addition to the descriptive questionnaires, respondents also assess their health today on a visual analogue scale (VAS), ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score will be summarized separately using descriptive statistics for baseline, each study evaluation, and change from baseline to each evaluation.

No imputation methods will be used to handle missing data, because the results are simply summarized over time as opposed to any formal hypothesis testing and analysis.

9.2.3 Haemo-QoL-A

The Haemo-QoL-A is a validated hemophilia A–specific instrument covering 6 areas (subscales):

- physical functioning
- role functioning
- worry
- consequences of bleeding
- positive affect
- treatment concerns

For each question, respondents select which statement best describes their hematology related QoL from a possible 6 options ("None of the time", "A little of the time", "Some of the time", "A good bit of the time" or "Most of the time"). Responses will be assigned to a specific scale and score based on the answers provided as set out in Table 8: Haemo-QoL-A Scoring for Individual Questions. Scoring is assigned based on the direction of the question, with a score of 1 indicating 'higher' quality of life and 6 being 'lower' quality of life (Rentz et al., 2008).

For scoring, where (R) is present in Table 8: Haemo-QoL-A Scoring for Individual Questions, the scoring has been reversed i.e. a recorded result of 6 will become a score of 1 and likewise a recorded result of 1 will become a score of 6.

The following scores will be calculated:

- **Raw score** (per subscale): This is to produce a score per subscale. Its range lies between the lowest possible (number of items (n) x 1) and highest possible (number of items(n) x 6) value of the respective scale.

- **Standardized scale score:** This is to enable comparisons across subscales. A value of 1 represents the highest possible quality of life rating and a value of 6 the lowest possible quality of life rating of the patient.

- **Transformed scale score (TSS):** This is to make it possible to express the scale score in percent between the lowest (0) and the highest (100) possible value. To be presented to 2 decimal places.

$$TSS = 100\ x\ \frac{Raw\ score - minimal\ of\ raw\ score\ (of\ the\ subscale)}{Range\ of\ raw\ score\ (of\ the\ subscale)}$$

Where the range of the raw score is the minimal of the raw score subtracted from the maximal of the raw score.

- **Total score:** Total score will be calculated by summing the subscale scores using all items, not just specific to a subscale, of the questionnaire.
  - **Raw:** as per Raw score, its range will lie between 41 (41x1) and 246 (41x6).
  - **Total score (Standardized):** as per standardized scale score.
  - **Total score (Transformed):** as per transformed scale score.

Data will not be imputed for missing results; the given scores will not be calculated where missing data exists.

The standardized and transformed subscale and total scores will be summarized by cohort and overall for the screening period and at the scheduled post-transfusion assessment as well as changes in the following assessments (post-gene transfer vs. baseline) over time. The appropriate measure for this response is mean, SD, range, minimum and maximum.

All data including the individual question responses and all calculated scores will be listed.

9.3 Patient Experience Analyses

9.3.1 VERITAS-Pro

The VERITAS-Pro is a self/parent-reported questionnaire to assess adherence to prophylactic treatment consisting of 24 questions on 6 (4-item) subscales:

- Time
- Dose
- Plan
- Remember
- Skip
- Communicate

For each question, respondents select from a five-point Likert scale (“Always”, “Often”, “Sometimes”, “Rarely” or “Never”), which statement best describes their response to the associated question. Responses will be assigned to a specific scale and score based on the answers provided as set out in Table 9: VERITAS-Pro Scoring for Individual Questions. Scoring is assigned based on adherence with a score of 1 indicating ‘best’ adherence and 5 being ‘worst’ adherence (Duncan et al., 2010).

Each subscale will have a score assigned, by summing all associated question scores, as well, a Total Scale score will be calculated, by summing all scores across subscales. Lower scores indicate better adherence.

For any missing data results, a score of 5 will be assigned in order to be conservative to the subscale and total scale scores. These results will be used for summaries.

Subscale and Total Scale scores will be summarized by cohort and overall for the baseline only. The appropriate measure for this response is mean, SD, range, minimum and maximum.

All data including the individual question responses and scores, as well as subscale and total scale scores will be listed. Imputed results will be flagged for easy identification.

9.3.2 HaemoPREF

The HaemoPREF is a 14-item questionnaire designed to measure ease of use and patients' preference for hemophilia treatment (Teal et al., 2014).

For each question, respondents will select from range of 0 to 10 as set out in Table 10: HaemoPREF Scoring for Individual Questions. In each case a higher score indicates greater satisfaction as response to the associated question.

The following scores will be calculated:

- **Global score:** a higher score indicates greater patient preference and treatment satisfaction (scores range from 0 to 140).
- **Ease of using clotting factor treatment score:** a higher score indicates greater ease of use (scores range from 0 to 40).
- **Burden of clotting factor treatment score:** a higher score indicates a lower burden of treatment (scores range from 0 to 20).
- **Impact of clotting factor treatment score:** a higher score indicates less negative impact on daily life (scores range from 0 to 30).
- **Risk associated with clotting factor treatment score:** a higher score indicates a lower level of worry associated with treatment (scores range from 0 to 30).
- **Influence of others on treatment choices score:** a higher score indicates a greater importance of the opinions or behavior of others (scores range from 0 to 20).

For scoring, where (R) is present in calculations the score will be reversed to the question result by subtracting 11 and taking the absolute value of the number i.e. a recorded result of 10 will become a score of 1 and likewise a recorded result of 1 will become a score of 10.

Scoring calculations:

- **Global score** = Item 1 + Item 2 + Item 3 + Item 4 + Item 5(R) + Item 6(R) + Item 7(R) + Item 8(R) + Item 9(R) + Item 10(R) + Item 11(R) + Item 12(R) + Item 13 + Item 14.
- **Ease of using clotting factor treatment score** = Item 1 + Item 2 + Item 3 + Item 4.
- **Burden of clotting factor treatment score** = Item 5(R) + Item 6(R).
- **Impact of clotting factor treatment score** = Item 7(R) + Item 8(R) + Item 9(R).
- **Risk associated with clotting factor treatment score** = Item 10(R) + Item 11(R) + Item 12 (R)**.**
- **Influence of others on treatment choices score** = Item 13 + Item 14.

Data will not be imputed for missing results; the given scores will not be calculated where missing data exists.

The 6 calculated scores will be summarized by cohort and overall for the baseline only. The appropriate measure for this response is mean, range and SD.

All data including the individual question responses and scores will be listed.

9.4 Patient Activity Level

Patient activity data will be summarized by cohort and overall, for the screening period and at the scheduled post-transfusion assessment as well as changes in the following assessments (post-gene transfer vs. baseline) over time.

10. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

An independent DMC will be set up to review the data on multiple occasions throughout the duration of the study.

For each cohort, once the second subject has reached week 4, a dose escalation/ cohort expansion decision will be made as described in the protocol.

In addition to a safety data review by the DMC, additional analyses on efficacy and safety data may be performed at study milestones (e.g., when the initial subject in the first cohort finishes the Week 14 visit), or otherwise up to 2 times every year for the duration of the study.

No formal interim analysis will be performed.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, interquartile ranges (Q1, Q3), minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Unless otherwise specified, decimal precision should be followed as:

- For measures of median and mean, use 1 decimal place beyond those used for the measurement.
- For measures of standard deviation and standard error of the mean, use 2 decimal places beyond those used for the measurement.
- For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
- BMI should be rounded to 1 decimal place for reporting.
- Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
- Averaged results (e.g. Diastolic/Systolic Blood Pressure and Pulse [when taken in triplicate]) should be rounded to 1 decimal place for reporting.
- Percentages should be reported in 1 decimal.

11.2 Definition of Reference Start Date and Study Day

Reference start date is defined as the date of administration of BAX888 and will be referred to as Study Day 1.

Study day will be calculated as described from the reference start date and will be used to show start and stop day of assessments and events. Study day will be calculated as:

$$Study\ Day = (Date\ of\ Event - Reference\ Start\ Date) + 1$$ (if the date of the event is on or after the reference start date).

In the situation where the assessment/event date is partial or missing, study day and corresponding durations will not be calculated.

11.3 Definition of Baseline

Baseline for all efficacy and safety analyses is defined as the last observed value for the efficacy assessment prior to the administration of the BAX 888 infusion (based on dates or date/times).

11.4 Definition of Visit Windows

All data will be presented by nominal visit as recorded in the eCRF. Visits will not be reassigned from the recorded nominal visit to any other visit based on dates.

11.5 Derived Efficacy Endpoints

Other than derivations described in Section 6.2.2, 6.2.3 and 9, there is no planned need for derivation of endpoint results on the study.

11.6 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

11.7 Handling of Missing, Unused, and Spurious Data

Except for the below specified, missing data will not be imputed.

11.7.1 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications, therapies and procedures, including Glucocorticoid use and Exogenous FVIII, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

11.7.1.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

11.7.1.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the BAX 888 infusion, then the day and month of the date of the BAX 888 infusion will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the BAX 888 infusion, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the BAX 888 infusion, then 01 January will be assigned to the missing fields.

11.7.1.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.7.1.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the BAX 888 infusion, then the day of the date of the BAX 888 infusion will be assigned to the missing day
- If either the year is before the year of the date of the BAX 888 infusion or if both years are the same but the month is before the month of the date of the BAX 888 infusion, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of the BAX 888 infusion or if both years are the same, but the month is after the month of the date of the BAX 888 infusion, then the first day of the month will be assigned to the missing day.

11.7.1.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

11.7.1.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the study termination, then the day and month of the date of the study termination will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the study termination, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the study termination, then 01 January will be assigned to the missing fields.

11.7.1.2.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.7.1.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the study termination, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the study termination or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the study termination or if both years are the same but the month is after the month of the date of the study termination, then the first day of the month will be assigned to the missing day.

11.7.2 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the BAX 888 infusion (Day 1~~0~~) , then the AE will be classified as treatment-emergent.

11.7.2.1 Incomplete Start Date

[Follow the same rules as in Section 11.7.1.1]

11.7.2.2 Incomplete Stop Date

[Follow the same rules as in Section 11.7.1.2]

11.7.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the BAX 888 infusion, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the BAX 888 infusion, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, indicated as imputed values will be used in data listings.

11.7.4 Missing Relationship to Investigational Product and Relationship to Prednisone or Prednisolone for Adverse Events

If the relationship to investigational product, Prednisone or Prednisolone is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, indicated as imputed values will be presented in data listings.

12. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Cohort 3 appeared in the protocol however the study enrollment was terminated before recruitment into this cohort

BAX 888 infusion day as the reference day will be changed from Day 0 to Day 1.

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14. APPENDICES

14.1 New Infusion Product list

Table 5: New Infusion Product list

Product Name		
Advate	GreenGeneF	MONOCLATE-P
ADYNOVATE	Greenjin	NEXGEN
ADYNOVI	Haemate-P	NovoEight
AFSTYLA	HELIXATE	NUWIQ
AleviateAlphanate	HELIXATE FS	OBIZUR
Autoplex	Helixate NexGen	Octagen/Ipsen
Beriate	Hemofil M	Octavi
Beriate P	Humate-P	PEGylated ADVATE
BIOCLATE	HYATE:C	RECOMBINATE
Biostate	Iblias	Recombinate
Cozinate FS	KOGENATE	ReFacto
ELOCTA	KOGENATE BIO-SET	ReFacto AF
ELOCTATE	KOGENATE FS	Voncento
Emoclot	KOGENATE PF	XYNTHA
Emowil	KOVALTRY	XYNTHA SOLOFUSE
GreenGene	Kovaltry	Zonovate

14.2 Questionnaire Scoring

14.2.1 SF-36

Table 6: SF-36 Scoring for Individual Questions

Question	Scale	Score
1. In general, would you say your health is:	General Health	Excellent: 5 Very Good: 4 Good: 3 Fair: 2 Poor: 1
2. Compared to one year ago, how would you rate your health in general now?	No Scale	Much better now than one year ago: 1 Somewhat better now than one year ago: 2 About the same as one year ago: 3 Somewhat worse now than one year ago: 4 Much worse now than one year ago: 5
3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?		
3a. Vigorous activities	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3b. Moderate activities	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3c. Lifting or carrying groceries	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3

Question	Scale	Score
3d. Climbing several flight of stairs	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3e. Climbing one flight of stairs	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3f. Bending, kneeling or stooping	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3g. Walking more than a mile	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3h. Walking several hundred yards	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3i. Walking one hundred yards	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
3j. Bathing or dressing yourself	Physical Functioning	Yes, limited a lot: 1 Yes, limited a little: 2 No, not limited at all: 3
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?		
4a. Cut down on the amount of time you spent on work or other activities	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4b. Accomplished less than you would like	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4c. Were limited in the kind of work or other activities	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
4d. Had difficulty performing the work or other activities (for example, it took extra effort)	Role-Physical	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		
5a. Cut down on the amount of time you spent on work or other activities.	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5

Question	Scale	Score
5b. Accomplished less than you would like	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
5c Did work or other activities less carefully than usual	Role-Emotional	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?	Social Functioning	Not at all: 5 Slightly: 4 Moderately: 3 Quite a bit: 2 Extremely: 1
7. How much bodily pain have you had during the past 4 weeks?	Bodily Pain	None: 6 Very mild: 5.4 Mild: 4.2 Moderate: 3.1 Severe: 2.2 Very severe: 1
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Bodily Pain	<u>If Question 7 Answered:</u> Not at all (and Question 7 = None): 6 Not at all (and Question 7 not None): 5 A little bit: 4 Moderately: 3 Quite a bit: 2 Extremely: 1 <u>If Question 7 Not Answered:</u> Not at all: 6 A little bit: 4.75 Moderately: 3.5 Quite a bit: 2.25 Extremely: 1
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...		
9a. Did you feel full of life?	Vitality	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9b. Have you been very nervous?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5

Question	Scale	Score
9c. Have you felt so down in the dumps that nothing could cheer you up?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9d. Have you felt calm and peaceful?	Mental Health	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9e. Did you have a lot of energy?	Vitality	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9f. Have you felt downhearted and depressed?	Mental Health	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9g. Did you feel worn out?	Vitality	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
9h. Have you been happy?	Mental Health	All of the time: 5 Most of the time: 4 Some of the time: 3 A little of the time: 2 None of the time: 1
9i. Did you feel tired?	Vitality	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
10. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?	Social Functioning	All of the time: 1 Most of the time: 2 Some of the time: 3 A little of the time: 4 None of the time: 5
11. How true or false is each of the following statements for you?		
11a. I seem to get sick a little easier than other people	General Health	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5

Question	Scale	Score
11b. I am as healthy as anybody I know	General Health	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1
11c. I expect my health to get worse	General Health	Definitely true: 1 Mostly true: 2 Don't know: 3 Mostly false: 4 Definitely false: 5
11d. My health is excellent	General Health	Definitely true: 5 Mostly true: 4 Don't know: 3 Mostly false: 2 Definitely false: 1

14.2.2 EQ-5D

Table 7: EQ-5D Scoring for Individual dimension

Scale	Score
Mobility	I have no problems walking: 1 I have slight problems walking: 2 I have moderate problems walking: 3 I have severe problems walking: 4 I am unable to walk: 5
Self-Care	I have no problems washing or dressing myself: 1 I have slight problems washing or dressing myself: 2 I have moderate problems washing or dressing myself: 3 I have severe problems washing or dressing myself: 4 I am unable to wash or dress myself: 5
Usual Activities (e.g. work, study, housework, family or leisure activities)	I have no problems doing my usual activities: 1 I have slight problems doing my usual activities: 2 I have moderate problems doing my usual activities: 3 I have severe problems doing my usual activities: 4 I am unable to do my usual activities: 5
Pain / Discomfort	I have no problems doing my usual activities: 1 I have slight problems doing my usual activities: 2 I have moderate problems doing my usual activities: 3 I have severe problems doing my usual activities: 4 I am unable to do my usual activities: 5
Anxiety / Depression	I am not anxious or depressed: 1 I am slightly anxious or depressed: 2 I am moderately anxious or depressed: 3 I am severely anxious or depressed: 4 I am extremely anxious or depressed: 5

14.2.3 Haemo-QoL-A

Table 8: Haemo-QoL-A Scoring for Individual Questions

Scale	Score	Reversed scoring (R)
Loss of joint mobility affects how I walk.	None of the time: 1	
	A little of the time: 2	
	Some of the time: 3	
	A good bit of the time: 4	
	Most of the time: 5	
	All the time: 6	
It is hard for me to climb the stairs.	None of the time: 1	
	A little of the time: 2	
	Some of the time: 3	
	A good bit of the time: 4	
	Most of the time: 5	
	All the time: 6	
It is easy for me to perform daily activities.	None of the time: 6	(R)
	A little of the time: 5	
	Some of the time: 4	
	A good bit of the time: 3	
	Most of the time: 2	
	All the time: 1	
I am unable to leave the house because of haemophilia.	None of the time: 1	
	A little of the time: 2	
	Some of the time: 3	
	A good bit of the time: 4	
	Most of the time: 5	
	All the time: 6	
I have to adjust my activities because of pain.	None of the time: 1	
	A little of the time: 2	
	Some of the time: 3	
	A good bit of the time: 4	
	Most of the time: 5	
	All the time: 6	
I am able to complete household tasks.	None of the time: 6	(R)
	A little of the time: 5	
	Some of the time: 4	
	A good bit of the time: 3	
	Most of the time: 2	
	All the time: 1	
It is easy for me to lift heavy objects.	None of the time: 6	(R)
	A little of the time: 5	
	Some of the time: 4	
	A good bit of the time: 3	
	Most of the time: 2	
	All the time: 1	

Scale	Score	Reversed scoring (R)
I depend on others to carry out activities around the home.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am able to participate in sports.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
I have difficulty traveling because of my haemophilia.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am afraid of being far from a health care center with emergency care facilities.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am hopeful about the future.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
I worry about accidents.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am afraid of being hit or bumped.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I feel less confident than others.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	

I enjoy life.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
I feel much older than my years.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am afraid of internal bleeding.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am in control of my life.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
I feel like I'm taking a risk when I do things.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I feel frustrated because I can't do what I want to do.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
Because of haemophilia, I have difficulty planning for the future.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I worry about finding or losing a job.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	

I worry about missing work or school because of my hemophilia.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I experience restrictions at work or school.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I feel like a burden to my family.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I worry about having children.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
Hemophilia interferes with my relationships with my friends.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I worry about not being able to provide for my family.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I am afraid to go to crowded places like concerts or bars for fear of being bumped or injured.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I feel different from others because of my haemophilia.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6

I feel I have the same opportunities to succeed in life as others.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
Others treat me differently.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I feel I can carry out a normal life like the rest of society.	None of the time: 6 A little of the time: 5 Some of the time: 4 A good bit of the time: 3 Most of the time: 2 All the time: 1	(R)
Hemophilia interferes with my ability to have intimate relationship with one another.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I am afraid of having a bleed in public.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
My haemophilia treatment interferes with my daily activities.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
My infusions for haemophilia are stressful.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	
I worry about the safety of my treatment.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6	

I worry about being treated by health care providers who do not know how to treat haemophilia.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6
I worry about the availability of haemophilia products.	None of the time: 1 A little of the time: 2 Some of the time: 3 A good bit of the time: 4 Most of the time: 5 All the time: 6

14.2.4 VERITAS-Pro

Table 9: VERITAS-Pro Scoring for Individual Questions

Scale	Score
Timing: I do prophylaxis infusions on the scheduled days.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Timing: I infuse the recommended number of times per week.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Timing: I do prophylaxis infusions in the morning as recommended.	Always:1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Timing: I do infusions according to the schedule provided by the treatment center.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Dosing: I use the doctor-recommended dose for infusions.	Always:1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Dosing: I infuse at a lower dose than prescribed.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1

Dosing: I increase or decrease the dose without calling the treatment center.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1
Dosing: I use the correct amount of factor boxes to total my recommended dose.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Planning: I plan ahead so I have enough factor at home.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Planning: I keep close track of how much factor and how many supplies I have at home.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Planning: I run out of factor and supplies before I order more.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1
Planning: I have a system for keeping track of factor and supplies at home.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Remembering: I forget to do prophylaxis infusions.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1
Remembering: Remembering to do prophylaxis is difficult.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1
Remembering: I remember to infuse on the schedule prescribed by the treatment center.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never: 5
Remembering: I miss recommended infusions because I forget about them.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never: 1

Skipping: I skip prophylaxis infusions.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never:1
Skipping: I choose to infuse less often than prescribed.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never:1
Skipping: If it is inconvenient to infuse, I skip the infusion that day.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never:1
Skipping: I miss recommended infusions because I skip them.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never:1
Communicating: I call the treatment center when I have questions about hemophilia or treatment.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never:5
Communicating: I call the treatment center when I have hemophilia-related health concerns or when changes occur.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never:5
Communicating: I make treatment decisions myself rather than calling the hemophilia center.	Always: 5 Often: 4 Sometimes: 3 Rarely: 2 Never:1
Communicating: I call the treatment center before medical interventions, such as dental extractions, colonoscopies, visits to the emergency room, or hospital stays.	Always: 1 Often: 2 Sometimes: 3 Rarely: 4 Never:5

14.2.5 HaemoPREF

Table 10: HaemoPREF Scoring for Individual Questions

Scale	Score
How easy is it to prepare your clotting factor treatment for injection?	0="Not at all easy" to 10="Very easy"
How easy is it to store your clotting factor treatment?	0="Not at all easy" to 10="Very easy"
How easy is It to get rid of the containers, syringes, needles and so on from your clotting factor treatment once you have used them?	0="Not at all easy" to 10="Very easy"
How easy is it to use your current clotting factor treatment?	0="Not at all easy" to 10="Very easy"
How time consuming is it to treat yourself with your clotting factor treatment?	0="Not at all time consuming" to 10="Very time consuming"
How difficult is it to find a vein that you can inject your clotting factor treatment info?	0="Not at all difficult" to 10="Very difficult"
How much does your clotting factor treatment make it difficult to travel (for holidays or for work)?	0="Not at all difficult" to 10="Very difficult"
How much does your clotting factor treatment make it difficult to do your daily activities including work or study?	0="Not at all difficult" to 10="Very difficult"
How much does your clotting factor treatment make it difficult to do social or leisure activities?	0="Not at all difficult" to 10="Very difficult"
How worried are you that your clotting factor treatment could infect you with other diseases?	0=" Not at all worried" to 10=" Very worried"
How worried are you that your clotting factor treatment could become contaminated while being prepared for injection?	0=" Not at all worried" to 10=" Very worried"
How worried are you about injecting yourself?	0=" Not at all worried" to 10=" Very worried"
How important is your family/partner's opinion about how you use your clotting factor treatment to you?	0="Not at all important" to 10="Very important"

STATISTICAL ANALYSIS PLAN- APPROVAL

Statistical Analysis Plan V1.0 (Dated 01OCT2024) for Protocol 201501.

	Name	Signature
Author:	[redacted]	[redacted]
Position:	[redacted]	
Company:	IQVIA	

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature
Approved By:	[redacted], PhD	[redacted]
Position:	[redacted], Biostatistics (SBR)	
Company:	IQVIA	
Approved By:	[redacted]	[redacted]
Position:	[redacted], Biostatistics	
Company:	Baxalta, now part of Takeda	
Approved By:	[redacted], PhD	[redacted]
Position:	[redacted], Statistical & Quantitative Sciences	
Company:	Baxalta, now part of Takeda	
Approved By:	[redacted]	[redacted]
Position:	[redacted], Clinical Science	
Company:	Baxalta, now part of Takeda	

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PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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