STATISTICAL ANALYSIS PLAN

NCT Number: NCT02764489

Study Title: A Phase 3b/4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of Tolerability and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and of Faster Infusion Rates in Patients With Hemophilia A or B With Inhibitors

Study Number: 091501

SAP Version and Date:

Version 2.0: 19-January-2022

STATISTICAL ANALYSIS PLAN

FEIBA
PHASE 3b/4

A Phase 3b/4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of Tolerability and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

PROTOCOL IDENTIFIER: 091501

Study Sponsor(s):

Baxalta US Inc.
300 Shire Way
Lexington, MA 02421,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

Author: [redacted], IQVIA (Version 1.0)

[redacted], IQVIA (Version 2.0)

Protocol: Amendment 4 (Global): 2018 MAR 07

SAP Version #: 2.0

SAP Date: 2022 JAN 19

Status: Final

REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2021 Jul 21	New Document
2.0	2022 Jan 19	• Added: subjects who received FEIBA during the blood sampling period shall be excluded from the Per-Protocol Analysis Set (Section 4.5). • Revised the treatment groups for the analyses of the questionnaires (Section 8). • FII Analyses (Section 9): *) Added guidance how to deal with FII results that are above the upper limit of quantification *) Added: unreliable FII results shall be excluded in the Per-Protocol-Analysis Set analysis *) If the standardized increase at a given time point results in a negative value, then only this value and not also all subsequent values should be set to zero.

TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BU	Bethesda units
CD4	cluster of differentiation 4
COVID-19	coronavirus disease 2019
CTMS	clinical trial management system
eCRF	electronic case report form
FAS	Full Analysis Set
FEIBA	Factor Eight Inhibitor Bypassing Activity
FII	Factor II
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IgM	immunoglobulin M
IP	investigational product
ISMC	Internal Safety Monitoring Committee
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects in each category
PPAS	Per-Protocol Analysis Set
PT	preferred term
Q1	first quartile
Q3	third quartile
rFVIIa	activated recombinant factor FVII
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SOC	system organ class
SWFI	sterile water for injection
TASI	time-averaged standardized increase
TAT	thrombin/anti-thrombin complex
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of tolerability and safety data as described in protocol amendment 4 for study 091501. Specifications for tables, figures, and listings are contained in a separate Outputs Template document.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate tolerability and safety of Factor Eight Inhibitor Bypassing Activity (FEIBA) reconstituted in a 50% reduced volume of sterile water for injection (SWFI) administered at the standard infusion rate of 2 U/kg/min and at increased rates of 4 and 10 U/kg/min, based on the occurrence of any adverse event (AE), in particular of thromboembolic events and hypersensitivity reactions.

2.1.2 Exploratory Objectives

1. To monitor pre- (within 60 min before the infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) activity of coagulation Factor II (FII).
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire.

2.2 Outcome Measures

2.2.1 Primary Outcome Measures

Tolerability and safety (local and general) related to infusion rate and volume of reconstitution will be assessed by the occurrence of all AEs including hypersensitivity, thromboembolic events and infusion site reactions, AEs leading to discontinuation, changes in vital signs and laboratory parameters which are considered AEs.

2.2.2 Exploratory Outcome Measures

1. To monitor pre- (within 60 min before the infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) activity of coagulation FII.
2. Evaluate subject treatment preference using TSQM and patient preference questionnaire.

3. STUDY DESIGN

3.1 General Description

This is a 2-part Phase 3b/4 (depending on market authorization status per country), prospective, open-label, multicenter study to compare tolerability and safety of FEIBA reconstituted in 50% reduced volume versus regular volume of SWFI, and to evaluate the safety of infusing reduced volume FEIBA at increased infusion rates of 4 and 10 U/kg/min in comparison with the standard rate of 2 U/kg/min, in 24 evaluable subjects with hemophilia A or B with inhibitors (≥ 0.6 Bethesda units [BU] in hemophilia A and B). There is no washout period prior to Part 1 or between infusions and between the two parts of the study. The overall study design for Part 1 is illustrated in Figure 1 and for Part 2 in Figure 2.

In Part 1, all subjects will be administered 2 different volumes of FEIBA every 48 hours (-8/+24 hours) in a 1:1 randomized, crossover manner. Both volumes will be given at the standard infusion rate of 2 U/kg/min. After infusion, subjects should be observed for at least 30 minutes at the study site. See section 10.3.2 of the protocol for additional details.

Treatment regimens during Part 1 of the study are:

- Part 1 Sequence A: FEIBA 2 U/kg/min in regular volume SWFI (i.e. infusions 1, 2 and 3) followed by FEIBA 2 U/kg/min in 50% reduced volume (i.e. infusions 4, 5, and 6) *or:*
- Part 1 Sequence B: FEIBA 2 U/kg/min in 50% reduced volume (i.e. infusions 1, 2, and 3) followed by FEIBA 2 U/kg/min in regular volume SWFI (i.e. infusions 4, 5, and 6)

Part 2 is non-randomized with sequential treatment of subjects who complete Part 1 to evaluate FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/kg/min. FEIBA infusions 7, 8, and 9 will be administered at the 4 U/kg/min rate followed by 3 infusions (Infusions 10, 11 and 12) of FEIBA at 10 U/kg/min.

The infusions will be administered every 48 hours (-8 hours/+24 hours) to allow time to monitor safety and tolerability of the higher infusion rate.

The treatment phases within Part 2 of the study are as follows:

1. First treatment phase: 4 U/kg/min (Infusions 7, 8, and 9)
2. Second treatment phase: 10 U/kg/min (Infusions 10, 11, and 12)

The dose of all infusions in Part 1 and Part 2 will be 85 ± 15 U/kg.
See section 8.2 of the protocol for additional details to the overall study design.

Figure 1 Study Flow Chart Part 1

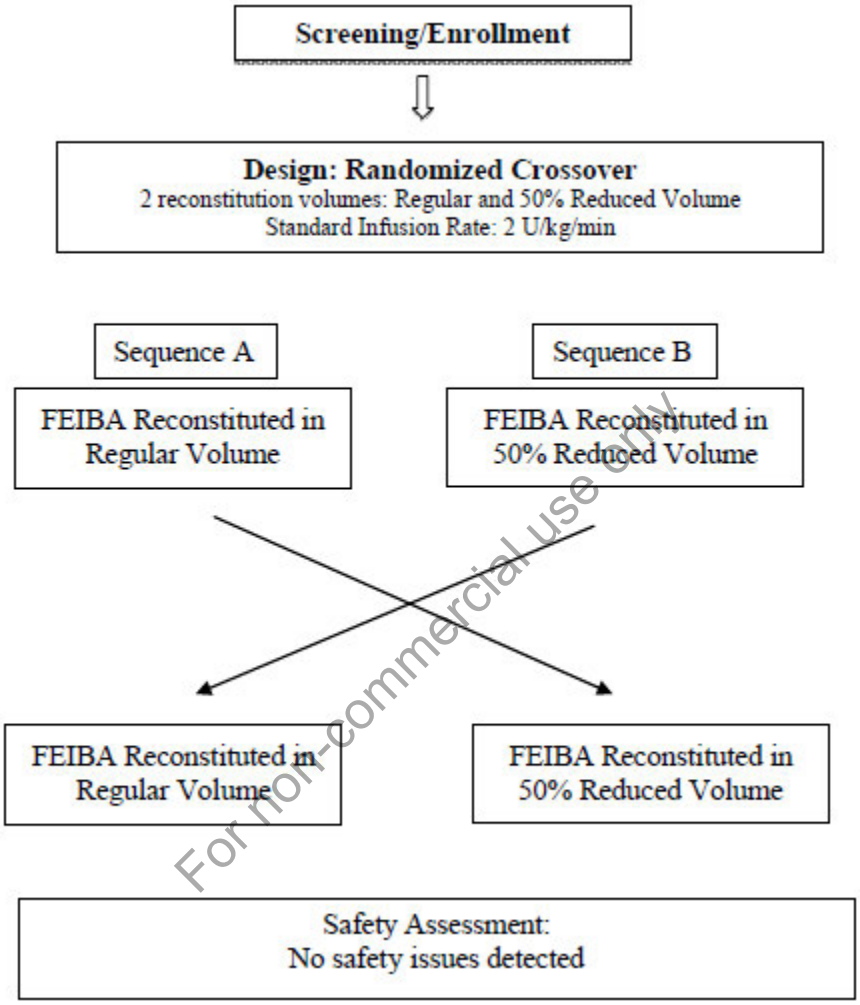
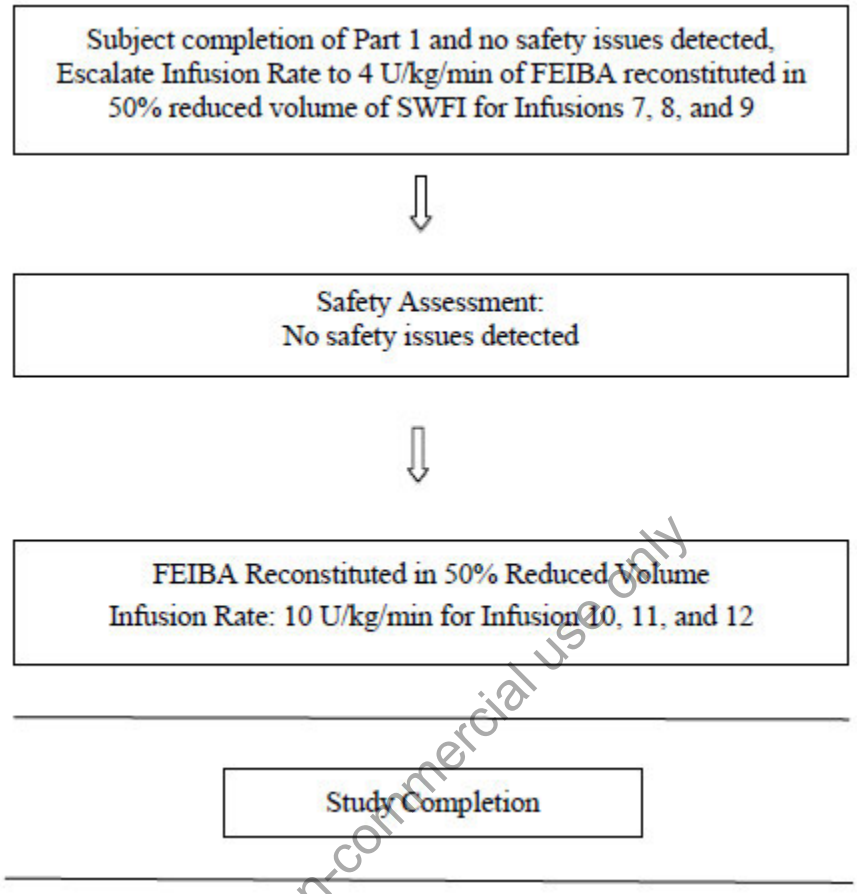


Figure 2 Study Flow Chart Part 2



3.2 Randomization and Blinding

Part 1 of this study is a randomized, crossover, active treatment clinical study. Subjects will be randomly assigned to 1 of 2 treatment sequences at a 1:1 ratio (Sequence A: FEIBA regular volume of SWFI followed by FEIBA reduced volume of SWFI or Sequence B: FEIBA reduced volume of SWFI followed by FEIBA regular volume of SWFI) . Part 2 of this study is an open-label, sequential, active treatment clinical study. In Part 2, all subjects will receive FEIBA reduced volume of SWFI at 2 varying rates of infusion.

3.3 Sample Size and Power Considerations

The sample size of 24 evaluable subjects for this safety study was determined by considering available patients and is not based on statistical power calculations. Evaluable subjects are all subjects who receive at least 2 infusions per sequence in Part 1 and at least 2 infusions per infusion rate in Part 2.

To allow a non-evaluable rate of 25%, 32 subjects will be enrolled.

4. STATISTICAL ANALYSIS SETS

4.1 Enrolled Analysis Set

The Enrolled Analysis Set will consist of all subjects who have signed informed consent as obtained from the *Screening* electronic case report form (eCRF).

4.2 Randomized Analysis Set

Randomized Analysis Set consists of all subjects in the Enrolled Analysis Set who have been randomized as obtained from the *Randomization* eCRF. Randomization is only applicable to Part 1.

4.3 Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) will include all subjects who received at least one dose of investigational product (IP) (i.e., FEIBA). All safety analyses will be performed on the SAS. Subjects will be evaluated according to the treatment (infusion volume and infusion rate) received.

4.4 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be comprised of all subjects who were randomized to study treatment in Part 1 and contains all subjects who received at least one dose of study product and have a pre-infusion FII level measurement as well as at least two post-infusion results for the same administration of infusion 1 or 3 or 4 or 6 or 9 or 12. Subjects will be evaluated according to the treatment (infusion volume and infusion rate) received.

4.5 Per-Protocol Analysis Set (PPAS)

The Per-Protocol Analysis Set (PPAS) is a subset of the FAS and contains all subjects who have no protocol violations that may affect the reliability of the FII level time profiles where subjects will be evaluated according to the treatment received.

As no eligibility criteria have an impact to the reliability of the FII levels, no subject will be excluded from the PPAS in case not all criteria are met. Nevertheless, following patients will be excluded for the exploratory analyses of the PPAS as these may affect the reliability of the FII level time profiles:

- Not treated according to the randomized treatment sequence within Part 1
- Not treated according to the planned treatment within Part 2
- No FII measurements available for the pre-infusion or corresponding 30 minutes post infusion time point
- Bleeding at start of infusion or during blood sampling period. This will be determined by using start and stop bleeding date collected in CRF.
- FEIBA or any other concomitant medication containing FII during the blood sampling period. The medical team will review all concomitant medications and will determine medications containing FII.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number of subjects who signed the informed consent as well as the screen failures will be presented in a summary table. In addition, the number and percentage of subjects who completed and prematurely discontinued the study will be presented for each study part, Part 1 will be presented by volume and Part 2 will be presented by infusion rate for subjects who received an infusion. Reasons for premature discontinuation as recorded on the *Completion/Termination* eCRF will be summarized (number and percentage) by study part, volume for Part 1 and infusion rate for Part 2. Subjects will be counted in Part 2 if they completed Part 1 and received at least 1 dose in Part 2.

A listing of all screen failures will be presented along with reasons for screen failure. In addition, the randomization assignments will be listed for the Randomized Analysis Set. Additionally, all subjects who prematurely discontinued during the study will be listed for the Enrolled Analysis Set.

The number of subjects enrolled, randomized and that completed each study part will be tabulated by site for the Enrolled Analysis Set.
A summary table showing number of subjects included in different analysis sets will also be presented.
In addition, the duration of enrollment in days, will be summarized for each site and

overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - date of informed consent + 1).

In addition, subjects that deviated from the inclusion/exclusion criteria and subjects excluded from the SAS, FAS and PPAS along with the reason for exclusion will be listed for the Enrolled Analysis Set.

The following derivations based on eCRF reported data will be performed:

- A subject is considered as completed Part 1 if "Was Part 1 completed?" from *Part 1 Completion* eCRF is "Yes" and considered as completed Part 2 if "Select one primary reason" from C*ompletion/Termination* eCRF is "Subject completed study".
- A subject is considered as discontinued in Part 1 if both following conditions are met:
    - the answer of "Was Part 1 completed?" from *Part 1 Completion* eCRF has not been answered or is equal to "No",
    - "Select one primary reason" on C*ompletion/Termination* eCRF has a reason other than "Subject completed study".
- A subject is considered as discontinued Part 2 if "Was Part 1 completed?" from *Part 1 Completion* eCRF is "Yes" and question "Select one primary reason" on C*ompletion/Termination* eCRF has a reason other than "Subject completed study".

If a subject does not complete completion/ termination visit and is lost to follow-up, the last infusion visit will be used to determine if a subject discontinued from Part 1 or Part 2.

5.2 Protocol Deviations

Protocol deviations will be recorded in the IQVIA Clinical Trial Management System (CTMS) and will be classified as critical, major or minor by the site staff and/or medical monitor. The study team will review the protocol deviations and their classification throughout the study and before treatment unblinding and database lock. Decisions of the review will include the accuracy of protocol deviations categorization based on the clinical and medical team review of the clinical database. Confirmed categorization of protocol deviations will be documented in the Protocol Deviation tracker for the study.

Critical/major/minor protocol deviations will be summarized by category and by site and overall, for the SAS. Protocol deviations will be listed for the SAS. In addition, a separate protocol deviation listing will be provided for deviations that are related to coronavirus disease 2019 (COVID-19).

Deviation categories will be included as part of the CTMS protocol deviations log and may include any of the following categories:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious AE criteria
- Visit schedule criteria
- IP compliance
- Administrative criteria
- Source document criteria
- Regulatory or ethics approval criteria
- Other criteria

5.3 Demographic and Other Screening Characteristics

Descriptive summaries of demographic and screening characteristics will be presented for all subjects in the SAS, FAS and PPAS.

Demographic and screening characteristics will be listed using the SAS.

Demographic variables will include age (year), sex, race, and ethnicity as reported on the *Demography* eCRF.

Screening characteristics, including laboratory tests that influence inclusion/ exclusion criteria, will be summarized and listed corresponding to the value which the subject was enrolled onto the study. These values will include:

- Height (cm) and weight (kg) as reported on the *Vital Signs* eCRF,
- Hemophilia type with severity and past annualized bleed rate as reported on the *Medical History Hemophilia* eCRF
- Karnofsky performance score (%) as reported on the *Karnofsky Index* eCRF
- Serum pregnancy test results as reported on the *Serum Pregnancy Test* eCRF
- FII activity, inhibitor level, hepatitis C virus antibody (including titer if positive), human immunodeficiency virus (HIV), cluster of differentiation 4 (CD4) count, platelet count from central laboratory results from external vendor.

Body mass index (BMI) will be derived (accurately to 1 decimal place) from eCRF recorded height and weight as follows for presentation in summaries and listings:

$$BMI(kg/m^2) = \frac{weight(kg)}{height(m)^2}.$$

5.4 FEIBA or rFVIIa Usage Before and During Screening

The number of subjects with a history of inhibitors as well as number of subjects who received any FEIBA or activated recombinant factor FVII (rFVIIa) within 3 weeks / within 12 months prior to screening will be summarized for all subjects in the SAS.

In addition, following listings will be presented for SAS:

- Details on history of inhibitors as well as on history of FEIBA or rFVIIa usage 3 weeks before screening and within 12 months of screening as collected on the *History of FEIBA or rFVIIa usage* eCRF
- FEIBA or rFVIIa usage during screening as collected on *Use of FEIBA or rFVIIa during the Screening Period* eCRF.

5.5 Medical and Hemophilia History

Medical history conditions as collected on the *Medical History* eCRF will be coded using Medical Dictionary for Regulatory Activities (MedDRA) as specified in the data management coding guidelines. The number and percentage of subjects for each medical history condition, as well as the number of events, will be tabulated by system organ class (SOC) and preferred term (PT) for all subjects in the SAS.

Listings for medical history and hemophilia history as collected on the *Medical History Hemophilia* eCRF will be presented for all subjects in the SAS.

5.6 Prior and Concomitant Medications, Therapies and Procedures

All data on medications, therapies and procedures will be obtained from the *Concomitant Medications/Non-Drug Therapy* eCRF. Medications and Non-Drug therapies will be coded using the version of the World Health Organization - Drug Dictionary (WHO-DD) as specified in the data management coding guidelines. Procedures will be coded using MedDRA.

Medications, therapies, and procedures will be assigned as prior or to a study stage (regular volume, reduced volume, 4 U/kg/min or 10 U/kg/min). Medications, therapies

and procedures will be assigned as prior if medication, therapy or procedure stopped prior to first administration of FEIBA.

Medications, therapies and procedures will be assigned as concomitant if they either:

- started on or after the first FEIBA administration, or
- started before the first FEIBA administration and are still ongoing, or
- started before the first FEIBA administration and ended after the first FEIBA administration

Refer to Section 11.4 for classification of medications, therapies and procedures. Since the medications, therapies and procedures can continue over more than one study stage, medications, therapies, and procedures can be assigned to more than one study stage.

No imputation on dates for medications, therapies or procedures will be performed. Where possible, the assignment of prior, regular volume, reduced volume, 4 U/kg/min and 10 U/kg/min will still be done if it is clear from the partial date to which category the medication, therapy or procedure belongs. If missing dates do not allow for assignments on above rules, unknown will be assigned.

The number and percentage of subjects for prior medications will be tabulated for all subjects in the SAS. Concomitant medications will be summarized for the SAS separated by groups as described in Section 7 as well as for all subjects in the SAS.

Medication, therapy, and procedure data will be listed for all subjects in the SAS.

5.7 Exposure to Investigational Product

Information on FEIBA administration will be obtained from *Study Drug Administration* eCRF.

The following derivations based on eCRF reported data will be performed:

- Body weight adjusted dose will be derived using the amount infused (U) and the last available body weight (kg) as obtained from *Vital Signs* eCRFs prior to the infusion as follows:

$$Body\ weight\ \ adjusted\ dose(U/kg) = \frac{Amount\ infused(U)}{Body\ weight(kg)}.$$

- The total number of infusions for each infusion reason and overall will be determined as the count of infusions per infusion reason.
- The average body weight adjusted dose (U/kg) per infusion reason will be derived as:

$$Average\ Body\ Weight\ Adjusted\ Dose(U/kg)\ per\ infusion\ reason = \frac{Total\ Body\ Weight\ Adjusted\ Dose\ Infused(U/kg)}{Number\ of\ Infusions}.$$

- The infusion rate (U/kg/min) will be derived for infusions that were not interrupted using the body weight adjusted dose (U/kg) and the time from infusion start to infusion end (min) as follows:

$$Infusion\ Rate\ (\mathrm{U/kg/min}) = \frac{Body\ Weight\ Adjusted\ Dose\ Infused(U/kg)}{Infusion\ End\ Time - Infusion\ Start\ Time\ (\mathrm{min})}.$$

Information on exposure will be summarized for the SAS separated by groups as described in Section 7 as well as for all subjects in the SAS. Information on study drug administration and exposure will be listed.

The compliance based on infusion rate will be derived from above mentioned formula based on the infusion start and stop time captured in eCRF.

The compliance based on infusion volume will be calculated based on the actual applied concentration (U/ml). For the regular volume, the expected concentration is 50 U/ml, for the reduced volume the expected concentration is 100 U/ml.

Compliance to FEIBA prophylactic infusions will be based on number of infusions, dose, rate and volume. The following infusions will be considered as non-compliant:

- Any infusion outside the recommended dose of 85 ± 15 U/kg: the compliance measure regarding dose is calculated as the number of infusions within ±15 U/kg of the planned dose of 85 U/kg divided by the total number of applied infusions.
- Any infusion outside ±10% of required infusion volume: the compliance measure regarding volume is calculated as the number of infusions within 10% of the planned volume divided by the total number of applied infusions.

- Any infusion outside ±10% of required infusion rate: the compliance measure regarding rate is calculated as the number of infusions that were not interrupted and were within 10% of the planned rate divided by the total number of applied infusions that were not interrupted (i.e. infusions that were interrupted will not be taken into account).

Descriptive statistics will be performed for the compliances regarding dose, volume and rate for the SAS separated by groups as described in Section 7 as well as for all subjects in the SAS. Additionally, the number of subjects with 0, 1, 2 or 3 applied infusions will be presented separately by groups 1-4 as described in Section 7. In addition, a listing of all non-compliant infusions will be listed for subjects in the SAS.

6. EFFICACY ANALYSES

Not applicable.

7. SAFETY ANALYSIS

The safety analysis will be performed using the SAS and will be summarized by the following groups as well as for all subjects:

- 1st group: regular volume and regular rate (i.e. 2 U/kg/min)
- 2nd group: reduced volume and regular rate (i.e. 2 U/kg/min)
- 3rd group: reduced volume and increased rate (i.e. 4 U/kg/min)
- 4th group: reduced volume and increased rate (i.e. 10 U/kg/min)
- 5th group: group 1 and 2 together (overall regular rate)
- 6th group: group 2, 3 and 4 together (overall reduced volume)

The first 4 groups from above will be derived based on the timing of each parameter, as described in Section 11.4, using the labels above. The pooled treatment groups will be derived by adding the number of subjects from each respective group (e.g. the overall regular rate will be derived by adding the number of subjects from group 1 and 2).

Safety variables include AEs, clinical laboratory variables and vital signs. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable. Refer to Section 11.3 for more details on baseline.

7.1 Adverse Events

AEs as obtained from the *Adverse Event* eCRF will be coded using the version of the MedDRA as specified in the data management coding guidelines. Information on infusion evaluation will be obtained from *Infusion Evaluation* eCRF. Infusion volume and infusion rate that subject was actually randomized to will be used for safety analysis.

An AE will be considered as treatment-emergent AE (TEAE) if it has started during or after first administration of FEIBA. If the start date is partially completed, it is expected that an indication is provided on the eCRF on whether the AE started prior to first administration of FEIBA or after. On the basis of AE start date, AEs will be also be categorized into regular volume, reduced volume, 4 U/kg/min or 10 U/kg/min (refer to Section 11.4 for more information on how AEs will be categorized to infusion volume and infusion rate). If start date be partially completed, it is expected that an indication is provided after which infusion the AE occurred and AEs will be assigned as follows:

- Regular volume: If infusion volume of last infusion before AE is regular and infusion rate is 2 U/kg/min
- Reduced volume: If infusion volume of last infusion before AE is reduced and infusion rate is 2 U/kg/min
- 4 U/kg/min: If infusion volume of last infusion before AE is reduced and infusion rate is 4 U/kg/min
- 10 U/kg/min: If infusion volume of last infusion before AE is reduced and infusion rate is 10 U/kg/min

No imputation of dates will be required to determine if an AE occurred during or after first administration of FEIBA or during which study stage (regular volume, reduced volume, 4 U/kg/min or 10 U/kg/min).

An overall summary of the number of subjects with TEAEs as well as the number of events presented for the SAS:

- All TEAEs
- TEAEs by maximum severity
- Serious TEAEs
- TEAEs related to FEIBA
- Serious TEAEs related to FEIBA
- TEAEs leading to death
- TEAEs leading to drug withdrawal
- TEAEs leading to study discontinuation

- TEAEs considered an allergic-type hypersensitivity reaction to FEIBA
- TEAEs considered an infusion site reaction
- TEAEs considered a thrombotic event
- TEAEs related to study procedures
- Local TEAEs
- Systemic TEAE
- Temporally associated TEAEs
- Temporally associated or potentially related TEAEs.

Definition of temporally associated TEAEs:

Temporally associated TEAEs are defined as AEs that begin during infusion or within 24 hours (or 1 day where time of onset is not available) after completion of infusion, irrespective of being related or not related to treatment.

Definition of temporally associated or potentially related TEAEs:

Temporally associated or potentially related TEAEs are defined as:

(a) an AE that began during infusion or within 24 hours (or 1 day where time of onset is not available) after completion of infusion, or

(b) an AE considered by either the investigator and/or the sponsor to be possibly or probably related to study drug, or

(c) an AE for which causality assessment was missing.

The following tables will be also created by SOC and PT and presented by descending incidence for SOC and PT in the overall group:

- All TEAEs
- Serious TEAEs
- TEAEs related to FEIBA
- Serious TEAEs related to FEIBA
- TEAEs considered an infusion site reaction
- TEAEs related to study procedures
- Local TEAEs
- Systemic TEAE
- Temporally associated TEAEs
- Temporally associated or potentially related TEAEs.

In addition, tables of TEAEs will be prepared to list each PT, the number of subjects who experienced a PT at least once, and the rate of subjects with PT(s). In these tables, the PTs will be grouped by SOC. Each TEAE will then be divided into defined severity

grades (mild, moderate, severe) and relationship to study drug (related, not related). Subject identifiers will be included within each PT. If the same subject experiences multiple TEAEs categorized under the same PT and relationship assessment, this TEAE is shown only once at its most serious severity. These tables will be sorted alphabetically and carried out for:

- All TEAEs
- Serious TEAEs
- TEAEs considered an infusion site reaction
- TEAEs related to study procedures
- Local TEAEs
- Systemic TEAE
- Temporally associated TEAEs
- Temporally associated or potentially related TEAEs.

The following listings will be presented:

- All TEAEs
- Serious TEAEs
- TEAEs leading to death
- TEAEs leading to drug withdrawal
- TEAEs leading to study discontinuation
- TEAEs considered a hypersensitivity reaction to study drug
- TEAEs considered a thromboembolic event
- TEAEs considered an infusion site reaction
- Pre-treatment AEs for subjects who were treated with IP
- Lab results considered as TEAEs
- Vital sign results considered as TEAEs
- AEs of subjects who were never treated with IP.

The following derivations based on eCRF reported data will be performed:

Relationship of AE:

The AE will be considered related to FEIBA if relationship is indicated as “Possibly related” or “Probably related” in the eCRF. AEs indicated as “Not related and “Unlikely related” will be summarized as “Not related”.

Handling of unknown causality assessment:

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned. The imputed values for relationship to IP will be used for summary tables but not for listings.

Severity of AE:

Severity of AEs will be summarized as reported in the eCRF.

Handling of unknown severity grades:

- If a subject experiences more than one AE categorized under the same PT, one of them is categorized as "severe" and one of them is categorized as "unknown", then the maximum severity for this PT will be counted as "severe".
- If a subject experiences more than one AE categorized under the same PT, one of them is categorized as "mild" or "moderate" and one of them is categorized as "unknown", then the maximum severity for this PT will be counted as "unknown". A row "Unknown" will be inserted for those AEs.

The imputed values for severity assessment will be used for summary tables but not for listings.

Duration of AE:

The duration of AE will be calculated as:

$$Duration(Hours) = (Stop\ Date\ and\ Time) - (Start\ Date\ and\ Time)$$

if time is available for both the start and stop dates of the AE. The duration will be presented in hours should the result be ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

If time is missing for either the start date or the stop date of the AE, or the duration as calculated above resulted in > 24 hours, then the duration will be presented in days, calculated as follows:

$$Duration(Days) = (Stop\ Date) - (Start\ Date) + 1.$$

If either the start date or stop date is partial or completely missing, no duration will be calculated.

Time since last FEIBA administration:

Time since last FEIBA administration will only be presented for TEAEs. The last FEIBA administration is defined as the administration immediately preceding the start of the AE. The start date of the preceding FEIBA administration will be used for all calculations.

Time since last FEIBA administration will be calculated as:

$$Time\ Since\ Last\ FEIBA\ Administartion(Hours) = (AE\ Start\ Date\ and\ Time) - (Date\ and\ Time\ of\ Last\ FEIBA\ Administartion)$$

if time is available for both the AE start date and last FEIBA administration. Time since last FEIBA administration will be presented in hours should the result be ≤ 24 hours. If the result is > 24 hours the result will be presented in days as described below.

If time is missing from either the AE start date or last FEIBA administration, or the time since last FEIBA administration is > 24 hours, then the result will be presented in days, calculated as follows:

$$Time\ Since\ FEIBA\ Administration(Days) = (AE\ Start\ Date) - (Date\ and\ Time\ of\ Last\ FEIBA\ Administartion) + 1.$$

7.2 Bleeding Episodes

Information on bleeding episodes as obtained from *Bleeding Episodes* eCRF will be summarized and listed.

7.3 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values as obtained from the central laboratory (in standardized units), their changes from baseline and shift tables from baseline will be presented. Refer to Section 11.3 for definition of baseline.

Table 4 of the protocol provide the details of clinical laboratory assessments.

Hematology, chemistry and serology will be presented by shift tables, baseline versus completion/ termination visit in low/normal/high values and in clinically significant/not clinically significant/total values.

Coagulation will be presented by line graphs over time for each subject. Normal ranges will be inserted into the graphs and information of clinical significance will be annotated.

The following clinical laboratory parameters will be included in analyses:

Hematology Complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count])] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet counts.

Chemistry Sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, glucose, gamma-glutamyl transpeptidase, and 5'-nucleotidase.

Coagulation Activated partial thromboplastin time (aPTT), prothrombin time, and thrombotic markers (D-Dimers, prothrombin fragment F 1+2, thrombin/anti-thrombin complex [TAT], and fibrinopeptide A).

Viral Serology HIV-1 and HIV-2 antibody, hepatitis A virus antibody, hepatitis B surface antigen, hepatitis C virus antibody (including titer if positive), parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).

All laboratory data including data from local laboratories will be listed for the SAS. In addition, abnormal laboratory data (i.e. outside reference range) will also be listed – in case a laboratory value is abnormal for a specific parameter and subject, then all results of that laboratory test will be listed for this subject.

Any quantitative laboratory measurement reported as "<X", i.e., below the limit of quantification, or ">X", i.e., above the upper limit of quantification will be presented as recorded, i.e., as "<X" or ">X" in listings.

All safety laboratory results except the FII measurements recorded as "<X" or ">X" will be summarized as "X". For FII measurements, values below the lower limit of

quantification (LLOQ) or above the upper limit of quantification (ULOQ) will be set as described in Section 9.

7.4 Vital Signs

Descriptive statistics for vital signs as obtained from the *Vital Signs* and *Vital Signs (Predose and Postdose)* eCRFs (e.g., body temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate) and their percent changes from baseline will be presented. The pre-infusion value of next visit will be used as nominal 48 hours' post timepoint. Change from baseline will be calculated by taking the average percent change from baseline to all post-infusion timepoints for each subject and group.

The percent change from baseline will be derived as:

$$Change\ from\ Baseline\ at\ Timepoint\ X\ (\%) =$$

$$\frac{(Value\ at\ Timepoint\ X) - (Value\ at\ Baseline)}{(Value\ at\ Baseline)} \times 100.$$

All vital signs data will be listed for the SAS.

8. QUESTIONNAIRES

Responses to individual questions from the *Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM)* and *Patient Preference Questionnaire* eCRFs will be summarized for the SAS separated by the groups described below:

- 1st group: After Screening Prior to Infusion 1
- 2nd group: Sequence A - After Regular Volume / Regular Rate 2 U/kg/min and Prior to 50% Reduced Volume / Regular Rate 2 U/kg/min
- 3rd group: Sequence B - After 50% Reduced Volume / Regular Rate 2 U/kg/min and Prior to Regular Volume / Regular Rate 2 U/kg/min
- 4th group: Sequence A - After 50% Reduced Volume / Regular Rate 2 U/kg/min and Prior to 50% Reduced Volume / Increased Rate 4 U/kg/min
- 5th group: Sequence B - After Regular Volume / Regular Rate 2 U/kg/min and Prior to 50% Reduced Volume / Increased Rate 4 U/kg/min
- 6th group: After 50% Reduced Volume / Increase Rate 4 U/kg/min and Prior to 50% Reduced Volume / Increased Rate 10 U/kg/min
- 7th group: After 50% Reduced Volume / Increased Rate 10 U/kg/min

For the TSQM, effectiveness, global satisfaction and convenience scores will be summarized by the groups as described above.

Effectiveness, global satisfaction and convenience scores will be computed as follows:

- Effectiveness
  - If there is no missing data for the first 3 items, then the effectiveness score is computed as $Score = \frac{[(TSQM01+TSQM02+TSQM03)-3]/18}{100}$
  - If there is 1 missing data for the first 3 items, then the effectiveness score is computed as $Score = \frac{[(TSQM01+TSQM02+TSQM03)-2]/12}{100}$
  - Missing if more than 1 item is missing among the first 3 items
- Convenience
  - If there is no missing data for the items 4 to 6, then the convenience score is computed as $Score = \frac{[(TSQM04+TSQM05+TSQM06)-3]/18}{100}$
  - If there is 1 missing data for the items 4 to 6, then the convenience score is computed as $Score = \frac{[(TSQM04+TSQM05+TSQM06)-2]/12}{100}$
  - Missing if more than 1 item is missing among items 4 to 6
- Global Satisfaction
  - If there is no missing data for the items 7 to 9, then the global satisfaction score is computed as $Score = \frac{[(TSQM07+TSQM08+TSQM09)-3]/14}{100}$
  - If TSQM07 or TSQM08 is missing, but TSQM09 isn't, then the global satisfaction score is computed as $Score = \frac{[(TSQM07+TSQM08+TSQM09)-2]/10}{100}$
  - If both TSQM07 and TSQM08 are not missing, but TSQM09 is, then the global satisfaction score is computed as $Score = \frac{[(TSQM07+TSQM08)-2]/8}{100}$
  - Missing if more than 1 item is missing among items 7 to 9

The following table will be used for TSQM item numbering:

TSQM0101	1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
TSQM0102	2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
TSQM0103	3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
TSQM0104	4. How easy or difficult is it to use the medication in its current form?
TSQM0105	5. How easy or difficult is it to plan when you will use the medication each time?
TSQM0106	6. How convenient or inconvenient is it to take the medication as instructed?
TSQM0107	7. Overall, how confident are you that taking this medication is a good thing for you?
TSQM0108	8. How certain are you that the good things about your medication outweigh the bad things?
TSQM0109	9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

9. FACTOR II (FII) LEVELS

Due to uncertainty around prior dosing/steady state and the unknown clinical relevance of FII as lead marker for FEIBA, FII levels will be analyzed as standardized increase from the corresponding pre-dose levels. The minimum, time-averaged up to 48 hours (for the nominal 48 hour time point, the pre-infusion value of the next infusion will be used), and maximum standardized increase from the pre-dose level will be analyzed for descriptive purposes only for the FAS as well as for the PPAS. In the PPAS analysis, unreliable FII results will be excluded. Unreliable FII results that will be excluded from the PPAS will be marked in the FII listing.

Standardized increase from pre-dose levels will be calculated with the following formula:

$$\text{Standardized Increase} = \frac{(C_t - C_{pre})}{dose}$$

where C_t refers to the FII level at time point t, C_{pre} refers to corresponding pre-dose level and dose to the weight adjusted dose. For the FII analyses, values below the LLOQ will be set to half of the LLOQ for calculation of standardized increase. FII concentration

values above the ULOQ will be set to missing for calculation of standardized increase. These samples will not be included in the analysis because the actual values are not reported. If the standardized increase at a given time point results in a negative value, then this value should be set to zero.

The minimum standardized increase is defined as the minimum value over the 48-hour sampling period, while the maximum standardized increase is defined as the maximum value over the 48-hour sampling period. The time-averaged standardized increase (TASI) up to 48 hours will be calculated based on the area under the curve (AUC) of the standardized increase up to 48 hours as

$$TASI = \frac{AUC_{0-48h}}{48\ h}$$

$AUC_{0\text{-}48h}$ will be calculated as:

$$AUC_{0-48h} = \sum_{i=1}^{x} \frac{1}{2}(y_i + y_{i-1})(t_i - t_{i-1})$$

where y_i is the standardized increase at the actual time t_i (i.e. after start of preceding infusion) and x is the number of timepoints for a given subject where $y_i = 0$ should be used for $t_i = 0$. For calculation of $AUC_{0\text{-}48h}$, the FII level at exactly 48 hours will be log-linearly interpolated/extrapolated from the two nearest sampling points from the same FII level profile for calculating the standardized increase at exactly 48 hours.

The minimum and maximum standardized increase will only be calculated following an infusion if at least the corresponding pre-infusion and at least one-post infusion FII result is available for that infusion. The time-averaged up to 48 hours increase will only be calculated following an infusion if at least the corresponding pre-infusion and at least two post-infusion FII results are available for that infusion.

For the purpose of estimating a potential impact of infusion volume (regular and reduced volume within Part 1) at an infusion rate of 2 U/kg/min on the minimum, time-averaged up to 48 hours, and maximum standardized increase, a linear mixed effects model will be used that models the sequence, infusion number, and volume as fixed effects and subject

nested within sequence as random effect. The following SAS® code will be used based on FII data after infusions 1, 3, 4 and 6:

```
proc mixed data = <Part1>;
  class subject sequence inf_number volume;
  model standardized_increase = sequence inf_number volume / ddfm
  = kr;
  random subject(sequence)/ type=VC;
  lsmeans volume / pdiff cl;
run;
```

where standardized_increase is either minimum, time-averaged up to 48 hours, or maximum standardized increase, sequence is either "Sequence A" or "Sequence B", volume is either "Regular" or "Reduced", and inf_number is either "Infusion 1", "Infusion 3", "Infusion 4" or "Infusion 6". Of note, study part 1 consists of two sequences each with 6 infusions (i.e. 6 periods) and the variable infusion number is in-line with the periods 1, 3, 4 and 6 where full FII profiles will be available.

For Part 1, the minimum, time-averaged up to 48 hours, and maximum standardized increase will be listed per subject and infusion (i.e. after infusion 1, 3, 4 and 6) and displayed graphically using subject profiles plot showing between-subject variability and the difference in the response between regular and reduced volume within each subject by sequence for the FAS and PPAS. The minimum, time-averaged up to 48 hours, and maximum standardized increase will be also summarized among subjects using the mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum grouped by sequence and infusion number where infusion numbers 1, 3 within sequence A and 4, 6 within sequence B refer to regular volume and infusion numbers 4, 6 within sequence A and 1, 3 within sequence B refer to reduced volume.

For the purpose of estimating a potential impact of infusion rates (4 and 10 U/kg/min within Part 2) with reduced volume on the minimum, time-averaged up to 48 hours, and maximum standardized increase, a linear mixed effects model that models infusion rate as fixed and subject as random effect will be used. The following SAS® code will be used

based on FII data after infusion 9 (i.e. infusion rate of 4 IU/kg/min) and infusion 12 (i.e. infusion rate of 10 U/kg/min):

```
proc mixed data = <Part2>;
  class subject infusion_rate;
  model standardized_increase = infusion_rate / ddfm = kr;
  random subject / type=VC;
  lsmeans infusion_rate / pdiff cl;
run;
```

where standardized_increase is either minimum, time-averaged up to 48 hours, or maximum standardized increase, and infusion_rate is either to "4 U/kg/min" or "10 U/kg/min".

For Part 2, the minimum, time-averaged up to 48 hours, and maximum standardized increase will be listed per subject and infusion rate (i.e. after infusion 9 and 12 for infusion rates of 4 and 10 U/kg/min, respectively) and displayed graphically using subject profiles plot showing between-subject variability and the difference in the response between infusion rates within each subject for the FAS and PPAS. The minimum, time-averaged up to 48 hours and maximum standardized increase will be also summarized among subjects using the mean, SD, median, Q1, Q3, minimum and maximum grouped by infusion rate (i.e. for infusion rates of 4 or 10 IU/kg/min following infusions 9 and 12, respectively).

The potential impact of infusion volume as well as the potential impact of infusion rates on the minimum, time-averaged up to 48 hours and maximum standardized increase will be assessed descriptively by least squares means for each infusion volume, for each infusion rate and their differences along with corresponding two-sided 95% confidence intervals obtained from the models described above.

Individual plots of FII levels as well as of the corresponding standardized increase over time will be also generated for the FAS.

10. INTERIM ANALYSIS/ INTERNAL SAFETY MONITORING COMMITTEE (ISMC)

Safety reviews will be performed by the Internal Safety Monitoring Committee (ISMC) during the trial, and no formal interim analysis will be performed. Analyses for the ISMC are described in a separate document.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

In case an analysis set is identical to another analysis set or if the difference is less or equal to 1 subject, then the respective table will not be repeated, but a statement within the respective tables will be added (e.g. in case the FAS is identical to the PPAS, tables on the PPAS will not be created, but the following statement within the respective tables will be added: "The Full Analysis Set is identical to the Per-Protocol Analysis Set, therefore this table was not repeated.").

Unless otherwise specified the default summary statistics for quantitative variables will be as follows:

- The number of subjects in each category (n)
- Mean
- SD
- Q1
- Median
- Q3
- Minimum
- Maximum

If the original data has N decimal places (as derived from the raw data) (i.e., decimal precision [N]) then the summary statistics will contain the following decimal places (with a maximum of three decimals):

- Minimum and maximum: N decimals
- Mean, median, Q1 and Q3: N + 1 decimals
- SD: N + 2 decimals

For qualitative variables the number (n) and percentage (%) of subjects in each category will be the default summary presentation. Unless otherwise specified, percentages will be calculated relative to the total number of subjects in the relevant analysis set with data available as described in the latest version of the Output Templates and this SAP.

All values will be rounded using the SAS® function ROUND. All computed percentages will be presented using one decimal place.

11.2 Reference Start Date and Study Days

The reference start date for presentation of study days in data listings will be the date of first FEIBA administration obtained from the *Study Drug Administration* eCRF. The reference start date will be referred to as Day 1.

If the date of the event is on or after the reference start date, then study day will be derived as:

$$Study\ Day = Date\ of\ Event - Reference\ Start\ Date + 1.$$

If the date of the event is prior to the reference start date, then study day will be derived as:

$$Study\ Day = Date\ of\ Event - Reference\ \text{Start}\ Date.$$

Phase start date will be the date of first FEIBA administration within each phase where phase refers to regular volume Part 1, 50% reduced volume Part 1, 4 U/kg/min Part 2 and 10 U/kg/min Part 2.

If the date of the event is on or after the phase start date, then phase day will be derived as:

$$Phase\ Day = (Date\ of\ Event) - (Phase\ Start\ Date) + 1.$$

If the date of the event is prior to the phase start date, then phase day will be derived as:

$$Phase\ Day = (Date\ of\ Event) - (Phase\ \text{Start}\ Date).$$

11.3 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to first IP infusion.

11.4 Classification of Events

An event in Part 1 will be assigned as regular or 50% reduced volume using the following rules:

- If subject started in sequence A:
  - Regular volume: if date/time of event is on or after date/time of first regular volume infusion, but prior to the date/time of first 50% reduced volume infusion.
  - 50% Reduced volume: if date/time of event is on or after date/time of first 50% reduced infusion, but prior to date/time of first infusion for Part 2.
- If subject started in sequence B:
  - 50% Reduced volume: if date/time of event is on or after date/time of first 50% reduced infusion, but prior to date/time of first regular volume infusion.
  - Regular volume: if date/time of event is on or after date/time of first regular infusion, but prior to date/time of first infusion for Part 2.

A subject is considered as started in sequence A if sequence is indicated as "Part 1 Sequence A" and considered as started in sequence B if sequence is indicated as "Part 1 Sequence B" as obtained from *Randomization* eCRF. The date/time of first regular volume infusion is the date/time of first infusion where volume infused is "Regular" and infusion rate is "2 U/kg/min" as obtained from *Study Drug Administration* eCRF. The date/time of first 50% reduced volume infusion is the date/time of first infusion where volume infused is "Reduced" and infusion rate is "2 U/kg/min" as obtained from *Study Drug Administration* eCRF. Date/time of first infusion for Part 2 is the date/time of first infusion where volume infused is "Reduced" and infusion rate is "4 U/kg/min" as obtained from *Study Drug Administration* eCRF.

An event in Part 2 will be assigned as 4 U/kg/min or 10 U/kg/min using the following rules:

- 4 U/kg/min: if date/time of event is on or after date/time of first infusion in Part 2 and prior to date/time of first 10 U/kg/min infusion.
- 10 U/kg/min: if date/time of event is on or after date/time of first 10 U/kg/min infusion.

Date/time of first 10 U/kg/min infusion is date/time of first infusion where volume infused is "Reduced" and infusion rate is "10 U/kg/min" as obtained from *Study Drug Administration* eCRF.

If time for infusion or event is not available, date without time will be used for both infusion and event.

11.5 Repeated or Unscheduled Assessments

In the case of retests, the last available measurement for that visit will be used for by-visit summaries.

In general, unscheduled results will not be included in summaries, unless a result is re-assessed it might be decided to use the re-assessed result instead of the original result. Unscheduled results will be included in subject listings.

11.6 Handling of Missing, Unused, and Spurious Data

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If data are considered spurious (e.g. for lack of biological plausibility), it will be documented along with the reason for exclusion and the analyses from which the data were excluded.

Subjects who withdraw prior to the last planned observation in the study period will be included in the analyses up to the time of withdrawal.

Outcome specific handling of missing data are described in the relevant section. Unless otherwise specified, no action will be made to handle missing data.

12. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 or higher of SAS®.

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Enrolled analysis set, randomized analysis set, FAS and PPAS have been added to keep only certain subjects for analyses.

14. REFERENCES

Not applicable.