CLINICAL STUDY PROTOCOL

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

Protocol Versions and Date:

Version 4.0: 07 March 2018
Version 3.0: 14 September 2017
Version 2.0: 04 August 2017
Version 1.0: 03 March 2016
Original Protocol: 08 October 2015

16.1.1 Protocol and Protocol Amendments

091501 Original Protocol 2015Oct08

091501 Protocol Amendment 1 2016Mar03

091501 Protocol Amendment 2 2017Aug04

091501 Protocol Amendment 3 2017Sep14

091501 Protocol Amendment 4 2018Mar07

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CLINICAL STUDY PROTOCOL

PRODUCT: Anti-inhibitor Coagulant Complex, FEIBA

STUDY TITLE: A Two-part, Phase 4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

STUDY SHORT TITLE: FEIBA Reconstitution Volume Reduction and Faster Infusion Study

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

ORIGINAL: 2015 OCT 08

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-004079-60
IND NUMBER: 13715

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Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted] MD
[redacted] Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

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2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

**ALL SAEs ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (ECRF)
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE ECRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.**

See SAE Protocol Sections for further information and SAER form for contact information.
Further details are also available in the study team roster.

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For definitions and information on the assessment of these events, refer to the following:

- Adverse Event, Section 12.1
- Serious Adverse Event, Section 12.1.1.1
- Assessment of Adverse Events, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	FEIBA, Anti-Inhibitor Coagulant Complex
Name(s) of Active Ingredient(s)	Coagulation factors II, X, IX, and VIIa
CLINICAL CONDITION(S)/INDICATION(S) • Hemophilia A or B with inhibitors	
PROTOCOL ID	091501
PROTOCOL TITLE	A Two-part, Phase 4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors
Short Title	FEIBA Reconstitution Volume Reduction and Faster Infusion Study
STUDY PHASE	Phase 4 (postmarketing)
PLANNED STUDY PERIOD	
Initiation	First Subject In: Q2 2016
Primary Completion	Last Subject In: Q1 2017
Study Completion	Last Subject Last Visit: Q1 2018
Duration	21 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose 1. To compare the pharmacokinetics (PK) of FEIBA (Factor Eight Inhibitor Bypassing Activity) component (Factor II [FII]) and safety of FEIBA reconstituted in a reduced volume of sterile water for injection (SWFI) versus regular volume SWFI, administered at the standard infusion rate of 2 U/min/kg 2. To evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison to the standard rate of 2 U/min/kg in Part 1	
Primary Objectives 1. Determine PK equivalence of FEIBA component (FII) reconstituted in 50% reduced volume SWFI and regular volume SWFI on area under the curve from time zero (preinfusion) to time 216 hours ($AUC_{0\text{-}216\ h}$) 2. Determine the occurrence of severe allergic reactions (e.g., anaphylaxis)	

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Secondary Objectives

1. Determine the safety and tolerability of 50% reduced volume FEIBA administered at the standard and escalated infusion rates, based on the occurrence of adverse events (AE)
2. Monitor clinically apparent thromboembolic events, changes in vital signs, infusion rate-related events, and infusion site reactions
3. Determine the effect of 50% reduced volume FEIBA component (FII) on incremental recovery (IR), area under the curve from time zero (preinfusion) extrapolated to infinity ($AUC_{0-\infty}$), area under the concentration-time curve from time zero (preinfusion) to time of last quantifiable concentration (AUC_{0-last}), terminal half-life ($t_{1/2}$), clearance (CL), mean residence time (MRT), volume of distribution at steady state (V_{ss}), maximum plasma concentration (C_{max}), and time to maximum observed plasma concentration (t_{max})

Exploratory Objective

[redacted]

2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

STUDY DESIGN

Study Type/ Classification/ Discipline	PK Equivalence, Pharmacokinetic, and Safety
Control Type	Active
Study Indication Type	Treatment
Intervention model	Part 1: Crossover Part 2: Sequential
Blinding/Masking	Part 1: Randomized, Open-label Part 2: Non-randomized, Open-label
Study Design	This study is a 2-part, Phase 4, prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.4 Bethesda units [BU] in hemophilia A and ≥ 0.6 BU in hemophilia B) for the primary PK assessment, (i.e., having the $AUC_{0-216\ h}$ of FEIBA component FII estimable from both PK infusions), with a planned enrollment of 32 subjects. In Part 1, subjects will be administered 2 different volumes of FEIBA in a randomized, crossover manner with a washout period between the treatments. Part 1 will evaluate the PK (FEIBA component FII) and safety of FEIBA reconstituted in 50% reduced volume of SWFI and administered at the standard infusion rate of 2 U/min/kg compared with FEIBA reconstituted in regular volume of SWFI at the standard infusion rate. All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria.

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	After a washout period (at least 12 days from last treatment with FEIBA, or at least 24 hours after last treatment with a recombinant activated clotting factor VII (rFVIIa) product [e.g., NovoSeven®]), eligible subjects will be randomized (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. Subjects will receive the first infusion for PK and safety analysis and the second and third infusions for collection of additional safety data. After a washout period of at least 12 days following the third infusion, subjects will crossover to the next treatment group where the fourth infusion will be for PK and safety analysis and the fifth and sixth infusions for collection of additional safety data. All evaluable subjects will be included in the safety analysis set. Pharmacokinetic equivalence of FEIBA reconstituted in reduced and regular volumes of SWFI in terms of $AUC_{0\text{-}216\ h}$ will be evaluated using the PK population. Once the first 12 subjects have completed Part 1, the data monitoring committee (DMC) will review the safety and PK data and will provide a recommendation on whether these subjects can proceed to Part 2 for evaluation of increased infusion rates. The DMC will meet again after the final subject has completed Part 1 of the study. The DMC will then review all safety and PK data from Part 1 and provide a recommendation on whether the remaining subjects can proceed to Part 2. During the interim period (while subjects are waiting to proceed to Part 2), subjects will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. A soft database lock will be in place on the records of the subjects who are undergoing DMC review. Subject recruitment and subjects in other phases of the study will not be affected by this database lock. Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1, to evaluate the safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/kg compared with the current standard rate of 2 U/min/kg. Subjects will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/min/kg rate. The infusions will be administered every 48 hours (+48 hours) to allow time to monitor safety and tolerability of the higher infusion rate. After the first 12 subjects have completed Infusion 9, the DMC will review the safety data and provide a recommendation on whether these subjects can proceed to the next higher infusion rate of 10 U/min/kg.

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	The DMC will meet again after the final subject has completed Infusion 9, and provide a recommendation on whether the remaining subjects can proceed to the faster infusion rate. A soft database lock will be in place on the records of the subjects who are undergoing DMC review. Subject recruitment and subjects in other phases of the study will not be affected by this database lock. Once subjects have been approved by the DMC to continue, they will then be given 3 infusions (Infusions 10, 11, and 12) of FEIBA at the 10 U/min/kg rate. Infusions will again be administered every 48 hours (+48 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion. All IP infusions will be administered at the hemophilia care centers/study sites. Each subject will receive a maximum of 14 IP infusions total (most subjects will receive 12 IP infusions, up to 14 is for subjects who have a bleeding episode during PK collections, and therefore have their PK infusion reinfused). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, and 6, and all Part 2 infusions). During study participation, subjects will be provided with standard of care FEIBA (by the sponsor) for the treatment of bleeding episodes, and will be provided with standard of care FEIBA prophylaxis and/or treatment (by the sponsor) during interim DMC breaks, as determined by the investigator.
Planned Duration of Subject Participation	Study enrollment is planned to initiate in Q2 of 2016. It is planned that each subject will spend approximately 60 days in each portion of the study. Additional time may be needed depending on the elapsed time between infusions, obtaining 12 evaluable subjects for DMC review, and the length of the DMC review period.
Primary Outcome Measure 1. $AUC_{0\text{-}216\ h}$ of FEIBA component FII in the subjects 2. Occurrence of severe allergic reactions (e.g., anaphylaxis)	
Secondary Outcome Measure(s) **Efficacy/Pharmacokinetics** 1. Incremental recovery of FEIBA component FII in subjects 2. $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max} of FEIBA component FII in subjects **Safety** 1. Evaluate occurrence of product-related AEs 2. Evaluate occurrence of infusion site reactions 3. Evaluate occurrence of all AEs occurring within 24 to 72 hours of IP infusion	

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4. Evaluate occurrence of thromboembolic AEs
5. Evaluation of thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, thrombin/anti-thrombin complex [TAT], and fibrinopeptide A)
6. Evaluate vital signs and clinical laboratory assessments

Exploratory Outcome Measure(s)

[redacted]

2. Evaluate responses to the TSQM and the patient preference questionnaire

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Active Product	**Dosage form:** kit; powder, lyophilized, for solution/suspension; injection **Dosage frequency:** 12-14 study infusions **Mode of Administration:** intravenous bolus

SUBJECT SELECTION

Targeted Accrual	Enroll 32 subjects (at least 24 evaluable for the primary PK assessment)
Number of Groups/Arms/Cohorts	1 cohort: at least 24 evaluable adult subjects (≥ 18 to ≤ 65 years old) for PK and safety evaluation

Inclusion Criteria

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa)
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable hepatic disease
4. Human immunodeficiency virus (HIV) negative; or HIV positive with stable disease and cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Subject is willing and able to comply with the requirements of the protocol

Exclusion Criteria

1. Known hypersensitivity to FEIBA or any of its components
2. Clinically symptomatic liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/mL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications

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8. Subject is taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy
9. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
10. Subject is a family member or employee of the investigator
11. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

STATISTICAL ANALYSIS

Sample Size Calculation

Part 1 (crossover) of this study will evaluate PK equivalence of FEIBA component (FII) in FEIBA reconstituted in 50% reduced volume versus regular volume of SWFI as measured by $AUC_{0\text{-}216\ h}$. The sample size was calculated for Type-1 (α) error level of 0.05 and a Type-II (β) error level of 0.1 or 90% power, under the assumption that the true (population) means are equivalent, i.e., the 90% confidence interval (CI) for the ratio of the geometric means between the 2 treatments are contained completely in the margins of equivalence defined as 80% to 125%. The within-subject variability was estimated by using the square root of mean square error (0.222) as in previous studies of EVIII. The required sample size was estimated to be 24 evaluable subjects. In order to obtain the required 24 subjects, Part 1 will randomize approximately 32 subjects for the crossover design, allowing for a possible 25% dropout rate.

With approximately 100 infusions for each treatment (reduced or regular volume of SWFI) administered for the study, the upper limit of the 95% CI of the rate of infusions with a specific AE is less than 3.3%, if the specific AE is not observed. The upper limit of the 95% CI of the rate of infusions for a specific AE is about 5% if 1 AE is observed.

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Planned Statistical Analysis

Primary Analysis

For Part 1, a formal equivalence test will be made for $AUC_{0\text{-}216\ h}$ of FII. All other PK parameters will be reported using descriptive statistics.

Log-transformed PK parameter $AUC_{0\text{-}216\ h}$ of FII from the Infusions 1 and 4 will be analyzed using a linear mixed-effects model with sequence, period, and treatment (FEIBA reconstituted in 50% reduced volume and regular volume of SWFI) as fixed effects and subject as a random effect. To establish the equivalence, the 90% CI for the ratio of the geometric means between the 2 treatments has to be contained completely in the margins of equivalence defined as 80% to 125%.

For Parts 1 and 2, the safety of treatment infusions will be evaluated primarily by the occurrence of severe allergic reactions and infusion site reactions by treatment for each study part. These will be statistically described and a 95% CI will be provided.

Secondary and Exploratory Analysis

Levels of FEIBA components FII, [redacted] will be displayed graphically over time for each subject and summarized by visit and treatment for each study part.

The $AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, t_{max}, and IR of FEIBA component FII will be summarized descriptively by visit and treatment for each study part.

The number and proportion of subjects experiencing serious and non-serious AEs up to study completion or subject withdrawal will be summarized by treatment. The number of product related serious and non-serious AEs will also be summarized by treatment for each study part.

Subgroup analyses will also be performed for events categorized as thromboembolic AEs. Thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, TAT, and fibrinopeptide A) will be summarized using descriptive statistics by treatment. Mean concentration plots will be presented by treatment and visit for each thrombotic marker and study part.

The results of the TSQM and the patient preference questionnaires will be summarized by descriptive statistics as appropriate.

Vital signs and clinical laboratory assessments will be summarized descriptively by treatment for each study part at each scheduled assessment and for the corresponding change from baseline. Shift tables will also be presented for clinical laboratory assessments by treatment for each study part at each scheduled assessment.

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0\text{-}216\ h}$	area under the curve from time zero (preinfusion) to time 216 hours
$AUC_{0\text{-}last}$	area under the curve from time zero (preinfusion) to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the curve from time zero (preinfusion) to infinity
BU	Bethesda units
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CRF	case report form
DMC	Data Monitoring Committee
EC	ethics committee
EOI	end-of-infusion
eCRF	electronic case report form
EDC	electronic data capture
EDTA	Ethylenediaminetetraacetic acid
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FEIBA VH	Factor Eight Inhibitor Bypassing Activity Vapor Heated
FII	Factor II
FIX	Factor IX
FVII	Factor VII
FVIII	Factor VIII

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Abbreviation	Definition
FVIII:CAg	Factor VIII C antigen
FX	Factor X
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immumoglobulin G
IgM	immunoglobulin M
IP	investigational product
IR	incremental recovery
IRB	Institutional Review Board
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
Min	minutes
MRT	mean residence time
NMC	non-medical complaint
PCR	polymerase chain reaction
PK	Pharmacokinetic(s)
PT	prothrombin time
rFVIIa	recombinant activated clotting factor VII
RBC	red blood cell
Rsq	r^2
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SI	serious injuries

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Abbreviation	Definition
SWFI	sterile water for injection
$t_{1/2}$	terminal half-life
TAT	thrombin/anti-thrombin complex
t_{max}	Time to maximum observed plasma concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
US CFR	US Code of Federal Regulations
V_{ss}	volume of distribution at steady state
WBC	white blood cell
λ_z	terminal rate constant
$\%AUC_{ex}$	percentage of AUC obtained by extrapolation

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6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

Note: Labeling has been updated since the Investigator Brochure (IB), and Factor Eight Inhibitor Bypassing Activity Nanofiltered (FEIBA NF) referenced in the background section is now referenced as FEIBA throughout the rest of the protocol.

The investigational product (IP), FEIBA NF[i] is a plasma derived, activated prothrombin complex concentrate, generically identified as an anti-inhibitor coagulant complex (AICC). FEIBA was developed to treat bleeding episodes and cover surgical interventions in hemophilia A and B patients with inhibitors and in non-hemophilia patients with acquired inhibitors.[ii] FEIBA was marketed beginning in 1978 and was superseded in 1985 by a 2-stage vapor heat-treated product, FEIBA VH. Nanofiltration was introduced to the manufacturing process in 2006 to produce FEIBA NF. Factor Eight Inhibitor Bypassing Activity Nanofiltered shares the same indications as FEIBA VH (control of bleeding episodes and to cover surgical interventions in hemophilia A and B patients with inhibitors), and is also intended for use as a prophylactic treatment for hemophilia A and B subjects with high-responding inhibitors and frequent joint bleeding.[iii,1,2,3]

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Replacement therapy for the treatment of hemophilia A, and less frequently hemophilia B, can be complicated by an immune response resulting in the production of inhibitory alloantibodies to Factor VIII (FVIII) or Factor IX (FIX), especially in patients with moderate to severe hemophilia. The development of such inhibitory antibodies currently represents the most serious complication of hemophilia treatment. The presence of inhibitors against FVIII generally precludes the efficacious use of human FVIII replacement therapy. A substantial portion of patients with FVIII inhibitors have high-responding, high-titer inhibitors (> 5 Bethesda units [BU]). These patients exhibit an anamnestic response after FVIII exposure, sometimes with a dramatic increase in inhibitory antibody titer.[4,5] The inability to provide FVIII replacement therapy predisposes this group of patients to increased morbidity and mortality compared with hemophilia patients without inhibitors.[4] Several therapeutic approaches are currently available in the management of hemorrhagic events in patients who have developed FVIII inhibitors. These include neutralization with high doses of human FVIII (low titer

[i] FEIBA NF is a trademark of Baxalta Inc. US and Baxalta Innovations GmbH.
[ii] Anti-Inhibitor Coagulant Complex, FEIBA Vapor Heated. Package Insert, Baxalta US Inc., Westlake Village, CA.
[iii] Protocol 090701. FEIBA NF: A Prospective, Open-label, Randomized, Parallel Study to Evaluate Efficacy and Safety of Prophylactic versus On-demand Treatment in Subjects with Hemophilia A and B and High Titer Inhibitor. 2013 Jan 14, Baxalta US Inc., (Westlake Village, CA).

inhibitor only), and treatment with bypassing agents such as Activated Prothrombin Complex Concentrates (APCCs), or activated recombinant factor VII (rFVIIa). Among these treatment options, only APCCs and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII or FIX. It has been proposed that FEIBA products achieve this goal principally by virtue of the presence of a "partial prothrombinase complex" consisting of activated Factor X (FX) and prothrombin.[6]

The active ingredient of FEIBA is a plasma-derived, freeze-dried APCC with FVIII inhibitor bypassing activity. The product FEIBA contains mainly non-activated forms of the 3 coagulation factors, Factor II (FII), FIX and FX, as well as activated FVII; and Factor III coagulant antigen present in a concentration of up to 0.1 U/1 U FEIBA. A solution containing 1 U FEIBA shortens the activated partial thromboplastin time (aPTT) of FVIII inhibitor plasma up to 50% of the buffer value. Additional details can be found in the FEIBA IB.[iv]

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6.2 Clinical Condition/Indication

Hemophilia is an X-linked, recessive, congenital bleeding disorder caused by deficient or defective coagulation due to a deficiency in FVIII (hemophilia A), or FIX (hemophilia B).The absence of FVIII or FIX leads to spontaneous bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury.[7,8] A serious complication in the treatment of hemophilia is inhibitor formation. Patients with inhibitors experience more difficulty in treating bleeds than those patients who do not develop inhibitors.

The intended indication for FEIBA NF is treatment and prophylaxis of bleeding in hemophilia A and B patients with inhibitors, and to cover surgical interventions.

6.3 Population to Be Studied

Adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B of any severity, of all races and ethnic groups will be studied. All subjects will have a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa). Subjects will either be hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease. Subjects will either be human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3.

[iv] Investigator's brochure. Anti-inhibitor coagulant complex nanofiltered; FEIBA NF. 2013 APR 22. Baxalta US Inc., (Westlake Village, CA).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

The nonclinical studies performed for FEIBA NF included a virus clearance study, which was performed to investigate the virus reduction capacity of the nanofiltration step in the manufacturing of FEIBA NF.

Preclinical studies have demonstrated FEIBA NF to have comparable activity and other biochemical properties to FEIBA VH.

Data from nonclinical studies can be found in the FEIBA NF IB.[iv] Preclinical studies have demonstrated FEIBA NF to have comparable activity and other biochemical properties to FEIBA VH.

6.4.2 Findings from Clinical Studies

The results of Baxalta clinical study 090701[iii] demonstrated that prophylaxis with FEIBA NF significantly reduced the annualized bleeding episode rates for spontaneous, traumatic, joint, non-joint, spontaneous-joint, spontaneous-non-joint, and traumatic-joint bleeding episodes when compared with on-demand treatment. A statistically significant reduction in the rate of bleeding episodes in new target joints in the prophylaxis arm versus the on-demand arm was also observed. An examination of adverse events (AEs), abnormal laboratory parameters for hematology and clinical chemistry and vital signs demonstrated that FEIBA NF was safe and well tolerated for prophylactic use. Clinically, these data suggest that both on-demand and prophylaxis regimens were safe and efficacious in the management of hemophilia A or B with persistent high- or low-titer inhibitors refractory to FVIII or FIX treatment, and further confirmed the safety and effectiveness of FEIBA NF for controlling and preventing bleeding episodes.

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Baxalta clinical study 091002 was an open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. This study was designed to document routine usage of FEIBA NF as an inhibitor-bypassing agent for on-demand or prophylactic treatment in everyday clinical practice and in surgical intervention. The safety results of this postauthorization safety study showed that treatment with FEIBA NF, administered in 81 subjects with hemophilia and requiring treatment with inhibitor-bypass therapy for bleed resolution or bleed prophylaxis, was well tolerated. Treatment-related AEs or serious adverse events (SAEs) were reported in 9.9% and in 3.7% of subjects, respectively. A deep venous thrombosis and a superficial thrombophlebitis were observed in 1 subject with acquired hemophilia. The hemostatic effectiveness was rated by the physicians as excellent or good in more

than 90% of total subjects, with the highest rates reported in subjects with FEIBA NF prescribed as regular prophylaxis. Additional details on this study can be found in the clinical study report.[v]

Additional observational, non-interventional studies were conducted with FEIBA NF. Additional details on clinical studies can be found in the FEIBA NF IB.[iv]

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

The FEIBA NF products can precipitate allergic-type hypersensitivity reactions that have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and a drop in blood pressure; these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. The most commonly reported adverse drug reactions described for FEIBA NF include increase in inhibitor titer, somnolence, dizziness, dysgeusia, dyspnea, nausea, chills, pyrexia, chest pain, and chest discomfort.

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The possibility of thrombotic events should be considered when systemic anti-fibrinolytics such as aminocaproic acid and tranexamic acid are used in combination with FEIBA NF. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours before or after the administration of FEIBA NF.

Animal reproduction studies have not been conducted with FEIBA NF. There are no adequate and well-controlled studies in pregnant women. It is also not known whether FEIBA NF can cause fetal harm when administered to a pregnant woman or an affect reproductive capacity. It is not known whether FEIBA NF is excreted in human milk.[9] Subjects within the study should be warned regarding this labeling information.

Additional safety experience for FEIBA is provided in the FEIBA NF IB.[iv]

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

[v] Clinical Study Report. Post-Authorization Safety Study of FEIBA NF (Factor VIII Inhibitor Bypassing Activity). An open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. 10 Oct 2014. Baxalta Inc. US and Baxalta Innovations GmbH.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is:

1. To compare the pharmacokinetics (PK) of FEIBA component (FII) and safety of FEIBA reconstituted in a reduced volume of sterile water for injection (SWFI) versus regular volume SWFI, administered at the standard infusion rate of 2 U/min/kg
2. To evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison to the standard rate of 2 U/min/kg in Part 1

7.2 Primary Objectives

The primary objectives are to determine PK equivalence of FEIBA component (FII) reconstituted in 50% reduced volume SWFI and regular volume SWFI on area under the curve from time zero (preinfusion) to time 216 hours ($AUC_{0\text{-}216\ h}$), and to determine the occurrence of severe allergic reactions (e.g., anaphylaxis).

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7.3 Secondary Objectives

1. Determine the safety and tolerability of 50% reduced volume FEIBA administered at the standard and escalated infusion rates, based on the occurrence of AEs
2. Monitor clinically apparent thromboembolic events, changes in vital signs, infusion rate-related events, and infusion site reactions
3. Determine the effect of 50% reduced volume FEIBA component (FII) on incremental recovery (IR), area under the curve from time zero (preinfusion) to extrapolated to infinity ($AUC_{0\text{-}\infty}$), area under the concentration time curve from time zero (preinfusion) to time of last quantifiable concentration ($AUC_{0\text{-last}}$), terminal half-life ($t_{1/2}$), clearance (CL), mean residence time (MRT), volume of distribution at steady state (V_{ss}), maximum plasma concentration (C_{max}), and time to maximum observed plasma concentration (t_{max})

7.4 Exploratory Objective

[redacted]

2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

8. STUDY DESIGN

8.1 Brief Summary

This is a 2-part Phase 4, prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.4 BU in hemophilia A and ≥ 0.6 BU in hemophilia B) for the primary PK assessment, (i.e., having the $AUC_{0\text{-}216\ h}$ of FEIBA component FII estimable from both PK infusions), with a planned enrollment of 32 subjects. All subjects will receive 3 infusions of FEIBA reconstituted in a regular volume of SWFI, and 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI, with all 6 of these infusions being given at a rate of 2 U/min/kg within Part 1 of the study. In Part 2 of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/min/kg followed by 3 infusions FEIBA reduced volume at a rate of 10 U/min/kg. All subjects will undergo PK evaluation in Part 1 of the study.

8.2 Study Design Rationale

This study has been designed as a 2-way crossover study in order to assess for PK bioequivalence analysis. By designing it as a crossover study, subjects serve as their own controls, reducing the number of subjects needed for the study by half. This study is open-label because it is a change in infusion volume and infusion rate, which would be difficult to properly blind. The goal of the study is to demonstrate PK bioequivalence of FEIBA in reduced volume SWFI to FEIBA regular volume SWFI, and then to increase the rate that this reduced volume can be infused. By being able to reduce the volume and speed of the infusion, subjects will be able to spend less time infusing.

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As there are washout periods, and interim breaks within the study design in which subjects will not be receiving IP, steps have been taken to protect them from bleeding episodes. If a subject has a bleeding episode during a washout period, he or she will be treated with standard of care FEIBA to control the bleeding, with a washout period beginning after the last infusion of FEIBA. Once the washout period is complete, the study can restart from the last infusion time point. During the interim period (data monitoring committee [DMC] review period), subjects will be provided with FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. Subjects will record their treatments and bleeding episodes in a subject diary for review by the study team.

8.3 Overall Study Design

This is a 2-part Phase 4, prospective, open-label, multicenter study to compare PK and safety of FEIBA reconstituted in reduced versus regular volume of SWFI, and to evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison with the standard rate of 2 U/min/kg, in approximately 32 subjects (at least 24 evaluable) with hemophilia A or B with inhibitors (≥ 0.4 BU in hemophilia A and ≥ 0.6 BU in hemophilia B), with the $AUC_{0\text{-}216\ h}$ of FEIBA component FII estimable from both PK infusions. The overall study design is illustrated in Figure 1 and Figure 2.

In Part 1, subjects will be administered 2 different volumes of FEIBA in a randomized, crossover manner with a washout period between the treatments. Both volumes will be given at the standard infusion rate of 2 U/min/kg. After infusion, subjects should be observed for 30 minutes in the clinic. For PK infusions and collections, accommodations can be made for convenience or to ensure compliance with PK sampling. See Section 10.3.2 for details. A DMC review will be conducted after the first 12 subjects have completed Part 1, and then again after the last subject has completed Part 1 of the study. The DMC will provide recommendations for proceeding to Part 2, for both subsets of subjects. During the interim period (DMC review period), subjects will be provided with FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. Subjects will record their treatments and bleeding episodes in a subject diary for review by the study team. A soft database lock will be in place on the records of the subjects who are undergoing DMC review. This soft lock will prevent new data or data changes for these subjects, which will be unlocked following DMC review. Subject recruitment and subjects in other phases of the study will not be affected by this soft database lock.

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Treatments regimens during Part 1 of the study are:

- Part 1 Sequence A:
    1. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in 50% reduced volume SWFI (Infusions 4, 5, and 6)
- Part 1 Sequence B:
    1. FEIBA 2 U/min/kg in 50% reduced volume SWFI (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 4, 5, and 6)

- Infusion dose:
    1. Infusions 1 and 4: 85 U/kg ± 100 U
    2. All other infusions: 85 ± 15 U/kg

Prior to the first infusion of FEIBA (Sequence A or B), subjects will undergo a washout period of at least 12 days from last treatment with APCC (e.g., FEIBA), or at least 1 day after the last treatment with an rFVIIa product (e.g., NovoSeven®).

Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1 to evaluate FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/kg. All subjects will receive the 4 U/min/kg treatment during the first treatment phase, then there will be an interim period for a DMC review (after the first 12 subjects have completed Infusion 9, and again after the last subject has completed Infusion 9). The DMC will then provide recommendations regarding each subset of subjects proceeding to the increased rate of 10 U/min/kg during the second treatment phase. During the interim period (DMC review period), subjects will be provided with FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. Subjects will record their treatments and bleeding episodes in a subject diary for review by the study team. A soft database lock will be in place on the records of the subjects who are undergoing DMC review. Subject recruitment and subjects in other phases of the study will not be affected by this database lock. The treatment phases within Part 2 of the study are as follows:

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- First treatment phase: 4 U/min/kg (3 infusions)
- Second treatment phase: 10 U/min/kg (3 infusions)

All infusions will be administered at the hemophilia care centers/study sites. Pharmacokinetic collections may be performed at the hemophilia care centers/study sites or appropriate ambulatory centers. Each subject will receive a maximum of 14 IP infusions total (most subjects will receive 6 in Part 1 and 6 in Part 2, the additional 2 infusions are for reinfusing PK infusions if a bleeding event occurred during the 9 day PK collection). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions). After each infusion, subjects should be observed for 30 minutes in the clinic. During study participation, subjects will be provided FEIBA for treatment of break-through bleeding (by the sponsor). Additional details on study design and timing are described in Section 8.8.3. For additional details on managing bleeding episodes, see Section 8.8.4.

8.4 Duration of Study Period(s) and Subject Participation

The overall duration of the study is 21 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 to 12 months.

The subject participation period is 8 to 10 months from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

8.5 Outcome Measures

8.5.1 Primary Outcome Measures

The primary outcome measures are:

1. $AUC_{0\text{-}216\ h}$ of FEIBA component FII in subjects
2. Occurrence of severe allergic reactions (e.g., anaphylaxis)

8.5.2 Secondary Outcome Measures

8.5.2.1 Efficacy/Pharmacokinetics

1. Incremental recovery of FEIBA component FII in subjects
2. $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max} of FEIBA component FII in subjects

8.5.2.2 Safety

1. Evaluate occurrence of product-related AEs
2. Evaluate occurrence of infusion site reactions
3. Evaluate occurrence of all AEs occurring within 24 to 72 hours of IP infusion
4. Evaluate occurrence of thromboembolic AEs
5. Evaluation of thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, thrombin/anti-thrombin complex [TAT], and fibrinopeptide A)
6. Evaluate vital signs and clinical laboratory assessments

8.5.3 Exploratory Outcomes Measure

[redacted]

2. Evaluate responses to the TSQM and the patient preference questionnaires

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8.6 Randomization and Blinding

Part 1 of this study is a randomized, crossover, active treatment clinical study. In order to minimize/avoid bias, subjects will be randomly assigned to 1 of 2 treatment regimens (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 SWFI) in equal numbers. 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.

8.7 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. If 2 or more subjects develop anaphylaxis following exposure to FEIBA (enrollment and treatment temporarily stopped pending further review by the DMC)
2. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk benefit
3. The sponsor or investigator considers continuation of the study unjustifiable for medical or ethical reasons
4. The DMC recommends study termination

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8.8 Investigational Product(s)

8.8.1 Packaging, Labeling, and Storage

Note: Labeling has been updated since the IB, and FEIBA NF as previously referenced in Section 6 is now referenced as FEIBA.

The active ingredient of FEIBA is a plasma-derived, freeze-dried, APCC with FVIII inhibitor bypassing activity. Factor Eight Inhibitor Bypassing Activity will be provided in vials containing 350 to 650 U/vial (nominal potency 500 U), 700 to 1300 U/vial (nominal potency 1,000 U) or 1750 to 3250 U/vial (nominal potency 2500 U). FEIBA contains mainly non-activated forms of the 3 coagulation factors, FII, FIX, and FX, as well as activated FVII; and Factor VIII coagulant antigen (FVIII:CAg) present in a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all. A solution containing 1 U FEIBA shortens the aPTT of FVIII inhibitor plasma to 50% of the buffer value. The product is supplied as freeze-dried powder or friable solid of white to off-white or pale green color.

Factor Eight Inhibitor Bypassing Activity can be stored at room temperature, not to exceed 25°C (77°F). Factor Eight Inhibitor Bypassing Activity should not be allowed to freeze, and should be protected from light. Although the chemical and physical stability of the reconstituted product has been demonstrated for 6 hours at room temperature (up to 25°C), in consideration of sterility, infusion of FEIBA should be commenced as promptly as practical, but must be completed within 3 hours following reconstitution. Reconstituted product must not be returned to the refrigerator.

Reconstitution can be performed using a BAXJECT II Hi-Flow needleless transfer device. For additional information, such as reconstitution instructions, please refer to the FEIBA product insert [9] and/or other specific instructions provided by the sponsor or sponsor's representative.

8.8.2 Administration

Following reconstitution, FEIBA should be administered using an intravenous needle or infusion set with a winged adapter (ensure the use of plastic luer lock syringes as proteins within FEIBA can adhere to glass). The standard infusion rate of FEIBA is a slow bolus injection, with an infusion rate of 2 U/kg body weight (BW) per minute, which in a 75-kg subject, corresponds to an infusion rate of approximately 2.4 to 7.5 mL/minute depending on the potency (see label on vial). This rate will be modified depending on which part of the study the subject is in. Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions). For additional details, see the FEIBA IB.[iv] Additional rates of 4 and 10 U/min/kg are also used in this study.

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Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. Information regarding lot used, the actual dose given, date of treatment, treatment start and stop times, as well as any infusion interruptions will be recorded in the electronic case report form (eCRF).

Subjects must be given the same lot for Infusion 1 and Infusion 4 in order to ensure comparable PK results.

8.8.3 Description of Treatment

Part 1

Part 1 of the study uses a crossover design to evaluate the PK of FEIBA component FII and to evaluate the safety of FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI (administered at the standard infusion rate of 2 U/min/kg). Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1. Part 2 will evaluate the safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/kg.

All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. The subject's medical history including hemophilia history, confirmation of inhibitors, bleeding episode history, and history of FEIBA or rFVIIa usage for the previous year will be collected at screening. Also recorded will be the date of last use of FEIBA or rFVIIa treatment. Results of the screening assessments will be used to establish a subject's eligibility for the study.

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After eligibility is established, the duration of the washout period will be determined. The washout period is based on the subject's last dose of FEIBA or rFVIIa. Due to the varying lengths of the half-lives of the components, subjects who have received FEIBA will need to wait 12 days from their last dose of FEIBA before they can receive Infusion 1 of the study. Subjects who have previously been treated with rFVIIa (e.g., NovoSeven), will need to wait at least 24 hours from the last dose of rFVIIa treatment before they can begin Infusion 1 of the study (in agreement with the reported half-life of 2.6 to 3.9 hours of FVII). Additional days beyond the minimum of 1 or 12 days (treatment dependent) is permissible since subjects have varying courses of treatments prior to their enrollment in the study (as long as screening procedures stay within the allotted time frame). Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. For subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day they used treatment. If they have a bleeding episode that requires treatment during the washout period, the washout period must be restarted before they can proceed with the study. For additional details on bleeding control, see Section 8.8.4.

After the washout period is complete, eligible subjects will be randomized (1:1) into Part 1 of the study by interactive voice response system to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. Subjects will receive the first infusion for PK and safety analysis and the second and third infusions for collection of additional safety data.

The first infusion will be given after randomization, and PK blood draws will be taken at the times described in Table 4. After the 216 hour PK draw (9 days after Infusion 1), subjects will receive Infusion 2, and subjects will receive Infusion 3 forty-eight (+48) hours after Infusion 2. If bleeding occurs during the 9-day PK collection period, the PK collection will be stopped and the subject will be treated with FEIBA. Once bleeding is resolved, subjects will undergo a 12-day washout period before having the IP infusion and PK assessments repeated. If bleeding occurs again, the subject will be treated with FEIBA and subjects will continue to the next IP infusion, see Section 8.8.4.

After Infusion 3, subjects will go through a washout period of at least 12 days before crossing over to the next treatment group for Infusion 4. The 12 days is based on Infusion 3, since all subjects receive FEIBA at Infusion 3. If bleeding occurs during the washout period it will be treated with FEIBA and the washout period will be restarted. If bleeding has not resolved 72 hours after treatment with FEIBA, the investigator will treat the subject as appropriate to control the bleeding. If multiple bleeding episodes occur during the washout period, the investigator and sponsor should decide if it is more beneficial for the subject to be taken off study, see Section 8.8.4.

Infusion 4 will be the beginning of the new treatment regimen in the crossover scheme, and PK assessment will be completed for this infusion. Infusion 4 must be administered using the same lot of IP as Infusion 1. Infusion 4 will be given after the minimum of 12-day washout period is complete, and PK blood draws will be taken at times described in Table 4. After the 216-hour PK draw (9 days after Infusion 4), subjects will receive Infusion 5, and subjects will receive Infusion 6 forty-eight (+48) hours after Infusion 5.

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Part 1 Treatment Summary:

- Part 1 Sequence A:
    1. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in 50% reduced volume (Infusions 4, 5, and 6)
- Part 1 Sequence B:
    1. FEIBA 2 U/min/kg in 50% reduced (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 4, 5, and 6)

- Infusion dose
    1. Infusions 1 and 4: 85 U/kg ± 100 U
    2. All other infusions: 85 ± 15 U/kg

Additional details on study visits for Part 1 can be found in Section 10.3 and Table 1.

DMC of Part 1

All evaluable subjects will be included in the DMC review, however to help with subject retention in the study, the DMC review of Part 1 will be conducted twice; once after the first 12 subjects have completed Part 1, and then again after the last subject has completed Part 1. Once the first 12 subjects have completed Part 1, the DMC will review the safety and PK data and will provide a recommendation on whether these subjects can proceed to Part 2 for evaluation of increased infusion rates. The DMC will meet again after the final subject has completed Part 1 of the study. The DMC will then review all safety and PK data from Part 1 and provide a recommendation on whether the remaining subjects can proceed to Part 2. A soft database lock will be in place on the records of the subjects who are undergoing review. Subject recruitment and subjects in other phases of the study will not be affected by this database lock.

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During the interim period, subjects who are on hold for DMC review will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. The subject will continue completing the electronic subject diary during the interim break. The study team will be able to monitor the subject through real-time reporting from the electronic diary recording. No other study procedures beyond the diary completion will be conducted during the interim period. After the DMC review, subjects who have been reviewed and approved to continue by the DMC can then be scheduled to proceed with Part 2 of the study. No washout period will be required before the commencement of Part 2 since there is no PK analysis in Part 2 of the study; however, subjects should wait at least 48 hours after their last dose of FEIBA before restarting IP.

After each subset of subjects have completed Part 1, PK equivalence of FEIBA reconstituted in reduced and regular volumes of SWFI in terms of $AUC_{0\text{-}216\,h}$ of FII will be evaluated.

Part 2

Part 2 is non-randomized and uses sequential enrollment of subjects who complete Part 1 of the study. Subjects in Part 2 will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/min/kg rate. Infusion 7 can be given as soon as possible once the DMC has released the subjects from review; however, if they have received FEIBA during the pause for DMC, they will need to wait at least 48 hours after their last FEIBA dose before beginning Infusion 7. The infusions in Part 2 will be administered every 48 hours (+48) to allow time to monitor safety and tolerability of the higher infusion rate. Infusion rates for the treatment phases in Part 2 are:

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

After the first 12 subjects have completed Infusion 9, the DMC will review the safety data and provide a recommendation on whether these subjects can proceed to the next higher infusion rate of 10 U/min/kg. The DMC will meet again after the final subject has completed Infusion 9, and provide a recommendation on whether the remaining subjects can proceed to the faster infusion rate.

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During the interim period, subjects who are on hold for DMC review will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. The subject will continue completing the electronic subject diary during the interim break. The study team will be able to monitor the subject through real-time reporting from the electronic diary recording. No other study procedures beyond the diary completion will be conducted during the interim period. After the DMC review, subjects who have been reviewed and approved to continue by the DMC can be scheduled to begin the 10 U/min/kg infusion. No washout period will be required before the commencement of the 10 U/min/kg infusion since there is no PK analysis in Part 2 of the study; however, subjects should wait at least 48 hours after their last dose of FEIBA before restarting IP.

Once subjects have been approved by the DMC to continue, they will be given 3 infusions (Infusions 10, 11, and 12) of FEIBA NF at the 10 U/min/kg rate. Infusions will be again administered every 48 (+48) hours to allow time to monitor safety and tolerability of the higher infusion rate. Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Additional details on study visits for Part 2 can be found in Section 10.3 and Table 2.

Additional Treatment and Visit Information

The Schedule of Study Procedures and Events Procedures listed in Table 1 and Table 2 have the visit windows listed in relation to the subjects' previous infusions instead of by study date. This is due to the variability in each subjects schedule based on previous therapy, bleeding events, and interim break periods.

All infusions will be administered at hemophilia care centers/study sites. Each subject will receive a maximum of 14 IP infusions (12 scheduled IP infusions, as well as the possibility of PK infusions being reinfused if the subject had a bleeding episode during PK collection). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions). During study participation, FEIBA will be used for control of break-through bleeding episodes. For additional information on break-through bleeding control, see Section 8.8.4.

Study visits will be completed concurrently with study infusions. After subjects have completed the 12 study infusions, they will complete a Study Completion/Termination Visit within 7 days but no sooner than 72 hours after Infusion 12. In case of early withdrawal or discontinuation the Study Completion/Termination Visit will need to be completed within 7 days but no sooner than 72 hours after the last IP infusion received.

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A subject diary will be utilized to capture break-through bleeding events, treatments, and AEs throughout the study and interim periods, for additional details see Section 10.6.

Two subject questionnaires will be administered during the study, a TSQM questionnaire and a patient preference questionnaire (see 10.5). These will be administered between Screening and Infusion 1, between Infusion 3 and Infusion 4, between Infusion 6 and Infusion 7, and after Infusion 12 to assess the subjects' satisfaction and preferences for treatments.

During study participation, subjects will be provided with standard of care FEIBA (by the sponsor) for the treatment of bleeding episodes, prophylaxis and/or treatment during interim pauses for DMC, as determined by the investigator. For additional details, see Section 8.8.4.

Detailed study flowcharts are presented in Table 1 and Table 2.

Investigational product may be interrupted or discontinued at any time during the study at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any infusion site reactions, regardless of causality, will be recorded on the AE eCRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate eCRF.

8.8.4 Management and Treatment of Break-Through Bleeding

Bleeding episodes are managed as described below for each section of the study (screening, PK assessments, washout, DMC period). In all cases, if the bleeding episode, of whatever severity, is not resolved within 72 hours after an infusion to control bleeding, the subject must contact the study site for further treatment recommendations.

Screening Washout

During screening, subjects will be asked to keep track of any FEIBA or rFVIIa usage, as the last dose is used to determine the date of the first infusion of IP. If a subject is on prophylaxis before the study, once eligibility is determined, the subject will discontinue their routine prophylaxis upon instruction of the investigator for the start of the washout period. If a subject experiences a bleeding episode during the washout period, subjects will be treated for the bleeding episode with FEIBA as determined by the investigator, and the washout period will be restarted. If the subject has a second bleeding episode during the washout period, the investigator should consider whether it is appropriate to include the subject into the study or whether they would be better served to remain on their current treatment regimen.

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Bleeding during PK Assessments

Subjects who have a bleeding episode during the PK assessment periods will not have subsequent PK blood samples collected in that specific PK assessment period and will be treated for the bleeding episode with FEIBA as determined by the investigator. Once the bleeding is resolved, subjects will have the IP infusion and PK assessments repeated. However, they should wait at least 12 days after their last dose of FEIBA before proceeding. If the subject bleeds again on the second PK collection attempt, bleeding will be treated with FEIBA as determined by the investigator, and subjects will move on to the next IP infusion after waiting at least 48 hours from their last dose of FEIBA. Subjects will have one re-attempt on each PK infusion and collection.

Washout Periods before Infusion 4

After Infusion 3, subjects will go through a washout period of at least 12 days before crossing over to the next treatment group for Infusion 4. The 12 days is based on Infusion 3, since all subjects receive FEIBA at Infusion 3. If bleeding occurs during the washout period, it will be treated with FEIBA and the washout period will be restarted. If bleeding has not resolved 72 hours after treatment with FEIBA, the investigator will treat the subject as appropriate to control the bleeding. If multiple bleeding episodes occur during the washout period, the investigator and sponsor should decide if it is more beneficial for the subject to be taken off the study.

DMC Periods

During the interim period, subjects who are on hold for DMC review will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. For subjects who are being treated for bleeding, if bleeding has not resolved 72 hours after treatment with FEIBA, the investigator will treat the subject as appropriate to control the bleeding.

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8.8.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.9 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

For additional information on study documentation and eCRFs, see Section 17.2. The use of subject diaries is described in Section 10.6.

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9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa)
3. HCV negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable hepatic disease
4. HIV negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Subject is willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, subject must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
    a. Abstain from sexual intercourse
    b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
    a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known hypersensitivity to FEIBA or any of its components
2. Clinically symptomatic liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/mL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Subject is taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy
9. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
10. Subject is a family member or employee of the investigator
11. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study case report form (eCRF). Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.7 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome
- In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose, should also be recorded following authorization from the subject's partner
- AE(s)/SAE(s) that in the investigator or sponsor opinion, poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study

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10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 091501) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 091501-020003. All study documents (e.g., eCRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in eCRFs, regardless of screening outcome. If a subject is re-screened, the End of Study eCRF should be completed, and a new ICF, new SIC and new eCRF are required for that subject.

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4 Schedule of Study Procedures and Assessments (Part 1 and Part 2, respectively) and Supplement 20.5 Clinical Laboratory Assessments. Pharmacokinetic assessment scheduling can be found in Table 4.

10.3.1 Screening and Baseline Assessments

After ICF has been obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in Section 9.1 and Section 9.2, respectively. Screening procedures must be performed within 56 days of Infusion 1.

At screening, subjects will receive instruction and educational materials on the symptoms of thromboembolic events. They will be instructed to contact the treatment center/hospital if they experience any symptoms of thromboembolism.

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Medical history, including
    - Hemophilia history, inhibitor development history, bleeding episodes history, history of FEIBA or rFVIIAa usage for a year prior to screening
    - Relevant medical and surgical history and all medications taken 4 weeks prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measurement body weight and height (see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (hematology, clinical chemistry, coagulation testing, and serology testing; see Section 12.7)
- PK assessments (see Section 11.1)
- Serum pregnancy test (female subjects of childbearing potential only)
- TSQM and patient preference questionnaires (see Section 10.5)

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After screening and eligibility is determined, the duration of the washout period will be determined. The washout period is based on the subjects' last dose of FEIBA or rFVIIa (e.g., NovoSeven). Due to the varying lengths of the half-lives of the components, subjects who have received FEIBA will need to wait 12 days from the last dose of FEIBA that they received before they can begin Infusion 1. For subjects who have previously been treated with rFVIIa, they will need to wait at least 24 hours from the last dose of rFVIIa before they can begin Infusion 1 of the study. Additional days beyond the minimum of 1 or 12 days (treatment dependent) is permissible (as long as the screening assessments stay within the window to Infusion 1) since subjects have varying courses of treatments prior to their enrollment in the study. Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. Subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day they used treatment, if they have a bleeding episode that requires treatment during the washout period, the washout period must be restarted before they can proceed with the study. For additional details on bleeding, see Section 8.8.4.

10.3.2 Treatment Visits

10.3.2.1 Infusion Visits

Randomization will occur at Infusion Visit 1 using interactive voice response system.

- Randomization of eligible subjects to the following treatment sequences:
  - Part 1 Sequence A: FEIBA 2 U/min/kg in regular volume SWFI (3 infusions), washout period, FEIBA NF 2 U/min/kg in 50% reduced volume (3 infusions)
  - Part 1 Sequence B: FEIBA 2 U/min/kg in 50% reduced volume (3 infusions), washout period, FEIBA NF 2 U/min/kg in regular volume SWFI (3 infusions)

For additional details on the description of treatment, see Section 8.8.3.

At Infusion Visit 1, subjects will be given a subject diary as described in Section 10.6.

During the study (Infusion Visits 1 to 12), subjects will return to the study site according to the schedule presented in Table 1 and Table 2. Prior to administration of IP, the following assessments will be performed at all visits unless otherwise indicated:

- Review of concomitant medications/non-drug therapies
- Review of subject diary
- AE monitoring
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
  - Before administration of IP
  - 30 minutes after administration of IP
- Clinical laboratory assessments (coagulation testing)
- PK assessments (Infusions 1 and 4): from 30 minutes before start of infusion through 8 hours after stop of infusion
  - At the discretion of the investigator, subjects may be given the option of staying overnight at study site facility and/or a hotel for convenience or to ensure compliance with the serial PK collections. Funding or reimbursement for hotel facilities may be provided as allowed by the Institutional Review Board (IRB) approved ICF and any applicable laws and regulations. Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures unrelated to AEs will not be considered as hospitalizations for SAE reporting purposes.

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- IP administration (infusion site should be monitored for 30 minutes [± 10 min] after infusion)
- Subjects should be reminded to complete their diaries between study visits, including monitoring of infusion site for 72 hours postinfusion, break-through bleeding episodes, AEs, and concomitant medications
- Subjects will be administered the TSQM and patient preference questionnaires after screening, between Infusion 3 and Infusion 4, between Infusion 6 and Infusion 7, and after Infusion 12

10.3.3 PK only Visits

Additional PK only visits will be performed between Infusion 1 and 2, and between Infusions 4 and 5 according to the schedule presented in Table 1 and Table 4. These times include 24 hours, 72 hours, 120 hours, 168 hours and 216 hours after Infusions 1 and 4. Exact time ranges can be found in Table 4. For details on treatment of bleeding episodes during PK assessments, see Section 8.8.4.

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10.3.4 Study Completion/Termination Visit

The Study Completion/Termination Visit will be performed within 7 days but no sooner than 72 hours after Infusion 12, or within 7 days but no sooner than 72 hours after the last infusion if the subject is discontinuing early. The following assessments will be performed:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Clinical laboratory assessments (hematology, clinical chemistry, coagulation testing, serology testing)
- Review of subject diary
- Subject diaries will be collected
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and body weight)

10.4 Medications and Non-Drug Therapies

Once subject eligibility has been confirmed for the study, subjects will begin a washout period as described in Section 8.8.3. The subject will discontinue their routine prophylaxis upon instruction of the investigator at the beginning of the washout period. Throughout the course of the study and during the interim periods of the study, subjects will be provided with FEIBA for break-through bleeding, as well as FEIBA for prophylaxis if indicated by the investigator. See Section 8.8.4 for instructions on bleeding control.

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

- Medications:
  - Any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) except anti-retroviral chemotherapy
  - Any investigational drug or device

A subject who has taken any of these medications or received any of these non-drug therapies will be withdrawn from further study participation.

Antifibrinolytics should not be used approximately 6 to 12 hours before or after the administration of FEIBA.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study (these are permitted; however, they should not be taken within 12 hours before or after administration of FEIBA)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
  - Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
  - Supplemental vitamins, minerals

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- Non-drug therapies:
  - Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Questionnaires

Two questionnaires will be administered to subjects within this study (TSQM [10] and a patient preference questionnaire). These questionnaires will be used to assess the subject's preferences on the IP, as well as their satisfaction with the IP, and will be collected in the eCRF or in the subject electronic diary. Both questionnaires will be administered after screening, between Infusion 3 and Infusion 4, between Infusion 6 and Infusion 7, and after Infusion 12.

10.6 Subject Diary

An electronic subject diary will be provided to each subject at the Infusion 1 visit to record the following information: The subject diary will be reviewed at each infusion visit and the Study Completion/Termination Visit.

- Break-through bleeding episodes (duration, severity, treatment)
  - Date and time of bleeding episode
  - Anatomic location of the bleeding episode: joint (identify exact joint), body cavity, deep muscle, superficial
  - Date and time of all infusions with dose and batch number of FEIBA used to control bleeding
  - Use of alternative hemostatic agents, if any
- Infusion site reactions: subjects will monitor the infusion site for 72 hours after each infusion and answer questions regarding AEs after infusion (see Section 10.5).
- Treatments and AEs during DMC interim break
  - Date and time of infusion with dose and batch number of FEIBA
- Untoward medical events
- Concomitant medications (including immunizations) and non-drug therapies

If the subject feels that the bleeding is severe, he must notify the study site. If the bleeding episode, of whatever severity, is not resolved within 72 hours after an infusion to control bleeding, the subject must contact the study site for further treatment recommendations.

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Subjects will be trained on use of the diary. The diary will be provided in electronic format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in PDF format.

The Investigator will review the diary for completeness and ask for missing information. Any unclear or implausible information should be immediately clarified with the subject at each study visit and instructions related to treatment and data entry should be reinforced.

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10.7 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems), DMC recommends a subject should not continue. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

Every effort will be made to have discontinued subjects complete the Study Completion/Termination Visit. If the Study Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Study Completion/Termination Visit. If a subject terminates participation in the study and does not return for the Study Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.5 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.8 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

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11. ASSESSMENT OF PHARMACOKINETICS

11.1 Sample Collection and Processing

Blood PK samples for the determination of FEIBA components FII, [redacted] will be taken at screening, at 30 and 15 minutes preinfusion, at end of infusion, and 30 and 60 minutes, 3, 8, 24, 72, 120, 168, and 216 hours after stop of infusion (see Table 4 for sampling time points and allowed sampling time deviations) following Infusions 1 and 4. The date and time of each sample collections will be documented in the subject's eCRF. Blood sample processing and handling details will be presented in a separate laboratory manual.

At the discretion of the investigator and with sponsor's approval, subjects may be given the option of staying overnight at study sites and/or a hotel for convenience or to ensure compliance with the serial PK collections. Funding or reimbursement for hotel facilities may be provided as allowed by the IRB-approved ICF and any applicable laws and regulations. Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures unrelated to AEs will not be considered as hospitalizations for SAE reporting purposes.

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11.2 Pharmacokinetic Evaluation and Pharmacokinetic Parameters

For PK assessments (Infusion 1 and 4), subjects will receive an infusion of 85 U/kg ± 100 U FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. There will be a washout period of at least 12 days following the Infusion 3 before subjects cross over to the next treatment group. For PK assessments, subjects are required to not be actively bleeding at the time of infusion.

Subjects who have a bleeding episode during the PK assessment periods will not have subsequent PK blood samples collected in that specific PK assessment period and will be treated for the bleeding episode with FEIBA as determined by the investigator. After a washout period of at least 12 days, the IP infusion and PK assessments will be repeated.

Pharmacokinetic parameters will be derived for baseline-corrected FII, [redacted] activity. Baseline-corrected FII, [redacted] activities will be calculated by subtracting the preinfusion value (or average of preinfusion values) from each measurement after infusion.

The following PK parameters will be calculated for FII, [redacted] using standard noncompartmental methods after administration with FEIBA reconstituted in regular volume of SWFI or FEIBA reconstituted in 50% reduced volume of SWFI:

- $AUC_{0\text{-}216\ h}$
- $AUC_{0\text{-}\infty}$
- $AUC_{0\text{-last}}$
- $t_{1/2}$
- MRT
- CL
- V_{ss}
- C_{max}
- t_{max}
- IR at C_{max}; defined as (observed C_{max} - $C_{preinfusion}$)/[total dose/body weight]

[redacted]

Additional PK parameters may be calculated at the discretion of the PK scientist and/or sponsor.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{1/2}$, Interval	The time interval of the log-linear regression used to determine the terminal rate constant lambda_z (λ_z)
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z
Rsq	Goodness-of-fit statistic for calculation of λ_z (coefficient of determination). If Rsq < 0.800, then λ_z and associated parameters will not be reported
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation. If $\%\ AUC_{ex} > 20.00\%$, then $AUC_{0\text{-}\infty}$ and associated parameters will not be reported

All PK analyses will use the actual sampling times, wherever possible. Actual sampling times will be defined as time from the start of infusion to the collection time of blood.

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12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

A SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

Additional events which should be reported as SAEs are as follows:

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19

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- Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE
- Thromboembolic events (myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke, transitory ischemic attack, etc.)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE. Any pregnancy occurring during the study should be reported to the sponsor within 24 hours of the site learning about the pregnancy. The pregnancy should be followed until completion of the pregnancy and up to 1 year postdelivery, if feasible. Pregnancies not considered an (S)AE as described above will be captured in the eCRF.

Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures as described in Section 10.3.2 for reasons unrelated to AEs will not be considered as hospitalization for SAE reporting purposes.

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12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE eCRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study termination/completion will be described on the AE eCRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, it is medically stabilized, or 30 days after the Study Completion/Termination Visit, whichever comes first, and the follow-up information is to be documented in the eCRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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Deviations from the protocol-specified dosage including overdosing (20% higher than the highest permitted dose), underdosing (20% lower than the lowest permitted dose), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion/termination, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on eCRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

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These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours after IP administration the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

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12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 2) and Section 12.1.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the EDC system by completing the relevant eCRF page(s) in English. Once the SAE has been recorded in the EDC system, the Sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24 hour timeline requirement (contacts and instructions to be provided in separate documentation).

Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE report form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAE Report Form, if applicable) must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the Investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting Investigator (for paper SAE Report Forms)

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12.1.3 Medical Device Safety reporting

The IP kit contains the BaxJect device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the Sponsor as an SAE in the same process as described above.

Serious injury is defined as:

- Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure.
- Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) is notified of the urgent measures taken in such cases according to local regulations.

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12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE eCRF (and SAE Report Form if eCRF is not available). These events will be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)

- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

General medical history will be collected for 4 weeks prior to screening. Any information on the subjects' hemophilia history will be collected a year prior to screening including documented history of hemophilia, confirmation of inhibitors, bleeding episodes history, and history of FEIBA or rFVIIa usage.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

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12.6 Physical Examinations

At screening (as described in Table 1 and Table 2), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Where applicable (see Section 15.6), assessments will be performed at a central laboratory, according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for additional testing. Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of 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.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, glucose, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase.

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Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening and at study completion/termination. Hematology and clinical chemistry assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, at the central laboratory.

In addition, serum samples for pregnancy tests for females of childbearing potential will be collected at screening.

12.7.2 Coagulation Testing

Blood will be obtained for the assessment of coagulation testing will consist of aPTT, PT, thrombotic markers (D-Dimers, prothrombin fragment F 1.2, TAT, fibrinopeptide A), FII, FX, FIX, FVII, and FVIII or FIX inhibitor level (Nijmegen assay). All coagulation testing will be performed at screening, during the study (Infusion Visits 1 to 12), and at the Study Completion/Termination Visit.

12.7.3 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, hepatitis A virus (HAV) antibody, hepatitis B virus (HBV) antibody, hepatitis B surface antigen (HBsAg), HCV antibody, parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening and at the Study Completion/Termination Visit.

12.7.4 CD4 Levels

At screening only, CD4 levels will be determined using flow cytometry in the case of a subject being HIV positive.

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE eCRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a pre-existing disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned:

- Backup samples for FII, [redacted] will be taken at screening, and at all pre and postinfusion timepoints for PK assessments

Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE. Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) measured once at screening and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and after administration of IP, at each Infusion study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE eCRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0-100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of subject status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease. In this scale, a high number performance status represents high functionality, and a lower number represents low functionality and likely rapid progression of disease.[11] Subjects will be scored using this scale at screening.

12.10 Infusion Site Evaluations

The current site of IP infusion will be assessed for immediate local reactions 30 minutes (±10 min) after infusion. In addition, infusion sites will be monitored by the subject for 72 hours after infusion, and any AEs will be captured in the subject electronic diary as described in Section 10.6.

Infusion sites will be monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations will be made by clinical staff or by the subject or caregiver. If an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Infusion sites will continue to be reviewed at each study visit, and any infusion site reactions will be followed until resolution. Each infusion site reaction will be categorized using the intensity grading described for AEs in Section 12.1.2.1.

12.11 Special Treatment Considerations

Subjects will be screened for eligibility in the study as described in Section 8.2 and Section 8.8.3, and will be informed of the study specific restrictions and requirements of the study. Subjects who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic reaction

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Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Sometimes, these reactions can be life-threatening. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute allergic/hypersensitivity reaction after an infusion of IP, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn to test for anti-drug antibodies.

Subjects who experience a potentially severe allergic reaction will be discontinued from IP. They will complete a Termination/Study Completion Visit, and will be monitored for stabilization or resolution of the AE. Premedication to prevent allergic reactions will not be permitted, as severe allergic reactions are an outcome measure for this study.

13. STATISTICS

Data handling will be the responsibility of the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

Part 1 (cross-over) of this study will evaluate PK equivalence of FEIBA component (FII) in FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI as measured by $AUC_{0\text{-}216\ h}$. The sample size was calculated for a Type-1 (α) error level of 0.05 and a Type-II (β) error level of 0.1 or 90% power, under the assumption that the true (population) means are equivalent, i.e., the 90% confidence interval (CI) for the ratio of the geometric means between the 2 treatments are contained completely in the margins of equivalence defined as 80% to 125%. The within-subject variability was estimated by using the square root of mean square error (0.222) as in previous studies of FVIII. The required sample size was estimated to be 24 evaluable subjects. In order to obtain the required 24 subjects, Part 1 will randomize approximately 32 subjects for the crossover PK study, allowing for a possible 25% dropout rate.

With approximately 100 infusions for each treatment (reduced or regular volume of SWFI) administered for the study, the upper limit of the 95% CI of the rate of infusions with a specific AE is less than 3.3%, if the specific AE is not observed. The upper limit of 95% CI of the rate of infusions for a specific AE is about 5% if 1 AE is observed.

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13.2 Datasets and Analysis Cohorts

Classification into the analysis sets will be conducted prior to the soft database lock for DMC in Part 1. For Part 2, the classification of the analysis sets will be conducted prior to database lock.

Major protocol violations will include, but are not limited to: violation of inclusion/exclusion criteria, administration of prohibited medications, and erroneous administration of study treatment. Subjects will be assigned to treatment groups based on randomization.

Safety: The safety population will include all subjects who received at least 1 dose of IP (FEIBA). All safety analyses will be performed on the safety population. Subjects will be evaluated according to the treatment received. The safety population will be defined separately for each part of the study.

PK: The PK population will include all subjects who received at least 1 dose of IP and have at least 1 measured concentration at a scheduled PK time point after start of dosing without protocol violations or events with potential to affect PK. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Statistical analyses of the primary PK endpoint will be based on the PK population.

13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed; no imputation method for missing values will be used. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of withdrawal.

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13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values. All PK parameters will be summarized by treatment using n, mean, standard deviation, geometric mean, % geometric coefficient of variation, minimum, median, and maximum, except that t_{max} will be reported with n, minimum, median, and maximum only.

A listing of PK blood sample collection times by individual, as well as derived sampling time deviations, will be provided. Pharmacokinetic concentrations/activities and derived PK parameters for FII, [redacted] will be summarized using descriptive statistics by treatment and nominal sampling time point. Plots of individual and mean plasma concentration-time profiles will be presented by treatment and visit. Plots of individual and geometric mean $AUC_{0\text{-}216\ h}$ will also be presented by treatment.

13.4.1 Primary Outcome Measure

13.4.1.1 Analysis of the Primary PK Outcome Measure (Part 1)

The primary PK outcome measure is the $AUC_{0\text{-}216\ h}$ of FEIBA component FII. $AUC_{0\text{-}216\ h}$ will be derived using noncompartmental methods as described in Section 11.2 and will be summarized by treatment using descriptive statistics. The 216 hour timepoint is critical and no imputation, interpolation, or extrapoloation of the FII concentration at time = 216 hours will be performed if no bioanalytical result is available or the sample is not quantifiable at that specific timepoint. In such cases, $AUC_{0\text{-}216\ h}$ will be set to missing. Missing datapoints may not prevent the calculation of $AUC_{0\text{-}216\ h}$. If at least the pre-infusion, end-of-infusion, 216 hour and at least one other timepoint is collected, $AUC_{0\text{-}216\ h}$ may be able to be calculated.

For subjects that require re-infusion due to bleeding episodes during the PK assessment, PK parameters will only be listed for the first, interrupted infusion, while those from the repeated infusion (if deemed evaluable) will be listed and used for descriptive and statistical analysis.

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Statistical analyses of the primary PK endpoint will be based on the PK population with evaluable $AUC_{0\text{-}216\ h}$ parameters.

Log-transformed PK parameter $AUC_{0\text{-}216\ h}$ from Infusions 1 and 4 will be analyzed using a linear mixed-effects model with sequence, period, and treatment (FEIBA reconstituted in 50% reduced volume and regular volume of SWFI) as fixed effects and subject as a random effect. Least-squares means with corresponding 95% CIs for the 2 treatments will be determined. The difference in least-squares means between the 2 treatments with reduced and standard volumes and corresponding 90% CI will also be determined. Back transformation will provide the ratio of the geometric means and corresponding CI for the treatment comparison (reduced to standard volumes). To establish the equivalence, the 90% CI for the ratio of the geometric means between the 2 treatments has to be contained completely in the margins of equivalence defined as 80% to 125%.

13.4.1.2 Analysis of the Primary Safety Outcome Measure (Parts 1 and 2)

The safety of treatment infusions will be evaluated primarily by the occurrence of severe allergic reactions and infusion site reactions. The number and proportion (95% exact CI) of subjects experiencing severe allergic reactions and infusion site reactions will be summarized by treatment for each study part.

13.4.2 Secondary Outcome Measures

13.4.2.1 Analysis of the Pharmacokinetic Outcome Measures

Secondary efficacy/PK outcome measures consist of the IR of FEIBA component FII in subjects as well as PK measurements ($AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max}) of FEIBA component FII. Pharmacokinetic parameters will be derived using noncompartmental methods as described in Section 11.2. The secondary outcome measures will be descriptively summarized by treatment.

13.4.2.2 Analysis of the Safety Outcome Measures

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per subject and treatment for each study part. If a subject reports the same AE more than once, it will be counted with its worst severity and closest relationship to the IP.

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The number and proportion of subjects experiencing serious and non-serious AEs up to study completion or subject withdrawal will be summarized by treatment for each study part. The number of product related serious and non-serious AEs will also be summarized by treatment for each study part.

Subgroup analyses will also be performed for events categorized as thromboembolic AEs. Thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, TAT, and fibrinopeptide A) will be summarized using descriptive statistics by treatment for each study part. Mean concentration plots will be presented by treatment and visit for each thrombotic marker and study part.

Vital signs and clinical laboratory assessments as well as the corresponding changes from baseline will be summarized descriptively by treatment at each scheduled assessment for each study part. Baseline will be defined as the last value prior to the first infusion for each treatment. Laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables by treatment at each scheduled assessment for each study part. All laboratory data will be listed with abnormal values flagged.

Individual listings presenting subjects by treatment will be presented for the safety parameters. The listings will be created for both change and absolute values, if appropriate.

13.4.3 Exploratory Outcome Measures

[redacted]

The results of the TSQM and the patient preference questionnaires will be summarized by descriptive statistics as appropriate.

13.5 Planned Interim Analysis of the Study

There is no planned interim analysis other than a safety and PK data review by the DMC.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

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15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

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15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

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16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

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16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 16.3).

16.4 Data Monitoring Committee

This study will be monitored by and internal Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the Baxalta DMC will be composed by appropriate members of clinical, safety, and biostatistics division that are not involved in the active execution of the trial. This internal DMC can stop a study if it finds toxicities or if treatment is proven to be not beneficial. The DMC will meet at 2 predetermined timepoints through the study for 2 subsets of subjects (subjects 1 through 12, and again for all subjects through the final subject), for a total of 4 meetings.

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Baxalta internal DMC Part 1

All evaluable subjects will be included in the DMC review, however to help with subject retention on the study, the DMC review of Part 1 will be conducted twice; once after the first 12 subjects have completed Part 1, and then again after the last subject has completed Part 1. Once the first 12 subjects have completed Part 1, the DMC will review the safety and PK data and will provide a recommendation on whether these subjects can proceed to Part 2 for evaluation of increased infusion rates. The DMC will meet again after the final subject has completed Part 1 of the study. The DMC will then review all safety and PK data from Part 1 and provide a recommendation on whether the remaining subjects can proceed to Part 2. A soft database lock will be in place on the records of the subjects who are undergoing review. Subject recruitment and subjects in other phases of the study will not be affected by this database lock.

Baxalta internal DMC Part 2

After the first 12 subjects have completed Infusion 9, the DMC will review the safety data and provide a recommendation on whether these subjects can proceed to the next higher infusion rate of 10 U/min/kg. The DMC will meet again after the final subject has completed Infusion 9, and provide a recommendation on whether the remaining subjects can proceed to the faster infusion rate.

Additional Baxalta internal DMC Meetings

Additional ad hoc meetings of the DMC may be convened as required.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.9), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, eCRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

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The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If eCRFs are provided by the sponsor, only authorized study site personnel will record or change data on the eCRFs. If data is not entered on the eCRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to an eCRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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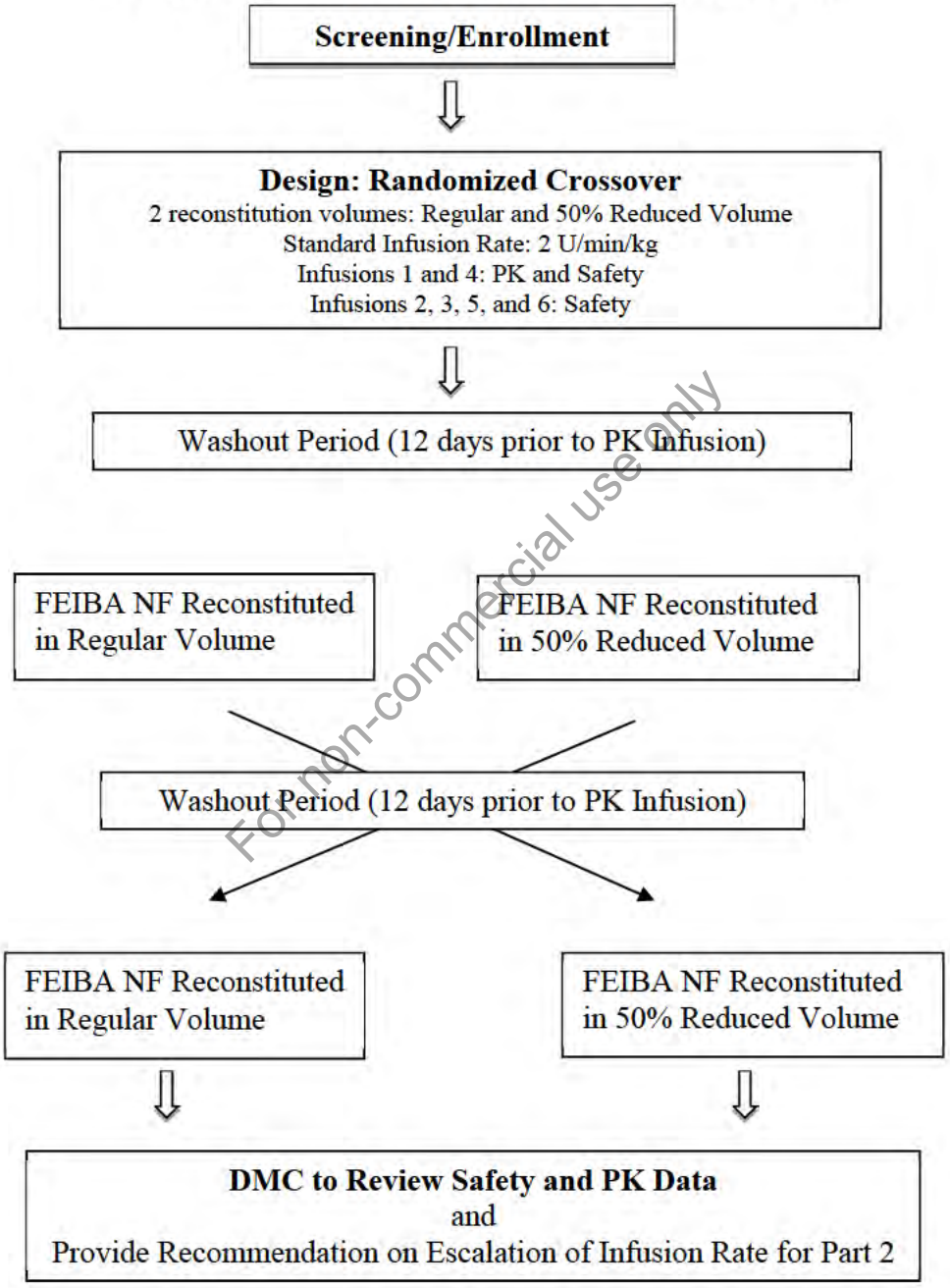
20. SUPPLEMENTS

20.1 Study Flow Chart Part 1

Figure 1
Study Design for Part 1 Baxalta Clinical Study 091501



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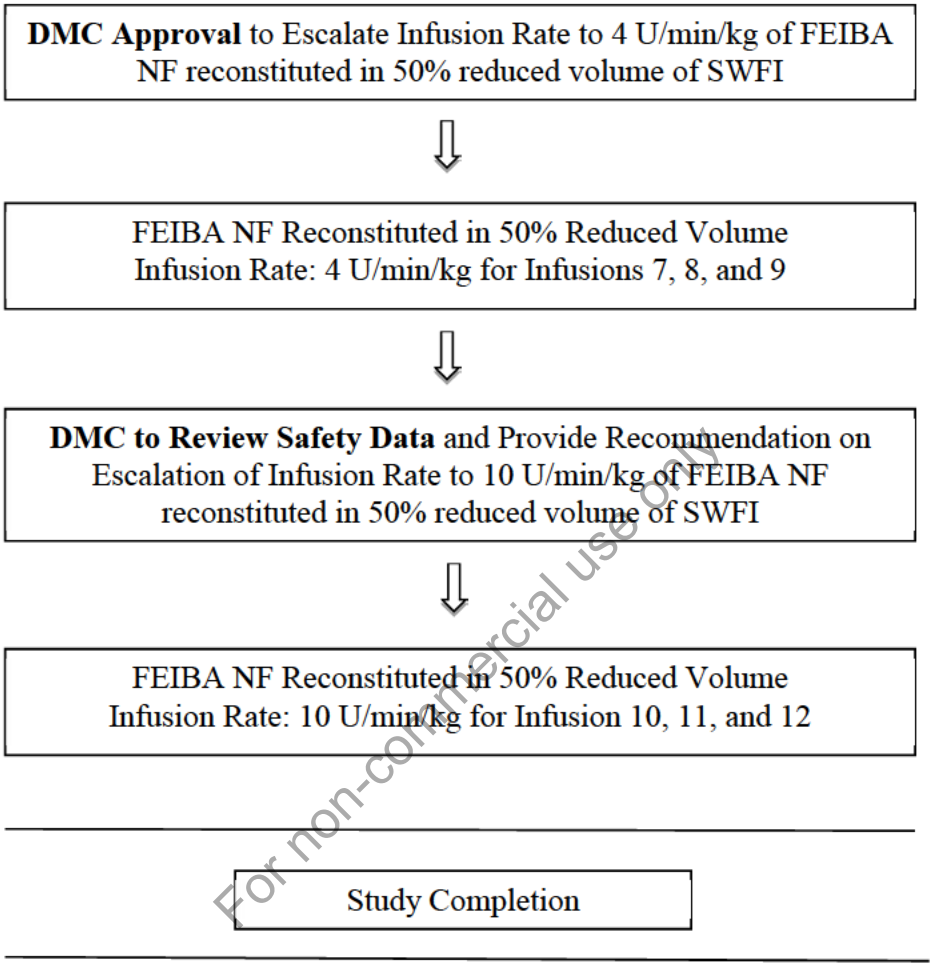
20.2 Study Flow Chart Part 2

Figure 2
Study Design for Part 2 Baxalta Clinical Study 091501



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20.3 Schedule of Study Procedures and Assessments (Part 1)

Table 1
Schedule of Study Procedures and Assessments (Part 1)

Procedures/ Assessments	Screening Assessments	Study Visits[a]										
		Washout Period 1[e]	Infusion #1	PK Visits[b]	Infusion #2	Infusion #3	Washout Period 2[f]	Infusion #4	PK Visits[a]	Infusion #5	Infusion #6	DMC Review[g]
Study Visit Windows[c]	A maximum of -56 days to 0		Day 1	Multiple Visits Day 1 through 9	9 (+1) days from Infusion 1	48 hr (+48) from Infusion 2		At least 12 days from Infusion 3	Multiple Visits up to 9 Days from Infusion 4	9 (+1) days from Infusion 4	48 hr (+48) from Infusion 5	
Informed Consent[d]	X											
Eligibility Criteria	X											
Medical History	X											
Medication and Non-drug Therapies	X		X		X	X		X		X	X	
Dispense/Collect Subject Diary			X									
Review Subject Diary					X	X		X		X	X	
Physical Examination	X											
Pregnancy Test	X											
Vital Signs[h]	X		X		X	X		X		X	X	
Karnofsky Performance Test	X											
Laboratory Assessments[i]	X		X		X	X		X		X	X	
PK Assessments[j]	X		X	X				X	X			
Adverse Events	X[k]		X	X	X	X		X	X	X	X	
IP Treatment			X		X	X		X		X	X	
TSQM and patient preference questionnaires[l]		X					X					X

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Continued

Abbreviations:DMC=Data Monitoring Committee; FEIBA=Factor Eight Inhibitor Bypassing Activity; ICF=informed consent form; IP=investigational product; PK=pharmacokinetic; rFVIIa=recombinant activated clotting factor VII; SAE=serious adverse event.

[a] A Study Completion/Termination Visit is to be completed in Part 1 only for subjects who withdraw or discontinue prior to the end of the study. If a subject withdraws or discontinues, this visit should be done in within 7 days but no sooner than 72 hours from the last infusion that he or she receives. Otherwise, the Study Completion/Termination Visit will occur at the end of Part 2 (see Table 2).

[b] Additional PK visits will occur between Infusions 1 and 2, and between Infusions 4 and 5, at 24, 72, 120, 168, and 216 hours after Infusion 1 or Infusion 4 as described in Table 4.

[c] Study Visit Windows:

1. Infusion 1: Infusion 1 can be scheduled after screening assessments have been completed and the appropriate washout period as defined in washout (footnote e) below has occurred. Scheduling will also need to ensure that PK timepoints can be collected as described in footnote a and Table 4.
2. Infusion 2: Infusion 2 is scheduled for 9 days (+1) after Infusion 1. All PK samples must be completed before Infusion 2 can begin. If the subject has a bleeding episode during the 9-day PK collection period, bleeding will be controlled as described in Section 8.8.4, and after a washout of at least 12 days, Infusion 1 and PK assessments will be repeated.
3. Infusion 3: Infusion 3 should be scheduled 48 hours (+48 hours) after Infusion 2.
4. Infusion 4: Infusion 4 should be at least 12 days after Infusion 3 (See footnote f on Washout Period 2 for restrictions).
5. Infusion 5: Infusion 5 should be 9 days (+1) after Infusion 4. All PK samples must be completed before Infusion 4 can begin. If the subject has a bleeding episode during the 9-day PK collection, bleeding will be controlled as described in Section 8.8.4, and after a washout of at least 12 days, Infusion 4 and PK assessments will be repeated..
6. Infusion 6: Infusion 6 should be scheduled for 48 hours (+48) after Infusion 5.

[d] Occurs at enrollment (prior to any study-specific procedure).

[e] Washout Period 1: Washout Period 1 is based on the subject's last dose of FEIBA or rFVIIa (e.g., NovoSeven). Due to the varying lengths of the half-lives of the drugs, subjects who have received FEIBA will need to wait 12 days from the last dose of FEIBA that they received before they can begin Infusion 1. For subjects who have previously been treated with rFVIIa, they will need to wait at least 24 hours from the last dose of rFVIIa before they can begin Infusion 1 of the study. Additional days of washout beyond the minimum of 12 days or 1 day for FEIBA or rFVIIa treatment subjects, respectively, are permissible (as long as the screening assessments stay within the window to Infusion 1). Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. For subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day of treatment. If the subject has a bleeding episode that requires treatment during the washout period, the washout period must be restarted before they can proceed with the study.

[f] Washout Period 2: Washout Period 2 is a minimum of 12 days from Infusion 3, since all subjects receive FEIBA at Infusion 3. If bleeding occurs during the washout period, the subject will be treated with FEIBA and the washout period will be restarted.

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[g] DMC break after Part 1: The DMC review of Part 1 will be conducted twice; once after the first 12 subjects have completed Part 1, and then again after the last subject has completed Part 1. Once the first 12 subjects have completed Part 1, the DMC will review the safety and PK data and will provide a recommendation on whether these subjects can proceed to Part 2 for evaluation of increased infusion rates. Therefore, subjects will be held in a DMC interim period until review as described in Section 8.8.3 after completion of Infusion 6. During this time subjects who are on hold will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator, see Section 8.8.4. The DMC process will not affect enrollment of new subjects or subjects who are in other parts of the study.

[h] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within 30 minutes after completion of the infusion. Height, measured once at Screening, will also be collected.

[i] For laboratory assessments, see Table 3.

[j] For PK assessments, see Section 11 for details.

[k] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[l] Questionnaires (TSQM and patient preference questionnaire) will be administered between Screening and Infusion 1, between Infusion 3 and 4, and between Infusion 6 and 7.

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20.4 Schedule of Study Procedures and Assessments (Part 2)

Table 2
Schedule of Study Procedures and Assessments (Part 2)

Procedures/ Assessments	Study Visits			
	Infusions 7, 8, and 9 Rate: 4 U/min/kg	DMC Review[d]	Infusions 10, 11, and 12 Rate: 10 U/min/kg	Study Completion/ Termination Visit[a]
Study Visit Windows	48 hours (+48) from previous infusion[b]		48 hours (+48) from previous infusion[c]	3 days (+ 4) from Infusion 12 (or last infusion)[a]
Medications and Non-drug Therapies	X		X	X
Review Subject Diary	X		X	X
Pregnancy Test				
Vital Signs[e]	X		X	X
Laboratory Assessments[f]	X		X	X
Adverse Events[g]	X		X	X
IP Treatment	X		X	
TSQM and patient preference questionnaires[h]			X[h]	

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Abbreviations: DMC=Data Monitoring Committee; FEIBA=Factor Eight Inhibitor Bypassing Activity; IP=investigational product.

[a] The Study Completion/Termination Visit includes cases of withdrawal or discontinuation. This visit should be done within 7 days but no sooner than 72 hours after Infusion 12). If a subject withdraws or discontinues, this visit should be done within 7 days but no sooner than 72 hours after the last infusion that the subject receives.

[b] Infusions 7, 8, and 9:

1. Infusion 7 will be scheduled as soon as possible from the subject being approved to proceed to Part 2 of the study by the DMC. However, if they have been receiving FEIBA treatment during the DMC interim period, wait at least 48 hours after the subject's previous infusion before Infusion 7 is given.
2. Infusion 8 will be scheduled 48 hours (+48) after Infusion 7.
3. Infusion 9 will be scheduled 48 hours (+48) after Infusion 8.

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[c] Infusions 10, 11, and 12:
Infusion 10 will be scheduled as soon as possible from the subject being approved to proceed to the next treatment arm (Infusion 10) of the study by the DMC. However, if they have been receiving FEIBA treatment during the DMC interim period, wait at least 48 hours after the subject's previous infusion before Infusion 10 is given.
Infusion 11 will be scheduled 48 hours (+48) after Infusion 10.
Infusion 12 will be scheduled 48 hours (+48) after Infusion 11.

[d] DMC review in Part 2: The DMC review of Part 2 treatment 1 will be conducted twice, once after the first 12 subjects have completed Infusion 9, and then again after the last subject has completed Infusion 9. The DMC will review the safety data for each subset of subjects and provide a recommendation on whether the subjects under review can proceed to Infusion 10. Once subjects have completed Infusion 9, they will be held in an interim period until the DMC review as described in Section 8.8.3. During this time, subjects who are on hold will be provided with standard of care FEIBA (by the sponsor) for the treatment or prevention of bleeding episodes as determined by the investigator. Subjects will continue to fill out their subject diary at this time. Subjects will move to the next treatment arm (Infusion 10) of the study upon approval by the DMC. The DMC process will not affect enrollment of new subjects or subjects who are in other parts of the study.

[e] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within 30 minutes after completion of the infusion. Height, measured once at Screening, will also be collected.

[f] For laboratory assessments, see Table 3.

[g] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[h] Subject questionnaires (TSQM and patient preference questionnaire) will be administered after Infusion 12.

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20.5 Clinical Laboratory Assessments

Table 3
Clinical Laboratory Assessments

Assessments	Screening Visit	Infusions 1 and 4	PK Visits[a] (multiple visits Day 1 through 9)	Infusions 2, 3, 5, 6, 7, 8, 9, 10, 11, and 12	Study Completion/ Termination Visit[b]
Hematology[c]	X				X
Clinical Chemistry[d]	X				X
Coagulation Testing[e]	X	X		X	X
Serology Testing[f]	X				X
PK Assessments[g]	X	X	X		
Pregnancy Test[h]	X				

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; FII=Factor II; FIX=Factor IX; FVII=Factor VII; FVIII=Factor VIII; FX=Factor X; GGT=gamma-glutamyl transpeptidase; HAV=hepatitis A virus; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; Hct=hematocrit; HCV=hepatitis C virus; Hgb=hemoglobin; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IgM=immunoglobulin M; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; TAT=thrombin/anti-thrombin complex; WBC=white blood cell.

[a] Additional PK visits will occur between Infusions 1 and 2, and between Infusions 4 and 5, at 24, 72, 120, 168, and 216 hours after Infusion 1 or Infusion 4 as described in Table 4.

[b] Includes cases of withdraw or discontinuation.

[c] Hematology assessments include: CBC (Hct, Hgb, RBC count, WBC count) with differential, MCV, MCHC, and platelet count.

[d] Clinical chemistry assessments include sodium, chloride, potassium, bicarbonate, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, GGT, 5'-nucleotidase.

[e] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1.2, TAT, fibrinopeptide A), FII, FX, FIX, FVII, and FVIII or FIX inhibitor level (Nijmegen assay).

[f] Serological testing will include: HIV-1 and HIV-2 antibodies (HIV+, check CD4 count–screening visit only), HAV antibodies, HBV antibody, HBsAg, HCV antibody, parvovirus B19 (IgM and IgG), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).

[g] PK assessments will include coagulation activity testing of: Factors II, [redacted] as described in Table 4.

[h] A serum pregnancy test will be performed for females of childbearing potential.

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20.6 Pharmacokinetic Assessments

Table 4
PK Assessments

Procedures/ Assessments	Screening Visit	Infusion 1	Infusion 4	Day from Infusion
PK Assessments: Factor II	X	**Preinfusion**		
		30 ± 5 min	30 ± 5 min	Day 0
		15 ± 5 min	15 ± 5 min	
[redacted]	X	**Postinfusion**[a]		
		EOI	EOI	Day 0
		30 ± 5 min[b]	30 ± 5 min[b]	
		60 ± 5 min	60 ± 5 min	
		3 h ± 30 min	3 h ± 30 min	
		8 h ± 30 min	8 h ± 30 min	
		24 ± 4 h[b]	24 ± 4 h[b]	Day 1
		72 ± 4 h	72 ±4 h	Day 3
		120 ± 6 h	120 ± 6 h	Day 5
		168 ± 6 h	168 ± 6 h	Day 7
		216 ± 6 h	216 ± 6 h	Day 9

Abbreviations: EOI=end-of-infusion; Factor II=FII; [redacted] h=hours; min=minutes; PK=pharmacokinetic.

Notes: PK assessments will be completed on FII, [redacted] at screening and all timepoints indicated before and after Infusion 1 and Infusion 4.

[a] Postinfusion sampling times are relative to the end of infusion.

[b] Blood sample for thrombotic marker analysis will be collected at either the 30-minute or 24-hour timepoint.

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21. REFERENCES

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INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered, FEIBA NF

STUDY TITLE: A Two-part, Phase 4, Prospective, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

ORIGINAL: 2015 OCT 08

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-004079-60
IND NUMBER: 13715

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered, FEIBA NF

STUDY TITLE: A Two-part, Phase 4, Prospective, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

ORIGINAL: 2015 OCT 08

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-004079-60
IND NUMBER: 13715

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: Anti-inhibitor Coagulant Complex, activated prothrombin complex concentrate, FEIBA

STUDY TITLE: A Two-part, Phase 4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

STUDY SHORT TITLE: FEIBA Reconstitution Volume Reduction and Faster Infusion Study

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PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

AMENDMENT 1 (Global): 2016 Mar 03

Replaces: Original: 2015 OCT 08

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted] MD
[redacted] Clinical Development
Baxalta US Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

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2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

**ALL SAEs ARE TO BE REPORTED ON THE ADVERSE EVENT ELECTRONIC CASE REPORT FORM (ECRF)
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT. IF THE ECRF IS NOT AVAILABLE THEN THE SAE MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT.**

See SAE Protocol Sections for further information and SAER form for contact information.
Further details are also available in the study team roster.

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For definitions and information on the assessment of these events, refer to the following:

- Adverse Event, Section 12.1
- Serious Adverse Event, Section 12.1.1.1
- Assessment of Adverse Events, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	FEIBA, Anti-Inhibitor Coagulant Complex
Name(s) of Active Ingredient(s)	Coagulation factors II, X, IX, and VIIa
CLINICAL CONDITION(S)/INDICATION(S) • Hemophilia A or B with inhibitors	
PROTOCOL ID	091501
PROTOCOL TITLE	A Two-part, Phase 4, Prospective, Multicenter, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors
Short Title	FEIBA Reconstitution Volume Reduction and Faster Infusion Study
STUDY PHASE	Phase 4 (postmarketing)
PLANNED STUDY PERIOD	
Initiation	First Subject In: Q2 2016
Primary Completion	Last Subject In: Q1 2017
Study Completion	Last Subject Last Visit: Q1 2018
Duration	13 to 16 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose 1. To compare the pharmacokinetics (PK) of Factor Eight Inhibitor Bypassing Activity (FEIBA component Factor II (FII) and safety of FEIBA reconstituted in a reduced volume of sterile water for injection (SWFI) versus regular volume SWFI, administered at the standard infusion rate of 2 U/min/kg 2. To evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison to the standard rate of 2 U/min/kg	
Primary Objectives 1. Determine PK equivalence of FEIBA component FII reconstituted in 50% reduced volume SWFI and regular volume SWFI on area under the concentration-time curve from time zero (preinfusion) to time 216 hours ($AUC_{0\text{-}216\ h}$) 2. Determine the occurrence of thromboembolic events and allergic-type hypersensitivity reactions	

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Secondary Objectives

1. Determine the safety and tolerability of 50% reduced volume FEIBA administered at the standard and escalated infusion rates, based on the occurrence of adverse events (AEs)
2. Monitor clinically apparent changes in vital signs, infusion rate-related events, and infusion site reactions
3. Determine the effect of 50% reduced volume FEIBA component FII on incremental recovery (IR), area under the concentration-time curve from time zero (preinfusion) extrapolated to infinity ($AUC_{0-\infty}$), area under the concentration-time curve from time zero (preinfusion) to time of last quantifiable concentration ($AUC_{0\text{-last}}$), terminal half-life ($t_{1/2}$), clearance (CL), mean residence time (MRT), volume of distribution at steady state (V_{ss}), maximum plasma concentration (C_{max}), and time to maximum observed plasma concentration (t_{max})

Exploratory Objective

[redacted]

2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

STUDY DESIGN

Study Type/ Classification/ Discipline	PK Equivalence, Pharmacokinetic, and Safety
Control Type	Active
Study Indication Type	Treatment
Intervention model	Part 1: Crossover Part 2: Sequential
Blinding/Masking	Part 1: Randomized, Open-label Part 2: Non-randomized, Open-label
Study Design	This study is a 2-part, Phase 4, prospective, open-label, multicenter study to be conducted in up to 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 Bethesda units [BU] in hemophilia A and ≥ 0.6 BU in hemophilia B) for the primary PK assessment, (i.e., having the $AUC_{0\text{-}216\ h}$ of FEIBA component FII estimable from both PK infusions), with a planned enrollment of up to 32 subjects. In Part 1, subjects will be administered 2 different volumes of FEIBA in a randomized, crossover manner with a washout period between the treatments. Part 1 will evaluate the PK (FEIBA component FII) and safety of FEIBA reconstituted in 50% reduced volume of SWFI and administered at the standard infusion rate of 2 U/min/kg compared with FEIBA reconstituted in regular volume of SWFI at the standard infusion rate. All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria.

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	After a washout period (at least 12 days from last treatment with APCC (e.g., FEIBA), or at least 24 hours after last treatment with a recombinant activated clotting factor VII (rFVIIa) product [e.g., NovoSeven®]), eligible subjects will be randomly assigned (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. Subjects will receive the first infusion for PK and safety analysis and the second and third infusions for collection of additional safety data. After a washout period of at least 12 days following the third infusion, subjects will crossover to the next treatment group where the fourth infusion will be for PK and safety analysis and the fifth and sixth infusions for collection of additional safety data. All subjects who received at least 1 dose of FEIBA will be included in the safety analysis set. Pharmacokinetic equivalence of FEIBA reconstituted in reduced and regular volumes of SWFI in terms of $AUC_{0\text{-}216\ h}$ will be evaluated using the PK population. Part 2 is non-randomized with sequential enrollment of subjects who complete Part 1, to evaluate the safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/kg. FEIBA Infusions 7, 8, and 9 will be administered at the 4 U/min/kg rate. The infusions will be administered every 48 hours (+48 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Subjects will follow with 3 infusions (Infusions 10, 11, and 12) of FEIBA at 10 U/min/kg rate. The infusions will be administered every 48 hours (+48 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion. All IP infusions will be administered at the hemophilia care centers/study sites. Each subject will receive a maximum of 14 IP infusions total (most subjects will receive 12 IP infusions, up to 14 is for subjects who have a bleeding episode during PK collections, and therefore have their PK infusion reinfused). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg. For PK infusions, every measure should be taken to ensure consistent dosing between Infusion 1 and Infusion 4. Partial vials may be used in order to maintain a consistent dose in case 85 U/kg ± 100 U can not be achieved by administration of whole vials. For infusions that are not PK infusions, whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate. Please refer to study documents for detailed instructions.

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	Safety monitoring for this study will be conducted by an Internal Safety Monitoring Committee (ISMC). All SAEs that occur will be reviewed by the Chair of the ISMC. Additionally, there are 3 scheduled ISMC meetings: 1. At least 48 hours after 6 subjects in Part 1 (3 subjects in each group) have completed Infusion 5 2. At least 48 hours after 6 subjects have completed Infusion 8 (Part 2) 3. At least 48 hours after 6 subjects have completed Infusion 11 (Part 2) ISMC preplanned meetings will be held concurrently with the ongoing study.
Planned Duration of Subject Participation	Study enrollment is planned to initiate in Q2 of 2016. It is planned that each subject will spend approximately 60-90 days in the study.

Primary Outcome Measure

1. $AUC_{0\text{-}216\ h}$ of FEIBA component FII in the subjects
2. Occurrence of thromboembolic events
3. Occurrence of allergic-type hypersensitivity reactions

Secondary Outcome Measure(s)

Efficacy/Pharmacokinetics

1. Incremental recovery of FEIBA component FII in subjects
2. $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max} of FEIBA component FII in subjects

Safety

1. Evaluate occurrence of all AEs and SAEs
2. Evaluate occurrence of AEs leading to discontinuation
3. Evaluate occurrence of infusion site reactions
4. Evaluate occurrence of all AEs occurring within 24 to 72 hours of IP infusion
5. Evaluation of thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, thrombin/anti-thrombin complex [TAT], and fibrinopeptide A)
6. Evaluate vital signs and clinical laboratory assessments

Exploratory Outcome Measure(s)

[redacted]

2. Evaluate responses to the TSQM and the patient preference questionnaire

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INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** kit; powder, lyophilized, for solution/suspension; injection **Dosage frequency:** Infusion 2 and 5 are 9 days (+ 1 day) from Infusion 1 and 4, respectively. Infusions 3, 6, 7, 8, 9, 10, 11, and 12 are 48 hr (+48 hr) from the previous infusion. See Section 20.3 and Section 20.4 for additional details. **Mode of Administration:** intravenous bolus
SUBJECT SELECTION	
Targeted Accrual	Enroll 32 subjects (at least 24 evaluable for the primary PK assessment)
Number of Groups/Arms/Cohorts	1 cohort: at least 24 evaluable adult subjects (≥ 18 to ≤ 65 years old) for PK and safety evaluation

Inclusion Criteria

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa)
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable hepatic disease
4. Human immunodeficiency virus (HIV) negative; or HIV positive with stable disease and cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Subject is willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, subject must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a Abstain from sexual intercourse
   b Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
   a Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
   b Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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Exclusion Criteria

1. Known hypersensitivity to FEIBA or any of its components
2. Clinically symptomatic liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Subject is taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except antiretroviral chemotherapy
9. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
10. Subject is a family member or employee of the investigator
11. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

STATISTICAL ANALYSIS

Sample Size Calculation

Part 1 (crossover) of this study will evaluate PK equivalence of FEIBA component FII in FEIBA reconstituted in 50% reduced volume versus regular volume of SWFI as measured by $AUC_{0\text{-}216\ h}$. The sample size was based on the premise of a true ratio of geometric means of test and reference of 1.0 using a within-subject coefficient of variation of 22.2%, to yield 90% power when equivalence is declared based on the 90% CI for the ratio of geometric means for the 2 treatments being completely contained in the margins of equivalence defined as 80% to 125%. In order to obtain the required 24 subjects, Part 1 will randomize up to 32 subjects for the crossover design, allowing for a possible 25% dropout rate.

With approximately 100 infusions for each treatment (reduced or regular volume of SWFI) administered for the study, the upper limit of the 95% CI of the rate of infusions with a specific AE is less than 3.3%, if the specific AE is not observed. The upper limit of the 95% CI of the rate of infusions for a specific AE is about 5% if 1 AE is observed.

Planned Statistical Analysis

Primary Analysis

For Part 1, an equivalence test will be made for $AUC_{0\text{-}216\ h}$ of FII. All other PK parameters will be reported using descriptive statistics

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$AUC_{0\text{-}216\ h}$ for FEIBA component FII of reduced volume and regular volume will be compared calculating the 90% two-sided confidence interval for the difference of the mean logarithms of $AUC_{0\text{-}216\ h}$ between reduced volume and regular volume. The error variance used to calculate these CIs will be obtained from an analysis of variance model that will consist of fixed effect terms that model the subject effect, the sequence effect, the period effect, and the drug effect. The antilogs of the confidence limits will constitute the 90% CI for the ratio of the geometric means (antilog of the means of the log). To establish equivalence, the 90% CI for the ratio of the geometric means of the 2 treatments has to be contained in the margins of equivalence defined as 80% to 125%.

For Parts 1 and 2, the safety of treatment infusions will be evaluated primarily by the occurrence of thromboembolic events and allergic-type hypersensitivity reactions, by treatment for each study part. These will be summarized and a 95% CI will be provided.

Secondary and Exploratory Analysis

Levels of FEIBA components FII, [redacted] will be displayed graphically over time for each subject and summarized by visit and treatment for each study part.

The $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, t_{max}, and IR of FEIBA component FII will be summarized descriptively by visit and treatment for each study part.

All safety analyses will be performed for each part separately as well as for the 2 parts together.

The number and proportion of subjects experiencing serious and non-serious AEs up to study completion or subject withdrawal will be summarized by treatment. The number of product related serious and non-serious AEs and number of AEs leading to discontinuation will also be summarized by treatment. A subgroup of all AEs occurring within 24 and 72 hours of IP infusion will be summarized by treatment. Additionally, subjects experiencing infusion-related AEs and infusion site reactions will be summarized by treatment.

Thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, TAT, and fibrinopeptide A) will be summarized using descriptive statistics by treatment. Mean concentration plots will be presented by treatment and visit for each thrombotic marker and study part.

The results of the TSQM and the patient preference questionnaires will be summarized by descriptive statistics as appropriate.

Vital signs and clinical laboratory assessments will be summarized descriptively by treatment for each study part at each scheduled assessment and for the corresponding change from baseline. Shift tables will also be presented for clinical laboratory assessments by treatment for each study part at each scheduled assessment.

Full details of the statistical analysis will be specified in the statistical analysis plan (SAP).

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0\text{-}216\ h}$	area under the concentration-time curve from time zero (preinfusion) to time 216 hours
$AUC_{0\text{-}last}$	area under the concentration-time curve from time zero (preinfusion) to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from time zero (preinfusion) extrapolated to infinity
BU	Bethesda units
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CRF	case report form
EC	ethics committee
EOI	end-of-infusion
eCRF	electronic case report form
EDC	electronic data capture
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FEIBA VH	Factor Eight Inhibitor Bypassing Activity Vapor Heated
FII	Factor II
FIX	Factor IX
FVII	Factor VII
FVIII	Factor VIII
FVIII:CAg	Factor VIII C antigen

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Abbreviation	Definition
Continued	
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSL	Global Safety Lead
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immumoglobulin G
IgM	immunoglobulin M
IP	investigational product
IR	incremental recovery
ISMC	Internal Safety Monitoring Committee
Min	minutes
MRT	mean residence time
NMC	non-medical complaint
PCR	polymerase chain reaction
PK	Pharmacokinetic(s)
PT	prothrombin time
rFVIIa	recombinant activated clotting factor VII
Rsq	r^2
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SI	serious injuries
SWFI	sterile water for injection

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Abbreviation	Definition
Continued	
$t_{1/2}$	terminal half-life
TAT	thrombin/anti-thrombin complex
t_{max}	Time to maximum observed plasma concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
V_{ss}	volume of distribution at steady state
λ_z	terminal rate constant
$\%AUC_{ex}$	percentage of AUC obtained by extrapolation

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6. BACKGROUND INFORMATION

6.1 Description of Investigational Product and Clinical Condition/Indication

Note: Labeling has been updated since the Investigator Brochure (IB), and Factor Eight Inhibitor Bypassing Activity Nanofiltered (FEIBA NF) referenced in the background section is now referenced as FEIBA throughout the rest of the protocol.

The investigational product (IP), FEIBA NF[i] is a plasma derived, activated prothrombin complex concentrate (APCC), generically identified as an anti-inhibitor coagulant complex (AICC). FEIBA was developed to treat bleeding episodes and cover surgical interventions in hemophilia A and B patients with inhibitors and in non-hemophilia patients with acquired inhibitors[ii] and is also intended for use as a prophylactic treatment for hemophilia A and B patients with high responding inhibitors and frequent joint bleeding. [iii,1,2,3]

FEIBA was marketed beginning in 1978 and was superseded in 1985 by a 2-stage vapor heat-treated product, FEIBA VH. Nanofiltration was introduced to the manufacturing process in 2006 to produce FEIBA NF. FEIBA NF shares the same indications as FEIBA VH.

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Hemophilia is an X-linked, recessive, congenital bleeding disorder caused by deficient or defective coagulation due to a deficiency in FVIII (hemophilia A), or FIX (hemophilia B). The absence of FVIII or FIX leads to spontaneous bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury.[4,5] Replacement therapy for the treatment of hemophilia A, and less frequently hemophilia B, can be complicated by an immune response resulting in the production of inhibitory alloantibodies to Factor VIII (FVIII) or Factor IX (FIX), especially in patients with moderate to severe hemophilia. The development of such inhibitory antibodies currently represents the most serious complication of hemophilia treatment. The presence of inhibitors against FVIII generally precludes the efficacious use of human FVIII replacement therapy. A substantial portion of patients with FVIII inhibitors have high-responding, high-titer inhibitors (> 5 Bethesda units [BU]). These patients exhibit an anamnestic response after FVIII exposure, sometimes with a dramatic increase in inhibitory antibody titer.[6,7] The inability to provide FVIII replacement therapy

[i] FEIBA NF is a trademark of Baxalta US Inc. and Baxalta Innovations GmbH.
[ii] Anti-Inhibitor Coagulant Complex, FEIBA Vapor Heated. Package Insert, Baxalta US Inc., Westlake Village, CA.
[iii] Protocol 090701. FEIBA NF: A Prospective, Open-label, Randomized, Parallel Study to Evaluate Efficacy and Safety of Prophylactic versus On-demand Treatment in Patients with Hemophilia A and B and High Titer Inhibitor. 2013 Jan 14, Baxalta US Inc., (Westlake Village, CA).

predisposes this group of patients to increased morbidity and mortality compared with hemophilia patients without inhibitors.[6] Several therapeutic approaches are currently available in the management of hemorrhagic events in patients who have developed FVIII inhibitors. These include neutralization with high doses of human FVIII (low titer inhibitor only), and treatment with bypassing agents such as Activated Prothrombin Complex Concentrates (APCCs), or activated recombinant factor VII (rFVIIa). Among these treatment options, only APCCs and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII or FIX. It has been proposed that FEIBA products achieve this goal principally by virtue of the presence of a "partial prothrombinase complex" consisting of activated Factor X (FX) and prothrombin.[8]

The active ingredient of FEIBA is a plasma-derived, freeze-dried APCC with FVIII inhibitor bypassing activity. The product FEIBA contains mainly non-activated forms of the 3 coagulation factors, Factor II (FII), FIX and FX, as well as activated FVII; and Factor III coagulant antigen present in a concentration of up to 0.1 U/1 U FEIBA. A solution containing 1 U FEIBA shortens the activated partial thromboplastin time (aPTT) of FVIII inhibitor plasma up to 50% of the buffer value. Additional details can be found in the FEIBA IB.[iv]

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6.2 Population to Be Studied

Adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B of any severity, of all races and ethnic groups will be studied. All subjects will have a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa). Subjects will either be hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease. Subjects will either be human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3. See additional details in the Inclusion and Exclusion Criteria in Section 9.1 and Section 9.2, respectively.

[iv] Investigator's brochure. Anti-inhibitor coagulant complex nanofiltered; FEIBA NF. 2013 APR 22. Baxalta US Inc., (Westlake Village, CA).

6.3 Findings from Nonclinical and Clinical Studies

6.3.1 Finding from Nonclinical Studies

The nonclinical studies performed for FEIBA NF included a virus clearance study, which was performed to investigate the virus reduction capacity of the nanofiltration step in the manufacturing of FEIBA NF.

Preclinical studies have demonstrated FEIBA NF to have comparable activity and other biochemical properties to FEIBA VH.

Data from nonclinical studies can be found in the FEIBA NF IB.[iv]

6.3.2 Findings from Clinical Studies

The results of Baxalta clinical study 090701[iii] demonstrated that prophylaxis with FEIBA NF significantly reduced the annualized bleeding episode rates for spontaneous and traumatic, joint/non-joint, bleeding episodes when compared with on-demand treatment. A statistically significant reduction in the rate of bleeding episodes in new target joints in the prophylaxis arm versus the on-demand arm was also observed. An examination of adverse events (AEs), abnormal laboratory parameters for hematology and clinical chemistry and vital signs demonstrated that FEIBA NF was safe and well tolerated for prophylactic use. Clinically, these data suggest that both on-demand and prophylaxis regimens were safe and efficacious in the management of hemophilia (congenital and acquired) A or B with persistent high- or low-titer inhibitors refractory to FVIII or FIX treatment, and further confirmed the safety and effectiveness of FEIBA NF for controlling and preventing bleeding episodes.

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Baxalta clinical study 091002 was an open-label, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. This study was designed to document routine usage of FEIBA NF as a bypassing agent for on-demand or prophylactic treatment in everyday clinical practice and in surgical intervention. The safety results of this postauthorization safety study showed that treatment with FEIBA NF, administered in 81 subjects with hemophilia and requiring treatment with inhibitor-bypass therapy for bleed resolution or bleed prophylaxis, was generally safe and well tolerated. The mean infusion rate of FEIBA under routine clinical practice during the study (3.7 U/kg per min, range 0.9 to 23.5) was higher than that recommended in the Summary of Product Characteristics of FEIBA (2.0 U/kg per min). A manual analysis of safety listings did not disclose any AEs associated with a higher infusion rate.[9] Treatment-related AEs or serious adverse events (SAEs) were reported in 9.9% and in 3.7% of subjects, respectively. A deep venous thrombosis and a superficial thrombophlebitis were observed in 1 subject with acquired hemophilia.

The hemostatic effectiveness was rated by the physicians as excellent or good in more than 90% of total subjects, with the highest rates reported in subjects with FEIBA NF prescribed as regular prophylaxis. Additional details on this study can be found in the clinical study report.[v]

Additional observational, non-interventional studies were conducted with FEIBA NF. Additional details on clinical studies can be found in the FEIBA NF IB.[iv]

6.4 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

The FEIBA NF products can precipitate allergic-type hypersensitivity reactions that have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and a drop in blood pressure; these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. The most commonly reported adverse drug reactions described for FEIBA NF include increase in inhibitor titer, somnolence, dizziness, dysgeusia, dyspnea, nausea, chills, pyrexia, chest pain, and chest discomfort.

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The possibility of thrombotic events should be considered when systemic anti-fibrinolytics such as aminocaproic acid and tranexamic acid are used in combination with FEIBA NF. Therefore, anti-fibrinolytics should not be used for approximately 6 to 12 hours before or after the administration of FEIBA NF.

Animal reproduction studies have not been conducted with FEIBA NF. There are no adequate and well-controlled studies in pregnant women. It is also not known whether FEIBA NF can cause fetal harm when administered to a pregnant woman or an affect reproductive capacity. It is not known whether FEIBA NF is excreted in human milk.[10] Subjects within the study should be warned regarding this labeling information.

Additional safety experience for FEIBA is provided in the FEIBA NF IB.[iv]

6.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

[v] Clinical Study Report. Post-Authorization Safety Study of FEIBA NF (Factor VIII Inhibitor Bypassing Activity). An open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. 10 Oct 2014. Baxalta US Inc. and Baxalta Innovations GmbH.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is:

1. To compare the pharmacokinetics (PK) of FEIBA component FII and safety of FEIBA reconstituted in a reduced volume of sterile water for injection (SWFI) versus regular volume SWFI, administered at the standard infusion rate of 2 U/min/kg
2. To evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison to the standard rate of 2 U/min/kg

7.2 Primary Objectives

1. Determine PK equivalence of FEIBA component FII reconstituted in 50% reduced volume SWFI and regular volume SWFI on area under the concentration-time curve from time zero (preinfusion) to time 216 hours ($AUC_{0\text{-}216\ h}$)
2. Determine the occurrence of thromboembolic events and allergic-type hypersensitivity reactions

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7.3 Secondary Objectives

1. Determine the safety and tolerability of 50% reduced volume FEIBA administered at the standard and escalated infusion rates, based on the occurrence of AEs
2. Monitor clinically apparent changes in vital signs, infusion rate-related events, and infusion site reactions
3. Determine the effect of 50% reduced volume FEIBA component FII on incremental recovery (IR), area under the concentration-time curve from time zero (preinfusion) to extrapolated to infinity ($AUC_{0\text{-}\infty}$), area under the concentration-time curve from time zero (preinfusion) to time of last quantifiable concentration ($AUC_{0\text{-}last}$), terminal half-life ($t_{1/2}$), clearance (CL), mean residence time (MRT), volume of distribution at steady state (V_{ss}), maximum plasma concentration (C_{max}), and time to maximum observed plasma concentration (t_{max})

7.4 Exploratory Objective

[redacted]

2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

8. STUDY DESIGN

8.1 Brief Summary

This is a 2-part Phase 4, prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 BU in hemophilia A and ≥ 0.6 BU in hemophilia B) for the primary PK assessment, (i.e., having the $AUC_{0\text{-}216\ h}$ of FEIBA component FII estimable from both PK infusions), with a planned enrollment of 32 subjects. All subjects will receive 3 infusions of FEIBA reconstituted in a regular volume of SWFI, and 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI, with all 6 of these infusions being given at a rate of 2 U/min/kg within Part 1 of the study. In Part 2 of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/min/kg followed by 3 infusions FEIBA reduced volume at a rate of 10 U/min/kg. All subjects will undergo PK evaluation in Part 1 of the study.

8.2 Study Design Rationale

This study has been designed as a 2-way crossover study in order to assess for PK equivalence analysis. By designing it as a crossover study, subjects serve as their own controls, reducing the number of subjects needed for the study by half. This study is open-label because it is a change in infusion volume and infusion rate, which would be difficult to properly blind. The goal of the study is to demonstrate PK equivalence of FEIBA in reduced volume SWFI to FEIBA regular volume SWFI, and then to increase the rate that this reduced volume can be infused. By being able to reduce the volume and speed of the infusion, subjects will be able to spend less time infusing.

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As there are washout periods within the study design in which subjects will not be receiving IP, steps have been taken to protect them from bleeding episodes, see Section 8.8.4 for details.

8.3 Overall Study Design

This is a 2-part Phase 4, prospective, open-label, multicenter study to compare PK and safety of FEIBA reconstituted in reduced versus regular volume of SWFI, and to evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison with the standard rate of 2 U/min/kg, in up to 32 subjects (up to 24 evaluable) with hemophilia A or B with inhibitors (≥ 0.6 BU in hemophilia A and ≥ 0.6 BU in hemophilia B), with the $AUC_{0\text{-}216\ h}$ of FEIBA component FII estimable from both PK infusions. The overall study design is illustrated in Figure 1 and Figure 2.

In Part 1, subjects will be administered 2 different volumes of FEIBA in a randomized, crossover manner with a washout period between the treatments. Both volumes will be given at the standard infusion rate of 2 U/min/kg. After infusion, subjects should be observed for 30 minutes in the clinic. For PK infusions and collections, accommodations can be made for convenience or to ensure compliance with PK sampling. See Section 10.3.2 for details.

Treatments regimens during Part 1 of the study are:

- Part 1 Sequence A:
    1. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in 50% reduced volume SWFI (Infusions 4, 5, and 6)
- Part 1 Sequence B:
    1. FEIBA 2 U/min/kg in 50% reduced volume SWFI (Infusions 1, 2, and 3)
    2. Washout period
    3. FEIBA 2 U/min/kg in regular volume SWFI (Infusions 4, 5, and 6)
- Infusion dose:
    1. Infusions 1 and 4: 85 U/kg ± 100 U
    2. All other infusions: 85 ± 15 U/kg

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Prior to the first infusion of FEIBA (Sequence A or B), subjects will undergo a washout period of at least 12 days from last treatment with APCC (e.g., FEIBA), or at least 24 hours after the last treatment with an rFVIIa product (e.g., NovoSeven®).

Part 2 is non-randomized with sequential enrollment of subjects who complete Part 1 to evaluate FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/ kg. FEIBA Infusions 7, 8, and 9 will be administered at the 4 U/min/kg rate. The infusions will be administered every 48 hours (+48 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Subjects will follow with 3 infusions (Infusions 10, 11, and 12) of FEIBA at 10 U/min/kg rate. The infusions will be administered every 48 hours (+48 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:

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

All infusions will be administered at the hemophilia care centers/study sites. Pharmacokinetic collections may be performed at the hemophilia care centers/study sites or appropriate ambulatory centers. Each subject will receive a maximum of 14 IP infusions total (most subjects will receive 12 IP infusions [6 in Part 1 and 6 in Part 2], the additional 2 infusions are for reinfusing PK infusions if a bleeding event occurred during the 9 day PK collection). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions), see Section 8.8.2. After each infusion, subjects should be observed for 30 minutes in the clinic. Additional details on study design and timing are described in Section 8.8.3. For additional details on managing bleeding episodes, see Section 8.8.4.

Please see Section 16.4 for additional details on the safety reviews performed by the Internal Safety Monitoring Committee (ISMC).

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8.4 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 13 to 16 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 to 12 months.

The subject participation period is approximately 60 to 90 days from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

8.5 Outcome Measures

8.5.1 Primary Outcome Measures

The primary outcome measures are:

1. $AUC_{0\text{-}216\ h}$ of FEIBA component FII in subjects
2. Occurrence of thromboembolic events
3. Occurrence of allergic-type hypersensitivity reactions

8.5.2 Secondary Outcome Measures

8.5.2.1 Efficacy/Pharmacokinetics

1. Incremental recovery of FEIBA component FII in subjects
2. $AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max} of FEIBA component FII in subjects

8.5.2.2 Safety

1. Evaluate occurrence of all AEs and SAEs
2. Evaluate occurrence of AEs leading to discontinuation
3. Evaluate occurrence of infusion site reactions
4. Evaluate occurrence of all AEs occurring within 24 to 72 hours of IP infusion
5. Evaluation of thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, thrombin/anti-thrombin complex [TAT], and fibrinopeptide A)
6. Evaluate vital signs and clinical laboratory assessments

8.5.3 Exploratory Outcomes Measure

[redacted]

2. Evaluate responses to the TSQM and the patient preference questionnaires

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8.6 Randomization and Blinding

Part 1 of this study is a randomized, crossover, active treatment clinical study. In order to minimize/avoid bias, subjects will be randomly assigned to 1 of 2 treatment regimens (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 SWFI) in equal numbers. 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.

8.7 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. If 2 or more subjects develop anaphylaxis following exposure to FEIBA (enrollment and treatment temporarily stopped pending further review by the ISMC)
2. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk benefit
3. The sponsor or investigator considers continuation of the study unjustifiable for medical or ethical reasons
4. The ISMC recommends study termination

8.8 Investigational Product(s)

8.8.1 Packaging, Labeling, and Storage

Note: Labeling has been updated since the IB, and FEIBA NF as previously referenced in Section 6 is now referenced as FEIBA.

The active ingredient of FEIBA is a plasma-derived, freeze-dried, APCC with FVIII inhibitor bypassing activity. FEIBA will be provided in vials containing 350 to 650 U/vial (nominal potency 500 U), 700 to 1300 U/vial (nominal potency 1,000 U) or 1750 to 3250 U/vial (nominal potency 2500 U). FEIBA contains mainly non-activated forms of the 3 coagulation factors, FII, FIX, and FX, as well as activated FVII; and Factor VIII coagulant antigen (FVIII:CAg) present in a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all. A solution containing 1 U FEIBA shortens the aPTT of FVIII inhibitor plasma to 50% of the buffer value. The product is supplied as freeze-dried powder or friable solid of white to off-white or pale green color.

FEIBA might be marketed locally with storage at room temperature or 2°C to 8°C. To standardize conditions in the study, FEIBA should be stored at 2°C to 8°C only. FEIBA should not be allowed to freeze, and should be protected from light. Although the chemical and physical stability of the reconstituted product has been demonstrated for 6 hours at room temperature (up to 25°C), in consideration of sterility, infusion of FEIBA should be commenced as promptly as practical, but must be completed within 3 hours following reconstitution. Reconstituted product must not be returned to the refrigerator.

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FEIBA will be provided in kits including SWFI for reconstitution. SWFI will be provided in different volumes for preparation of FEIBA infusions at regular volume or reduced volume. For additional information, such as reconstitution instructions, please refer to the FEIBA product insert [10] and/or other specific instructions provided by the sponsor or sponsor's representative.

8.8.2 Administration

Following reconstitution, FEIBA should be administered using an intravenous needle and syringes provided by the sponsor for this study. The standard infusion rate of FEIBA is a slow bolus injection, with an infusion rate of 2 U/kg body weight (BW) per minute, which in a 75-kg subject, corresponds to an infusion rate of approximately 2.4 to 7.5 mL/minute depending on the potency (see label on vial). In order to standardize administration within the study, it is recommended that study drug be administered with an infusion pump. Details regarding pump qualification will be provided in the study documents.

This rate will be modified depending on which part of the study the subject is in. Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions). For additional details, see Table 1 for general information on product preparation, as well as the study documents, and the FEIBA IB.[iv] Additional rates of 4 and 10 U/min/kg are also used in this study.

Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. Information regarding lot used, the actual dose given, date of treatment, treatment start and stop times, as well as any infusion interruptions will be recorded in the electronic case report form (eCRF).

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Table 1
FEIBA Product Preparation

FEIBA	Diluent for Regular Volume FEIBA	Diluent for 50% Reduced Volume FEIBA
500 U	10 mL	5 mL
1000 U	20 mL	10 mL
2500 U	50 mL	25 mL

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity.

Every effort should be made for subjects to be given the same FEIBA lot for Infusion 1 and Infusion 4 in order to ensure comparable PK results. Please note that the diluent used for reconstitution might not be the same lot between the 2 infusions.

For PK infusions, every measure should be taken to ensure consistent dosing between Infusion 1 and Infusion 4. Partial vials may be used in order to maintain a consistent dose in case 85 U/kg ± 100 U can not be achieved by administration of whole vials. For infusions that are not PK infusions, different FEIBA lots may be mixed within an infusion, and whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate. Please refer to study documents for detailed instructions.

Please note that the availability of potencies may vary among countries and regions. Dose calculations should be made based on potencies available at site.

8.8.3 Description of Treatment

Part 1 of the study uses a crossover design to evaluate the PK of FEIBA component FII and to evaluate the safety of FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI (administered at the standard infusion rate of 2 U/min/kg). Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1. Part 2 will evaluate the safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/min/kg.

All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. The subject's medical history including hemophilia history, confirmation of inhibitors, bleeding episode history, and history of FEIBA or rFVIIa usage for the previous year will be collected at screening. Also recorded will be the date of last use of FEIBA or rFVIIa treatment. Results of the screening assessments will be used to establish a subject's eligibility for the study.

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Part 1

After eligibility is established, the duration of the washout period will be determined. The washout period is based on the subject's last dose of FEIBA or rFVIIa. Due to the varying lengths of the half-lives of the components, subjects who have received FEIBA will need to wait 12 days from their last dose of FEIBA before they can receive Infusion 1 of the study. Subjects who have previously been treated with rFVIIa (e.g., NovoSeven), will need to wait at least 24 hours from the last dose of rFVIIa treatment before they can begin Infusion 1 of the study (in agreement with the reported half-life of 2.6 to 3.9 hours of FVII). Additional days beyond the minimum of 1 or 12 days (treatment dependent) is permissible since subjects have varying courses of treatments prior to their enrollment in the study (as long as screening procedures stay within the allotted time frame). Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. For subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day they used treatment. For management of bleeding episodes during Screening Washout see Section 8.8.4.

After the washout period is complete, eligible subjects will be randomly assigned (1:1) into Part 1 of the study by interactive web response system to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. Subjects will receive the first and fourth infusion for PK and safety analysis and the second, third, fifth, and sixth infusions for collection of additional safety data. The first infusion will be given after randomization,

and PK blood draws will be taken at the times described in Table 5. After the 216 hour PK draw (9 days after Infusion 1), subjects will receive Infusion 2, and subjects will receive Infusion 3 forty-eight (+48) hours after Infusion 2. For management of bleeding episodes during PK assessments see Section 8.8.4.

After Infusion 3, subjects will go through a washout period of at least 12 days before crossing over to the next treatment group for Infusion 4. The 12 days is based on Infusion 3, since all subjects receive FEIBA at Infusion 3. For management of bleeding episodes during washouts see Section 8.8.4.

Infusion 4 will be the beginning of the new treatment regimen in the crossover scheme, and PK assessment will be completed for this infusion. Infusion 4 must be administered using the same lot of IP as Infusion 1. Infusion 4 will be given after the minimum of 12-day washout period is complete, and PK blood draws will be taken at times described in Table 5. After the 216-hour PK draw (9 days after Infusion 4), subjects will receive Infusion 5, and subjects will receive Infusion 6 forty-eight (+48) hours after Infusion 5.

Additional details on study visits for Part 1 can be found in Section 10.3 and Table 2.

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Part 2

Part 2 is non-randomized and uses sequential enrollment of subjects who complete Part 1 of the study. Subjects in Part 2 will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/min/kg rate, followed by 3 infusions (Infusions 10, 11, and 12) of FEIBA at the 10 U/min/kg rate. Infusion 7 will be administered 48 hours after Infusion 6. The infusions in Part 2 will be administered every 48 hours (+48) to allow time to monitor safety and tolerability of the higher infusion rate. Infusion rates for the treatment phases in Part 2 are:

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

Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Additional details on study visits for Part 2 can be found in Section 10.3 and Table 3.

Additional Treatment and Visit Information

The Schedule of Study Procedures and Events Procedures listed in Table 2 and Table 3 have the visit windows listed in relation to the subjects' previous infusions instead of by study date. This is due to the variability in each subjects schedule based on previous therapy and bleeding events.

All infusions will be administered at hemophilia care centers/study sites. Each subject will receive a maximum of 14 IP infusions (12 scheduled IP infusions, as well as the possibility of PK infusions being reinfused if the subject had a bleeding episode during PK collection). Subjects will receive FEIBA at a dose of 85 U/kg ± 100 U for all PK infusions (Infusions 1 and 4) and 85 ± 15 U/kg for all other infusions (Infusions 2, 3, 5, 6, and all Part 2 infusions). For specifications on dosing and administration, see Section 8.8.2. For information on break-through bleeding control, see Section 8.8.4.

Study visits will be completed concurrently with study infusions. After subjects have completed the 12 study infusions, they will complete a Study Completion/Termination Visit within 7 days but no sooner than 72 hours after Infusion 12. In case of early withdrawal or discontinuation the Study Completion/Termination Visit will need to be completed within 7 days but no sooner than 72 hours after the last IP infusion received.

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During each visit, the study staff will inquire with the subject about break-through bleeding events, treatments, and AEs throughout the study and washout periods. Subjects are encouraged to report AEs to the site during the time spans between visits.

Two subject questionnaires will be administered 4 times during the study, a TSQM questionnaire and a patient preference questionnaire to assess the subjects' satisfaction and preferences for treatments, for additional details see Section 10.5.

Detailed study flowcharts are presented in Table 2 and Table 3.

Investigational product may be interrupted or discontinued at any time during the study at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any infusion site reactions, regardless of causality, will be recorded on the AE eCRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate eCRF.

For details on the safety review by ISMC see Section 16.4.

8.8.4 Management and Treatment of Break-Through Bleeding

Bleeding episodes are managed as described below for each section of the study (screening, PK assessments, and washout). In all cases, if the bleeding episode, of whatever severity, is not resolved within 72 hours after an infusion to control bleeding, the subject must contact the study site for further treatment recommendations.

Screening Washout

During screening, subjects will be asked to keep track of any FEIBA or rFVIIa usage, as the last dose is used to determine the date of the first infusion of IP. If a subject is on prophylaxis before the study, once eligibility is determined, the subject will discontinue their routine prophylaxis upon instruction of the investigator for the start of the washout period. If a subject experiences a bleeding episode during the washout period, subjects will be treated for the bleeding episode per standard of care as determined by the investigator, and the washout period will be restarted. If the subject has a second bleeding episode during the washout period, the investigator should consider whether it is appropriate to include the subject into the study or whether they would be better served to remain on their current treatment regimen.

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Bleeding during PK Assessments

Subjects who have a bleeding episode during the PK assessment periods will not have subsequent PK blood samples collected in that specific PK assessment period and will be treated for the bleeding episode per standard of care as determined by the investigator. Once the bleeding is resolved, subjects will have the IP infusion and PK assessments repeated. However, they should wait at least 12 days after their last dose of FEIBA, or at least 24 hours after last treatment with an rFVIIa product before proceeding. If the subject bleeds again on the second PK collection attempt, bleeding will be treated per standard of care as determined by the investigator, and subjects will move on to the next IP infusion after waiting at least 48 hours from their last dose of FEIBA. Subjects will have one re-attempt on each PK infusion and collection.

Washout Periods before Infusion 4

After Infusion 3, subjects will go through a washout period of at least 12 days before crossing over to the next treatment group for Infusion 4. The 12 days is based on Infusion 3, since all subjects receive FEIBA at Infusion 3. If bleeding occurs during the washout period, it will be treated per standard of care and the washout period will be restarted (at least 12 days after their last dose of FEIBA, or at least 24 hours after last treatment with an rFVIIa product). If rFVIIa is administered, a washout period of 12 days after their last dose of FEIBA (i.e. Infusion 3) should still be observed.

If multiple bleeding episodes occur during the washout period, the investigator and sponsor should decide if it is appropriate for the subject to be taken off the study or continue with the study.

Bleeding during the study at times other than washout periods and PK collection period

If bleeding occurs during any period other than the washout periods and PK assessment periods described above (e.g., between Infusions 5 6), it will be treated per standard of care. For bleeding events treated with FEIBA, a time window of 48 hours post treatment for bleeding should be observed before resuming study infusions. If rFVIIa was used for the bleeding event, a time window of 24 hours post treatment should be observed in combination with the 48 hour time window since last study administration of FEIBA before resuming study infusions per protocol. The subject will resume their treatment regimen and visits after control of the bleeding and following the administration windows mentioned above. Depending on the clinical circumstances (e.g., treatment of uncontrolled bleeding due to injury and associated complications), the investigator and sponsor should decide if it is appropriate for the subject to be taken off the study or continue with the study.

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8.8.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.9 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the eCRF.

For additional information on study documentation and eCRFs, see Section 17.2.

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9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Subject is ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented history of inhibitors requiring the use of bypassing agents (FEIBA or rFVIIa)
3. HCV negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable hepatic disease
4. HIV negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Subject is willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, subject must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
    a. Abstain from sexual intercourse
    b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
    a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known hypersensitivity to FEIBA or any of its components
2. Clinically symptomatic liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Subject is taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy
9. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
10. Subject is a family member or employee of the investigator
11. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study eCRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The ISMC determines a subject should be taken off the study
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome
- In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose, should also be recorded following authorization from the subject's partner
- AE(s)/SAE(s) that in the investigator or sponsor opinion, poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study

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10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 091501) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 091501-020003. All study documents (e.g., eCRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in eCRFs, regardless of screening outcome. If a subject is re-screened, the End of Study eCRF should be completed, and a new ICF, new SIC and new eCRF are required for that subject.

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4 Schedule of Study Procedures and Assessments (Part 1 and Part 2, respectively) and Supplement 20.5 Clinical Laboratory Assessments. Pharmacokinetic assessment scheduling can be found in Table 5.

10.3.1 Screening and Baseline Assessments

After ICF has been obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in Section 9.1 and Section 9.2, respectively. Screening procedures must be performed within 56 days of Infusion 1.

At screening, subjects will be instructed on the symptoms of thromboembolic events by the investigator, and to contact the treatment center/hospital if they experience any symptoms of thromboembolism.

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Medical history, including
    - Hemophilia history, inhibitor development history, bleeding episodes history, history of FEIBA or rFVIIAa usage for a year prior to screening
    - Relevant medical and surgical history and all medications taken 4 weeks prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measurement body weight and height (see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (hematology, clinical chemistry, coagulation testing, and serology testing; see Section 12.7)
- PK assessments (see Section 11.1)
- Serum pregnancy test (female subjects of childbearing potential only)
- TSQM and patient preference questionnaires (see Section 10.5)

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After screening and eligibility is determined, the duration of the washout period will be determined. The washout period is based on the subjects' last dose of FEIBA or rFVIIa (e.g., NovoSeven). Due to the varying lengths of the half-lives of the components, subjects who have received FEIBA will need to wait 12 days from the last dose of FEIBA that they received before they can begin Infusion 1. For subjects who have previously been treated with rFVIIa, they will need to wait at least 24 hours from the last dose of rFVIIa before they can begin Infusion 1 of the study. Additional days beyond the minimum of 1 or 12 days (treatment dependent) is permissible (as long as the screening assessments stay within the window to Infusion 1) since subjects have varying courses of treatments prior to their enrollment in the study. Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. Subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day they used treatment, if they have a bleeding episode that requires treatment during the washout period, the washout period must be restarted before they can proceed with the study. For additional details on bleeding, see Section 8.8.4.

10.3.2 Treatment Visits

10.3.2.1 Infusion Visits

Randomization will occur at Infusion Visit 1 using interactive web response system.

- Randomization of eligible subjects to the following treatment sequences:
  - Part 1 Sequence A: FEIBA 2 U/min/kg in regular volume SWFI (3 infusions), washout period, FEIBA 2 U/min/kg in 50% reduced volume (3 infusions)
  - Part 1 Sequence B: FEIBA 2 U/min/kg in 50% reduced volume (3 infusions), washout period, FEIBA 2 U/min/kg in regular volume SWFI (3 infusions)

For additional details on the description of treatment, see Section 8.8.3.

During the study (Infusion Visits 1 to 12), subjects will return to the study site according to the schedule presented in Table 2 and Table 3. Prior to administration of IP, the following assessments will be performed at all visits unless otherwise indicated:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measure body weight)
  - Before administration of IP
  - 30 minutes after administration of IP
- Clinical laboratory assessments (coagulation testing)
- PK assessments (Infusions 1 and 4): from 30 minutes before start of infusion through 8 hours after stop of infusion
  - At the discretion of the investigator, subjects may be given the option of staying overnight at study site facility and/or a hotel for convenience or to ensure compliance with the serial PK collections. Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures unrelated to AEs will not be considered as hospitalizations for SAE reporting purposes unless the hospitalization is prolonged.
- IP administration (infusion site should be monitored for 30 minutes [± 10 min] after infusion)

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- Break-through bleed monitoring
- Subjects will be administered the TSQM and patient preference questionnaires prior to Infusion 1, Infusion 4, and Infusion 7, and after Infusion 12, prior to or up to the completion of the Study Completion/Termination Visit

10.3.3 PK only Visits

Additional PK only visits will be performed between Infusion 1 and 2, and between Infusions 4 and 5 according to the schedule presented in Table 2 and Table 5. These times include 24 hours, 72 hours, 120 hours, 168 hours and 216 hours after Infusions 1 and 4. Exact time ranges can be found in Table 5. For details on treatment of bleeding episodes during PK assessments, see Section 8.8.4.

See also information on administration (Section 8.8.2).

10.3.4 Study Completion/Termination Visit

The Study Completion/Termination Visit will be performed within 7 days but no sooner than 72 hours after Infusion 12, or within 7 days but no sooner than 72 hours after the last infusion if the subject is discontinuing early. The following assessments will be performed:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Breakthrough bleeds monitoring
- Concomitant medication monitoring
- Clinical laboratory assessments (hematology, clinical chemistry, coagulation testing, serology testing)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and body weight)

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10.4 Medications and Non-Drug Therapies

Once subject eligibility has been confirmed for the study, subjects will begin a washout period as described in Section 8.8.3. The subject will discontinue their routine prophylaxis upon instruction of the investigator at the beginning of the washout period. See Section 8.8.4 for instructions on bleeding control.

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

- Medications:
  - Any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) except anti-retroviral chemotherapy
  - Any investigational drug or device

A subject who has taken any of these medications or received any of these non-drug therapies will be withdrawn from further study participation.

Antifibrinolytics should not be used approximately 6 to 12 hours before or after the administration of FEIBA.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study (these are permitted; however, they should not be taken within 12 hours before or after administration of FEIBA)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
  - Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
  - Supplemental vitamins, minerals
  - Any standard of care to treat breakthrough bleeds
- Non-drug therapies:
  - Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

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10.5 Subject Questionnaires

Two questionnaires will be administered to subjects within this study (TSQM [11] and a patient preference questionnaire). These questionnaires will be used to assess the subject's preferences on the IP, as well as their satisfaction with the IP, and will be collected in the eCRF or on paper. Both questionnaires will be administered:

- After screening prior to Infusion 1
- After Infusion 3 prior to Infusion 4
- After Infusion 6 prior to Infusion 7
- After Infusion 12, prior to or up to the completion of the Study Completion/Termination Visit

These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.

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10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when the subject ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems, and severe allergic reaction), ISMC recommends a subject should not continue. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

Every effort will be made to have discontinued subjects complete the Study Completion/Termination Visit. If the Study Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Study Completion/Termination Visit. If a subject terminates participation in the study and does not return for the Study Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.5 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

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11. ASSESSMENT OF PHARMACOKINETICS

11.1 Sample Collection and Processing

Blood PK samples for the determination of FEIBA components FII, [redacted] will be taken 30 and 15 minutes preinfusion, at end of infusion, and 30 and 60 minutes, 3, 8, 24, 48, 96, 168, and 216 hours after stop of infusion (see Table 5 for sampling time points and allowed sampling time windows) following Infusions 1 and 4. The date and time of each sample collections will be documented in the subject's eCRF. Blood sample processing and handling details will be presented in a separate laboratory manual. Information on accommodations (i.e., hotel stays and hospitalization) for PK assessments can be found in Section 10.3.2.1.

11.2 Pharmacokinetic Evaluation and Pharmacokinetic Parameters

For PK assessments (Infusion 1 and 4), subjects will receive an infusion of 85 U/kg ± 100 U FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa. There will be a washout period of at least 12 days following the Infusion 3 before subjects cross over to the next treatment group. For PK assessments, subjects are required to not be actively bleeding at the time of infusion.

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Subjects who have a bleeding episode during the PK assessment periods will not have subsequent PK blood samples collected in that specific PK assessment period. Bleeding and additional washouts will be managed as described in Section 8.8.4. After a washout period as described in Section 8.8.4, the IP infusion and PK assessments will be repeated.

Pharmacokinetic parameters will be derived for baseline-corrected FII, [redacted] activity. Baseline-corrected FII, [redacted] activities will be calculated by subtracting the preinfusion value (or average of preinfusion values) from each measurement after infusion.

The following PK parameters will be calculated for FII, [redacted] using standard noncompartmental methods after administration with FEIBA reconstituted in regular volume of SWFI or FEIBA reconstituted in 50% reduced volume of SWFI:

- $AUC_{0\text{-}216\ h}$
- $AUC_{0\text{-}\infty}$
- $AUC_{0\text{-}last}$
- $t_{1/2}$
- MRT

- CL
- V_{ss}
- C_{max}
- t_{max}
- IR at C_{max}; defined as (observed C_{max} - $C_{preinfusion}$)/[total dose/body weight]

[redacted]

Additional PK parameters may be calculated at the discretion of the PK scientist and/or sponsor.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

$t_{1/2}$, Interval	The time interval of the log-linear regression used to determine the terminal rate constant lambda_z (λ_z)
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z
Rsq	Goodness-of-fit statistic for calculation of λ_z (coefficient of determination). If Rsq < 0.800, then λ_z and associated parameters will not be reported
%AUC_{ex}	Percentage of $AUC_{0-\infty}$ obtained by extrapolation. If % $AUC_{ex} > 20.00\%$, then $AUC_{0-\infty}$ and associated parameters will not be reported

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All PK analyses will use the actual sampling times, wherever possible. Actual sampling times will be defined as time from the start of infusion to the collection time of blood.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

A SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

Additional events which should be reported the same way as SAEs are as follows:

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19

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- Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE
- Any thromboembolic event
- Allergic-type hypersensitivity reactions (e.g., analyphylaxis)

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE. Any pregnancy occurring during the study should be reported to the sponsor within 24 hours of the site learning about the pregnancy. The pregnancy should be followed until completion of the pregnancy and up to 1 year postdelivery, if feasible. Pregnancies not considered an (S)AE as described above will be captured in the eCRF.

Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures as described in Section 10.3.2 for reasons unrelated to AEs will not be considered as hospitalization for SAE reporting purposes unless the hospitalization is prolonged.

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12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE eCRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study termination/completion will be described on the AE eCRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE eCRF. Recovering/resolving AEs will be followed until resolution, it is medically stabilized, or 30 days after the Study Completion/Termination Visit, whichever comes first, and the follow-up information is to be documented in the eCRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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Deviations from the protocol-specified dosage including overdosing (20% higher than the highest permitted dose), underdosing (20% lower than the lowest permitted dose), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion/termination, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on eCRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

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These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

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For events assessed as not related or unlikely related and occurring within 72 hours after IP administration the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 3) and Section 12.1.

Adverse Events/SAEs are to be recorded on the AE page of the eCRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported via the EDC system by completing the relevant eCRF page(s) in English. Once the SAE has been recorded in the electronic data capture (EDC) system, the sponsor and other designated recipients will be informed of the event automatically. For instances in which the EDC may become unavailable, SAEs must be reported using the back-up paper SAE Report Form to meet the 24-hour timeline requirement (contacts and instructions to be provided in separate documentation). Once the EDC becomes available, the site must enter all SAE data as reported on the back-up paper SAE report form on the applicable eCRF pages.

The initial SAE information reported on the applicable eCRF pages (or back-up SAE Report Form, if applicable) must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting investigator (for paper SAE Report Forms)

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12.1.3 Medical Device Safety Reporting

The IP kit contains the BaxJect II Hi-Flow needleless transfer device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

- Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure.
- Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

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The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE eCRF (and SAE Report Form if eCRF is not available). These events will be considered as SAEs and will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims
- Medication errors: an error (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication e.g., administration of incorrect dose

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

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12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

General medical history will be collected for 4 weeks prior to screening. Any information on the subjects' hemophilia history will be collected a year prior to screening including documented history of hemophilia, confirmation of inhibitors, bleeding episodes history, and history of FEIBA or rFVIIa usage.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

12.6 Physical Examinations

At screening (as described in Table 2 and Table 3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Where applicable (see Section 15.6), assessments will be performed at a central laboratory, according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for additional testing. Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

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Details of blood sampling volumes are presented in the laboratory manual and master ICF.

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of 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.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening and at study completion/termination. Hematology and clinical chemistry assessments will be performed on ethylenediaminetetraacetic acid-anticoagulated whole blood and serum, respectively, at the central laboratory.

In addition, serum samples for pregnancy tests for females of childbearing potential will be collected at screening.

12.7.2 Coagulation Testing

Blood will be obtained for the assessment of coagulation testing and consist of aPTT, PT, thrombotic markers (D-Dimers, prothrombin fragment F 1.2, TAT, fibrinopeptide A), FII, FX, FIX, FVII, and FVIII or FIX inhibitor level (Nijmegen assay). All coagulation testing will be performed at screening, during the study (Infusion Visits 1 to 12), and at the Study Completion/Termination Visit.

12.7.3 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, hepatitis A virus (HAV) antibody, hepatitis B virus (HBV) antibody, hepatitis B surface antigen (HBsAg), HCV antibody, parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening and at the Study Completion/Termination Visit.

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12.7.4 CD4 Levels

At screening only, CD4 levels will be determined using flow cytometry in the case of a subject being HIV positive.

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE eCRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a pre-existing disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned:

- Backup samples for FII, [redacted] will be taken at screening, and at all pre and postinfusion timepoints for PK assessments

Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE. Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) measured once at screening and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and after administration of IP, at each Infusion study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE eCRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0-100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of subject status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease. In this scale, a high number performance status represents high functionality, and a lower number represents low functionality and likely rapid progression of disease.[12] Subjects will be scored using this scale at screening.

12.10 Infusion Site Evaluations

The current site of IP infusion will be assessed for immediate local reactions 30 minutes (±10 min) after infusion. In addition, infusion sites will be monitored by the subject for 72 hours after infusion, and will be discussed with the site staff during the next study visit.

Infusion sites will be monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations will be made by clinical staff or by the subject or caregiver. If an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Infusion sites will continue to be reviewed at each study visit, and any infusion site reactions will be followed until resolution. Each infusion site reaction will be categorized using the intensity grading described for AEs in Section 12.1.2.1.

12.11 Special Treatment Considerations

Subjects will be screened for eligibility in the study as described in Section 8.2 and Section 8.8.3, and will be informed of the study specific restrictions and requirements of the study. Subjects who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

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All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic reaction

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Thromboembolic events have been observed with bypassing agents including FEIBA. Clinical manifestations of these events may include, but not limited to:

- myocardial infarction
- deep vein thrombosis
- pulmonary embolism
- stroke and
- transitory ischemic attack, etc.

Sometimes, these reactions can be life-threatening. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute allergic/hypersensitivity reaction after an infusion of IP, the subject should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn to test for anti-drug antibodies.

Subjects who experience a potentially severe allergic reaction will be discontinued from IP. They will complete a Termination/Study Completion Visit, and will be monitored for stabilization or resolution of the AE. Premedication to prevent allergic reactions will not be permitted, as severe allergic reactions are an outcome measure for this study.

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13. STATISTICS

Data handling will be the responsibility of the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

Part 1 (cross-over) of this study will evaluate PK equivalence of FEIBA component FII in FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI as measured by $AUC_{0\text{-}216\ h}$. The sample size was based on the premise of a true ratio of geometric means of test and reference of 1.0 using a within-subject coefficient of variation of 22.2%, to yield 90% power when equivalence is declared based on the 90% CI for the ratio of geometric means for the 2 treatments being completely contained in the margins of equivalence defined as 80% to 125%. The within-subject variability (0.222) was estimated by using the square root of mean square error as in previous studies of FVIII. The required sample size was estimated to be 24 evaluable subjects. In order to obtain the required 24 subjects, Part 1 will randomize up to 32 subjects for the crossover PK study, allowing for a possible 25% dropout rate.

With approximately 100 infusions for each treatment (reduced or regular volume of SWFI) administered for the study, the upper limit of the 95% CI of the rate of infusions with a specific AE is less than 3.3%, if the specific AE is not observed. The upper limit of 95% CI of the rate of infusions for a specific AE is about 5% if 1 AE is observed.

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13.2 Datasets and Analysis Cohorts

Classification into the safety analysis sets will be conducted prior to database lock.

Major protocol violations will include, but are not limited to: violation of inclusion/exclusion criteria, administration of prohibited medications, and erroneous administration of study treatment. Subjects will be assigned to treatment groups based on randomization.

Safety: The safety population will include all subjects who received at least 1 dose of IP (FEIBA). All safety analyses will be performed on the safety population. Subjects will be evaluated according to the treatment received. The safety population will be defined separately for each part of the study.

PK: The PK population will include all subjects who received at least 1 dose of IP and have at least 1 measured concentration at a scheduled PK time point after start of dosing without protocol violations or events with potential to affect PK.

13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of withdrawal.

For the calculation of $AUC_{0\text{-}216\ h}$, non quantifiable PK results will be extrapolated.

13.4 Methods of Analysis

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), mean, standard deviation, median, minimum, and maximum values. All PK parameters will be summarized by treatment using n, mean, standard deviation, geometric mean, % geometric coefficient of variation, minimum, median, and maximum, except that t_{max} will be reported with n, minimum, median, and maximum only.

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A listing of PK blood sample collection times by individual, as well as derived sampling time deviations, will be provided. Pharmacokinetic concentrations/activities and derived PK parameters for FII, [redacted] will be summarized using descriptive statistics by treatment and nominal sampling time point. Plots of individual and mean plasma concentration-time profiles will be presented by treatment and visit. Plots of individual and geometric mean $AUC_{0\text{-}216\ h}$ will also be presented by treatment.

Details and rules for evaluable data in the PK analysis, and subsequent summary statistics and inferential statistics will be defined in the SAP.

13.4.1 Primary Outcome Measure

13.4.1.1 Analysis of the Primary PK Outcome Measure (Part 1)

The primary PK outcome measure is the $AUC_{0\text{-}216\ h}$ of FEIBA component FII. $AUC_{0\text{-}216\ h}$ will be derived using noncompartmental methods as described in Section 11.2 and will be summarized by treatment using descriptive statistics. The 216 hour timepoint is critical. Interpolation or extrapolation of the FII concentration at time = 216 hours will be performed. Additional details can be found in the SAP.

For subjects who require re-infusion due to bleeding episodes during the PK assessment, PK parameters will only be listed for the first, interrupted infusion, while those from the repeated infusion (if deemed evaluable) will be listed and used for descriptive and statistical analysis.

Statistical analyses of the primary PK endpoint will be based on the PK population.

$AUC_{0\text{-}216\ h}$ for FEIBA component FII of reduced volume and regular volume will be compared calculating the 90% two-sided CI for the difference of the mean logarithms of $AUC_{0\text{-}216\ h}$ between reduced volume and regular volume. The error variance used to calculate these CIs will be obtained from an analysis of variance model that will consist of fixed effect terms that model the subject effect, the sequence effect, the period effect, and the drug effect. The antilogs of the confidence limits will constitute the 90% CI for the ratio of the geometric means (antilog of the means of the log). To establish equivalence, the 90% CI for the ratio of the geometric means of the 2 treatments has to be contained in the margins of equivalence defined as 80% to 125%.

13.4.1.2 Analysis of the Primary Safety Outcome Measure (Parts 1 and 2)

The safety of treatment infusions will be evaluated primarily by the occurrence of thromboembolic events and allergic-type hypersensitivity reactions. The number and proportion (95% exact CI) of subjects experiencing thromboembolic events and allergic-type hypersensitivity reactions will be summarized by treatment for each study part as well as for the 2 parts together.

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13.4.2 Secondary Outcome Measures

13.4.2.1 Analysis of the Pharmacokinetic Outcome Measures

Secondary efficacy/PK outcome measures consist of the IR of FEIBA component FII in subjects as well as PK parameters ($AUC_{0\text{-}\infty}$, $AUC_{0\text{-last}}$, $t_{1/2}$, CL, MRT, V_{ss}, C_{max}, and t_{max}) of FEIBA component FII. Pharmacokinetic parameters will be derived using noncompartmental methods as described in Section 11.2. The secondary outcome measures will be descriptively summarized by treatment.

13.4.2.2 Analysis of the Safety Outcome Measures

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. In the summaries, AEs will be counted only once per subject and treatment for each study part. If a subject reports the same AE more than once, it will be counted with its worst severity and closest relationship to the IP.

All safety analyses will be performed for each part separately as well as for the two parts together.

The number and proportion of subjects experiencing serious and non-serious AEs up to study completion or subject withdrawal will be summarized by treatment for each study part. The number of product related serious and non-serious AEs, and number of AEs leading to discontinuation will also be summarized by treatment. A subgroup of all AEs occurring within 24 and 72 hours of IP infusion will be summarized by treatment. Additionally, subjects experiencing infusion-related AEs and infusion site reactions will be summarized by treatment.

Thrombotic markers (e.g., D-Dimers, prothrombin fragment F 1.2, TAT, and fibrinopeptide A) will be summarized using descriptive statistics by treatment. Mean concentration plots will be presented by treatment and visit for each thrombotic marker.

Vital signs and clinical laboratory assessments as well as the corresponding changes from baseline will be summarized descriptively by treatment at each scheduled assessment for each study part. Baseline will be defined as the last value prior to the first infusion for each treatment. Laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables by treatment at each scheduled assessment for each study part. All laboratory data will be listed with abnormal values flagged.

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Individual listings presenting subjects by treatment will be presented for the safety parameters. The listings will be created for both change and absolute values, if appropriate.

Full details of the statistical analysis will be specified in the SAP.

13.4.3 Exploratory Outcome Measures

[redacted]

The results of the TSQM and the patient preference questionnaires will be summarized by descriptive statistics as appropriate.

13.5 Planned Interim Analysis of the Study

There is no planned interim analysis other than a safety and PK data review by the ISMC.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

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15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

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15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

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16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

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16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 16.3).

16.4 Internal Safety Monitoring Committee

This study will be monitored by an ISMC. The ISMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the Baxalta ISMC will be composed by appropriate members of clinical, safety, and biostatistics division that are not involved in the active execution of the trial. The ISMC can stop a study if it finds toxicities or if treatment is proven to be not beneficial.

All SAEs will be reviewed by the Chair of the ISMC. There are 3 planned ISMC meetings:

1. At least 48 hours after 6 subjects in Part 1 (3 subjects in each group) have completed Infusion 5
2. At least 48 hours after 6 subjects have completed Infusion 8 (Part 2)
3. At least 48 hours after 6 subjects have completed Infusion 11 (Part 2)

ISMC preplanned meetings will be held concurrently with the ongoing study. Subjects can continue with their scheduled therapy and assessments unless the ISMC warrants that the trial needs to be suspended due to safety concerns. Additional ad hoc meetings of the ISMC may be convened as appropriate per ongoing safety evaluations.

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17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.9), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, eCRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

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The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If eCRFs are provided by the sponsor, only authorized study site personnel will record or change data on the eCRFs. If data is not entered on the eCRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to an eCRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of eCRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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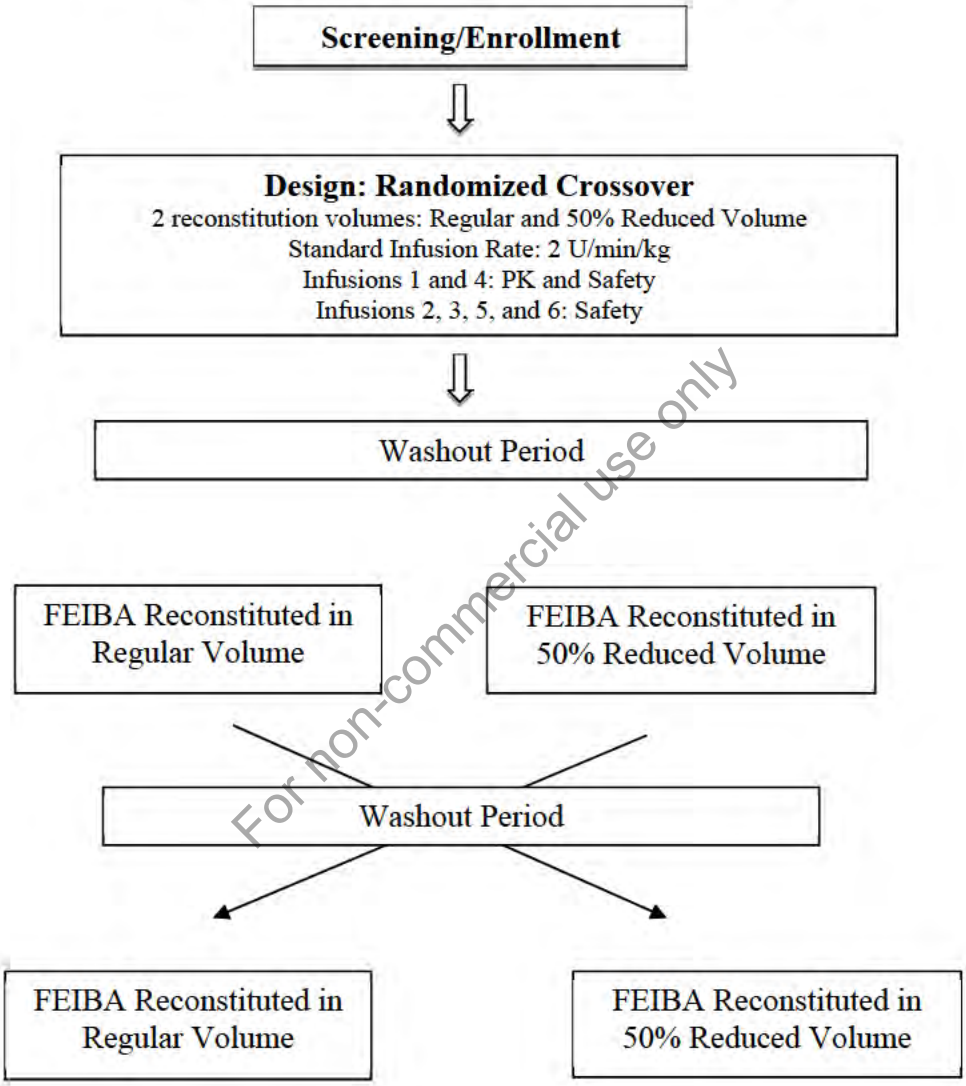
20. SUPPLEMENTS

20.1 Study Flow Chart Part 1

Figure 1
Study Design for Part 1 Baxalta Clinical Study 091501



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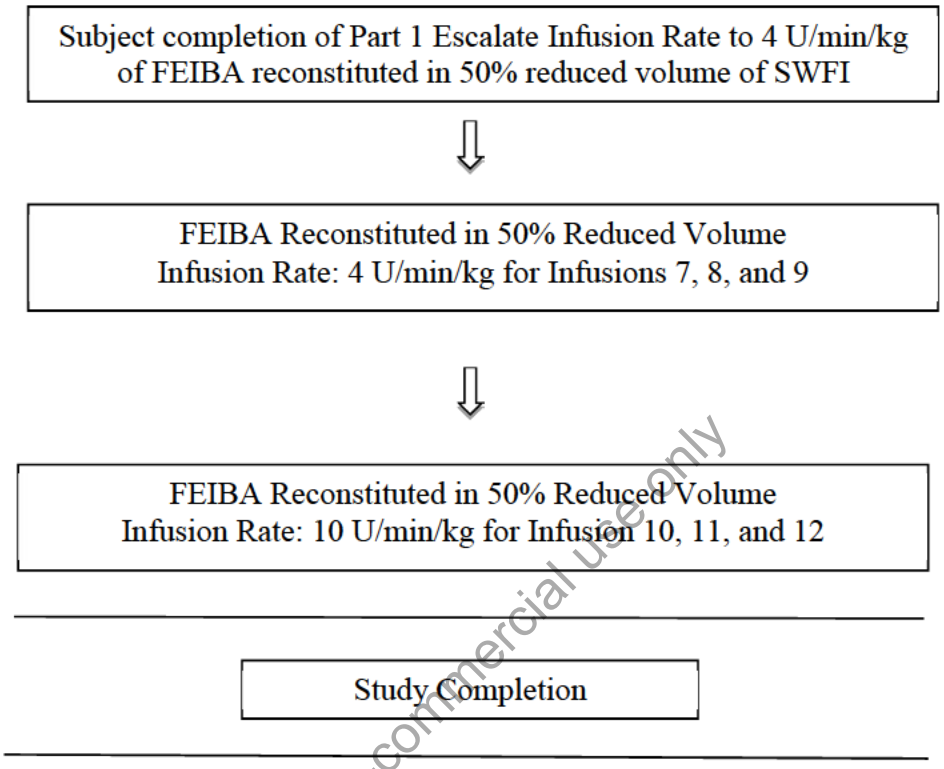
20.2 Study Flow Chart Part 2

Figure 2
Study Design for Part 2 Baxalta Clinical Study 091501



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20.3 Schedule of Study Procedures and Assessments (Part 1)

Table 2
Schedule of Study Procedures and Assessments (Part 1)

Procedures/ Assessments	Screening Assessments	Study Visits[a]									
		Washout Period 1[e]	Infusion #1	PK Visits[b]	Infusion #2	Infusion #3	Washout Period 2[f]	Infusion #4	PK Visits[a]	Infusion #5	Infusion #6
Study Visit Windows[c]	A maximum of -56 days to 0		Day 1	Multiple Visits Day 1 through 9	9 (+1) days from Infusion 1	48 hr (+48) from Infusion 2		At least 12 days from Infusion 3	Multiple Visits up to 9 Days from Infusion 4	9 (+1) days from Infusion 4	48 hr (+48) from Infusion 5
Informed Consent[d]	X										
Eligibility Criteria	X										
Medical History	X										
Medication and Non-drug Therapies	X		X		X	X		X		X	X
Physical Examination	X										
Pregnancy Test	X										
Vital Signs[g]	X		X		X	X		X		X	X
Karnofsky Performance Test	X										
Laboratory Assessments[h]	X		X		X	X		X		X	X
PK Assessments[i]	X		X	X				X	X		
Adverse Events, breakthrough bleeds, and site infusion reactions	X[j]		X	X	X	X		X	X	X	X
IP Treatment			X		X	X		X		X	X
TSQM and patient preference questionnaires[k]		X					X				

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity; ICF=informed consent form; IP=investigational product; PK=pharmacokinetic; rFVIIa=recombinant activated clotting factor VII; SAE=serious adverse event.

[a] A Study Completion/Termination Visit is to be completed in Part 1 only for subjects who withdraw or discontinue prior to the end of the study. If a subject withdraws or discontinues, this visit should be done in within 7 days but no sooner than 72 hours from the last infusion that the subject receives. Otherwise, the Study Completion/Termination Visit will occur at the end of Part 2 (see Table 3).

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Continued

[b] Additional PK visits will occur between Infusions 1 and 2, and between Infusions 4 and 5, at 24, 48, 96, 168, and 216 hours after Infusion 1 or Infusion 4 as described in Table 5

[c] Study Visit Windows:

1. Infusion 1: Infusion 1 can be scheduled after screening assessments have been completed and the appropriate washout period as defined in washout (footnote e) below has occurred. Scheduling will also need to ensure that PK timepoints can be collected as described in footnote a and Table 5. If the subject has a bleeding episode during the 9-day PK collection period, bleeding will be controlled, and the washout period restarted as described in Section 8.8.4, Infusion 1 and PK assessments will have one re-attempt.
2. Infusion 2: Infusion 2 is scheduled for 9 days (+1) after Infusion 1. All PK samples from Infusion 1 must be completed before Infusion 2 can begin, except in cases of multiple bleeding episodes, see Section 8.8.4.
3. Infusion 3: Infusion 3 should be scheduled 48 hours (+48 hours) after Infusion 2.
4. Infusion 4: Infusion 4 should be at least 12 days after Infusion 3 (See footnote f on Washout Period 2 for restrictions). If the subject has a bleeding episode during the 9-day PK collection, bleeding will be controlled, and the washout period restarted as described in Section 8.8.4, Infusion 4 and PK assessments will have one re-attempt.
5. Infusion 5: Infusion 5 should be 9 days (+1) after Infusion 4. All PK samples from Infusion 4 must be completed before Infusion 5 can begin, except in cases of multiple bleeding episodes, see Section 8.8.4.
6. Infusion 6: Infusion 6 should be scheduled for 48 hours (+48) after Infusion 5.

[d] Occurs at enrollment (prior to any study-specific procedure).

[e] Washout Period 1: Washout Period 1 is based on the subject's last dose of FEIBA or rFVIIa (e.g., NovoSeven). Due to the varying lengths of the half-lives of the drugs, subjects who have received FEIBA will need to wait 12 days from the last dose of FEIBA that they received before they can begin Infusion 1. For subjects who have previously been treated with rFVIIa, they will need to wait at least 24 hours from the last dose of rFVIIa before they can begin Infusion 1 of the study. Additional days of washout beyond the minimum of 12 days or 1 day for FEIBA or rFVIIa treatment subjects, respectively, are permissible (as long as the screening assessments stay within the window to Infusion 1). Subjects who are on prophylactic therapy before the study, will need to have an appropriate washout period once eligibility is determined. For subjects who are on an on-demand treatment to control bleeding, the washout begins from the last day of treatment. If the subject has a bleeding episode that requires treatment during the washout period, the washout period must be restarted before they can proceed with the study.

[f] Washout Period 2: Washout Period 2 is a minimum of 12 days from Infusion 3, since all subjects receive FEIBA at Infusion 3. If bleeding occurs during the washout period, the subject will be treated per standard of care and the washout period will be restarted (at least 12 days from their last dose of FEIBA, or at least 24 hours after last treatment with an rFVIIa product. If rFVIIa is administered, a washout period of 12 days after their last dose of FEIBA [i.e., Infusion 3] should still be observed).

[g] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within 30 minutes after completion of the infusion. Height, measured once at Screening, will also be collected.

[h] For laboratory assessments, see Table 4.

[i] For PK assessments, see Section 11 for details.

[j] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[k] Questionnaires (TSQM and patient preference questionnaire) will be administered after Screening prior to the start of Infusion 1, and after Infusion 3 prior to the start of Infusion 4

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20.4 Schedule of Study Procedures and Assessments (Part 2)

Table 3
Schedule of Study Procedures and Assessments (Part 2)

Procedures/ Assessments	Study Visits						
	Infusions 7	**Infusion 8**	**Infusion 9**	**Infusion 10**	**Infusion 11**	**Infusions 12**	**Study Completion/ Termination Visit[a]**
Rate of Infusion	**Rate: 4 U/min/kg**			**Rate: 10 U/min/kg**			
Study Visit Windows	48 hours (+48) from previous infusion[b]	48 hours (+48) from previous infusion[b]	48 hours (+48) from previous infusion[b]	48 hours (+48) from previous infusion[b]	48 hours (+48) from previous infusion[b]	48 hours (+48) from previous infusion[b]	3 days (+ 4) from Infusion 12 (or last infusion)[a]
Medications and Non-drug Therapies	X	X	X	X	X	X	X
Pregnancy Test							
Vital Signs[c]	X	X	X	X	X	X	X
Laboratory Assessments[d]	X	X	X	X	X	X	X
Adverse Events, breakthrough bleeds, and site infusion reactions[e]	X	X	X	X	X	X	X
IP Treatment	X	X	X	X	X	X	
TSQM and patient preference questionnaires[f]	X						X

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity; IP=investigational product.

[a] The Study Completion/Termination Visit includes cases of withdrawal or discontinuation. This visit should be done within 7 days but no sooner than 72 hours after Infusion 12). If a subject withdraws or discontinues, this visit should be done within 7 days but no sooner than 72 hours after the last infusion that the subject receives.

[b] Infusions 7, through 12: All infusions in Part 2 will be scheduled for 48 hours (+48) after their previous infusion.

[c] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate, and weight. Blood will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within 30 minutes after completion of the infusion. Height, measured once at Screening, will also be collected.

[d] For laboratory assessments, see Table 4.

[e] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[f] Subject questionnaires (TSQM and patient preference questionnaire) will be administered after Infusion 6 prior to the start of Infusion 7, and after Infusion 12 prior to or up to the completion of the Study Termination/Completion Visit.

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20.5 Clinical Laboratory Assessments

Table 4
Clinical Laboratory Assessments

Assessments	Screening Visit	Infusions 1 and 4	PK Visits[a] (multiple visits Day 1 through 9)	Infusions 2, 3, 5, 6, 7, 8, 9, 10, 11, and 12	Study Completion/ Termination Visit[b]
Hematology[c]	X				X
Clinical Chemistry[d]	X				X
Coagulation Testing[e]	X	X		X	X
Serology Testing[f]	X				X
PK Assessments[g]	X	X	X		
Pregnancy Test[h]	X				

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; FII=Factor II; FIX=Factor IX; FVII=Factor VII; FVIII=Factor VIII; FX=Factor X; GGT=gamma-glutamyl transpeptidase; HAV=hepatitis A virus; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; Hct=hematocrit; HCV=hepatitis C virus; Hgb=hemoglobin; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IgM=immunoglobulin M; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; TAT=thrombin/anti-thrombin complex; WBC=white blood cell.

[a] Additional PK visits will occur between Infusions 1 and 2, and between Infusions 4 and 5, at 24, 48, 96, 168, and 216 hours after Infusion 1 or Infusion 4 as described inTable 5 .

[b] Includes cases of withdraw or discontinuation.

[c] Hematology assessments include: CBC (Hct, Hgb, RBC count, WBC count) with differential, MCV, MCHC, and platelet count.

[d] Clinical chemistry assessments include sodium, chloride, potassium, bicarbonate, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, GGT, 5'-nucleotidase.

[e] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1.2, TAT, fibrinopeptide A), FII, FX, FIX, FVII, and FVIII or FIX inhibitor level (Nijmegen assay).

[f] Serological testing will include: HIV-1 and HIV-2 antibodies (HIV+, check CD4 count–screening visit only), HAV antibodies, HBV antibody, HBsAg, HCV antibody, parvovirus B19 (IgM and IgG), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).

[g] PK assessments will include coagulation activity testing of: Factors II, [redacted] as described in Table 5.

[h] A serum pregnancy test will be performed for females of childbearing potential.

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20.6 Pharmacokinetic Assessments

Table 5
PK Assessments

Procedures/ Assessments	Screening Visit	Infusion 1	Infusion 4	Day from Infusion
PK Assessments: Factor II	X	**Preinfusion**		
		30 ± 5 min	30 ± 5 min	Day 0
		15 ± 5 min	15 ± 5 min	
[redacted]	X	**Postinfusion**[a]		
		EOI	EOI	Day 0
		30 ± 5 min[b]	30 ± 5 min[b]	
		60 ± 5 min	60 ± 5 min	
		3 h ± 30 min	3 h ± 30 min	
		8 h ± 30 min	8 h ± 30 min	
		24 ± 4 h[b]	24 ± 4 h[b]	Day 1
		48 ± 4 h	48 ±4 h	Day 2
		96 ± 6 h	96 ± 6 h	Day 4
		168 ± 6 h	168 ± 6 h	Day 7
		216 ± 6 h	216 ± 6 h	Day 9

Abbreviations: EOI=end-of-infusion; Factor II=FII; [redacted] h=hours; min=minutes; PK=pharmacokinetic.

Notes: PK assessments will be completed on FII, [redacted] at screening and all timepoints indicated before and after Infusion 1 and Infusion 4.

[a] Postinfusion sampling times are relative to the end of infusion.

[b] Blood sample for thrombotic marker analysis will be collected at the 30-minute timepoint.

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21. REFERENCES

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22. SUMMARY OF CHANGES

Protocol 091501 Amendment 1 (Global) 2016 FEB 09

Replaces: Original: 2015 OCT 08

In this section, changes made in this amendment from the previous version of the protocol, dated 2015 OCT 08, are described and their rationale is given.

1. Throughout the document:
   Description of Change**:** Minor grammatical and/or administrative changes were made.
   Purpose of Change**:** To improve clarity in the protocol.

2. Title page, Investigator Acknowledgement
   Description of Change: The EudraCT Number was updated to 2015-005781-39.
   Purpose of Change: To correct the EudraCT number.

3. Synopsis, Section 8.1 Brief Summary, Section 8.3 Overall Study Design:
   Description of Change: The criteria for subjects with hemophilia A was changed from ≥0.4 to ≥0.6 BU.
   Purpose of Change: The change was made based on the availability of validated assays and their detection level.

4. Synopsis, Section 8.2 Study Design Rationale, Section 8.3 Overall Study Design, Section 8.8.3 Description of Treatment, Section 8.8.4 Management and Treatment of Break-Through Bleeding, Section 10.6 Subject Diary, Section 16.4 Internal Safety Monitoring Committee; Section 20.3 Schedule of Study Procedures and Assessments (Part 1), Section 20.4 Schedule of Study Procedures and Assessments (Part 2)
   Description of Change: Text describing the previous 4 DMC reviews, and interim breaks was removed. Text was simplified to be described in just the synopsis and Section 16.4 Data Monitoring Committee which was updated to Internal Safety Monitoring Committee with this change. Text was added to define the 3 safety reviews as well as continuous monitoring.
   Purpose of Change: An operational decision was made to reduce the formal DMC reviews from 4 DMC reviews with treatment breaks, to ongoing continual monitoring with 3 ISMCs and no break in treatment. This change is in an effort to increase the safety monitoring while reducing the total length of time of the study.

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5. Throughout the document
Description of Change: All references of DMC were removed and updated to ISMC.
Purpose of Change: The change was made to align the text to the updated operational design.

6. Synopsis, Section 8.2 Study Design Rationale, Section 8.3 Overall Study Design, Section 11.2 Pharmacokinetic Evaluation and Pharmacokinetic Parameters, Section 8.8.3 Description of Treatment, Section 8.8.4 Management and Treatment of Break-Through Bleeding
Description of Change: Text specifying washout periods was simplified and duplications within the text deleted. References to sponsor providing FEIBA was removed and replaced with allowing subjects to be given standard of care treatment for bleeding during washout periods.
Purpose of Change: Updates to the washout descriptions were made to align with the deletion of the DMC, as well as add clarity and simplify the text. In addition, with the removal of the DMC there are no long interim breaks, hence the sponsor has decided it is unnecessary to provide FEIBA and that allowing the investigator to choose the treatment for bleeding control for subjects will increase safety, as the investigator can choose which product they know works best for the subject.

7. Section 8.8.4 Management and Treatment of Break-Through Bleeding
Description of Change: The phrase "during the interim period, subjects who are on hold for DMC review" was updated to "During the interim period for DMC review, subjects".
Purpose of Change: This change was made to align the text with the DMC changes described in Section 16.4 Data Monitoring Committee.

8. Synopsis
Description of Change: Inclusion criteria 7 and 8 were added to the synopsis.
Purpose of Change: Inclusion criteria 7 and 8 were in the main body of the text but not the synopsis, this change is to update the sections to match.

9. List of Abbreviations, Section 6.5 Compliance Statement
Description of Change: ICH was updated from International "Conference on" Harmonisation to "Council for".
Purpose of Change: The definition of ICH was recently updated, and this was reflected within this protocol amendment.

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10. Section 8.8.1 Packaging, Labeling, and Storage
Description of Change: Text was added to describe how the sites will receive FEIBA and SWFI within a kit.
Purpose of Change: To add clarity.

11. Section 8.8.2:Adminstration
Description of Change: More detail, including a table was added to describe how the study drug will be prepared and administered.
Purpose of Change: Improve clarity and investigator compliance.

12. Section 8.8.2 Administration
Description of Change: Wording was changed from "must" to "every effort should be made" when describing using the same lot numbers for Infusion 1 and Infusion 4. Additional details were added to include that the diluent does not need to be the same lot.
Purpose of Change: To increase clarity and investigator compliance.

13. Section 8.8.3 Description of Treatment
Description of Change: Redundant text was removed and hyperlinks to the information in other sections were added.
Purpose of Change: To simplify and add clarity to the protocol

14. Synopsis, Section 8.4 Duration of Study Period(s) and Subject Participation
Description of Change: The duration of time the subjects will be on study was clarified by Part 1 and Part 2. Text referencing extension of time for the DMC was deleted.
Purpose of Change: This change was to update and align with the new ISMC text.

15. Section 10.6 Subject Diary, Throughout the protocol
Description of Change: The use of subject diaries was removed from the protocol.
Purpose of Change: The use of diaries is no longer needed due to the removal of the DMC breaks. This will simplify the study and make participation easier for the subjects.

16. Section 12.10 Infusion Site Evaluations
Description of Change: A statement was added to describe discussions of the subject with site staff to capture infusion site reactions.
Purpose of Change: To replace what was previously going to be collected by the subject diary.

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17. Section 13.2 Datasets and Analysis Cohorts
Description of Change: The word "safety" was added in relation to the analysis sets, and reference to the soft database lock and DMC were deleted.
Purpose of Change: This change was to align with the change from DMC to ISMC.

18. Section 20.3 Schedule of Study Procedures and Assessments (Part 1)
Description of Change: Footnote text regarding PK sampling timing was moved from footnote 5 to footnote 4.
Purpose of Change: This change was to improve clarity.

19. Title page
Description of Change: The words "activated prothrombin complex concentrate" were added.
Purpose of Change: To add clarity for the investigators.

20. Synopsis, Section 7.1 Study Purpose
Description of Change: The text "in Part 1" was deleted from the 2nd study purpose "To evaluate the safety of infusing reduced volume FEIBA at increased rates of 4 and 10 U/min/kg in comparison to the standard rate of 2 U/min/kg in Part 1".
Purpose of Change: This change was added in order to increase flexibility in analysis.

21. Synopsis, Section 7.2 Primary Objectives
Description of Change: The occurrence of thromboembolic events was added to the primary objectives, and allergic reactions were renamed to allergic-type hypersensitivity reactions.
Purpose of Change: This was a medical and safety decision to more closely monitor and study the thromboembolic events based on the known information regarding FEIBA, and to capture a broader range of allergic reactions.

22. Synopsis, Section 7.3 Secondary Objectives
Description of Change: Thromboembolic events were deleted from secondary objectives.
Purpose of Change: Thromboembolic events were moved to primary objectives, in order to more closely assess their incidence.

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23. Synopsis, Section 8.5.1 Primary Outcome Measures
Description of Change: Thromboembolic events were added to the primary outcome measures, and it was separated from allergic-type hypersensitivity reactions.
Purpose of Change: The purpose of this change was to align it to the updated primary objectives, and to make the text more readable.

24. Synopsis, Section 8.5.2 Secondary Outcome Measures
Description of Change: The outcome measure of evaluating product-related AEs was updated to all AEs and SAEs, an additional outcome measure of evaluating the occurrence of AEs leading to discontinuation was added, and evaluating the occurrence of thromboembolic AEs was deleted.
Purpose of Change: The purpose of this change was to better evaluate the AEs and SAEs of this study. The deletion of the thromboembolic AEs was to not duplicate effort already being done in the primary outcome measures.

25. Synopsis
Description of Change: A more precise description of infusion frequency was added.
Purpose of Change: To add clarity and increase compliance.

26. Synopsis, Section 8.4 Duration of Study Period(s) and Subject Participation
Description of Change: Timing of planned duration of subject participation was updated.
Purpose of Change: The modification of the DMC to ISMC, and removal of the interim breaks shortens the duration of subject participation and time on study.

27. Section 6 Background Information
Description of Change: Background information was rearranged and duplicate text was deleted.
Purpose of Change: To add clarity and simplify the protocol text.

28. Section 6.2 Population to Be Studied
Description of Change: Previous Section 6.3 was updated to 6.2 based on updates to Section 6.1 and 6.2. A line referring to the Inclusion/Exclusion Criteria was added.
Purpose of Change: To increase specificity of the study population.

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29. Section 7.2 Primary Objectives
Description of Change: The section was rearranged into numbered format, and text updated to match Synopsis wording exactly.
Purpose of Change: To add clarity and simplify the text.

30. Section 8.8.4 Management and Treatment of Break-Through Bleeding, Section 20.3 Schedule of Study Procedures and Assessments (Part 1)
Description of Change: Additional text was added to describe the washout period depending on whether the subject is treated with FEIBA or rFVIIa, as well as for management of bleeding episodes during treatment periods.
Purpose of Change: This update was due to the sponsor no longer requiring the use of FEIBA for treatment of bleeding, therefore additional text needed to be added to specify what would occur depending on which treatment was administered.

31. Section 8.8.4 Management and Treatment of Break-Through Bleeding
Description of Change: The following sentence was updated: from "If multiple bleeding episodes occur during the washout period, the investigator and sponsor should decide if it is beneficial for the subject to be taken off the study" to "If multiple bleeding episodes occur during the washout period, the investigator and sponsor should decide if it is appropriate for the subject to be taken off the study or continue with the study".
Purpose of Change: To clarify and increase investigator compliance.

32. Section 9.3 Withdrawal and Discontinuation
Description of Change: The following withdrawal criterion was added "The ISMC determines a subject should be taken off study".
Purpose of Change: To align with the text in other sections of the protocol.

33. Section 10.3.1 Screening and Baseline Assessments
Description of Change: The text was updated from "subjects will receive instruction and educational materials on the symptoms of thromboembolic events" to "subjects will be instructed on the symptoms of thromboembolic events by the investigator".
Purpose of Change: This was an operational decision in case educational materials were not available in all languages that the study would need.

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34. Section 8.8.3 Description of Treatment, Section 10.3.2.1 Infusion Visits
Description of Change: The procedure for randomization was updated from interactive voice response system to interactive web response system.
Purpose of Change: This was an operational decision.

35. Section 10.3.2.1 Infusion Visits, Section 11.1 Sample Collection and Processing
Description of Change: The following sentence was deleted "Funding or reimbursement for hotel facilities may be provided as allowed by the Institutional Review Board approved ICF and any applicable laws and regulations".
Purpose of Change: This was determined to be common knowledge that did not need to be specified within the protocol text.

36. Section 10.3.2.1 Infusion Visits, Section 10.5 Patient Questionnaires, Section 20.3 Schedule of Study Procedures and Assessments (Part 1), Section 20.4 Schedule of Study Procedures and Assessments (Part 2)
Description of Change: Timing for questionnaire administration was updated from "between" visits, to "prior to the start of the next infusion".
Purpose of Change: This was to add clarity on when the questionnaires needed to be administered.

37. Section 12.1.1.1 Serious Adverse Event
Description of Change: Wording was changed from "should be reported as SAEs" to "should be reported the same way as SAEs" "Additional events which should be reported as SAEs": The following was removed "Thromboembolic events (myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke, transitory ischemic attack, etc.), and replaced with "Any thromboembolic event, allergic-type hypersensitivity reactions (e.g., analyphylaxis)"
Purpose of Change: To add clarity and align with the safety profile of the study infusions.

38. Section 12.4 Non-Medical Complaints
Description of Change: Medication errors were added to the list of NMCs.
Purpose of Change: This was a medical decision to include this additional NMC.

39. Section 12.11 Special Treatment Considerations
Description of Change: Thromboembolic events were added as a special treatment consideration.
Purpose of Change: For safety purposes and to align with the primary outcome measures, thromboembolic events have been upgraded special treatment considerations.

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40. Section 20.1 Study Flow Chart Part 1, Section 20.2 Study Flow Chart Part 2, Section 20.3 Schedule of Study Procedures and Assessments (Part 1), Section 20.4 Schedule of Study Procedures and Assessments (Part 2)
Description of Change: Specific timing was removed from the figure for washout periods as this has many different timings and is not exactly 12 days, as well as references to the DMC were removed.
Purpose of Change: These figures and tables were updated to align with the changes in washout periods and removal of the DMC.

41. Section 6.5 Compliance Statement
Description of Change: Template text was updated from "European Clinical Trial Directive" to "EU Directives".
Purpose of Change: Template language was updated since the drafting of the protocol. These updates were included into this amendment.

42. Section 8.9 Source Data
Description of Change: The sentence "No data will be entered directly onto the eCRF" was added.
Purpose of Change: Template language was updated since the drafting of the protocol. These updates were included into this amendment.

43. Section 12.2 Urgent Safety Measures
Description of Change: Additional language was added to include relevant competent authority(s) in addition to responsible EC will be notified of urgent safety measures.
Purpose of Change: Template language was updated since the drafting of the protocol. These updates were included into this amendment.

44. Section 8.8.3 Description of Treatment
Description of Change: The following sentence was deleted "After each subset of subjects have completed Part I, PK equivalence of FEIBA reconstituted in reduced and regular volumes of SWFI in terms of $AUC_{0\text{-}216\ h}$ of FII will be evaluated."
Purpose of Change: This was removed with the removal of the 4 DMCs. Additional details were left to Section 13 Statistics.

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45. Section 13.2 Datasets and Analysis Cohorts
Description of Change: A sentence regarding handling of data for noncompliant subjects were removed.
Purpose of Change: It was felt that this was overly detailed and unnecessary for the protocol, and will instead be updated and included into the SAP as necessary.

46. Section 13.4 Methods of Analysis
Description of Change: An additional sentence was added to refer to the SAP.
Purpose of Change: To add clarity to the protocol.

47. Synopsis, Section 13.2 Datasets and Analysis Cohorts
Description of Change: Clarification was added to which subjects were included into the safety analysis set.
Purpose of Change: To add clarity to the protocol.

48. Synopsis, Section 13.4.2.2 Analysis of the Safety Outcome Measures
Description of Change: Text was updated from: "The number of product-related serious and non-serious AEs will also be summarized by treatment for each study part. Subgroup analysis will also be performed for events categorized as thromboembolic AEs." to "The number of product related serious and non-serious AEs and number of AEs leading to discontinuation will also be summarized by treatment. A subgroup of all AEs occurring within 24 and 72 hours of IP infusion will be summarized by treatment". An additional line was added earlier in the section to apply throughout the section "All safety analyses will be performed for each part separately as well as for the 2 parts together."
Purpose of Change: To align the statistics to the updates in the outcome measures.

49. Section 13.4.1.2 Analysis of the Primary Safety Outcome Measures (Parts 1 and 2)
Description of Change: Thromboembolic events were added into the primary safety outcome measures.
Purpose of Change: To align with the changes in the outcome measures.

50. Synopsis, Section 8.3 Overall Study Design, Section 8.8.3 Description of Treatment
Description of Change: Additional text describing study infusions and their timing was added.
Purpose of Change: Due to the deletion of the DMC text, additional text had to be pulled out and reworded from this section. This change was to keep accurate descriptions of the treatments.

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51. Section 8.3 Overall Study Design
Description of Change: Infusion numbers were written out in the treatment phase description, and 12 IP infusions was clarified.
Purpose of Change: To add clarity to the protocol.

52. Synopsis, Section 8.8.2 Administration, Section 8.8.3 Description of Treatment
Description of Change: Text was added to allow for the use of partial vials for PK infusions and the recommendation to use full vials for non-PK infusions.
Purpose of Change: To simplify the dosing calculations and prevent treatment errors.

53. Section 8.8.1 Packaging, Labeling, and Storage
Description of Change: Changes to the storage conditions were added.
Purpose of Change: To standardize the storage conditions across countries.

54. Section 8.8.3 Description of Treatment
Description of Change: The bulleted list of treatment summary was removed.
Purpose of Change: This was redundant text and was removed to simplify the protocol.

55. Synopsis, Section 13.4 Methods of Analysis, Section 13.4.1.1 Analysis of the Primary PK Outcome Measure (Part 1)
Description of Change: The planned statistical analysis of the primary analysis was updated.
Purpose of Change: Unnecessary detail was removed from the protocol, and the analysis of the $AUC_{0\text{-}216\ h}$ was changed from a linear mixed effects model to a fixed effect. A reference to additional details in the SAP was added.

56. Section 10.3.4 Study Completion/Termination Visit
Description of Change: Review of subject diary and diary collection was removed and replaced with breakthrough bleeds monitoring and concomitant medication monitoring.
Purpose of Change: To ensure the data will be captured as necessary without the use of a subject diary.

57. Section 10.4 Medications and Non-Drug Therapies
Description of Change: A reference to the sponsor providing FEIBA for bleeding episodes was removed. Additionally, standard of care medication for bleeding episodes was introduced into the protocol to allow for this change in study design.
Purpose of Change: The study design has changed to allow the use of standard of care for bleeding episodes.

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58. Synopsis, Section 13.4.1.2 Analysis of the Primary Safety Outcome Measure (Part 1 and 2), Section 13.4.2.2 Analysis of the Safety Outcome Measures
Description of Change: Infusion site reactions was moved from the primary analysis to the secondary analysis.
Purpose of Change: To align the statistical text with the objectives of the protocol.

59. Section 8.8.4 Management and Treatment of Break-Through Bleeding
Description of Change: Additional text was added to describe the scenario of bleeding during times other than washout periods and PK collection periods.
Purpose of Change: To give guidance to the investigators and add clarity to the protocol.

60. Section 10.7 Subject Completion/Discontinuation
Description of Change: Severe allergic reaction was added as a reason for completion/discontinuation.
Purpose of Change: This was a decision for subject safety.

61. Section 11.1 Sample Collection and Processing, Section 20.5 Clinical Laboratory Assessments, Section 20.6 Pharmacokinetic Assessments
Description of Change: PK timepoints were updated.
Purpose of Change: To allow for easier draw times for subjects while preserving the integrity of the data.

62. Section 13.3 Handling of Missing, Unused, and Spurious Data
Description of Change: The phrase "no imputation method for missing values will be used" was deleted, and the following sentence was added "For the calculation of $AUC_{0\text{-}216\ h}$, non quantifiable PK results will be extrapolated".
Purpose of Change: To clarify the statistical analysis.

63. Synopsis, Section 13.1 Sample Size and Power Calculations
Description of Change: The sample size calculation was reworded and clarified, adding in the coefficient of variation and the margins of equivalence.
Purpose of Change: To add clarity to the protocol.

64. Section 20.6 Pharmacokinetic Assessments
Description of Change: Blood sample for thrombotic marker analysis will be collected at either the 30-minute or 24-hour timepoint. Was updated to just the 30 minutes timepoint.
Purpose of Change: This was an operational change designed to make decisions on which sample to collect easier.

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INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered, FEIBA

STUDY TITLE: A Two-part, Phase 4, Prospective, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

AMENDMENT 1 (Global): 2016 Mar 03

Replaces: Original: 2015 OCT 08

For non-commercial use only

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered, FEIBA

STUDY TITLE: A Two-part, Phase 4, Prospective, Open-label, Randomized, Crossover Study of the PK and Safety of FEIBA Reconstituted in Regular or 50% Reduced Volume and the Safety of Faster Infusion Rates in Patients with Hemophilia A or B with Inhibitors

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 4

AMENDMENT 1 (Global): 2016 Mar 03

Replaces: Original: 2015 OCT 08

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

For non-commercial use only

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD
[redacted], Clinical Development

CLINICAL STUDY PROTOCOL

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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 SHORT TITLE: FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 2 (Global): 2017 AUG 04

Replaces: Amendment 1 2016 MAR 03

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ALL VERSIONS:
Amendment 2 (Global): 2017 AUG 04
Amendment 1 (Global): 2016 MAR 03
Original: 2015 OCT 08

OTHER ID(s)
NCT Number: 02764489
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted] MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

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2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report From

Refer to SAE Protocol Sections and the study team roster for further information.

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For definitions and information on the assessment of these events, refer to the following:

- Adverse Event, Section 12.1
- Serious Adverse Event, Section 12.1.1.1
- Assessment of Adverse Events, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	**Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]), FEIBA NF. Referred to as FEIBA throughout the protocol.**
Name(s) of Active Ingredient(s)	Coagulation factors II, X, IX, and VIIa
CLINICAL CONDITION(S)/INDICATION(S) FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with • inhibitors for: ➢ Control and prevention of bleeding episodes ➢ Perioperative management ➢ Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. • FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.[1]	
PROTOCOL ID	091501
PROTOCOL 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**
Short Title	FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)
STUDY PHASE	Phase 3b/4, depending on market authorization status per country
PLANNED STUDY PERIOD	
Initiation	First Subject In: Q 1 2018
Primary Completion	Last Subject In: Q 4 2018
Study Completion	Last Subject Last Visit: Q 4 2018
Duration	6 to 11 weeks

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STUDY OBJECTIVES AND PURPOSE	
Study Purpose To evaluate the tolerability and safety of infusing reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume	
Primary Objectives To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions	
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) concentration of coagulation factor II with 50% reduced volume of FEIBA and faster infusion rates 2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Tolerability and Safety
Control Type	Active
Study Indication Type	Treatment
Intervention model	Part 1: Crossover Part 2: Sequential
Blinding/Masking	Part 1: Randomized, Open-label Part 2: Non-Randomized, Open-label

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Study Design	A 2-part, Phase 3b/4, prospective, open-label, multicenter study to be conducted in 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 Bethesda units [BU] for the primary tolerability and safety assessments. **Part 1:** In Part 1, subjects will be administered two different volumes of FEIBA in a randomized, crossover design every 48 hours (-8, +24 hours) intervals. Part 1 will monitor the tolerability, safety, pre (within 60 min before the infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) concentration of coagulation factor II (FII) reconstituted in 50% reduced volume of SWFI and administered at the standard infusion rate of 2 U/kg/min compared with FEIBA reconstituted in regular volume of SWFI at the standard infusion rate. All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. Eligible subjects will be randomly assigned (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI or regular volume SWFI (Period 1). Patients finishing 3 infusions in Period 1 (Sequence A or B), will either switch from FEIBA reconstituted in reduced volume to 3 infusions of FEIBA in regular volume SWFI or vice versa (Sequence A or B) depending on randomization. All patients completing Part 1 will move to Part 2. Evaluable patients from Part 1 are all subjects who receive 4 of the 6 planned infusions, at least 2 infusions in each sequence. Tolerability and safety data will be collected before, during and after each infusion and between infusions; Clinically apparent changes in vital signs, laboratory parameters, infusion site reactions and infusion rate-related reactions will be monitored.

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	FII concentration will be monitored by analyzing concentrations before (within 60 min before the infusion) and at 30 min after each infusion and at hours 1, 2, 6, 8 and 12 after infusion 1,3,4 and 6 as outlined in Section 20.6. **Part 2:** Part 2 is non-randomized with sequential treatment of all evaluable subjects who complete Part 1, will receive at least 4 of the 6 infusions. Subjects will receive FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/kg/min in a non-randomized fashion, at 48 hours (-8, +24 hours) intervals, to evaluate the tolerability and safety of infusing 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 and infusions 10, 11 and 12 will be administered at 10 U/kg/min. Following the last infusion (infusion 12), a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion. Tolerability and safety data will be collected before, during and after each infusion and between the infusions; Clinically apparent changes in vital signs, infusion rate-related events, and infusion site reactions will be monitored. Concentration of coagulation factor II will be assessed before (within 60 minutes before the infusion) and at 30 min after each infusion, and at hours 1, 2, 6, 8 and 12 after infusions 9, and 12 as outlined in Section 20.6. The infusions in both parts will be administered every 48 hours (-8 hours /+24 hours) to allow time to monitor tolerability and safety of the higher infusion rate.

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	All IP infusions will be administered at the hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions (6 in each part). There is no washout period before Part 1, between infusions or parts of the study. Subjects will receive FEIBA at a dose of 85 U/kg ± 15 U/kg for all infusions. For infusions, whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate. Please refer to study documents for detailed instructions. Safety monitoring for this study will be conducted concurrently by an Internal Safety Monitoring Committee (ISMC). All SAEs that occur will be reviewed by the Chair of the ISMC with the Medical Director within 24 hours. Planned ISMC meetings will be held concurrently with the ongoing study.
Planned Duration of Subject Participation	It is planned that each subject will spend approximately 6 to 11 weeks in the study.
Outcome Measure (s) **Primary** Assess tolerability and safety (local and general) related to the infusion and volume of reconstitution: 1. Occurrence of any adverse event: all AEs and SAEs, and AEs leading to discontinuation 2. Thromboembolic events and hypersensitivity reactions 3. Vital signs and Clinical laboratory data 4. Infusion site and infusion related reactions	
Exploratory Outcome Measure(s) 1. To monitor pre (within 60 min before the infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) concentration of coagulation factor II. 2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire	

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INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** kit; powder, lyophilized, for solution/suspension; injection **Dosage frequency:** IP will be infused every 48 hours (-8 hours/+24 hours). **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Enroll 24 evaluable subjects for the assessments
Number of Groups/Arms/Cohorts	1 cohort: at least 24 evaluable adult subjects (≥ 18 to ≤ 65 years old) for tolerability and safety evaluation

Inclusion Criteria

Subject is/has:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom

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8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
    a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

Exclusion Criteria

Subject is/has:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
9. Herbal supplements that contain anti-platelet activity
10. Participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
11. A family member or employee of the investigator
12. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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STATISTICAL ANALYSIS

Sample Size Calculation

The projected sample size of 24 evaluable subjects for this tolerability and safety study was determined by considering available patients, and is not based on statistical power calculations.

Planned Statistical Analysis

Statistical analysis for this study will be descriptive in nature.

Primary Analysis

AEs, SAEs and AEs leading to discontinuation, thromboembolic events and hypersensitivity reactions that occur during or after the IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be provided for temporally associated adverse events; and for potentially related adverse events as assessed by the investigators.

Shift tables and summary statistics will be presented for the results of clinical laboratory data. All abnormal lab results will be listed.

Summary statistics of vital signs, infusion site and infusion related reactions will be carried out.

Exploratory Analysis

All exploratory outcome measures will be analyzed descriptively.

Full details of the statistical analysis will be specified in the statistical analysis plan (SAP).

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4. TABLE OF CONTENTS

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Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BU	Bethesda units
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
EC	ethics committee
EOI	end-of-infusion
CRF	case report form
EDC	electronic data capture
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FEIBA VH	Factor Eight Inhibitor Bypassing Activity Vapor Heated
FII	Factor II
FIX	Factor IX
FVII	Factor VII
FVIII	Factor VIII
FVIII:CAg	Factor VIII C antigen
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSL	Global Safety Lead
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen

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Abbreviation	Definition
HBV	hepatitis B
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	Immumoglobulin G
IgM	immunoglobulin M
IP	investigational product
ISMC	Internal Safety Monitoring Committee
Min	minutes
NMC	non-medical complaint
PCR	polymerase chain reaction
PT	prothrombin time
rFVIIa	recombinant activated clotting factor VII
Rsq	r^2
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SI	serious injuries
SWFI	sterile water for injection
TAT	thrombin/anti-thrombin complex
TSQM	Treatment Satisfaction Questionnaire for Medication

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6. BACKGROUND INFORMATION

6.1 Description of Investigational Product and Clinical Condition/Indication

The investigational product (IP), FEIBA[i] is a plasma derived, activated prothrombin complex concentrate (APCC), generically identified as an anti-inhibitor coagulant complex (AICC). FEIBA was developed to treat bleeding episodes and cover surgical interventions in hemophilia A and B patients with inhibitors and in non-hemophilia patients with acquired inhibitors[ii] and is also intended for use as a prophylactic treatment for hemophilia A and B patients with high responding inhibitors and frequent joint bleeding.[iii,2,3,4]

Baxalta's first licensed FEIBA product, AICC FEIBA, was marketed beginning in 1975 and was superseded in 1985 by a 2-stage vapor heat-treated product, AICC FEIBA VH. Nanofiltration was introduced to the manufacturing process in 2006 to produce FEIBA NF, now called FEIBA.

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6.2 Clinical Condition/Indication

Hemophilia is an X-linked, recessive, congenital bleeding disorder caused by deficient or defective coagulation due to a deficiency in FVIII (hemophilia A), or FIX (hemophilia B). The absence of FVIII or FIX leads to spontaneous bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury.[5,6] Replacement therapy for the treatment of hemophilia A, and less frequently hemophilia B, can be complicated by an immune response resulting in the production of inhibitory alloantibodies to Factor VIII (FVIII) or Factor IX (FIX), especially in patients with moderate to severe hemophilia. The development of such inhibitory antibodies currently represents the most serious complication of hemophilia treatment. The presence of inhibitors against FVIII generally precludes the efficacious use of human FVIII replacement therapy. A substantial portion of patients with FVIII inhibitors have high-responding, high-titer inhibitors (> 5 Bethesda units [BU]). These patients exhibit an anamnestic response after FVIII exposure, sometimes with a dramatic increase in inhibitory antibody titer.[7,8] The inability to provide FVIII replacement therapy predisposes this group of patients to increased morbidity and mortality compared with hemophilia patients without inhibitors.[7]

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[i] FEIBA NF is a trademark of Baxalta Inc. US and Baxalta Innovations GmbH.

[ii] Anti-Inhibitor Coagulant Complex, FEIBA Vapor Heated. Package Insert, Baxalta US Inc., Westlake Village, CA.

[iii] Protocol 090701. FEIBA NF: A Prospective, Open-label, Randomized, Parallel Study to Evaluate Efficacy and Safety of Prophylactic versus On-demand Treatment in Patients with Hemophilia A and B and High Titer Inhibitor. 2013 Jan 14, Baxalta US Inc.,(Westlake Village, CA).

Several therapeutic approaches are currently available in the management of hemorrhagic events in patients who have developed FVIII inhibitors. These include neutralization with high doses of human FVIII (low titer inhibitor only), and treatment with bypassing agents such as Activated Prothrombin Complex Concentrate (APCC), or activated recombinant factor VII (rFVIIa). Among these treatment options, only APCCs and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII or FIX. It has been proposed that FEIBA products achieve this goal principally by virtue of the presence of a "partial prothrombinase complex" consisting of activated Factor X (FX) and prothrombin.[9]

The active ingredient of FEIBA is a plasma-derived, freeze-dried APCC with FVIII inhibitor bypassing activity. Recent studies have demonstrated that FEIBA is a multicomponent therapeutic agents with activities potentially targeting different sites in the coagulation system.[10] FEIBA contains mainly non-activated forms of the vitamin K - dependent proteins Factor II (FII), FVII, FIX and FX, as well as small amounts of activated prothrombin complex proteins; and Factor VIII coagulant antigen present in a concentration of up to 0.1 U/1 U FEIBA. From a number of confirmed studies it became clear that the FII–FXa complex is one of the key components in this system of different proteins.[11] A solution containing 1 U FEIBA shortens the activated partial thromboplastin time (aPTT) of FVIII inhibitor plasma up to 50% of the buffer value. Additional details can be found in the FEIBA IB.[iv]

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6.3 Population to Be Studied

Adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B (congenital or acquired) of any severity, of all races and ethnic groups will be studied. All subjects will have a documented history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa); subjects with no documented history will require testing of the inhibitor level before entering the study. Subjects will either be hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease. Subjects will either be human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3. See additional details in the Inclusion and Exclusion Criteria in Section 9.1 and Section 9.2, respectively.

[iv] Investigator's brochure. Anti-inhibitor coagulant complex nanofiltered; FEIBA NF. 2016 FEB 24. Baxalta US Inc., (Westlake Village, CA).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

The nonclinical studies included a virus clearance study, which was performed to investigate the virus reduction capacity of the nanofiltration step in the manufacturing of FEIBA NF.

Data from nonclinical studies can be found in the FEIBA NF IB.[iv]

6.4.2 Findings from Clinical Studies

The results of Baxalta clinical study 090701[iii] demonstrated that prophylaxis with FEIBA significantly reduced the annualized bleeding rates for all bleed types and for spontaneous, traumatic, joint, and non-joint, bleeding episodes when compared with on-demand treatment. A statistically significant reduction in the rate of bleeding episodes in new target joints in the prophylaxis arm versus the on-demand arm was also observed. An examination of adverse events (AEs), abnormal laboratory parameters for hematology and clinical chemistry and vital signs demonstrated that FEIBA was safe and well tolerated for prophylactic use. Clinically, these data suggest that FEIBA is safe and efficacious in the management of hemophilia A or B with persistent high-titer inhibitors or low-titer inhibitors refractory to FVIII or FIX treatment, and further confirmed the safety and effectiveness of FEIBA for controlling and preventing bleeding episodes.

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Baxalta clinical study 091002 was an open-label, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. This study was designed to document routine usage of FEIBA NF as a bypassing agent for on-demand or prophylactic treatment in everyday clinical practice and in surgical intervention. The safety results of this postauthorization safety study showed that treatment with FEIBA NF, administered in 81 subjects with hemophilia, requiring treatment with inhibitor-bypass therapy for bleed resolution or bleed prophylaxis, was generally safe and well tolerated. The mean infusion rate of FEIBA under routine clinical practice during the study (3.7 U/kg per min, range 0.9 to 23.5) was higher than that recommended in the Summary of Product Characteristics of FEIBA (2.0 U/kg per min). A manual analysis of safety listings did not disclose any AEs associated with a higher infusion rate.[12] Treatment-related AEs or serious adverse events (SAEs) were reported in 9.9% and in 3.7% of subjects, respectively. A deep venous thrombosis and a superficial thrombophlebitis were observed in 1 subject with acquired hemophilia.

The hemostatic effectiveness was rated by the physicians as excellent or good in more than 90% of total subjects, with the highest rates reported in subjects with FEIBA NF prescribed as regular prophylaxis. Additional details on this study can be found in the clinical study report.[v]

FEIBA consists of zymogens and traces of activated forms of procoagulant factors II, VII, IX, X, anticoagulants protein C and TFPI, and small amounts of cofactors FV, FVIII and protein S, in a balanced ratio. As mentioned before, FII-FXa complex plays a key role in FEIBA's mode of action (MoA). A recently published study has shown that although the FII-FXa complex are the key components other procoagulant components of FEIBA were necessary to achieve an optimal activity. However prothrombin (FII) is the lead procoagulant component of FEIBA.[1,11]

Due to the complex nature of the composition of FEIBA, pharmacokinetic information cannot be determined by measurement of a single component. In recent studies where FEIBA was used as a comparator product surrogate markers of coagulation were used to determine pharmacokinetics. These surrogate markers of coagulation included determination of thrombin generation, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin–antithrombin complex (TAT) and prothrombin fragment F_{1+2} (F1+2), and aPTT clot waveform analysis, maximum levels of these surrogate markers following FEIBA administration were seen after 10 or at 30 min with variable results at later time points.[10] In another study where thrombin generation was measured in patients following infusion of FEIBA peak thrombin levels were seen predominantly 30 and 60 minutes after infusion.[13] Thus, determination of peak plasma concentrations of components of FEIBA seems to be most appropriate performed at 30 or 60 minutes after infusion.

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Additional observational, non-interventional studies were conducted with FEIBA NF. Additional details on clinical studies can be found in the FEIBA NF IB.[iv]

[v] Clinical Study Report. Post-Authorization Safety Study of FEIBA NF (Factor VIII Inhibitor Bypassing Activity). An open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. 10 Oct 2014. Baxalta Inc. US and Baxalta Innovations GmbH.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Uncommon, hypersensitivity reactions observed after infusion of FEIBA have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; these reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. The most commonly reported adverse drug reactions described for FEIBA NF include increased inhibitor titer, somnolence, dizziness, dysgeusia, dyspnea, nausea, chills, pyrexia, chest pain, and chest discomfort.

The possibility of thrombotic events should be considered when FEIBA is used in combination with systemic anti-fibrinolytics such as aminocaproic acid and tranexamic acid. Therefore, anti-fibrinolytics should not be used for approximately 6 to 12 hours before or after the administration of FEIBA.

Animal reproduction studies have not been conducted with FEIBA. There are no adequate, well-controlled studies in pregnant women. It is also not known whether FEIBA can cause fetal harm when administered to a pregnant woman or an affect on reproductive capacity. It is also not known whether FEIBA is excreted in human milk.[1] Subjects within the study should be provided with labeling information and a detailed discussion of benefit risk profile.

Additional safety experience for FEIBA is provided in the FEIBA NF IB.[iv]

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6.6 Compliance Statement

The study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is:

To evaluate the tolerability and safety of infusing 50% reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume

7.2 Primary Objectives

To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions

7.3 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) concentration of coagulation factor II
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

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8. STUDY DESIGN

8.1 Brief Summary and Study Design Rationale

This is a 2-part Phase 3b/4 (depending on market authorization status per country), prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 BU in hemophilia A and B) to determine the tolerability and safety of FEIBA component FII with a planned enrollment of 24 evaluable subjects. Evaluable subjects are defined as the ones who complete both parts of the study (i.e. received at least 8 of the 12 infusions; 4 in each part and 2 in each sequence in Part 1).

All subjects will receive 3 infusions of FEIBA reconstituted in a regular volume of SWFI, and 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI, with all 6 of these infusions being given at a rate of 2 U/kg/min within Part 1 of the study. In Part 2 of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/kg/min followed by 3 infusions FEIBA reduced volume at a rate of 10 U/kg/min.

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This study has been designed as a 2-way crossover study in order to assess primarily tolerability and safety of FEIBA. By designing it as a crossover study, subjects serve as their own controls. In addition, having received 6 infusions at 2U/Kg/min in Part 1, patients will be near to or at steady state (post 6 infusion of FEIBA) prior to starting Part 2. This study is open-label because it is a change in infusion volume and infusion rate, which would not make it feasible to properly blind. The goal of the study is to determine tolerability and safety of FEIBA in 50% reduced volume SWFI to FEIBA regular volume SWFI, and increase rate of the 50% reduced volume at 4U/kg/min and 10U/kg/min. By being able to reduce the volume and speed of the infusion, subjects will be able to spend less time infusing and reduce infusion burden during the regular use.

The exploratory objectives include pre (within 60 min before infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) concentration of coagulation factor II (FII); the effect of 50% reduced volume FEIBA and faster infusion rate on coagulation parameters.

FII (prothrombin) was chosen as a lead marker for FEIBA for several reasons:

1. In previously published studies it has been demonstrated that FII is a key protein component of the active ingredient of FEIBA

2. Amongst the vitamin K-dependent proteins, FII has the highest relative plasma concentration as it has the lowest specific activity, and therefore the absolute amount of FII in FEIBA measured as protein mass is higher than for any other vitamin K-dependent protein
3. The half life of FII is longer than that of any other vitamin K-dependent protein contained in FEIBA.

8.2 Overall Study Design

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 with hemophilia A or B with inhibitors (≥ 0.6 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 is illustrated in Figure 1 and Figure 2.

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In Part 1, 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 for details.

Treatments regimens during Part 1 of the study are:

- Part 1 Sequence A:
    1. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 1, 2, and 3)
    2. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 1, 2, and 3)
- Part 1 Sequence B, patients from sequence A cross over to:
    1. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 4, 5, and 6)
    2. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 4, 5, and 6)
- Infusion dose:

  All infusions: 85 ± 15 U/kg

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 rate.

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:

- First treatment phase: 4 U/kg/min (Infusions 7, 8, 9)
- Second treatment phase: 10 U/kg/min Infusions 10, 11, 12)
- Infusion dose:

  All infusions: 85 ± 15 U/kg

All infusions will be administered at the hemophilia care centers/study sites. Sample collections may be performed at the hemophilia care centers/study sites, appropriate ambulatory centers or at home. Each subject will receive a maximum of 12 IP infusions total [6 in Part 1 and 6 in Part 2]. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions see Section 8.7.2. After each infusion, subjects should be observed for 30 minutes at the study site. Additional details on study design and timing are described in Section 8.7.3. For additional details on managing bleeding episodes, see Section 8.7.4.

See Section 15.4 for additional details on the safety reviews performed by the Internal Safety Monitoring Committee (ISMC).

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8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is expected to be approximately 10 to 13 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 to 11 months.

The subject participation period is approximately 6 to 11 weeks from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measures

Tolerability and safety (local and general) related to the infusion and volume of reconstitution:

1. Occurrence of any adverse event: all AEs and SAEs, and AEs leading to discontinuation
2. Thromboembolic events and hypersensitivity reactions
3. Vital signs and Clinical laboratory data
4. Infusion site and infusion related reactions

8.4.2 Exploratory Outcomes Measure

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

8.5 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 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.

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8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. If 2 or more subjects develop anaphylaxis and / or thromboembolic events following exposure to FEIBA (enrollment and treatment temporarily stopped pending further review by the ISMC)
2. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk benefit
3. The sponsor or investigator considers continuation of the study unjustifiable for medical or ethical reasons
4. The ISMC recommends study termination

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

The active ingredient of FEIBA is a plasma-derived, freeze-dried, APCC with FVIII inhibitor bypassing activity. FEIBA will be provided in vials with a nominal potency of 500 U/vial, 1,000 U/vialand 2,500 U/vial). FEIBA contains mainly non-activated forms of the 3 coagulation factors, FII, FIX, and FX, as well as activated FVII; and Factor VIII coagulant antigen (FVIII:CAg) present in a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all. A solution containing 1 U FEIBA shortens the aPTT of FVIII inhibitor plasma to 50% of the buffer value. The product is supplied as freeze-dried powder or friable solid of white to off-white or pale green color.

To standardize conditions in the study, FEIBA should be stored at 2°C to 8°C only. FEIBA should not be allowed to freeze, and should be protected from light. Aseptic techniques must be used for reconstituting and administering FEIBA. Although the chemical and physical stability of the reconstituted product has been demonstrated for 3 hours at room temperature (up to 25°C), however, the solution should be used immediately as the preparation does not contain preservatives. Reconstituted product must not be returned to the refrigerator.

FEIBA will be provided in kits including SWFI for reconstitution. SWFI will be provided in different volumes for preparation of FEIBA infusions at regular volume or reduced volume. For additional information, such as reconstitution instructions, please refer to the FEIBA product insert [1] and/or other specific instructions provided by the sponsor or sponsor's representative.

8.7.2 Administration

Following reconstitution, FEIBA should be administered immediately using an intravenous needle and syringes provided by the sponsor for this study. The standard infusion rate of FEIBA is 2 U/kg body weight (BW) per minute, which in a 75kg subject, corresponds to an infusion rate of approximately 2.4 to 7.5 mL/minute depending on the potency (see label on vial).

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In order to standardize administration within the study, it is recommended that study drug be administered with an infusion pump. The infusion rate will be modified depending on which part of the study the subject is in, rates of 4 and 10 U/kg/min are also used in this study.

Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions every 48 hours (-8 hours/+24 hours). Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. FEIBA lots may be mixed within an infusion, and whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate.

For additional details, see Table 1 for general information on product preparation, as well as the study documents, and the FEIBA IB.[iv]

Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. Information regarding lot used, the actual dose given, date of treatment, treatment start and stop times, as well as any infusion interruptions will be recorded in the case report form (CRF).

Table 1
FEIBA Product Preparation

FEIBA	Diluent for Regular Volume FEIBA	Diluent for 50% Reduced Volume FEIBA
500 U	10 mL	5 mL
1000 U	20 mL	10 mL
2500 U	50 mL	25 mL

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity.

Please note that the availability of potencies may vary among countries and regions. Dose calculations should be made based on potencies available at site.

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8.7.3 Description of Treatment

Part 1 of the study uses a crossover design to evaluate the tolerability and safety of FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI (administered at the standard infusion rate of 2 U/kg/min). Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1. Part 2 will evaluate the tolerability and safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased infusion rates of 4 and 10 U/kg/min.

All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. The subject's medical history including hemophilia history, confirmation of inhibitors, bleeding episode history, concomitant medications and history of FEIBA or rFVIIa usage for the previous year will be collected at screening. Also recorded will be the date of last use of FEIBA or rFVIIa treatment. Results of the screening assessments will be used to establish a subject's eligibility for the study.

Part 1

After eligibility is established, the eligible subjects will be randomly assigned (1:1) into Part 1 of the study to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa every 48 hours (-8 hours/+24 hours).

Additional details on study visits for Part 1 can be found in Section 10.3 and Table 2.

Part 2

Part 2 is non-randomized and uses sequential enrollment of subjects who complete Part 1 of the study. Subjects in Part 2 will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/kg/min rate, followed by 3 infusions (Infusions 10, 11, and 12) of FEIBA at the 10 U/kg/min rate. Infusion 7 will be administered 48 hours (-8 hours/+24 hours) after Infusion 6. The infusions in Part 2 will be administered every 48 hours (-8 hours/+24 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Infusion rates for the treatment phases in Part 2 are:

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

Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Additional details on study visits for Part 2 can be found in Section 10.3 and Table 3.

Additional Treatment and Visit Information

The Schedule of Study Procedures and Events Procedures listed in Table 2 and Table 3 have the visit windows listed in relation to the subject's previous infusion. This is due to the variability in each subjects schedule based on previous therapy and bleeding events.

All infusions will be administered at hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions. For specifications on dosing and administration, see Section 8.7.2. For information on break-through bleeding control, see Section 8.7.4.

Study visits will be completed concurrently with study infusions. After subjects have completed the 12 study infusions, they will complete a Study Completion/ Termination Visit within 7 days but no sooner than 72 hours after Infusion 12.
In case of early withdrawal or discontinuation the Study Completion/Termination Visit will need to be completed within 7 days but no sooner than 72 hours after the last IP infusion received.

During each visit, the study staff will inquire with the subject about break-through bleeding events, treatments, and AEs throughout the study. Subjects are encouraged to report AEs to the site during the time spans between visits.

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Two subject questionnaires will be administered 5 times during the study, a TSQM questionnaire and a patient preference questionnaire to assess the subjects' satisfaction and preferences for treatments, for additional details see Section 10.5.

Detailed study flowcharts are presented in Table 2 and Table 3.

Investigational product may be interrupted or discontinued at any time during the study at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any infusion site reactions, regardless of causality, will be recorded on the AE CRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate CRF.

For details on the safety review by ISMC see Section 15.4.

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8.7.4 Management and Treatment of Break-Through Bleeding

Bleeding episodes are managed as described below for each part of the study. In all cases, if the bleeding episode, of whatever severity, is not resolved within 48 hours after an infusion to control bleeding, the subject must contact the hemophilia treatment center/study site for further treatment recommendations.

Screening

During screening, subjects will be asked to keep track of any FEIBA or rFVIIa usage, as the last dose may be used to determine the date of the first infusion of IP. If a subject experiences a bleeding episode during the screening period, subjects will be treated for the bleeding episode per standard of care as determined by the investigator and the patient will be randomized after resolution of bleeding episode.

Bleeding during the study

If bleeding occurs during the study, it will be treated per standard of care. For bleeding events treated with FEIBA or rFVIIa, a time window of 48 hours post treatment for bleeding should be observed before resuming study infusions. The subject will resume their treatment regimen and visits after control of the bleeding and following the administration window mentioned above. Depending on the clinical circumstances (e.g., treatment of uncontrolled bleeding due to injury and associated complications), the investigator and sponsor should decide if it is appropriate for the subject to continue in the study.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

Subject questionnaires may be entered directly onto the CRF.

For additional information on study documentation and CRFs, see Section 17.2.

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9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
   a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
   b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
9. Herbal supplements that contain anti-platelet activity
10. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
11. Family member or employee of the investigator
12. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The ISMC recommends a subject should be taken off the study
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome
- AE(s)/SAE(s) that the investigator or sponsor feels poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study

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10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: protocol identifier (e.g., 091501) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 091501-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4 Schedule of Study Procedures and Assessments (Part 1 and Part 2, respectively) and Supplement 0 Clinical Laboratory Assessments. FII concentration scheduling can be found in Section 20.6.

10.3.1 Screening and Baseline Assessments

After ICF is obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in Section 9.1 and Section 9.2, respectively. Screening procedures must be performed within 35 days of Infusion 1.

At screening, subjects will be instructed on the symptoms of thromboembolic and systemic hypersensitivity events by the investigator, and to contact the treatment center/hospital if they experience any symptoms.

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Medical history, including
    - Hemophilia history, inhibitor development history, bleeding episodes history, history of FEIBA or rFVIIa usage for a year prior to screening
    - Relevant medical and surgical history and all medications taken 4 weeks prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measurement body weight and height (see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (hematology, clinical chemistry, , serology testing and inhibitor level if no documentation is available ≥ 3 months prior to screening; see Section 12.7)
- Serum pregnancy test (female subjects of childbearing potential only)
- TSQM and patient preference questionnaires (see Section 10.5)

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After screening and eligibility sare determined, the subject will be enrolled in the study. For additional details on bleeding, see Section 8.7.4.

10.3.2 Treatment Visits

10.3.2.1 Infusion Visits

Randomization will occur after the subject has been confirmed to be eligible and prior to the first infusion.

- Randomization of eligible subjects to the following treatment sequences:
    - Part 1 Sequence A: FEIBA 2 U/kg/min in regular volume SWFI (3 infusions), FEIBA 2 U/kg/min in 50% reduced volume (3 infusions)
    - Part 1 Sequence B: FEIBA 2 U/kg/min in 50% reduced volume (3 infusions), FEIBA 2 U/kg/min in regular volume SWFI (3 infusions)

For additional details on the description of treatment, see Section 8.7.3.

During the study (Infusion Visits 1 to 12), subjects will return to the study site according to the schedule presented in Table 2 and Table 3. Prior to administration of IP, the following assessments will be performed at all visits unless otherwise indicated:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Vital signs (body temperature, pulse rate, blood pressure and respiratory rate)
    - Before administration of IP
    - at 30 minutes after administration of IP
- Clinical laboratory assessments Table 4
- IP administration (infusion site should be monitored for at 30 minutes [± 10 min] after infusion)
- Break-through bleed monitoring
- Subjects will be administered the TSQM and patient preference questionnaires:
    - After screening prior to Infusion 1
    - After Infusion 3 prior to Infusion 4
    - After Infusion 6 prior to Infusion 7
    - After Infusion 9, prior to infusion 10
    - After infusion 12 or up to the completion of the Study Completion/Termination Visit
- Prothrombin II levels will be drawn within 60 min before IP administration and at 30 min, hours 1, 2, 6, 8 and 12 after IP administration, as outlined in Table 5 See also information on administration (Section 8.7.2).

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10.3.3 Study Completion/Termination Visit

The Study Completion/Termination Visit including if the subject is discontinuing early will be performed within 7 days but no sooner than 72 hours after Infusion 12, or the last infusion if discontinued early. The following assessments will be performed:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Breakthrough bleeds monitoring
- Concomitant medication monitoring

- Clinical laboratory assessments see Table 4
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and body weight)

10.4 Medications and Non-Drug Therapies

Once subject eligibility has been confirmed for the study, the following medications and non-drug therapies are not permitted during the course of the study:

- Medications:
  - Any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) except anti-retroviral chemotherapy
  - Any investigational drug or device

A subject who receive any of these therapies will be withdrawn from further study participation.

Antifibrinolytics should not be used approximately 6 to 12 hours before or after the administration of FEIBA.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study (these are permitted; however, they should not be taken within 6 to 12 hours before or after administration of FEIBA)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
  - Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
  - Supplemental vitamins, minerals
  - Any standard of care to treat breakthrough bleeds

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- Non-drug therapies:
    - Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Questionnaires

Two questionnaires will be administered to subjects within this study (TSQM [14] and a patient preference questionnaire). These questionnaires will be used to assess the subject's preferences on the IP, as well as their satisfaction with the IP, and will be collected in the CRF or on paper. Both questionnaires will be administered:

- After screening prior to Infusion 1
- After Infusion 3 prior to Infusion 4
- After Infusion 6 prior to Infusion 7
- After Infusion 9, prior to infusion 10
- After infusion 12 or up to the completion of the Study Completion/Termination Visit

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These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when the subject ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion / Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems, and severe hypersensitivity reaction), ISMC recommends a subject should not continue. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the Study Completion/Termination Visit. If the Study Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Study Completion/Termination Visit. If a subject terminates participation in the study and does not return for the Study Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 0 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

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10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF PHARMACOKINETICS

Pharmacokinetics will not be evaluated in this study.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

Additional events which should be reported the same way as SAEs are as follows:

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19

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- Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE
- Any thromboembolic event
- Hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE. Any pregnancy occurring during the study should be reported to the sponsor within 24 hours of the site learning about the pregnancy. The pregnancy should be followed until completion of the pregnancy and up to 1 year postdelivery, if feasible. Pregnancies not considered an (S)AE as described above will be captured in the CRF.

Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures as described in Section 10.3.2 for reasons unrelated to AEs will not be considered as hospitalization for SAE reporting purposes unless the hospitalization is prolonged.

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12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study termination/completion will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, it is medically stabilized, or 30 days after the Study Completion/Termination Visit, whichever comes first, and the follow-up information is to be documented in the CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

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Deviations from the protocol-specified dosage including overdosing (20% higher than the highest permitted dose), underdosing (20% lower than the lowest permitted dose), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion/termination, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
    - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
    - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
    - The AE produces limited impairment of function and may require therapeutic intervention.
    - The AE produces no sequela/sequelae.
- Severe
    - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
    - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

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These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

- Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).

- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

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For events assessed as not related or unlikely related and occurring within 72 hours after IP administration the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 3) and Section 12.1.

Adverse Events/SAEs are to be recorded on the AE page of the CRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported by completing the relevant CRF page(s) in English. Once the SAE has been recorded, SAEs must be reported to the sponsor to meet the 24-hour timeline requirement (contacts and instructions to be provided in separate documentation).

The initial SAE information reported on the applicable CRF pages (must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting investigator (for paper SAE Report Forms)

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12.1.3 Medical Device Safety Reporting

The IP kit contains the BaxJect II Hi-Flow needleless transfer device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

- Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure.
- Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

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The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF . These events will be considered as SAEs but will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims
- Medication errors: an error (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication e.g., administration of incorrect dose

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

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12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

General medical history will be collected for 4 weeks prior to screening. Any information on the subjects' hemophilia history will be collected a year prior to screening including documented history of hemophilia, confirmation of inhibitors, bleeding episodes history, and history of FEIBA or rFVIIa usage.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening (as described in Table 2 and Table 3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Assessments will be performed at a central laboratory (see Section 15.7), according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for any additional testing as needed (see Section 12.7.6). Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

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12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of 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.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening and at study completion/termination.

In addition, serum samples for pregnancy tests for females of childbearing potential will be collected at screening.

12.7.2 Concentration of FII and Coagulation Testing

Blood samples for the determination of FEIBA components FII will be taken within 60 (±15) min before and at 30 (±10) min, after completion of each infusion. In addition hours 1 (±15min), 2 (±30min), 6 (±1hour), 8 (±2hours) and 12 (±4hours) samples will be taken after infusion 1,3,4,6,9 and 12 (see Section 20.6 for sampling time points and allowed sampling time windows). The date and time of each sample collections will be documented in the subject's CRF.

Blood will be obtained for the assessment of coagulation testing and consist of aPTT, PT, thrombotic markers (D-Dimers, prothrombin fragment F 1+2, TAT, fibrinopeptide A), and FII concentration. Coagulation testing will be performed, during the study and samples at hours 1 (±15min), 6 (±1hour) and 12 (±4 hours) will be taken after infusion 1,3,4,6,9 and 12 (see Section 20.6 for sampling time points and allowed sampling time windows).

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12.7.3 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, hepatitis A virus (HAV) antibody, hepatitis B virus (HBV) antibody, hepatitis B surface antigen (HBsAg), HCV antibody, parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening and at the Study Completion/Termination Visit.

12.7.4 CD4 Levels

At screening only, CD4 levels will be determined using flow cytometry in the case of a subject being HIV positive.

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a pre-existing disease, due to a lab error, or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE. Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) measured once at screening and weight (lb or kg) measured at screening and completion/termination will also be collected.

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Vital signs will be measured at screening and within 30 minutes before and after (except weight) administration of IP, at each Infusion study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0-100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of subject status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease. In this scale, a high number performance status represents high functionality, and a lower number represents low functionality and likely rapid progression of disease.[15] Subjects will be scored using this scale at screening.

12.10 Infusion Site Evaluations

The current site of IP infusion will be assessed for immediate local reactions at 30 minutes (±10 min) after infusion. In addition, infusion sites will be monitored by the subject for up to 12 hours after infusion, and will be discussed with the site staff during the next study visit.

Infusion sites will be monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations will be made by clinical staff or by the subject or caregiver. If an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Infusion sites will continue to be reviewed at each study visit, and any infusion site reactions will be followed until resolution. Each infusion site reaction will be categorized using the intensity grading described for AEs in Section 12.1.2.1.

12.11 Special Treatment Considerations

Subjects will be screened for eligibility in the study as described in Section 9.1 and Section 8.7.3, and will be informed of the study specific restrictions and requirements of the study. Subjects who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

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All biological agents carry the risk of hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic reaction

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Thromboembolic events have been observed with bypassing agents including FEIBA. Clinical manifestations of these events may include, but not limited to:

- myocardial infarction
- deep vein thrombosis
- pulmonary embolism
- stroke and
- transitory ischemic attack

Sometimes, these reactions can be life-threatening. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute hypersensitivity reaction after an infusion of IP, the subject should be managed appropriately and given instruction to receive relevant supportive care.

Subjects who experience a potentially severe hypersensitivity reaction will be discontinued from IP. They will complete a Termination/Study Completion Visit, and will be monitored for stabilization or resolution of the AE. Premedication to prevent allergic reactions will not be permitted, as severe hypersensitivity reactions are an outcome measure for this study.

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13. STATISTICS

Data handling will be conducted by the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

Statistical analysis for this study will be descriptive in nature. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

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.

13.2 Datasets and Analysis Cohorts

Safety: The safety analysis set will include all subjects who received at least 1 dose of IP (FEIBA). All safety analyses will be performed on the safety analysis set. Subjects will be evaluated according to the treatment received.

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13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

13.4.1.1 Analysis of the Primary Outcome Measure (Parts 1 and 2)

AEs, SAEs and AEs leading to discontinuation, thromboembolic events and hypersensitivity reactions that occurred during or after IP infusions will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or potentially related adverse events as assessed by the investigators. Temporally associated AEs 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.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s).

AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related to the infusion and those considered unrelated. These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Shift tables and summary statistics will be presented for the results of clinical laboratory data. All abnormal lab results will be listed.

Summary statistics of vital signs, infusion site and infusion related reactions will be carried out.

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13.4.2 Exploratory Outcome Measures

All exploratory outcome measures will be analyzed descriptively.

Full details of the statistical analysis will be specified in the SAP.

13.5 Planned Interim Analysis of the Study

There is no planned interim analysis other than a safety data review by the ISMC.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

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15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

Primary objective of the study is to monitor safety parameters throughout the study with a special emphasis on hypersensitivity and thromboembolic events. Adverse event data will be collected at each visit assessed and documented on the CRFs as outlined in section 12.1.2.3.

Serious adverse events are monitored and reported per the safety reporting guidelines as outlined in section 12.1.2.3.

This study will be monitored by an ISMC. The ISMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from the ongoing clinical study. For this study, the ISMC will be composed by appropriate members of clinical, safety, and biostatistics division that are not involved in the active execution of the trial. The ISMC can stop a study if it finds toxicities or if treatment is proven to be not beneficial.

All SAEs will be reviewed within 24 hours by the Chair of the ISMC. There are 3 planned ISMC meetings:

1. Within 24 hours after 6 subjects in Part 1 (3 subjects in each group) have completed Infusion 5
2. Within 24 hours after 6 subjects have completed Infusion 7 (Part 2)
3. Within 24 hours after 6 subjects have completed Infusion 10 (Part 2)

ISMC preplanned meetings will be held concurrently with the ongoing study.

Subjects can continue with their scheduled therapy and assessments unless the ISMC warrants that the trial needs to be suspended due to safety concerns. Additional ad hoc meetings of the ISMC may be convened as appropriate per ongoing safety evaluations.

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15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided to patients will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

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If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements.

Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

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17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper/electronic format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper/electronic format, and this documentation will be considered source documentation. Changes to an CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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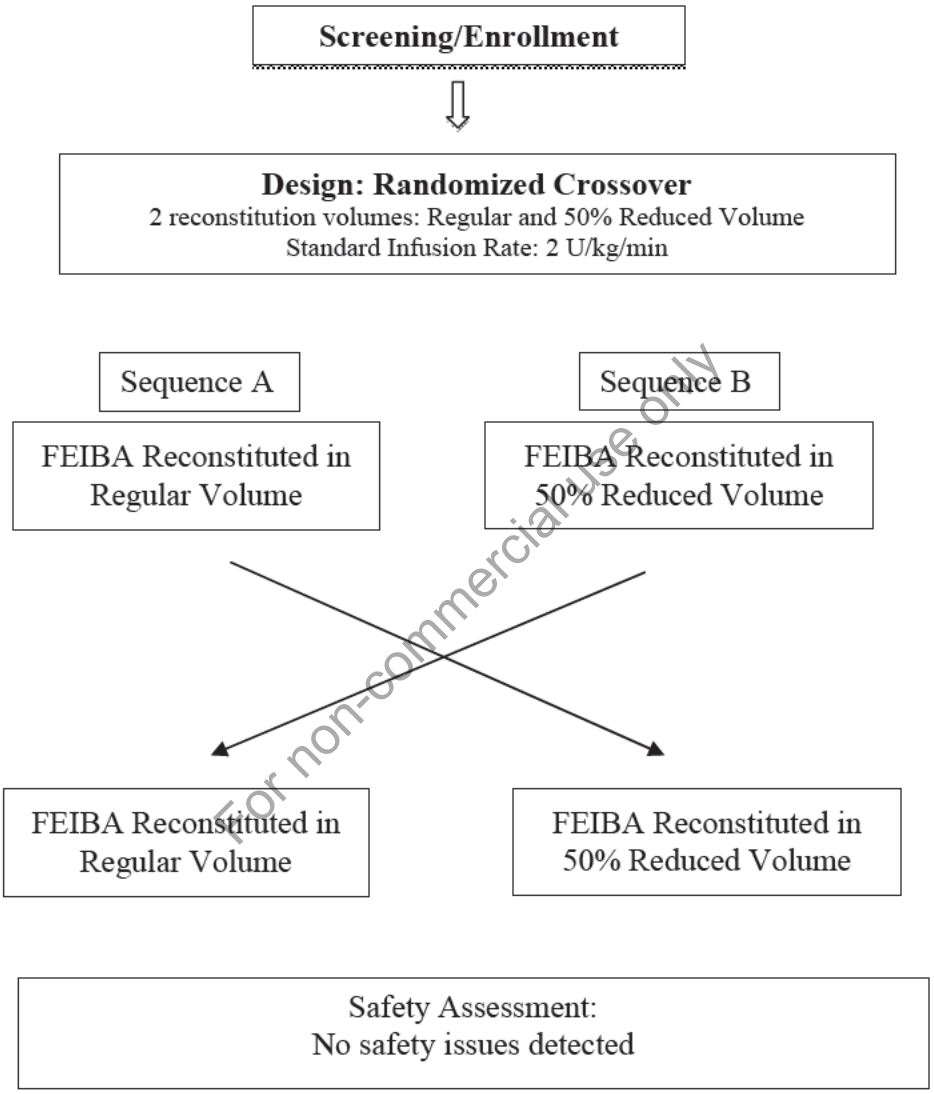
20. SUPPLEMENTS

20.1 Study Flow Chart Part 1

Figure 1
Study Design for Part 1 Baxalta Clinical Study 091501



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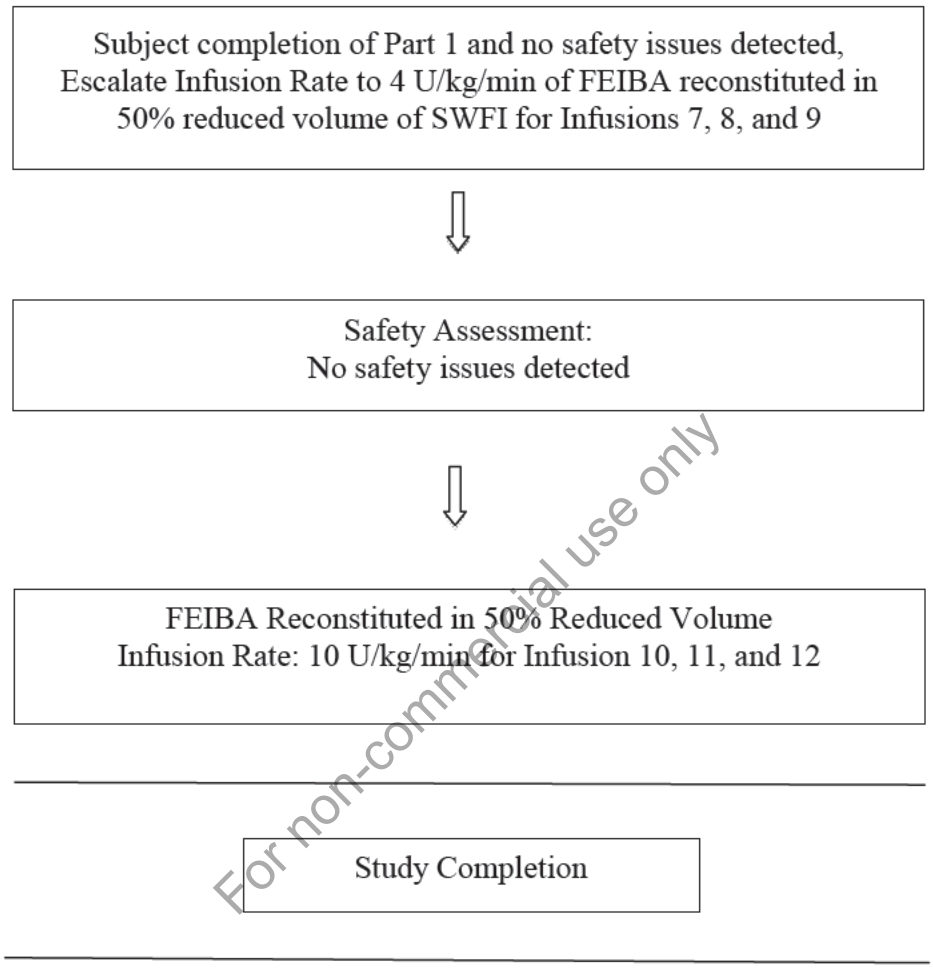
20.2 Study Flow Chart Part 2

Figure 2
Study Design for Part 2 Baxalta Clinical Study 091501



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20.3 Schedule of Study Procedures and Assessments (Part 1)

Table 2
Schedule of Study Procedures and Assessments (Part 1)

Procedures/ Assessments	Screening Assessments		Study Visits[a]						
			Infusion #1	Infusion #2	Infusion #3		Infusion #4	Infusion #5	Infusion #6
Study Visit Windows[b]	A maximum of -35 days to 0		Day 1	within 48 hrs (-8/+24) from Infusion 1	48 hrs (-8/+24) from Infusion 2		48 hrs (-8/+24) from Infusion 3	48 hrs (-8/+24) from Infusion 4	48 hrs (-8/+24) from Infusion 5
Informed Consent[c]	X								
Eligibility Criteria	X								
Medical History	X								
Medication and Non-drug Therapies	X		X	X	X		X	X	X
Physical Examination	X								
Pregnancy Test	X								
Vital Signs[d]	X		X	X	X		X	X	X
Karnofsky Performance Test	X								
Laboratory Assessments[e]	X		X	X	X		X	X	X
Inhibitor level if no documentation	X								
Factor II levels[f]			X		X		X		X
Adverse Events, breakthrough bleeds, and infusion site reactions[g]	X		X	X	X		X	X	X
IP Treatment			X	X	X		X	X	X
TSQM and patient preference questionnaires[h]		X				X			
Coagulation testing[i]			X		X		X		X

Randomization

Abbreviations: ICF=informed consent form; IP=investigational product

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[a] A Study Completion/Termination Visit is to be completed in Part 1 only for subjects who withdraw or discontinue prior to the end of the study. If a subject withdraws or discontinues, this visit should be completed within 7 days but no sooner than 72 hours from the last infusion that the subject received. Otherwise, the Study Completion/Termination Visit will occur at the end of Part 2 (see Table 3).

[b] Study Visit Windows:
Infusion 1 can be scheduled after screening assessments have been completed; all other infusions will occur within 48 hours (-8/+24hours) from the previous infusion.

[c] Occurs at enrollment (prior to any study-specific procedure).

[d] Vital signs will include body temperature, pulse rate, blood pressure, and respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[e] For laboratory assessments, see Section 0.

[f] FII levels within 60 minutes (±15min) before and 30 mins (±10min) and all timepoint within 60 min (±15 min) before and at 30 min (±10 min), hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour), and 12 (±4hours) after infusions 1, 3, 4 and 6.

[g] The infusion site will be monitored for AEs for 30 ±10 minutes after each study infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[h] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.. See Section 10.5 for details.

[i] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) post-infusion at 1 hr ± 15 min (mentioned in Section 12.7.2).

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20.4 Schedule of Study Procedures and Assessments (Part 2)

Table 3
Schedule of Study Procedures and Assessments (Part 2)

Procedures/ Assessments	Study Visits									
		Infusions 7	**Infusion 8**	**Infusion 9**		**Infusion 10**	**Infusion 11**	**Infusions 12**		**Study Completion/ Termination Visit[a]**
Rate of Infusion		**Rate: 4 U/kg/min**				**Rate: 10 U/kg/min**				
Study Visit Windows[b]		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		72 h to 7 days from Infusion 12 (or last infusion)
Medications and Non-drug Therapies		X	X	X		X	X	X		X
Vital Signs[c]		X	X	X		X	X	X		X
Laboratory Assessments[d]		X	X	X		X	X	X		X
Factor II levels[e]				X				X		
Adverse Events, breakthrough bleeds, and infusion site, infusion related reactions[f]		X	X	X		X	X	X		X
IP Treatment		X	X	X		X	X	X		
TSQM and patient preference questionnaires[g]	X				X				X	
Coagulation testing[h]				X				X		

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[a] The Study Completion/Termination Visit includes cases of withdrawal or discontinuation. This visit should be done within 7 days but no sooner than 72 hours after Infusion 12). If a subject withdraws or discontinues, this visit should be done within 7 days but no sooner than 72 hours after the last infusion that the subject receives.

[b] Infusions will occur within 48 hours (+-8/+24hours) from the previous infusion.

[c] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[d] For laboratory assessments, see Section 0.

[e] FII levels within 60 minutes (±15min) before and 30 mins (±10min) and all timepoint within 60 min (±15 min) before and at 30 min (±10 min), hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour), and 12 (±4hours) after infusions 9 and 12.

[f] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[g] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit. See Section 10.5 for details.

[h] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) (mentioned in Section 12.7.2).

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20.5 Clinical Laboratory Assessments

Table 4
Clinical Laboratory Assessments

Assessments	Screening Visit	Infusions 1, 3, 4, 6, 9, 12	Study Completion/ TerminationVisit[a]
Hematology[b]	X		X
Clinical Chemistry[c]	X		X
Coagulation Testing[d]		X	
Serological Testing[e] and CD4[f]	X		X
Pregnancy Test[g]	X		

[a] Includes cases of withdraw or discontinuation.
[b] Hematology assessments include: CBC (Hct, Hgb, RBC count, WBC count) with differential, MCV, MCHC, and platelet count.
[c] Clinical chemistry assessments include sodium, chloride, potassium, bicarbonate, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, GGT, 5'-nucleotidase.
[d] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A (mentioned in Section 12.7.2).
[e] Serological testing will include: HIV-1 and HIV-2 antibodies (HIV+, check CD4 count–screening visit only), HAV antibodies, HBV antibody, HBsAg, HCV antibody, parvovirus B19 (IgM and IgG), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).
[f] CD4 at screening in case of positive HIV test results.
[g] A serum pregnancy test will be performed for females of childbearing potential.

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20.6 Concentrations of FII and Coagulation testing

Table 5
FII and Coagulation Testing Time Frame

Procedures/Assessments	**PART 1** **Infusions 1, 3, 4, 6**	**PART 2** **Infusions 9, 12**	**Infusions** **2, 5, 7, 8, 10, 11**
FII concentration	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min
Coagulation testing: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A)	Infusions 1, 3, 4, 6, 9, and 12 Post infusion: 1 hr ± 15 min 6 hr ± 1 hr 12 hr ± 4 hr		

Abbreviations: EOI=end-of-infusion; Factor II, h=hours; min=minutes;

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22. SUMMARY OF CHANGES

Protocol 091501 AMENDMENT 2 (Global): 2017 AUG 04

Replaces: Protocol 091501 Amendment 1 (Global): 2016 MAR 03

In this section, changes made in this amendment from the previous version of the protocol, dated **2016 MAR 03**, are described and their rationale is given.

1. Throughout the document
   Description of Change**:** Minor grammatical and/or administrative changes were made.
   Purpose of Change**:** To improve clarity in the protocol.

2. Study title and throughout the document
   Description of Change: The phase of the study was changed from 3b to 3b/4.
   Purpose of Change: To reflect the study phase per registration status in differnet countries.

3. Study title and throughout the document
   Description of Change: The words “two-part” and “the safety” were removed from the title and PK was changed to Tolerability.
   Purpose of Change: To align with the sduty design and provide clarity.

4. Serious Adverse Event Reporting, Section 2
   Description of Change: SAE reporting via eCRF removed.
   Purpose of Change: To clarify that only SAER Forms will be used.

5. Name of IP, Section 2 (Synopsis)
   Description of Change: The sentence, Referred to as FEIBA throughout the protocol, was added.
   Purpose of Change: To provide clarity to reader.

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6. CLINICAL CONDITION(S)/INDICATION(S), Section 3 (Synopsis)
Description of Change: The following was added to this section and the reference was updated to 12:
   1. FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:
   2. Control and prevention of bleeding episodes
   3. Perioperative management
   4. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
   5. FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.

   Purpose of Change: Provide full range of indications as mentioned in the USPI and update the reference to USPI at the end of this document.

7. Short title, Section 3 (Synopsis)
Description of Change: Added FEIBA STAR.
Purpose of Change: Further shortened the title for ease of reading.

8. STUDY PHASE, Section 3 (Synopsis)
Description of Change: Added the sentence, "Phase 3b/4, depending on market authorization status per country".
Purpose of Change: To provide clear understanding of phase of the study depending on product registration status per country.

9. PLANNED STUDY PERIOD, Section 3 (Synopsis)
Description of Change: Updated timelines for initiation, primary completion, study completion and duration.
Purpose of Change: Provide updated timelines for study.

10. STUDY OBJECTIVES AND PURPOSE, Section 3 (Synopsis) and throughout the document
Description of Change: Updated study purpose, primary objectives and exploratory objectives to include Tolerability and Safety and remove PK and secondary objectives.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

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11. STUDY DESIGN, Section 3 (Synopsis) and throughout the document
Description of Change: Study design changed to Tolerability and Safety from PK Comparability, Pharmacokinetic and Safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

12. Planned Duration of Subject Participation, Section 3 (Synopsis) and throughout the document
Description of Change: Each subject will spend approximately 6 to 11 weeks in the study.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

13. Outcome Measure (s), Section 3 (Synopsis) and throughout the document
Description of Change: Changed Primary and Exploratory Outcome Measure(s). Removed secondary outcome measure (s).
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

14. INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION, Active Product, Section 3 (Synopsis)
and throughout the document
Description of Change: Dosage frequency updated to IP will be infused every 48 hours (-8 hours/+24 hours).
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

15. SUBJECT SELECTION, Targeted Accrual, Section 3 (Synopsis)
Description of Change: Changed to enroll 24 evaluable subjects for the assessments.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

16. Primary Objective, Section 3 (Synopsis)
Description of Change: Anaphylaxis was removed as an example from primary objective 2.
Purpose of Change: Provide the reader with clarity.

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17. Exclusion Criteria, Section 3 (Synopsis) and throughout the document
Description of Change: From clinically symptomatic liver disease changed to Advanced liver disease and prothrombin time [PT] 5 seconds above upper limit of normal was included.
Purpose of Change: The change was made to exclude patients with PT 5 seconds and above ULN with advanced liver disease.

18. Exclusion Criteria and throughout the document
Description of Change: Herbal supplements containing anti-platelet activity has been added as an exclusion criteria.
Purpose of Change: The change was made to align the text to the updated operational design.

19. STATISTICAL ANALYSIS, Sample size calculation, Section 3 (Synopsis)
Description of Change: Updated sample size calculation and Planned Statistical Analysis.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

20. Section 6.2
Description of Change: References 9 and 10 added. Recent studies have demonstrated that FEIBA is a multicomponent therapeutic agents with activities potentially targeting different sites in the coagulation system and From a number of confirmed studies it became clear that the FII–FXa complex is one of the key components in this system of different proteins, was added.
Purpose of Change: To provide clarity on FEIBA MOA and importance of FII-FXa complex.

21. Section 6,
Description of Change: Some text was adapted to improve consistency of text with current Investigators' Brochure content.
Purpose of Change: To ensure consistency between this protocol and the current Investigator's Brochure.

22. Description of Treatment, Section 8.7.3
Description of Change: Updated Part 1 and 2 as per design change from PK to tolerability and safety evaluation.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

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23. Management and Treatment of Break-Through Bleeding, Section 8.7.4
Description of Change: Updated bleeding episode to be resolved in 48 hours and washout period removed during screening.
Purpose of Change: To provide early treatment recommendation to patients and not to withdraw therapy from patients during screening washout.

24. Source Data, Section 8.8
Description of Change: Subject questionnaires may be entered directly onto the CRF.
Purpose of Change: To provide clarification.clarify .

25. Screening and Baseline Assessments, Section 9.3.1
Description of Change: Updated as per change in design to tolerability and safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

26. Infusion Visits, Section 10.3.2.1 and through out the document
Description of Change: Changed to randomization will occur after the subject has been confirmed to be eligible and prior to the first infusion. Added breakthrough bleeding monitoring. Added Prothrombin II levels to be drawn at various times related to IP administration.
Purpose of Change: Electronic randomization systems will not be used. Breakthough bleeding and Prothrombin II levels will be a measure of tolerability and safety.

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27. Source Data, Section 12.7.2 and through out the document
Description of Change: Updated as per change in design to tolerability and safety. Timelines for blood samples to determination of FEIBA component FII and Coagulation testing have been defined.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

28. Biobanking, Section 12.7.6
Description of Change: Updated to exclude need for samples to be used for re-testing, further evaluation of an AE, or follow-up of other results.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

29. Infusion Site Evaluations, Section 12.10
Description of Change: Updated infusion sites monitoring by subjects from 72 to 48 hours.
Purpose of Change: Infusions will be given every 48 hours.

30. Statistics, Section 13.
Description of Change: The entire statistics section was revised in line with the change in study design from PK to tolerability and safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

31. Study Flow Chart Part 1 and 2, Section 20.1 and 20.2.
Description of Change: Updated in line with the change in study design from PK to tolerability and safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

32. Schedule of Study Procedures and Assessments (Part 1) and (Part 2), Section 20.3 and 20.4 .
Description of Change: Updated in line with the change in study design from PK to tolerability and safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

33. Table 4: Clinical Laboratory Assessments, Section 20.5
Description of Change: Updated in line with the change in study design from PK to tolerability and safety.
Purpose of Change: To align with change in design of study from PK to Tolerability and Safety.

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INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 2 (Global): 2017 AUG 04

Replaces
Amendment 1 (Global): 2016 MAR 03

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OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 2 (Global): 2017 AUG 04

Replaces
Amendment 1 (Global): 2016 MAR 03

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted], MD, [redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH / Baxalta US Inc.

CLINICAL STUDY PROTOCOL

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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 SHORT TITLE: FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 3 (Global): 2017 SEP 14

Replaces:

AMENDMENT 2 (Global): 2017 AUG 04

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ALL VERSIONS:
AMENDMENT 3 (Global): 2017 SEP 14
Amendment 2 (Global): 2017 AUG 04
Amendment 1 (Global): 2016 MAR 03
Original: 2015 OCT 08

OTHER ID(s)
NCT Number: 02764489
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

Study Sponsor(s):

Baxalta US Inc.
One Baxter Way
Westlake Village, CA 91362,
UNITED STATES

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna,
AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

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2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report From

Refer to SAE Protocol Sections and the study team roster for further information.

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For definitions and information on the assessment of these events, refer to the following:

- Adverse Event, Section 12.1
- Serious Adverse Event, Section 12.1.1.1
- Assessment of Adverse Events, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	**Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]), FEIBA NF. Referred to as FEIBA throughout the protocol.**
Name(s) of Active Ingredient(s)	Coagulation factors II, X, IX, and VIIa
CLINICAL CONDITION(S)/INDICATION(S) FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with • inhibitors for: ➢ Control and prevention of bleeding episodes ➢ Perioperative management ➢ Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. • FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.[1]	
PROTOCOL ID	091501
PROTOCOL 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**
Short Title	FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)
STUDY PHASE	Phase 3b/4, depending on market authorization status per country
PLANNED STUDY PERIOD	
Initiation	First Subject In: Q 1 2018
Primary Completion	Last Subject In: Q 4 2018
Study Completion	Last Subject Last Visit: Q 4 2018
Duration	6 to 11 weeks

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STUDY OBJECTIVES AND PURPOSE
Study Purpose To evaluate the tolerability and safety of infusing reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume
Primary Objectives To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions
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) concentration of coagulation factor II with 50% reduced volume of FEIBA and faster infusion rates 2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

STUDY DESIGN	
Study Type/ Classification/ Discipline	Tolerability and Safety
Control Type	Active
Study Indication Type	Treatment
Intervention model	Part 1: Crossover Part 2: Sequential
Blinding/Masking	Part 1: Randomized, Open-label Part 2: Non-Randomized, Open-label

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Study Design	A 2-part, Phase 3b/4, prospective, open-label, multicenter study to be conducted in 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 Bethesda units [BU] for the primary tolerability and safety assessments. **Part 1:** In Part 1, subjects will be administered two different volumes of FEIBA in a randomized, crossover design every 48 hours (-8, +24 hours) intervals. Part 1 will monitor the tolerability, safety, pre (within 60 min before the infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) concentration of coagulation factor II (FII) reconstituted in 50% reduced volume of SWFI and administered at the standard infusion rate of 2 U/kg/min compared with FEIBA reconstituted in regular volume of SWFI at the standard infusion rate. All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. Eligible subjects will be randomly assigned (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI or regular volume SWFI (Period 1). Patients finishing 3 infusions in Period 1 (Sequence A or B), will either switch from FEIBA reconstituted in reduced volume to 3 infusions of FEIBA in regular volume SWFI or vice versa (Sequence A or B) depending on randomization. All patients completing Part 1 will move to Part 2. Evaluable patients from Part 1 are all subjects who receive 4 of the 6 planned infusions, at least 2 infusions in each sequence. Tolerability and safety data will be collected before, during and after each infusion and between infusions; Clinically apparent changes in vital signs, laboratory parameters, infusion site reactions and infusion rate-related reactions will be monitored.

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	FII concentration will be monitored by analyzing concentrations before (within 60 min before the infusion) and at 30 min after each infusion and at hours 1, 2, 6, 8 and 12 after infusion 1,3,4 and 6 as outlined in Section 20.6. **Part 2:** Part 2 is non-randomized with sequential treatment of all evaluable subjects who complete Part 1, will receive at least 4 of the 6 infusions. Subjects will receive FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/kg/min in a non-randomized fashion, at 48 hours (-8, +24 hours) intervals, to evaluate the tolerability and safety of infusing 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 and infusions 10, 11 and 12 will be administered at 10 U/kg/min. Following the last infusion (infusion 12), a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion. Tolerability and safety data will be collected before, during and after each infusion and between the infusions; Clinically apparent changes in vital signs, infusion rate-related events, and infusion site reactions will be monitored. Concentration of coagulation factor II will be assessed before (within 60 minutes before the infusion) and at 30 min after each infusion, and at hours 1, 2, 6, 8 and 12 after infusions 9, and 12 as outlined in Section 20.6. The infusions in both parts will be administered every 48 hours (-8 hours /+24 hours) to allow time to monitor tolerability and safety of the higher infusion rate.

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	All IP infusions will be administered at the hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions (6 in each part). There is no washout period before Part 1, between infusions or parts of the study. Subjects will receive FEIBA at a dose of 85 U/kg ± 15 U/kg for all infusions. For infusions, whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate. Please refer to study documents for detailed instructions. Safety monitoring for this study will be conducted concurrently by an Internal Safety Monitoring Committee (ISMC). All SAEs that occur will be reviewed by the Chair of the ISMC with the Medical Director within 24 hours. Planned ISMC meetings will be held concurrently with the ongoing study.
Planned Duration of Subject Participation	It is planned that each subject will spend approximately 6 to 11 weeks in the study.

Outcome Measure (s)

Primary

Assess tolerability and safety (local and general) related to the infusion and volume of reconstitution:

1. Occurrence of any adverse event: all AEs and SAEs, and AEs leading to discontinuation
2. Thromboembolic events and hypersensitivity reactions
3. Vital signs and Clinical laboratory data
4. Infusion site and infusion related reactions

Exploratory Outcome Measure(s)

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

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INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** kit; powder, lyophilized, for solution/suspension; injection **Dosage frequency:** IP will be infused every 48 hours (-8 hours/+24 hours). **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Enroll 24 evaluable subjects for the assessments
Number of Groups/Arms/Cohorts	1 cohort: at least 24 evaluable adult subjects (≥ 18 to ≤ 65 years old) for tolerability and safety evaluation

Inclusion Criteria

Subject is/has:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom

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8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
   a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
   b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

Exclusion Criteria

Subject is/has:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
9. Herbal supplements that contain anti-platelet activity
10. Participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
11. A family member or employee of the investigator
12. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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STATISTICAL ANALYSIS

Sample Size Calculation

The projected sample size of 24 evaluable subjects for this tolerability and safety study was determined by considering available patients, and is not based on statistical power calculations.

Planned Statistical Analysis

Statistical analysis for this study will be descriptive in nature.

Primary Analysis

AEs, SAEs and AEs leading to discontinuation, thromboembolic events and hypersensitivity reactions that occur during or after the IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be provided for temporally associated adverse events; and for potentially related adverse events as assessed by the investigators.

Shift tables and summary statistics will be presented for the results of clinical laboratory data. All abnormal lab results will be listed.

Summary statistics of vital signs, infusion site and infusion related reactions will be carried out.

Exploratory Analysis

All exploratory outcome measures will be analyzed descriptively.

Full details of the statistical analysis will be specified in the statistical analysis plan (SAP).

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4. TABLE OF CONTENTS

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Tables

Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BU	Bethesda units
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
EC	ethics committee
EOI	end-of-infusion
CRF	case report form
EDC	electronic data capture
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FEIBA VH	Factor Eight Inhibitor Bypassing Activity Vapor Heated
FII	Factor II
FIX	Factor IX
FVII	Factor VII
FVIII	Factor VIII
FVIII:CAg	Factor VIII C antigen
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSL	Global Safety Lead
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen

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Abbreviation	Definition
HBV	hepatitis B
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	Immumoglobulin G
IgM	immunoglobulin M
IP	investigational product
ISMC	Internal Safety Monitoring Committee
Min	minutes
NMC	non-medical complaint
PCR	polymerase chain reaction
PT	prothrombin time
rFVIIa	recombinant activated clotting factor VII
Rsq	r^2
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SI	serious injuries
SWFI	sterile water for injection
TAT	thrombin/anti-thrombin complex
TSQM	Treatment Satisfaction Questionnaire for Medication

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6. BACKGROUND INFORMATION

6.1 Description of Investigational Product and Clinical Condition/Indication

The investigational product (IP), FEIBA[i] is a plasma derived, activated prothrombin complex concentrate (APCC), generically identified as an anti-inhibitor coagulant complex (AICC). FEIBA was developed to treat bleeding episodes and cover surgical interventions in hemophilia A and B patients with inhibitors and in non-hemophilia patients with acquired inhibitors[ii] and is also intended for use as a prophylactic treatment for hemophilia A and B patients with high responding inhibitors and frequent joint bleeding.[iii,2,3,4]

Baxalta's first licensed FEIBA product, AICC FEIBA, was marketed beginning in 1975 and was superseded in 1985 by a 2-stage vapor heat-treated product, AICC FEIBA VH. Nanofiltration was introduced to the manufacturing process in 2006 to produce FEIBA NF, now called FEIBA.

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6.2 Clinical Condition/Indication

Hemophilia is an X-linked, recessive, congenital bleeding disorder caused by deficient or defective coagulation due to a deficiency in FVIII (hemophilia A), or FIX (hemophilia B). The absence of FVIII or FIX leads to spontaneous bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury.[5,6] Replacement therapy for the treatment of hemophilia A, and less frequently hemophilia B, can be complicated by an immune response resulting in the production of inhibitory alloantibodies to Factor VIII (FVIII) or Factor IX (FIX), especially in patients with moderate to severe hemophilia. The development of such inhibitory antibodies currently represents the most serious complication of hemophilia treatment. The presence of inhibitors against FVIII generally precludes the efficacious use of human FVIII replacement therapy. A substantial portion of patients with FVIII inhibitors have high-responding, high-titer inhibitors (> 5 Bethesda units [BU]). These patients exhibit an anamnestic response after FVIII exposure, sometimes with a dramatic increase in inhibitory antibody titer.[7,8] The inability to provide FVIII replacement therapy predisposes this group of patients to increased morbidity and mortality compared with hemophilia patients without inhibitors.[7]

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[i] FEIBA NF is a trademark of Baxalta Inc. US and Baxalta Innovations GmbH.

[ii] Anti-Inhibitor Coagulant Complex, FEIBA Vapor Heated. Package Insert, Baxalta US Inc., Westlake Village, CA.

[iii] Protocol 090701. FEIBA NF: A Prospective, Open-label, Randomized, Parallel Study to Evaluate Efficacy and Safety of Prophylactic versus On-demand Treatment in Patients with Hemophilia A and B and High Titer Inhibitor. 2013 Jan 14, Baxalta US Inc.,(Westlake Village, CA).

Several therapeutic approaches are currently available in the management of hemorrhagic events in patients who have developed FVIII inhibitors. These include neutralization with high doses of human FVIII (low titer inhibitor only), and treatment with bypassing agents such as Activated Prothrombin Complex Concentrate (APCC), or activated recombinant factor VII (rFVIIa). Among these treatment options, only APCCs and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII or FIX. It has been proposed that FEIBA products achieve this goal principally by virtue of the presence of a "partial prothrombinase complex" consisting of activated Factor X (FX) and prothrombin.[9]

The active ingredient of FEIBA is a plasma-derived, freeze-dried APCC with FVIII inhibitor bypassing activity. Recent studies have demonstrated that FEIBA is a multicomponent therapeutic agents with activities potentially targeting different sites in the coagulation system.[10] FEIBA contains mainly non-activated forms of the vitamin K - dependent proteins Factor II (FII), FVII, FIX and FX, as well as small amounts of activated prothrombin complex proteins; and Factor VIII coagulant antigen present in a concentration of up to 0.1 U/1 U FEIBA. From a number of confirmed studies it became clear that the FII–FXa complex is one of the key components in this system of different proteins.[11] A solution containing 1 U FEIBA shortens the activated partial thromboplastin time (aPTT) of FVIII inhibitor plasma up to 50% of the buffer value. Additional details can be found in the FEIBA IB.[iv]

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6.3 Population to Be Studied

Adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B (congenital or acquired) of any severity, of all races and ethnic groups will be studied. All subjects will have a documented history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa); subjects with no documented history will require testing of the inhibitor level before entering the study. Subjects will either be hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease. Subjects will either be human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3. See additional details in the Inclusion and Exclusion Criteria in Section 9.1 and Section 9.2, respectively.

[iv] Investigator's brochure. Anti-inhibitor coagulant complex nanofiltered; FEIBA NF. 2016 FEB 24. Baxalta US Inc., (Westlake Village, CA).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

The nonclinical studies included a virus clearance study, which was performed to investigate the virus reduction capacity of the nanofiltration step in the manufacturing of FEIBA NF.

Data from nonclinical studies can be found in the FEIBA NF IB.[iv]

6.4.2 Findings from Clinical Studies

The results of Baxalta clinical study 090701[iii] demonstrated that prophylaxis with FEIBA significantly reduced the annualized bleeding rates for all bleed types and for spontaneous, traumatic, joint, and non-joint, bleeding episodes when compared with on-demand treatment. A statistically significant reduction in the rate of bleeding episodes in new target joints in the prophylaxis arm versus the on-demand arm was also observed. An examination of adverse events (AEs), abnormal laboratory parameters for hematology and clinical chemistry and vital signs demonstrated that FEIBA was safe and well tolerated for prophylactic use. Clinically, these data suggest that FEIBA is safe and efficacious in the management of hemophilia A or B with persistent high-titer inhibitors or low-titer inhibitors refractory to FVIII or FIX treatment, and further confirmed the safety and effectiveness of FEIBA for controlling and preventing bleeding episodes.

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Baxalta clinical study 091002 was an open-label, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. This study was designed to document routine usage of FEIBA NF as a bypassing agent for on-demand or prophylactic treatment in everyday clinical practice and in surgical intervention. The safety results of this postauthorization safety study showed that treatment with FEIBA NF, administered in 81 subjects with hemophilia, requiring treatment with inhibitor-bypass therapy for bleed resolution or bleed prophylaxis, was generally safe and well tolerated. The mean infusion rate of FEIBA under routine clinical practice during the study (3.7 U/kg per min, range 0.9 to 23.5) was higher than that recommended in the Summary of Product Characteristics of FEIBA (2.0 U/kg per min). A manual analysis of safety listings did not disclose any AEs associated with a higher infusion rate.[12] Treatment-related AEs or serious adverse events (SAEs) were reported in 9.9% and in 3.7% of subjects, respectively. A deep venous thrombosis and a superficial thrombophlebitis were observed in 1 subject with acquired hemophilia.

The hemostatic effectiveness was rated by the physicians as excellent or good in more than 90% of total subjects, with the highest rates reported in subjects with FEIBA NF prescribed as regular prophylaxis. Additional details on this study can be found in the clinical study report.[v]

FEIBA consists of zymogens and traces of activated forms of procoagulant factors II, VII, IX, X, anticoagulants protein C and TFPI, and small amounts of cofactors FV, FVIII and protein S, in a balanced ratio. As mentioned before, FII-FXa complex plays a key role in FEIBA's mode of action (MoA). A recently published study has shown that although the FII-FXa complex are the key components other procoagulant components of FEIBA were necessary to achieve an optimal activity. However prothrombin (FII) is the lead procoagulant component of FEIBA.[1,11]

Due to the complex nature of the composition of FEIBA, pharmacokinetic information cannot be determined by measurement of a single component. In recent studies where FEIBA was used as a comparator product surrogate markers of coagulation were used to determine pharmacokinetics. These surrogate markers of coagulation included determination of thrombin generation, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin–antithrombin complex (TAT) and prothrombin fragment F_{1+2} (F1+2), and aPTT clot waveform analysis, maximum levels of these surrogate markers following FEIBA administration were seen after 10 or at 30 min with variable results at later time points.[10] In another study where thrombin generation was measured in patients following infusion of FEIBA peak thrombin levels were seen predominantly 30 and 60 minutes after infusion.[13] Thus, determination of peak plasma concentrations of components of FEIBA seems to be most appropriate performed at 30 or 60 minutes after infusion.

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Additional observational, non-interventional studies were conducted with FEIBA NF. Additional details on clinical studies can be found in the FEIBA NF IB.[iv]

[v] Clinical Study Report. Post-Authorization Safety Study of FEIBA NF (Factor VIII Inhibitor Bypassing Activity). An open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. 10 Oct 2014. Baxalta Inc. US and Baxalta Innovations GmbH.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Uncommon, hypersensitivity reactions observed after infusion of FEIBA have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; these reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. The most commonly reported adverse drug reactions described for FEIBA NF include increased inhibitor titer, somnolence, dizziness, dysgeusia, dyspnea, nausea, chills, pyrexia, chest pain, and chest discomfort.

The possibility of thrombotic events should be considered when FEIBA is used in combination with systemic anti-fibrinolytics such as aminocaproic acid and tranexamic acid. Therefore, anti-fibrinolytics should not be used for approximately 6 to 12 hours before or after the administration of FEIBA.

Animal reproduction studies have not been conducted with FEIBA. There are no adequate, well-controlled studies in pregnant women. It is also not known whether FEIBA can cause fetal harm when administered to a pregnant woman or an affect on reproductive capacity. It is also not known whether FEIBA is excreted in human milk.[1] Subjects within the study should be provided with labeling information and a detailed discussion of benefit risk profile.

Additional safety experience for FEIBA is provided in the FEIBA NF IB.[iv]

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6.6 Compliance Statement

The study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is:

To evaluate the tolerability and safety of infusing 50% reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume

7.2 Primary Objectives

To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions

7.3 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) concentration of coagulation factor II
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

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8. STUDY DESIGN

8.1 Brief Summary and Study Design Rationale

This is a 2-part Phase 3b/4 (depending on market authorization status per country), prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 BU in hemophilia A and B) to determine the tolerability and safety of FEIBA component FII with a planned enrollment of 24 evaluable subjects. Evaluable subjects are defined as the ones who complete both parts of the study (i.e. received at least 8 of the 12 infusions; 4 in each part and 2 in each sequence in Part 1).

All subjects will receive 3 infusions of FEIBA reconstituted in a regular volume of SWFI, and 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI, with all 6 of these infusions being given at a rate of 2 U/kg/min within Part 1 of the study. In Part 2 of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/kg/min followed by 3 infusions FEIBA reduced volume at a rate of 10 U/kg/min.

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This study has been designed as a 2-way crossover study in order to assess primarily tolerability and safety of FEIBA. By designing it as a crossover study, subjects serve as their own controls. In addition, having received 6 infusions at 2U/Kg/min in Part 1, patients will be near to or at steady state (post 6 infusion of FEIBA) prior to starting Part 2. This study is open-label because it is a change in infusion volume and infusion rate, which would not make it feasible to properly blind. The goal of the study is to determine tolerability and safety of FEIBA in 50% reduced volume SWFI to FEIBA regular volume SWFI, and increase rate of the 50% reduced volume at 4U/kg/min and 10U/kg/min. By being able to reduce the volume and speed of the infusion, subjects will be able to spend less time infusing and reduce infusion burden during the regular use.

The exploratory objectives include pre (within 60 min before infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) concentration of coagulation factor II (FII); the effect of 50% reduced volume FEIBA and faster infusion rate on coagulation parameters.

FII (prothrombin) was chosen as a lead marker for FEIBA for several reasons:

1. In previously published studies it has been demonstrated that FII is a key protein component of the active ingredient of FEIBA

2. Amongst the vitamin K-dependent proteins, FII has the highest relative plasma concentration as it has the lowest specific activity, and therefore the absolute amount of FII in FEIBA measured as protein mass is higher than for any other vitamin K-dependent protein
3. The half life of FII is longer than that of any other vitamin K-dependent protein contained in FEIBA.

8.2 Overall Study Design

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 with hemophilia A or B with inhibitors (≥ 0.6 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 is illustrated in Figure 1 and Figure 2.

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In Part 1, 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 for details.

Treatments regimens during Part 1 of the study are:

- Part 1 Sequence A:
    1. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 1, 2, and 3)
    2. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 1, 2, and 3)
- Part 1 Sequence B, patients from sequence A cross over to:
    1. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 4, 5, and 6)
    2. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 4, 5, and 6)
- Infusion dose:

    All infusions: 85 ± 15 U/kg

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 rate.

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:

- First treatment phase: 4 U/kg/min (Infusions 7, 8, 9)
- Second treatment phase: 10 U/kg/min Infusions 10, 11, 12)
- Infusion dose:

  All infusions: 85 ± 15 U/kg

All infusions will be administered at the hemophilia care centers/study sites. Sample collections may be performed at the hemophilia care centers/study sites, appropriate ambulatory centers or at home. Each subject will receive a maximum of 12 IP infusions total [6 in Part 1 and 6 in Part 2]. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions see Section 8.7.2. After each infusion, subjects should be observed for 30 minutes at the study site. Additional details on study design and timing are described in Section 8.7.3. For additional details on managing bleeding episodes, see Section 8.7.4.

See Section 15.4 for additional details on the safety reviews performed by the Internal Safety Monitoring Committee (ISMC).

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8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is expected to be approximately 10 to 13 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 to 11 months.

The subject participation period is approximately 6 to 11 weeks from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measures

Tolerability and safety (local and general) related to the infusion and volume of reconstitution:

1. Occurrence of any adverse event: all AEs and SAEs, and AEs leading to discontinuation
2. Thromboembolic events and hypersensitivity reactions
3. Vital signs and Clinical laboratory data
4. Infusion site and infusion related reactions

8.4.2 Exploratory Outcomes Measure

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

8.5 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 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.

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8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. If 2 or more subjects develop anaphylaxis and / or thromboembolic events following exposure to FEIBA (enrollment and treatment temporarily stopped pending further review by the ISMC)
2. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk benefit
3. The sponsor or investigator considers continuation of the study unjustifiable for medical or ethical reasons
4. The ISMC recommends study termination

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

The active ingredient of FEIBA is a plasma-derived, freeze-dried, APCC with FVIII inhibitor bypassing activity. FEIBA will be provided in vials with a nominal potency of 500 U/vial, 1,000 U/vialand 2,500 U/vial). FEIBA contains mainly non-activated forms of the 3 coagulation factors, FII, FIX, and FX, as well as activated FVII; and Factor VIII coagulant antigen (FVIII:CAg) present in a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all. A solution containing 1 U FEIBA shortens the aPTT of FVIII inhibitor plasma to 50% of the buffer value. The product is supplied as freeze-dried powder or friable solid of white to off-white or pale green color.

To standardize conditions in the study, FEIBA should be stored at 2°C to 8°C only. FEIBA should not be allowed to freeze, and should be protected from light. Aseptic techniques must be used for reconstituting and administering FEIBA. Although the chemical and physical stability of the reconstituted product has been demonstrated for 3 hours at room temperature (up to 25°C), however, the solution should be used immediately as the preparation does not contain preservatives. Reconstituted product must not be returned to the refrigerator.

FEIBA will be provided in kits including SWFI for reconstitution. SWFI will be provided in different volumes for preparation of FEIBA infusions at regular volume or reduced volume. For additional information, such as reconstitution instructions, please refer to the Investigator's Brochure and/or other specific instructions provided by the sponsor or sponsor's representative.

8.7.2 Administration

Following reconstitution, FEIBA should be administered immediately using an intravenous needle and syringes provided by the sponsor for this study. The standard infusion rate of FEIBA is 2 U/kg body weight (BW) per minute, which in a 75kg subject, corresponds to an infusion rate of approximately 2.4 to 7.5 mL/minute depending on the potency (see label on vial).

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In order to standardize administration within the study, it is recommended that study drug be administered with an infusion pump. The infusion rate will be modified depending on which part of the study the subject is in, rates of 4 and 10 U/kg/min are also used in this study.

Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions every 48 hours (-8 hours/+24 hours). Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. FEIBA lots may be mixed within an infusion, and whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate.

For additional details, see Table 1 for general information on product preparation, as well as the study documents, and the FEIBA IB.[iv]

Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. Information regarding lot used, the actual dose given, date of treatment, treatment start and stop times, as well as any infusion interruptions will be recorded in the case report form (CRF).

Table 1
FEIBA Product Preparation

FEIBA	Diluent for Regular Volume FEIBA	Diluent for 50% Reduced Volume FEIBA
500 U	10 mL	5 mL
1000 U	20 mL	10 mL
2500 U	50 mL	25 mL

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity.

Please note that the availability of potencies may vary among countries and regions. Dose calculations should be made based on potencies available at site.

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8.7.3 Description of Treatment

Part 1 of the study uses a crossover design to evaluate the tolerability and safety of FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI (administered at the standard infusion rate of 2 U/kg/min). Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1. Part 2 will evaluate the tolerability and safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased infusion rates of 4 and 10 U/kg/min.

All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. The subject's medical history including hemophilia history, confirmation of inhibitors, bleeding episode history, concomitant medications and history of FEIBA or rFVIIa usage for the previous year will be collected at screening. Also recorded will be the date of last use of FEIBA or rFVIIa treatment. Results of the screening assessments will be used to establish a subject's eligibility for the study.

Part 1

After eligibility is established, the eligible subjects will be randomly assigned (1:1) into Part 1 of the study to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa every 48 hours (-8 hours/+24 hours).

Additional details on study visits for Part 1 can be found in Section 10.3 and Table 2.

Part 2

Part 2 is non-randomized and uses sequential enrollment of subjects who complete Part 1 of the study. Subjects in Part 2 will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/kg/min rate, followed by 3 infusions (Infusions 10, 11, and 12) of FEIBA at the 10 U/kg/min rate. Infusion 7 will be administered 48 hours (-8 hours/+24 hours) after Infusion 6. The infusions in Part 2 will be administered every 48 hours (-8 hours/+24 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Infusion rates for the treatment phases in Part 2 are:

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

Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Additional details on study visits for Part 2 can be found in Section 10.3 and Table 3.

Additional Treatment and Visit Information

The Schedule of Study Procedures and Events Procedures listed in Table 2 and Table 3 have the visit windows listed in relation to the subject's previous infusion. This is due to the variability in each subjects schedule based on previous therapy and bleeding events.

All infusions will be administered at hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions. For specifications on dosing and administration, see Section 8.7.2. For information on break-through bleeding control, see Section 8.7.4.

Study visits will be completed concurrently with study infusions. After subjects have completed the 12 study infusions, they will complete a Study Completion/ Termination Visit within 7 days but no sooner than 72 hours after Infusion 12.
In case of early withdrawal or discontinuation the Study Completion/Termination Visit will need to be completed within 7 days but no sooner than 72 hours after the last IP infusion received.

During each visit, the study staff will inquire with the subject about break-through bleeding events, treatments, and AEs throughout the study. Subjects are encouraged to report AEs to the site during the time spans between visits.

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Two subject questionnaires will be administered 5 times during the study, a TSQM questionnaire and a patient preference questionnaire to assess the subjects' satisfaction and preferences for treatments, for additional details see Section 10.5.

Detailed study flowcharts are presented in Table 2 and Table 3.

Investigational product may be interrupted or discontinued at any time during the study at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any infusion site reactions, regardless of causality, will be recorded on the AE CRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate CRF.

For details on the safety review by ISMC see Section 15.4.

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8.7.4 Management and Treatment of Break-Through Bleeding

Bleeding episodes are managed as described below for each part of the study. In all cases, if the bleeding episode, of whatever severity, is not resolved within 48 hours after an infusion to control bleeding, the subject must contact the hemophilia treatment center/study site for further treatment recommendations.

Screening

During screening, subjects will be asked to keep track of any FEIBA or rFVIIa usage, as the last dose may be used to determine the date of the first infusion of IP. If a subject experiences a bleeding episode during the screening period, subjects will be treated for the bleeding episode per standard of care as determined by the investigator and the patient will be randomized after resolution of bleeding episode.

Bleeding during the study

If bleeding occurs during the study, it will be treated per standard of care. For bleeding events treated with FEIBA or rFVIIa, a time window of 48 hours post treatment for bleeding should be observed before resuming study infusions. The subject will resume their treatment regimen and visits after control of the bleeding and following the administration window mentioned above. Depending on the clinical circumstances (e.g., treatment of uncontrolled bleeding due to injury and associated complications), the investigator and sponsor should decide if it is appropriate for the subject to continue in the study.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

Subject questionnaires may be entered directly onto the CRF.

For additional information on study documentation and CRFs, see Section 17.2.

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9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate peripheral venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
   a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
   b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Clinical or laboratory evidence of disseminated intravascular coagulation
6. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
7. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
8. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
9. Herbal supplements that contain anti-platelet activity
10. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
11. Family member or employee of the investigator
12. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The ISMC recommends a subject should be taken off the study
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome
- AE(s)/SAE(s) that the investigator or sponsor feels poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study

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10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: protocol identifier (e.g., 091501) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 091501-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4 Schedule of Study Procedures and Assessments (Part 1 and Part 2, respectively) and Supplement 20.5 Clinical Laboratory Assessments. FII concentration scheduling can be found in Section 20.6.

10.3.1 Screening and Baseline Assessments

After ICF is obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in Section 9.1 and Section 9.2, respectively. Screening procedures must be performed within 35 days of Infusion 1.

At screening, subjects will be instructed on the symptoms of thromboembolic and systemic hypersensitivity events by the investigator, and to contact the treatment center/hospital if they experience any symptoms.

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Medical history, including
    - Hemophilia history, inhibitor development history, bleeding episodes history, history of FEIBA or rFVIIa usage for a year prior to screening
    - Relevant medical and surgical history and all medications taken 4 weeks prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measurement body weight and height (see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (hematology, clinical chemistry, , serology testing and inhibitor level if no documentation is available ≥ 3 months prior to screening; see Section 12.7)
- Serum pregnancy test (female subjects of childbearing potential only)
- TSQM and patient preference questionnaires (see Section 10.5)

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After screening and eligibility sare determined, the subject will be enrolled in the study. For additional details on bleeding, see Section 8.7.4.

10.3.2 Treatment Visits

10.3.2.1 Infusion Visits

Randomization will occur after the subject has been confirmed to be eligible and prior to the first infusion.

- Randomization of eligible subjects to the following treatment sequences:
    - Part 1 Sequence A: FEIBA 2 U/kg/min in regular volume SWFI (3 infusions), FEIBA 2 U/kg/min in 50% reduced volume (3 infusions)
    - Part 1 Sequence B: FEIBA 2 U/kg/min in 50% reduced volume (3 infusions), FEIBA 2 U/kg/min in regular volume SWFI (3 infusions)

For additional details on the description of treatment, see Section 8.7.3.

During the study (Infusion Visits 1 to 12), subjects will return to the study site according to the schedule presented in Table 2 and Table 3. Prior to administration of IP, the following assessments will be performed at all visits unless otherwise indicated:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Vital signs (body temperature, pulse rate, blood pressure and respiratory rate)
    - Before administration of IP
    - at 30 minutes after administration of IP
- Clinical laboratory assessments Table 4
- IP administration (infusion site should be monitored for at 30 minutes [± 10 min] after infusion)
- Break-through bleed monitoring
- Subjects will be administered the TSQM and patient preference questionnaires:
    - After screening prior to Infusion 1
    - After Infusion 3 prior to Infusion 4
    - After Infusion 6 prior to Infusion 7
    - After Infusion 9, prior to infusion 10
    - After infusion 12 or up to the completion of the Study Completion/Termination Visit
- Prothrombin II levels will be drawn within 60 min before IP administration and at 30 min, hours 1, 2, 6, 8 and 12 after IP administration, as outlined in Table 5 See also information on administration (Section 8.7.2).

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10.3.3 Study Completion/Termination Visit

The Study Completion/Termination Visit including if the subject is discontinuing early will be performed within 7 days but no sooner than 72 hours after Infusion 12, or the last infusion if discontinued early. The following assessments will be performed:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Breakthrough bleeds monitoring
- Concomitant medication monitoring

- Clinical laboratory assessments see Table 4
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and body weight)

10.4 Medications and Non-Drug Therapies

Once subject eligibility has been confirmed for the study, the following medications and non-drug therapies are not permitted during the course of the study:

- Medications:
  - Any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) except anti-retroviral chemotherapy
  - Any investigational drug or device

A subject who receive any of these therapies will be withdrawn from further study participation.

Antifibrinolytics should not be used approximately 6 to 12 hours before or after the administration of FEIBA.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study (these are permitted; however, they should not be taken within 6 to 12 hours before or after administration of FEIBA)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
  - Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition
  - Supplemental vitamins, minerals
  - Any standard of care to treat breakthrough bleeds

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- Non-drug therapies:
    - Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Questionnaires

Two questionnaires will be administered to subjects within this study (TSQM [14] and a patient preference questionnaire). These questionnaires will be used to assess the subject's preferences on the IP, as well as their satisfaction with the IP, and will be collected in the CRF or on paper. Both questionnaires will be administered:

- After screening prior to Infusion 1
- After Infusion 3 prior to Infusion 4
- After Infusion 6 prior to Infusion 7
- After Infusion 9, prior to infusion 10
- After infusion 12 or up to the completion of the Study Completion/Termination Visit

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These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when the subject ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion / Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems, and severe hypersensitivity reaction), ISMC recommends a subject should not continue. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the Study Completion/Termination Visit. If the Study Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Study Completion/Termination Visit. If a subject terminates participation in the study and does not return for the Study Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.5 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

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10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF PHARMACOKINETICS

Pharmacokinetics will not be evaluated in this study.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

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Additional events which should be reported the same way as SAEs are as follows:

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19
- Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE
- Any thromboembolic event
- Hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE. Any pregnancy occurring during the study should be reported to the sponsor within 24 hours of the site learning about the pregnancy. The pregnancy should be followed until completion of the pregnancy and up to 1 year postdelivery, if feasible. Pregnancies not considered an (S)AE as described above will be captured in the CRF.

Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures as described in Section 10.3.2 for reasons unrelated to AEs will not be considered as hospitalization for SAE reporting purposes unless the hospitalization is prolonged.

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12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study termination/completion will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

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For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, it is medically stabilized, or 30 days after the Study Completion/Termination Visit, whichever comes first, and the follow-up information is to be documented in the CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage including overdosing (20% higher than the highest permitted dose), underdosing (20% lower than the lowest permitted dose), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion/termination, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

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These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility.

For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
    - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
    - Has little or no temporal relationship to the IP
    - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
    - Follows a reasonable temporal relationship to the administration of IP
    - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
    - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
        - Reappearance of a similar reaction upon re-administration (positive rechallenge)
        - Positive results in a drug sensitivity test (skin test, etc.)
        - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours after IP administration the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

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12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 3) and Section 12.1.

Adverse Events/SAEs are to be recorded on the AE page of the CRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported by completing the relevant CRF page(s) in English. Once the SAE has been recorded, SAEs must be reported to the sponsor to meet the 24-hour timeline requirement (contacts and instructions to be provided in separate documentation).

The initial SAE information reported on the applicable CRF pages (must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting investigator (for paper SAE Report Forms)

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12.1.3 Medical Device Safety Reporting

The IP kit contains the BaxJect II Hi-Flow needleless transfer device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

- Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure.
- Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

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The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF . These events will be considered as SAEs but will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims
- Medication errors: an error (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication e.g., administration of incorrect dose

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

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12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

General medical history will be collected for 4 weeks prior to screening. Any information on the subjects' hemophilia history will be collected a year prior to screening including documented history of hemophilia, confirmation of inhibitors, bleeding episodes history, and history of FEIBA or rFVIIa usage.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening (as described in Table 2 and Table 3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Assessments will be performed at a central laboratory (see Section 15.7), according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for any additional testing as needed (see Section 12.7.6). Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

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12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of 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.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening and at study completion/termination.

In addition, serum samples for pregnancy tests for females of childbearing potential will be collected at screening.

12.7.2 Concentration of FII and Coagulation Testing

Blood samples for the determination of FEIBA components FII will be taken within 60 (±15) min before and at 30 (±10) min, after completion of each infusion. In addition hours 1 (±15min), 2 (±30min), 6 (±1hour), 8 (±2hours) and 12 (±4hours) samples will be taken after infusion 1,3,4,6,9 and 12 (see Section 20.6 for sampling time points and allowed sampling time windows). The date and time of each sample collections will be documented in the subject's CRF.

Blood will be obtained for the assessment of coagulation testing and consist of aPTT, PT, thrombotic markers (D-Dimers, prothrombin fragment F 1+2, TAT, fibrinopeptide A), and FII concentration. Coagulation testing will be performed, during the study and samples at hours 1 (±15min), 6 (±1hour) and 12 (±4 hours) will be taken after infusion 1,3,4,6,9 and 12 (see Section 20.6 for sampling time points and allowed sampling time windows).

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12.7.3 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, hepatitis A virus (HAV) antibody, hepatitis B virus (HBV) antibody, hepatitis B surface antigen (HBsAg), HCV antibody, parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening and at the Study Completion/Termination Visit.

12.7.4 CD4 Levels

At screening only, CD4 levels will be determined using flow cytometry in the case of a subject being HIV positive.

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a pre-existing disease, due to a lab error, or due to another issue that will be specified.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE. Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) measured once at screening and weight (lb or kg) measured at screening and completion/termination will also be collected.

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Vital signs will be measured at screening and within 30 minutes before and after (except weight) administration of IP, at each Infusion study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0-100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of subject status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease. In this scale, a high number performance status represents high functionality, and a lower number represents low functionality and likely rapid progression of disease.[15] Subjects will be scored using this scale at screening.

12.10 Infusion Site Evaluations

The current site of IP infusion will be assessed for immediate local reactions at 30 minutes (±10 min) after infusion. In addition, infusion sites will be monitored by the subject for up to 12 hours after infusion, and will be discussed with the site staff during the next study visit.

Infusion sites will be monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations will be made by clinical staff or by the subject or caregiver. If an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Infusion sites will continue to be reviewed at each study visit, and any infusion site reactions will be followed until resolution. Each infusion site reaction will be categorized using the intensity grading described for AEs in Section 12.1.2.1.

12.11 Special Treatment Considerations

Subjects will be screened for eligibility in the study as described in Section 9.1 and Section 8.7.3, and will be informed of the study specific restrictions and requirements of the study. Subjects who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

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All biological agents carry the risk of hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic reaction

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Thromboembolic events have been observed with bypassing agents including FEIBA. Clinical manifestations of these events may include, but not limited to:

- myocardial infarction
- deep vein thrombosis
- pulmonary embolism
- stroke and
- transitory ischemic attack

Sometimes, these reactions can be life-threatening. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute hypersensitivity reaction after an infusion of IP, the subject should be managed appropriately and given instruction to receive relevant supportive care.

Subjects who experience a potentially severe hypersensitivity reaction will be discontinued from IP. They will complete a Termination/Study Completion Visit, and will be monitored for stabilization or resolution of the AE. Premedication to prevent allergic reactions will not be permitted, as severe hypersensitivity reactions are an outcome measure for this study.

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13. STATISTICS

Data handling will be conducted by the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

Statistical analysis for this study will be descriptive in nature. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

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.

13.2 Datasets and Analysis Cohorts

Safety: The safety analysis set will include all subjects who received at least 1 dose of IP (FEIBA). All safety analyses will be performed on the safety analysis set. Subjects will be evaluated according to the treatment received.

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13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

13.4.1.1 Analysis of the Primary Outcome Measure (Parts 1 and 2)

AEs, SAEs and AEs leading to discontinuation, thromboembolic events and hypersensitivity reactions that occurred during or after IP infusions will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or potentially related adverse events as assessed by the investigators. Temporally associated AEs 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.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s).

AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related to the infusion and those considered unrelated. These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Shift tables and summary statistics will be presented for the results of clinical laboratory data. All abnormal lab results will be listed.

Summary statistics of vital signs, infusion site and infusion related reactions will be carried out.

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13.4.2 Exploratory Outcome Measures

All exploratory outcome measures will be analyzed descriptively.

Full details of the statistical analysis will be specified in the SAP.

13.5 Planned Interim Analysis of the Study

There is no planned interim analysis other than a safety data review by the ISMC.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

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15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

Primary objective of the study is to monitor safety parameters throughout the study with a special emphasis on hypersensitivity and thromboembolic events. Adverse event data will be collected at each visit assessed and documented on the CRFs as outlined in Section 12.1.2.3.

Serious adverse events are monitored and reported per the safety reporting guidelines as outlined in Section 12.1.2.3.

This study will be monitored by an ISMC. The ISMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from the ongoing clinical study. For this study, the ISMC will be composed by appropriate members of clinical, safety, and biostatistics division that are not involved in the active execution of the trial. The ISMC can stop a study if it finds toxicities or if treatment is proven to be not beneficial.

All SAEs will be reviewed within 24 hours by the Chair of the ISMC. There are 3 planned ISMC meetings:

1. Within 24 hours after 6 subjects in Part 1 (3 subjects in each group) have completed Infusion 5
2. Within 24 hours after 6 subjects have completed Infusion 7 (Part 2)
3. Within 24 hours after 6 subjects have completed Infusion 10 (Part 2)

ISMC preplanned meetings will be held concurrently with the ongoing study.

Subjects can continue with their scheduled therapy and assessments unless the ISMC warrants that the trial needs to be suspended due to safety concerns. Additional ad hoc meetings of the ISMC may be convened as appropriate per ongoing safety evaluations.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

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15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

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16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided to patients will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

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16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper/electronic format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

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The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper/electronic format, and this documentation will be considered source documentation. Changes to an CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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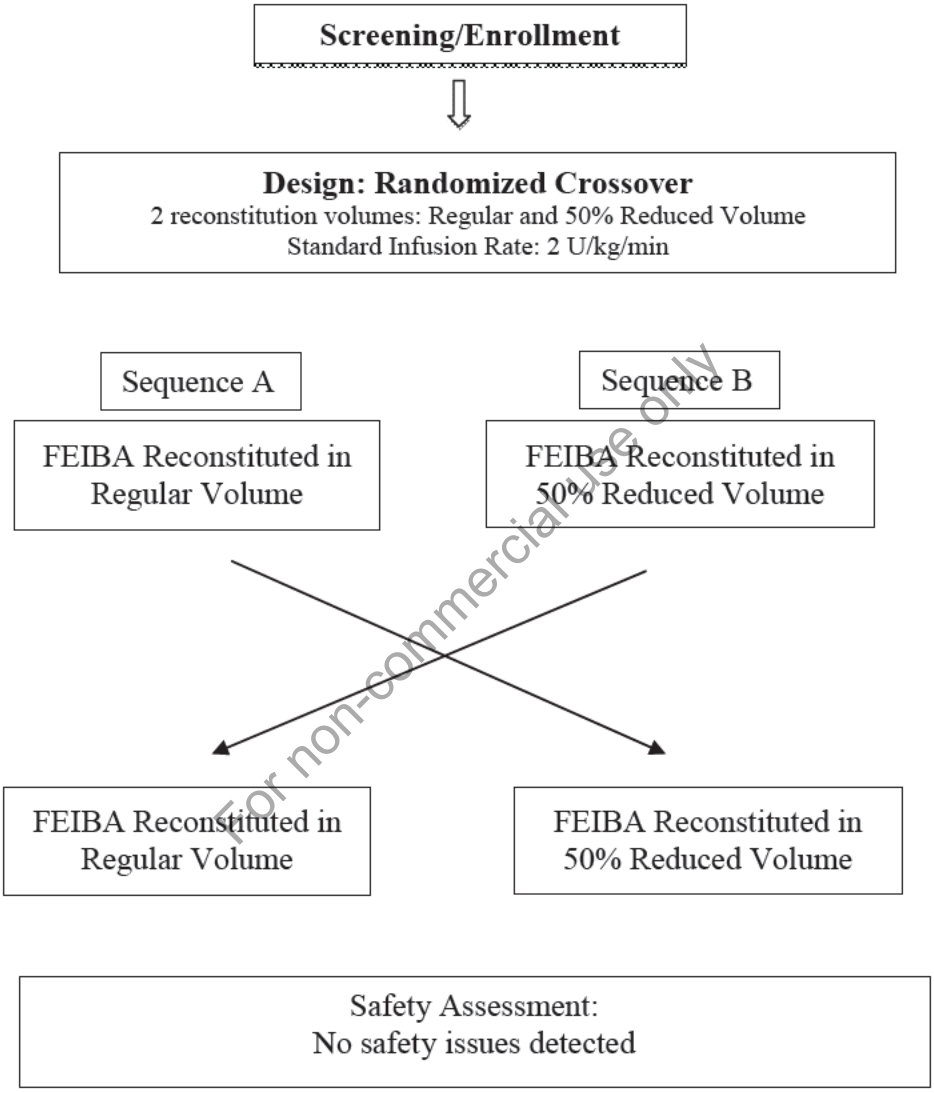
20. SUPPLEMENTS

20.1 Study Flow Chart Part 1

Figure 1
Study Design for Part 1 Baxalta Clinical Study 091501



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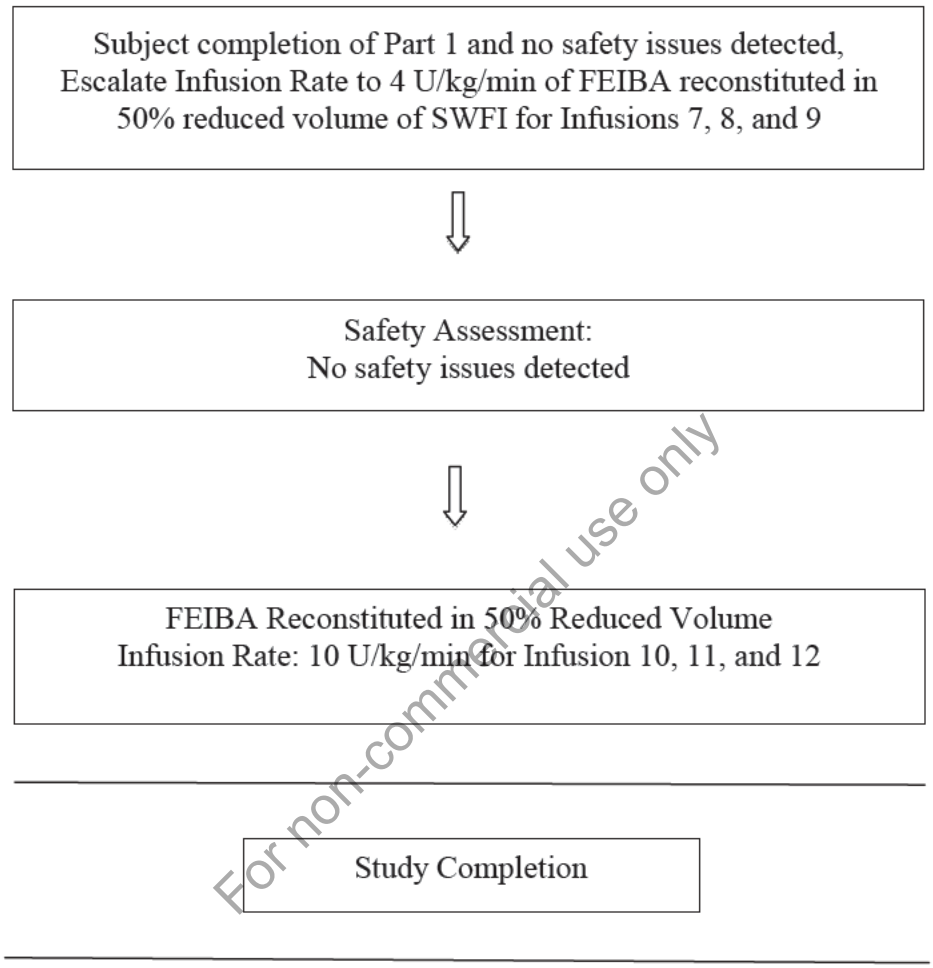
20.2 Study Flow Chart Part 2

Figure 2
Study Design for Part 2 Baxalta Clinical Study 091501



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20.3 Schedule of Study Procedures and Assessments (Part 1)

Table 2
Schedule of Study Procedures and Assessments (Part 1)

Procedures/ Assessments	Screening Assessments	Randomization	Study Visits[a]						
			Infusion #1	Infusion #2	Infusion #3		Infusion #4	Infusion #5	Infusion #6
Study Visit Windows[b]	A maximum of -35 days to 0		Day 1	within 48 hrs (-8/+24) from Infusion 1	48 hrs (-8/+24) from Infusion 2		48 hrs (-8/+24) from Infusion 3	48 hrs (-8/+24) from Infusion 4	48 hrs (-8/+24) from Infusion 5
Informed Consent[c]	X								
Eligibility Criteria	X								
Medical History	X								
Medication and Non-drug Therapies	X		X	X	X		X	X	X
Physical Examination	X								
Pregnancy Test	X								
Vital Signs[d]	X		X	X	X		X	X	X
Karnofsky Performance Test	X								
Laboratory Assessments[e]	X		X	X	X		X	X	X
Inhibitor level if no documentation	X								
Factor II levels[f]			X		X		X		X
Adverse Events, breakthrough bleeds, and infusion site reactions[g]	X		X	X	X		X	X	X
IP Treatment			X	X	X		X	X	X
TSQM and patient preference questionnaires[h]		X				X			
Coagulation testing[i]			X		X		X		X

Abbreviations: ICF=informed consent form; IP=investigational product

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[a] A Study Completion/Termination Visit is to be completed in Part 1 only for subjects who withdraw or discontinue prior to the end of the study. If a subject withdraws or discontinues, this visit should be completed within 7 days but no sooner than 72 hours from the last infusion that the subject received. Otherwise, the Study Completion/Termination Visit will occur at the end of Part 2 (see Table 3).

[b] Study Visit Windows:
Infusion 1 can be scheduled after screening assessments have been completed; all other infusions will occur within 48 hours (-8/+24hours) from the previous infusion.

[c] Occurs at enrollment (prior to any study-specific procedure).

[d] Vital signs will include body temperature, pulse rate, blood pressure, and respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[e] For laboratory assessments, see Section 20.5.

[f] FII levels within 60 minutes (±15min) before and 30 mins (±10min) and all timepoint within 60 min (±15 min) before and at 30 min (±10 min), hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour), and 12 (±4hours) after infusions 1, 3, 4 and 6.

[g] The infusion site will be monitored for AEs for 30 ±10 minutes after each study infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[h] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.. See Section 10.5 for details.

[i] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) post-infusion at 1 hr ± 15 min (mentioned in Section 12.7.2).

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20.4 Schedule of Study Procedures and Assessments (Part 2)

Table 3
Schedule of Study Procedures and Assessments (Part 2)

Procedures/ Assessments	Study Visits									
		Infusions 7	**Infusion 8**	**Infusion 9**		**Infusion 10**	**Infusion 11**	**Infusions 12**		**Study Completion/ Termination Visit[a]**
Rate of Infusion		**Rate: 4 U/kg/min**				**Rate: 10 U/kg/min**				
Study Visit Windows[b]		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		72 h to 7 days from Infusion 12 (or last infusion)
Medications and Non-drug Therapies		X	X	X		X	X	X		X
Vital Signs[c]		X	X	X		X	X	X		X
Laboratory Assessments[d]		X	X	X		X	X	X		X
Factor II levels[e]				X				X		
Adverse Events, breakthrough bleeds, and infusion site, infusion related reactions[f]		X	X	X		X	X	X		X
IP Treatment		X	X	X		X	X	X		
TSQM and patient preference questionnaires[g]	X				X				X	
Coagulation testing[h]				X				X		

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[a] The Study Completion/Termination Visit includes cases of withdrawal or discontinuation. This visit should be done within 7 days but no sooner than 72 hours after Infusion 12). If a subject withdraws or discontinues, this visit should be done within 7 days but no sooner than 72 hours after the last infusion that the subject receives.

[b] Infusions will occur within 48 hours (+-8/+24hours) from the previous infusion.

[c] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[d] For laboratory assessments, see Section 20.5.

[e] FII levels within 60 minutes (±15min) before and 30 mins (±10min) and all timepoint within 60 min (±15 min) before and at 30 min (±10 min), hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour), and 12 (±4hours) after infusions 9 and 12.

[f] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs will be collected from ICF signing but will not be included in the analysis of SAEs. See Section 12.3 for details.

[g] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit. See Section 10.5 for details.

[h] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) (mentioned in Section 12.7.2).

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20.5 Clinical Laboratory Assessments

Table 4
Clinical Laboratory Assessments

Assessments	Screening Visit	Infusions 1, 3, 4, 6, 9, 12	Study Completion/ TerminationVisit[a]
Hematology[b]	X		X
Clinical Chemistry[c]	X		X
Coagulation Testing[d]		X	
Serological Testing[e] and CD4[f]	X		X
Pregnancy Test[g]	X		

[a] Includes cases of withdraw or discontinuation.
[b] Hematology assessments include: CBC (Hct, Hgb, RBC count, WBC count) with differential, MCV, MCHC, and platelet count.
[c] Clinical chemistry assessments include sodium, chloride, potassium, bicarbonate, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, GGT, 5'-nucleotidase.
[d] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A (mentioned in Section 12.7.2).
[e] Serological testing will include: HIV-1 and HIV-2 antibodies (HIV+, check CD4 count–screening visit only), HAV antibodies, HBV antibody, HBsAg, HCV antibody, parvovirus B19 (IgM and IgG), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).
[f] CD4 at screening in case of positive HIV test results.
[g] A serum pregnancy test will be performed for females of childbearing potential.

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20.6 Concentrations of FII and Coagulation testing

Table 5
FII and Coagulation Testing Time Frame

Procedures/Assessments	**PART 1** **Infusions 1, 3, 4, 6**	**PART 2** **Infusions 9, 12**	**Infusions** **2, 5, 7, 8, 10, 11**
FII concentration	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min
Coagulation testing: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A)	Infusions 1, 3, 4, 6, 9, and 12 Post infusion: 1 hr ± 15 min 6 hr ± 1 hr 12 hr ± 4 hr		

Abbreviations: EOI=end-of-infusion; Factor II; h=hours; min=minutes

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22. SUMMARY OF CHANGES

Protocol 091501 AMENDMENT 3 (Global): 2017 SEP 14

Replaces: Protocol 091501 AMENDMENT 2 (Global): 2017 AUG 04

In this section, changes made in this amendment from the previous version of the protocol, dated **2017 AUG 04**, are described and their rationale is given.

1. **Packaging, Labeling, and Storage, Section 8.7.1**
   Description of Change: Product Insert changed to Investigator's Brochure
   Purpose of Change: Reconstitution details of the Investigational Product will be provided in the Investigator's Brochure and not the Product Insert.

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INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 3 (Global): 2017 SEP 14

Replaces

AMENDMENT 2 (Global): 2017 AUG 04

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 3 (Global): 2017 SEP 14

Replaces

AMENDMENT 2 (Global): 2017 AUG 04

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OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted] MD,
[redacted]
Global Clinical Development Operations

CLINICAL STUDY PROTOCOL

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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 SHORT TITLE: FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 4 (Global): 2018 MAR 07

Replaces:

AMENDMENT 3 (Global): 2017 SEP 14

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ALL VERSIONS:
Amendment 4 (Global): 2018 MAR 07
Amendment 3 (Global): 2017 SEP 14
Amendment 2 (Global): 2017 AUG 04
Amendment 1 (Global): 2016 MAR 03
Original: 2015 OCT 08

OTHER ID(s)
NCT Number: 02764489
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

Study Sponsor(s):	**Baxalta US Inc.**	**Baxalta Innovations GmbH**
	300 Shire Way, Lexington, MA 02421, UNITED STATES	Industriestrasse 67 A-1221 Vienna, AUSTRIA

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory)/Responsible Party

[redacted], MD
[redacted]
Global Clinical Development Operations
Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

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2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report From

Refer to SAE Protocol Sections and the study team roster for further information.

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For definitions and information on the assessment of these events, refer to the following:

- Adverse Event, Section 12.1
- Serious Adverse Event, Section 12.1.1.1
- Assessment of Adverse Events, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	**Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]), FEIBA NF. Referred to as FEIBA throughout the protocol.**
Name(s) of Active Ingredient(s)	Coagulation factors II, Xa, IX, and VIIa
CLINICAL CONDITION(S)/INDICATION(S) FEIBA is an Anti-Inhibitor Coagulant Complex (AICC) indicated for use in hemophilia A and B patients with • inhibitors for: ➢ Control and prevention of bleeding episodes ➢ Perioperative management ➢ Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. • FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX (FIX).[1]	
PROTOCOL ID	091501
PROTOCOL 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**
Short Title	FEIBA Reconstitution Volume Reduction and Faster Infusion Study (FEIBA STAR)
STUDY PHASE	Phase 3b/4, depending on market authorization status per country
PLANNED STUDY PERIOD	
Initiation	First Subject In: Q 3 2018
Primary Completion	Last Subject In: Q1 2020
Study Completion	Last Subject Last Visit: Q2 2020
Duration	6 to 11 weeks

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STUDY OBJECTIVES AND PURPOSE
Study Purpose To evaluate the tolerability and safety of infusing reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume
Primary Objectives To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions
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 with 50% reduced volume of FEIBA and faster infusion rates 2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

STUDY DESIGN	
Study Type/ Classification/ Discipline	Tolerability and Safety
Control Type	Active
Study Indication Type	Treatment
Intervention model	Part 1: Crossover Part 2: Sequential
Blinding/Masking	Part 1: Randomized, Open-label Part 2: Non-Randomized, Open-label

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Study Design	A 2-part, Phase 3b/4, prospective, open-label, multicenter study to be conducted in 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 Bethesda units [BU]) for the primary tolerability and safety assessments. **Part 1:** In Part 1, subjects will be administered two different volumes of FEIBA in a randomized, crossover design every 48 hours (-8, +24 hours) intervals. Part 1 will monitor the tolerability, safety, 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) reconstituted in 50% reduced volume of SWFI and administered at the standard infusion rate of 2 U/kg/min compared with FEIBA reconstituted in regular volume of SWFI at the standard infusion rate. All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. Eligible subjects will be randomly assigned (1:1) to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI or regular volume SWFI (Period 1). Patients finishing 3 infusions in Period 1 (Sequence A or B), will either switch from FEIBA reconstituted in reduced volume to 3 infusions of FEIBA in regular volume SWFI or vice versa (Sequence A or B) depending on randomization. All patients completing Part 1 will move to Part 2. Evaluable patients from Part 1 are all subjects who receive 4 of the 6 planned infusions, at least 2 infusions in each sequence. Tolerability and safety data will be collected before, during and after each infusion and between infusions; Clinically apparent changes in vital signs, laboratory parameters, infusion site reactions and infusion rate-related reactions will be monitored.

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	FII activity will be monitored by analyzing concentrations before (within 60 min before the infusion) and at 30 min after each infusion and at hours 1, 2, 6, 8 and 12 after infusion 1,3,4 and 6 as outlined in Section 20.6. **Part 2:** Part 2 is non-randomized with sequential treatment of all evaluable subjects who complete Part 1. Subjects will receive FEIBA reconstituted in 50% reduced volume of SWFI at increased rates of 4 and 10 U/kg/min in a non-randomized fashion, at 48 hours (-8, +24 hours) intervals, to evaluate the tolerability and safety of infusing 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 and infusions 10, 11 and 12 will be administered at 10 U/kg/min. Following the last infusion (infusion 12), a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion. Evaluable patients from Part 2 are all subjects who receive 4 of the 6 planned infusions, at least 2 infusions per infusion rate. Tolerability and safety data will be collected before, during and after each infusion and between the infusions; Clinically apparent changes in vital signs, infusion rate-related events, and infusion site reactions will be monitored. Activity of coagulation factor II will be assessed before (within 60 minutes before the infusion) and at 30 min after each infusion, and at hours 1, 2, 6, 8 and 12 after infusions 9, and 12 as outlined in Section 20.6.

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	The infusions in both parts will be administered every 48 hours (-8 hours /+24 hours) to allow time to monitor tolerability and safety of the higher infusion rate. All IP infusions will be administered at the hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions (6 in each part). There is no washout period before Part 1, between infusions or parts of the study. Subjects will receive FEIBA at a dose of 85 U/kg ± 15 U/kg for all infusions. For infusions, whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate. Please refer to study documents for detailed instructions. Safety monitoring for this study will be conducted concurrently by an Internal Safety Monitoring Committee (ISMC). All serious adverse events (SAEs) that occur will be reviewed by the Chair of the ISMC with the Medical Director within 24 hours. Planned ISMC meetings will be held concurrently with the ongoing study.
Planned Duration of Subject Participation	It is planned that each subject will spend approximately 6 to 11 weeks in the study.

Outcome Measure (s)

Primary

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.

Exploratory Outcome Measure(s)

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.
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

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INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** kit; powder, lyophilized, for solution/suspension; injection **Dosage frequency:** IP will be infused every 48 hours (-8 hours/+24 hours). **Mode of Administration:** intravenous
SUBJECT SELECTION	
Targeted Accrual	Enroll 32 subjects to have 24 evaluable subjects for the assessments
Number of Groups/Arms/Cohorts	1 cohort: at least 24 evaluable adult subjects (≥ 18 to ≤ 65 years old) for tolerability and safety evaluation

Inclusion Criteria

Subject is/has:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom

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8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
    a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

Exclusion Criteria

Subject is/has:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Taking Emicizumab (Hemlibra) for bleed prevention
6. Clinical or laboratory evidence of disseminated intravascular coagulation based on medical history
7. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
8. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
9. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
10. Herbal supplements that contain anti-platelet activity
11. Participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. A family member or employee of the investigator

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13. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

STATISTICAL ANALYSIS

Sample Size Calculation

The projected sample size of 24 evaluable subjects for this tolerability and safety study was determined by considering available patients, and is not based on statistical power calculations. Evaluable patients 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.

Planned Statistical Analysis

Statistical analysis for this study will be descriptive in nature.

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Primary Analysis

AEs, SAEs and AEs leading to discontinuation, thromboembolic events, hypersensitivity and infusion site reactions that occur during or after the IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be provided for temporally associated adverse events; and for potentially related adverse events as assessed by the investigators.

Lab results and vital signs which are considered AEs will be listed.

Exploratory Analysis

All exploratory outcome measures will be analyzed for descriptive purposes only.

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 48 hour time point, the pre-infusion value of the next infusion will be taken), and maximum standardized increase from the pre-dose level will be analyzed for descriptive purposes only.

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, period and volume as fixed effect and subject nested within sequence as random effect.

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 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 described using point estimates for infusion volume and rates with corresponding two-sided 95% confidence intervals (CI) obtained from the models above.

Full details of the statistical analysis will be specified in the statistical analysis plan (SAP).

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Figures

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	anti-inhibitor coagulant complex
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BU	Bethesda units
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CD4	cluster of differentiation 4
CI	confidence interval
EC	ethics committee
CRF	case report form
FEIBA	Factor Eight Inhibitor Bypassing Activity
FEIBA NF	Factor Eight Inhibitor Bypassing Activity Nanofiltered
FEIBA VH	Factor Eight Inhibitor Bypassing Activity Vapor Heated
FII	Factor II
FIX	Factor IX
FVII	Factor VII
FVIII	Factor VIII
FVIII:CAg	Factor VIII C antigen
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
Hct	hematocrit
HCV	hepatitis C virus

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Abbreviation	Definition
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	Immumoglobulin G
IgM	immunoglobulin M
IP	investigational product
ISMC	Internal Safety Monitoring Committee
Min	minutes
NMC	non-medical complaint
PCR	polymerase chain reaction
PT	prothrombin time
rFVIIa	activated recombinant factor VII
SAE	serious adverse event
SAER	serious adverse event report
SIC	subject identification code
SI	serious injuries
SWFI	sterile water for injection
TAT	thrombin/anti-thrombin complex
TSQM	Treatment Satisfaction Questionnaire for Medication

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6. BACKGROUND INFORMATION

6.1 Description of Investigational Product and Clinical Condition/Indication

The investigational product (IP), FEIBA[i] is a plasma derived, activated prothrombin complex concentrate (APCC), generically identified as an anti-inhibitor coagulant complex (AICC). FEIBA was developed to treat bleeding episodes and cover surgical interventions in hemophilia A and B patients with inhibitors and in non-hemophilia patients with acquired inhibitors[ii] and is also intended for use as a prophylactic treatment for hemophilia A and B patients with high responding inhibitors and frequent joint bleeding.[iii,2,3,4]

Baxalta's first licensed FEIBA product, AICC FEIBA, was marketed beginning in 1975 and was superseded in 1985 by a 2-stage vapor heat-treated product, AICC FEIBA VH. Nanofiltration was introduced to the manufacturing process in 2006 to produce FEIBA NF, now called FEIBA.

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6.2 Clinical Condition/Indication

Hemophilia is an X-linked, recessive, congenital bleeding disorder caused by deficient or defective coagulation due to a deficiency in FVIII (hemophilia A), or FIX (hemophilia B). The absence of FVIII or FIX leads to spontaneous bleeding episodes (occurring primarily in joints, muscles, and less commonly, in soft tissues) and to excessive bleeding following trauma or injury.[5,6] Replacement therapy for the treatment of hemophilia A, and less frequently hemophilia B, can be complicated by an immune response resulting in the production of inhibitory alloantibodies to Factor VIII (FVIII) or Factor IX (FIX), especially in patients with moderate to severe hemophilia. The development of such inhibitory antibodies currently represents the most serious complication of hemophilia treatment. The presence of inhibitors against FVIII generally precludes the efficacious use of human FVIII replacement therapy. A substantial portion of patients with FVIII inhibitors have high-responding, high-titer inhibitors (> 5 Bethesda units [BU]). These patients exhibit an anamnestic response after FVIII exposure, sometimes with a dramatic increase in inhibitory antibody titer.[7,8] The inability to provide FVIII replacement therapy predisposes this group of patients to increased morbidity and mortality compared with hemophilia patients without inhibitors.[7]

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[i] FEIBA NF is a trademark of Baxalta Inc. US and Baxalta Innovations GmbH.

[ii] Anti-Inhibitor Coagulant Complex, FEIBA Vapor Heated. Package Insert, Baxalta US Inc., Westlake Village, CA.

[iii] Protocol 090701. FEIBA NF: A Prospective, Open-label, Randomized, Parallel Study to Evaluate Efficacy and Safety of Prophylactic versus On-demand Treatment in Patients with Hemophilia A and B and High Titer Inhibitor. 2013 Jan 14, Baxalta US Inc.,(Westlake Village, CA).

Several therapeutic approaches are currently available in the management of hemorrhagic events in patients who have developed FVIII inhibitors. These include neutralization with high doses of human FVIII (low titer inhibitor only), and treatment with bypassing agents such as Activated Prothrombin Complex Concentrate (APCC), or activated recombinant factor VII (rFVIIa). Among these treatment options, only APCCs and rFVIIa are able to control acute hemorrhages in hemophilia patients with high titer inhibitors. These agents control bleeding by promoting the conversion of prothrombin to thrombin with subsequent fibrin polymerization and clot formation via mechanisms that do not require FVIII or FIX. It has been proposed that FEIBA products achieve this goal principally by virtue of the presence of a "partial prothrombinase complex" consisting of activated Factor X (FX) and prothrombin.[9]

The active ingredient of FEIBA is a plasma-derived, freeze-dried APCC with FVIII inhibitor bypassing activity. Recent studies have demonstrated that FEIBA is a multicomponent therapeutic agents with activities potentially targeting different sites in the coagulation system.[10] FEIBA contains mainly non-activated forms of the vitamin K -dependent proteins Factor II (FII), FVII, FIX and FX, as well as small amounts of activated prothrombin complex proteins; and Factor VIII coagulant antigen present in a concentration of up to 0.1 U/1 U FEIBA. From a number of confirmed studies it became clear that the FII–FXa complex is one of the key components in this system of different proteins.[11] A solution containing 1 U FEIBA shortens the activated partial thromboplastin time (aPTT) of FVIII inhibitor plasma up to 50% of the buffer value. Additional details can be found in the FEIBA IB.[iv]

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6.3 Population to Be Studied

Adult subjects (age ≥ 18 to ≤ 65 years) with hemophilia A or B (congenital or acquired) of any severity, of all races and ethnic groups will be studied. All subjects will have a documented history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa); subjects with no documented history will require testing of the inhibitor level before entering the study. Subjects will either be hepatitis C virus (HCV) negative or HCV positive with stable hepatic disease. Subjects will either be human immunodeficiency virus (HIV) negative or HIV positive with stable disease and a cluster of differentiation 4 (CD4) count ≥ 200 cell/mm^3. See additional details in the Inclusion and Exclusion Criteria in Section 9.1 and Section 9.2, respectively.

[iv] Investigator's brochure. Anti-inhibitor coagulant complex nanofiltered; FEIBA NF. 2016 FEB 24. Baxalta US Inc., (Westlake Village, CA).

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Finding from Nonclinical Studies

The nonclinical studies included a virus clearance study, which was performed to investigate the virus reduction capacity of the nanofiltration step in the manufacturing of FEIBA NF.

Data from nonclinical studies can be found in the FEIBA NF IB.[iv]

6.4.2 Findings from Clinical Studies

The results of Baxalta clinical study 090701[iii] demonstrated that prophylaxis with FEIBA significantly reduced the annualized bleeding rates for all bleed types and for spontaneous, traumatic, joint, and non-joint, bleeding episodes when compared with on-demand treatment. A statistically significant reduction in the rate of bleeding episodes in new target joints in the prophylaxis arm versus the on-demand arm was also observed. An examination of adverse events (AEs), abnormal laboratory parameters for hematology and clinical chemistry and vital signs demonstrated that FEIBA was safe and well tolerated for prophylactic use. Clinically, these data suggest that FEIBA is safe and efficacious in the management of hemophilia A or B with persistent high-titer inhibitors or low-titer inhibitors refractory to FVIII or FIX treatment, and further confirmed the safety and effectiveness of FEIBA for controlling and preventing bleeding episodes.

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Baxalta clinical study 091002 was an open-label, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. This study was designed to document routine usage of FEIBA NF as a bypassing agent for on-demand or prophylactic treatment in everyday clinical practice and in surgical intervention. The safety results of this post-authorization safety study showed that treatment with FEIBA NF, administered in 81 subjects with hemophilia, requiring treatment with inhibitor-bypass therapy for bleed resolution or bleed prophylaxis, was generally safe and well tolerated. The mean infusion rate of FEIBA under routine clinical practice during the study (3.7 U/kg per min, range 0.9 to 23.5) was higher than that recommended in the Summary of Product Characteristics of FEIBA (2.0 U/kg per min). A manual analysis of safety listings did not disclose any AEs associated with a higher infusion rate.[12] Treatment-related AEs or serious adverse events (SAEs) were reported in 9.9% and in 3.7% of subjects, respectively. A deep venous thrombosis and a superficial thrombophlebitis were observed in 1 subject with acquired hemophilia.

The hemostatic effectiveness was rated by the physicians as excellent or good in more than 90% of total subjects, with the highest rates reported in subjects with FEIBA NF prescribed as regular prophylaxis. Additional details on this study can be found in the clinical study report.[v]

FEIBA consists of zymogens and traces of activated forms of procoagulant factors II, VII, IX, X, anticoagulants protein C and TFPI, and small amounts of cofactors FV, FVIII and protein S, in a balanced ratio. As mentioned before, FII-FXa complex plays a key role in FEIBA's mode of action (MoA). A recently published study has shown that although the FII-FXa complex are the key components other procoagulant components of FEIBA were necessary to achieve an optimal activity. However prothrombin (FII) is the lead procoagulant component of FEIBA.[1,11]

Due to the complex nature of the composition of FEIBA, pharmacokinetic information cannot be determined by measurement of a single component. In recent studies where FEIBA was used as a comparator product surrogate markers of coagulation were used to determine pharmacokinetics. These surrogate markers of coagulation included determination of thrombin generation, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin–antithrombin complex (TAT) and prothrombin fragment F_{1+2} (F1+2), and aPTT clot waveform analysis, maximum levels of these surrogate markers following FEIBA administration were seen after 10 or at 30 min with variable results at later time points.[10] In another study where thrombin generation was measured in patients following infusion of FEIBA peak thrombin levels were seen predominantly 30 and 60 minutes after infusion.[13] Thus, determination of peak plasma levels of components of FEIBA seems to be most appropriate performed at 30 or 60 minutes after infusion.

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Additional observational, non-interventional studies were conducted with FEIBA NF. Additional details on clinical studies can be found in the FEIBA NF IB.[iv]

[v] Clinical Study Report. Post-Authorization Safety Study of FEIBA NF (Factor VIII Inhibitor Bypassing Activity). An open, uncontrolled, non-interventional observational cohort study of FEIBA NF in hemophiliacs with inhibitors. 10 Oct 2014. Baxalta Inc. US and Baxalta Innovations GmbH.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Uncommon, hypersensitivity reactions observed after infusion of FEIBA have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; these reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. The most commonly reported adverse drug reactions described for FEIBA NF include increased inhibitor titer, somnolence, dizziness, dysgeusia, dyspnea, nausea, chills, pyrexia, chest pain, and chest discomfort.

The possibility of thrombotic events should be considered when FEIBA is used in combination with systemic anti-fibrinolytics such as aminocaproic acid and tranexamic acid. Therefore, anti-fibrinolytics should not be used for approximately 6 to 12 hours before or after the administration of FEIBA.

Animal reproduction studies have not been conducted with FEIBA. There are no adequate, well-controlled studies in pregnant women. It is also not known whether FEIBA can cause fetal harm when administered to a pregnant woman or an affect on reproductive capacity. It is also not known whether FEIBA is excreted in human milk.[1] Subjects within the study should be provided with labeling information and a detailed discussion of benefit risk profile.

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Additional safety experience for FEIBA is provided in the FEIBA NF IB.[iv]

6.6 Compliance Statement

The study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP (R2), Nov 2016), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is:

To evaluate the tolerability and safety of infusing 50% reduced volume FEIBA at the standard infusion rate of 2 U/kg/min, and at increased rates of 4 and 10 U/kg/min, in comparison to the standard rate of 2 U/kg/min at the regular volume

7.2 Primary Objectives

To evaluate tolerability and safety of 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, in particular of thromboembolic events and hypersensitivity reactions

7.3 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
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

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8. STUDY DESIGN

8.1 Brief Summary and Study Design Rationale

This is a 2-part Phase 3b/4 (depending on market authorization status per country), prospective, open-label, multicenter study to be conducted in at least 24 evaluable hemophilia A or B subjects with inhibitors (≥ 0.6 BU in hemophilia A and B) to determine the tolerability and safety of FEIBA with a planned enrollment of 24 evaluable subjects. Evaluable subjects are defined as the ones who complete both parts of the study (i.e. received at least 8 of the 12 infusions; 4 in each part: 2 in each sequence in Part 1 and 2 in each infusion rate in Part 2).

All subjects will receive 3 infusions of FEIBA reconstituted in a regular volume of SWFI, and 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI, with all 6 of these infusions being given at a rate of 2 U/kg/min within Part 1 of the study. In Part 2 of the study, all subjects will receive 3 infusions of FEIBA reconstituted in 50% reduced volume of SWFI at 4 U/kg/min followed by 3 infusions FEIBA reduced volume at a rate of 10 U/kg/min.

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This study has been designed as a 2-way crossover study in order to assess primarily tolerability and safety of FEIBA. By designing it as a crossover study, subjects serve as their own controls. In addition, having received 6 infusions at 2U/Kg/min in Part 1, patients will be near to or at steady state (post 6 infusion of FEIBA) prior to starting Part 2. This study is open-label because it is a change in infusion volume and infusion rate, which would not make it feasible to properly blind. The goal of the study is to determine tolerability and safety of FEIBA in 50% reduced volume SWFI to FEIBA regular volume SWFI, and increase rate of the 50% reduced volume at 4U/kg/min and 10U/kg/min. By being able to reduce the volume and speed of the infusion, subjects will be able to spend less time infusing and reduce infusion burden during the regular use.

The exploratory objectives include pre (within 60 min before infusion) and post-infusion (at 30 min, hours 1, 2, 6, 8 and 12) activity of coagulation factor II (FII); the effect of 50% reduced volume FEIBA and faster infusion rate on coagulation parameters.

FII (prothrombin) was chosen as a lead marker for FEIBA for several reasons:

1. In previously published studies it has been demonstrated that FII is a key protein component of the active ingredient of FEIBA

2. Amongst the vitamin K-dependent proteins, FII has the highest relative plasma level as it has the lowest specific activity, and therefore the absolute amount of FII in FEIBA measured as protein mass is higher than for any other vitamin K-dependent protein
3. The half life of FII is longer than that of any other vitamin K-dependent protein contained in FEIBA.

8.2 Overall Study Design

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 with hemophilia A or B with inhibitors (≥ 0.6 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 is illustrated in Figure 1 and Figure 2.

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In Part 1, 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 for details.

Treatments regimens during Part 1 of the study are:

- Part 1 Sequence A:
    1. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 1, 2, and 3)
    2. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 1, 2, and 3)
- Part 1 Sequence B, patients from sequence A cross over to:
    1. FEIBA 2 U/kg/min in 50% reduced volume SWFI (Infusions 4, 5, and 6)
    2. FEIBA 2 U/kg/min in regular volume SWFI (Infusions 4, 5, and 6)
- Infusion dose:

    All infusions: 85 ± 15 U/kg

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 rate.

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:

- First treatment phase: 4 U/kg/min (Infusions 7, 8, 9)
- Second treatment phase: 10 U/kg/min Infusions 10, 11, 12)
- Infusion dose:

  All infusions: 85 ± 15 U/kg

All infusions will be administered at the hemophilia care centers/study sites. Sample collections may be performed at the hemophilia care centers/study sites, appropriate ambulatory centers and in certain geographies, may also be available at home. Each subject will receive a maximum of 12 IP infusions total [6 in Part 1 and 6 in Part 2]. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions see Section 8.7.2. After each infusion, subjects should be observed for 30 minutes at the study site. Additional details on study design and timing are described in Section 8.7.3. For additional details on managing bleeding episodes, see Section 8.7.4.

See Section 15.4 for additional details on the safety reviews performed by the Internal Safety Monitoring Committee (ISMC).

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8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is expected to be approximately 10 to 13 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is expected to be approximately 9 to 11 months.

The subject participation period is approximately 6 to 11 weeks from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 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.

8.4.2 Exploratory Outcomes Measure

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
2. Evaluate subject treatment preference using Treatment Satisfaction Questionnaire for Medication (TSQM) and patient preference questionnaire

8.5 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 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.

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8.6 Study Stopping Rules

This study will be stopped if 1 or more of the following criteria are met:

1. If 2 or more subjects develop anaphylaxis and / or thromboembolic events following exposure to FEIBA (enrollment and treatment temporarily stopped pending further review by the ISMC)
2. The sponsor or investigator, based on emerging data, considers there to be an unfavorable risk benefit
3. The sponsor or investigator considers continuation of the study unjustifiable for medical or ethical reasons
4. The ISMC recommends study termination

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

The active ingredient of FEIBA is a plasma-derived, freeze-dried, APCC with FVIII inhibitor bypassing activity. FEIBA will be provided in vials with a nominal potency of 500 U/vial, 1,000 U/vial and 2,500 U/vial). FEIBA contains mainly non-activated forms of the 3 coagulation factors, FII, FIX, and FX, as well as activated FVII; and Factor VIII coagulant antigen (FVIII:CAg) present in a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all.

A solution containing 1 U FEIBA shortens the aPTT of FVIII inhibitor plasma to 50% of the buffer value. The product is supplied as freeze-dried powder or friable solid of white to off-white or pale green color.

To standardize conditions in the study, FEIBA should be stored at 2°C to 8°C only. FEIBA should not be allowed to freeze, and should be protected from light. Aseptic techniques must be used for reconstituting and administering FEIBA. Although the chemical and physical stability of the reconstituted product has been demonstrated for 3 hours at room temperature (up to 25°C), however, the solution should be used immediately as the preparation does not contain preservatives. Reconstituted product must not be returned to the refrigerator.

FEIBA will be provided in kits including SWFI for reconstitution. SWFI will be provided in different volumes for preparation of FEIBA infusions at regular volume or reduced volume. For additional information, such as reconstitution instructions, please refer to the Investigator's Brochure, the study specific pharmacy manual and/or other specific instructions provided by the sponsor or sponsor's representative.

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8.7.2 Administration

Following reconstitution, FEIBA should be administered immediately using an intravenous needle and syringes provided by the sponsor for this study. The standard infusion rate of FEIBA is 2 U/kg body weight (BW) per minute, which in a 75kg subject, corresponds to an infusion rate of approximately 2.4 to 7.5 mL/minute depending on the potency (see label on vial).

In order to standardize administration within the study, it is recommended that study drug be administered with an infusion pump. The infusion rate will be modified depending on which part of the study the subject is in, rates of 4 and 10 U/kg/min are also used in this study.

Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions every 48 hours (-8 hours/+24 hours). Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. FEIBA lots may be mixed within an infusion, and whole vials should be rounded up or down to be as close as possible to the accurate dosage, as appropriate.

For additional details, see Table 1 for general information on product preparation, as well as the study documents, and the FEIBA IB.[iv]

Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

Dose calculation for FEIBA will be based on the stated actual potency on vials in respective lots. Information regarding lot used, the actual dose given, date of treatment, treatment start and stop times, as well as any infusion interruptions will be recorded in the case report form (CRF).

Table 1
FEIBA Product Preparation

FEIBA	Diluent for Regular Volume FEIBA	Diluent for 50% Reduced Volume FEIBA
500 U	10 mL	5 mL
1000 U	20 mL	10 mL
2500 U	50 mL	25 mL

Abbreviations: FEIBA=Factor Eight Inhibitor Bypassing Activity.

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Please note that the availability of potencies may vary among countries and regions. Dose calculations should be made based on potencies available at site.

8.7.3 Description of Treatment

Part 1 of the study uses a crossover design to evaluate the tolerability and safety of FEIBA reconstituted in 50% reduced volume SWFI versus regular volume of SWFI (administered at the standard infusion rate of 2 U/kg/min). Part 2 is a non-randomized study with sequential enrollment of subjects who complete Part 1. Part 2 will evaluate the tolerability and safety of infusing FEIBA reconstituted in 50% reduced volume of SWFI at increased infusion rates of 4 and 10 U/kg/min.

All subjects will be screened for eligibility based on the listed inclusion and exclusion criteria. The subject's medical history including hemophilia history, confirmation of inhibitors, bleeding episode history, concomitant medications and history of FEIBA or rFVIIa (dose and frequency) usage for the previous year will be collected at screening. Also recorded will be the use of FEIBA or rFVIIa (dose and frequency) during the screening period, date of last use of FEIBA or rFVIIa treatment and any bleeding episodes experienced. Results of the screening assessments will be used to establish a subject's eligibility for the study.

Part 1

After eligibility is established, the eligible subjects will be randomly assigned (1:1) into Part 1 of the study to receive 3 infusions of FEIBA reconstituted in 50% reduced volume SWFI followed by regular volume SWFI or vice versa every 48 hours (-8 hours/+24 hours).

Additional details on study visits for Part 1 can be found in Section 10.3 and Table 2.

Part 2

Part 2 is non-randomized and uses sequential enrollment of subjects who complete Part 1 of the study. Subjects in Part 2 will first be administered 3 infusions (Infusions 7, 8, and 9) of FEIBA at the 4 U/kg/min rate, followed by 3 infusions (Infusions 10, 11, and 12) of FEIBA at the 10 U/kg/min rate. Infusion 7 will be administered 48 hours (-8 hours/+24 hours) after Infusion 6. The infusions in Part 2 will be administered every 48 hours (-8 hours/+24 hours) to allow time to monitor safety and tolerability of the higher infusion rate. Infusion rates for the treatment phases in Part 2 are:

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

Following the last infusion, a study termination visit will be conducted within 7 days but no sooner than 72 hours after the last infusion.

Additional details on study visits for Part 2 can be found in Section 10.3 and Table 3.

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Additional Treatment and Visit Information

The Schedule of Study Procedures and Events Procedures listed in Table 2 and Table 3 have the visit windows listed in relation to the subject's previous infusion. This is due to the variability in each subjects schedule based on previous therapy and bleeding events.

All infusions will be administered at hemophilia care centers/study sites. Each subject will receive a maximum of 12 IP infusions. Subjects will receive FEIBA at a dose of 85 ± 15 U/kg for all infusions. For specifications on dosing and administration, see Section 8.7.2. For information on break-through bleeding control, see Section 8.7.4.

Study visits will be completed concurrently with study infusions. After subjects have completed the 12 study infusions, they will complete a Study Completion/ Termination Visit within 7 days but no sooner than 72 hours after Infusion 12.

In case of early withdrawal or discontinuation the Study Completion/Termination Visit will need to be completed within 7 days but no sooner than 72 hours after the last IP infusion received.

During each visit, the study staff will inquire with the subject about break-through bleeding events, treatments, and AEs throughout the study. Subjects are encouraged to report AEs to the site during the time spans between visits.

Two subject questionnaires will be administered 5 times during the study, a TSQM questionnaire and a patient preference questionnaire to assess the subjects' satisfaction and preferences for treatments, for additional details see Section 10.5.

Detailed study flowcharts are presented in Figure 1 and Figure 2.

Investigational product may be interrupted or discontinued at any time during the study at the discretion of the investigator based on his/her evaluation of the subject's condition or safety. No dose modification is permitted for this study.

Any infusion site reactions, regardless of causality, will be recorded on the AE CRF. Any concomitant medications, including those used to treat AE(s), will be recorded on the appropriate CRF.

For details on the safety review by ISMC see Section 15.4.

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8.7.4 Management and Treatment of Break-Through Bleeding

Bleeding episodes are managed as described below for each part of the study. In all cases, if the bleeding episode, of whatever severity, is not resolved within 48 hours after an infusion to control bleeding, the subject must contact the hemophilia treatment center/study site for further treatment recommendations.

Screening

During screening, subjects will be asked to keep track of any FEIBA or rFVIIa usage, as the last dose may be used to determine the date of the first infusion of IP. If a subject experiences a bleeding episode during the screening period, subjects will be treated for the bleeding episode per standard of care as determined by the investigator and the patient will be randomized after resolution of bleeding episode.

Bleeding during the study

If bleeding occurs during the study, it will be treated per standard of care.

For bleeding events treated with FEIBA or rFVIIa, a time window of 48 hours post treatment for bleeding should be observed before resuming study infusions. The subject will resume their treatment regimen and visits after control of the bleeding and following the administration window mentioned above. Depending on the clinical circumstances (e.g., treatment of uncontrolled bleeding due to injury and associated complications), the investigator and sponsor should decide if it is appropriate for the subject to continue in the study.

8.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (e.g., infusion center; home, as applicable per study design). Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

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8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

Subject questionnaires may be entered directly onto the CRF.

For additional information on study documentation and CRFs, see Section 17.2.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. ≥ 18 to ≤ 65 years old at the time of screening
2. Hemophilia A or B of any severity, with a documented ≥ 3 months history of inhibitors (≥ 0.6 BU) requiring the use of bypassing agents (FEIBA or rFVIIa) prior to screening. Inhibitor level will be tested at screening if no documented history is available.
3. Hepatitis C virus (HCV) negative, either by antibody testing or polymerase chain reaction (PCR); or HCV positive with stable liver disease
4. Human immune deficiency virus (HIV) negative; or HIV positive with stable disease and CD4 count ≥ 200 cell/mm^3 at screening
5. Adequate venous access
6. Willing and able to comply with the requirements of the protocol
7. If a female of childbearing potential, must have a negative blood pregnancy test and agrees to employ adequate birth control measures for the duration of the study, such as:
   a. Abstain from sexual intercourse
   b. Use a reliable method of contraception (contraception such as an intrauterine device, barrier method [e.g., diaphragm or sponge; female condom not permitted] with spermicide, oral contraceptive, injectable progesterone, sub dermal implant), and have their male partner use a condom
8. If female of non-childbearing potential, confirmed at screening by fulfilling 1 of the following criteria:
   a. Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone levels within the laboratory-defined postmenopausal range or postmenopausal with amenorrhea for at least 24 months and on hormonal replacement therapy
   b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral tubal ligation (with no subsequent pregnancy at least 1 year from bilateral tubal ligation), or bilateral salpingectomy

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9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known hypersensitivity to FEIBA or any of its components
2. Advanced liver disease (e.g., liver biopsy confirmed diagnosis of cirrhosis, portal vein hypertension, ascites, prothrombin time [PT] 5 seconds above upper limit of normal)
3. Planned elective surgery during participation in this study (excluding minor procedures that will not need preventative bleeding treatments, such as exchanges of peripherally inserted central catheters)
4. Platelet count < 100,000/μL
5. Taking Emicizumab (Hemlibra) for bleed prevention
6. Clinical or laboratory evidence of disseminated intravascular coagulation based on medical history
7. Prior history or evidence of thromboembolic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism, etc.
8. Diagnosis of advanced atherosclerosis, malignancy, and/or other diseases that may increase the subject's risk of thromboembolic complications
9. Taking any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) within 30 days prior to enrollment except anti-retroviral chemotherapy.
10. Herbal supplements that contain anti-platelet activity
11. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. Family member or employee of the investigator
13. Clinically significant medical, psychiatric or cognitive illness, or recreational drug/alcohol use that, in the opinion of the investigator, would affect subject safety or compliance

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9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.3.3 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to drop-out (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The ISMC recommends a subject should be taken off the study
- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year postdelivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome
- AE(s)/SAE(s) that the investigator or sponsor feels poses an unacceptable risk for continued dosing in the subject
- Participation in another clinical study involving an IP during the course of the study

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10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the informed consent form [ICF] and assent form, if applicable) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 091501) to be provided by the sponsor, 2- or 3-digit number study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 091501-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

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10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.3 and Supplement 20.4 Schedule of Study Procedures and Assessments (Part 1 and Part 2, respectively) and Supplement 20.5 Clinical Laboratory Assessments. FII activity scheduling can be found in Section 20.6.

10.3.1 Screening and Baseline Assessments

After ICF is obtained, subjects will be screened on-site for eligibility based on the inclusion and exclusion criteria defined in Section 9.1 and Section 9.2, respectively. Screening procedures must be performed within 35 days of Infusion 1.

At screening, subjects will be instructed on the symptoms of thromboembolic and systemic hypersensitivity events by the investigator, and to contact the treatment center/hospital if they experience any symptoms.

Screening assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Medical history, including
  - Hemophilia history, inhibitor development history, bleeding episodes history, history of FEIBA or rFVIIa usage for a year prior to screening
  - Relevant medical and surgical history and all medications including bypassing agents (dose and frequency) taken 4 weeks prior to screening
- Review of concomitant medications/non-drug therapies
- Complete physical examination (see Section 12.6)
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and measurement body weight and height (see Section 12.8)
- Karnofsky performance test assessment (see Section 12.9)
- Clinical laboratory assessments (hematology, FII activity, clinical chemistry, serology testing and inhibitor level if no documentation is available ≥ 3 months prior to screening; see Section 12.7)
- Serum pregnancy test (female subjects of childbearing potential only)
- TSQM and patient preference questionnaires (only at randomization; see Section 10.5)

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After screening and eligibility are determined, the subject will be enrolled in the study. For additional details on bleeding, see Section 8.7.4.

10.3.2 Treatment Visits

10.3.2.1 Infusion Visits

Randomization will occur after the subject has been confirmed to be eligible and prior to the first infusion.

- Randomization of eligible subjects to the following treatment sequences:
  - Part 1 Sequence A: FEIBA 2 U/kg/min in regular volume SWFI (3 infusions), FEIBA 2 U/kg/min in 50% reduced volume (3 infusions)
  - Part 1 Sequence B: FEIBA 2 U/kg/min in 50% reduced volume (3 infusions), FEIBA 2 U/kg/min in regular volume SWFI (3 infusions)

For additional details on the description of treatment, see Section 8.7.3.

During the study (Infusion Visits 1 to 12), subjects will return to the study site according to the schedule presented in Table 2 and Table 3. Prior to administration of IP, the following assessments will be performed at all visits unless otherwise indicated:

- Review of concomitant medications/non-drug therapies
- AE monitoring
- Vital signs (body temperature, pulse rate, blood pressure and respiratory rate)
  - Before administration of IP
  - at 30 minutes after administration of IP
- Clinical laboratory assessments Table 4
- IP administration (infusion site should be monitored for at 30 minutes [± 10 min] after infusion)
- Break-through bleed monitoring
- Coagulation testing
- Infusion site reactions.
- Subjects will be administered the TSQM and patient preference questionnaires:
  - After screening prior to Infusion 1
  - After Infusion 3 prior to Infusion 4
  - After Infusion 6 prior to Infusion 7
  - After Infusion 9, prior to infusion 10
  - After infusion 12 or up to the completion of the Study Completion/Termination Visit
- Factor II levels will be drawn within 60 min before IP administration and at 30 min, hours 1, 2, 6, 8 and 12 after IP administration, as outlined in Table 5. See also information on administration (Section 8.7.2).

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10.3.3 Study Completion/Termination Visit

The Study Completion/Termination Visit including if the subject is discontinuing early will be performed within 7 days but no sooner than 72 hours after Infusion 12, or the last infusion if discontinued early. The following assessments will be performed:

- Review of concomitant medications/non-drug therapies
- AE monitoring

- Breakthrough bleeds monitoring
- Clinical laboratory assessments see Table 4
- Vital signs (body temperature, pulse rate, blood pressure, respiratory rate, and body weight)

10.4 Medications and Non-Drug Therapies

Once subject eligibility has been confirmed for the study, the following medications and non-drug therapies are not permitted during the course of the study:

- Medications:
  - Concomitant use of Emicizumab (Hemlibra)
  - Any immunomodulating drug (e.g., corticosteroid agents at a dose equivalent to hydrocortisone > 10 mg/day, or α-interferon) except anti-retroviral chemotherapy
  - Any investigational drug or device

A subject who receive any of these therapies will be withdrawn from further study participation.

Antifibrinolytics should not be used approximately 6 to 12 hours before or after the administration of FEIBA.

Avoid concomitant use of rFVIIa, except when used to treat breakthrough bleeds that do not respond to FEIBA.

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The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
  - Hemostatic agents, such as tranexamic acid, are permitted, as indicated by the subject's treating physician, to treat mucosal bleeding during the study (these are permitted; however, they should not be taken within 6 to 12 hours before or after administration of FEIBA)
  - Any medications deemed necessary by the subject's physician to treat or prevent any medical condition (with the exception of those listed as not permitted)
  - Any over-the-counter medication used by the subject to treat symptoms or signs of any medical condition

- Supplemental vitamins, minerals
- Any standard of care to treat breakthrough bleeds

- Non-drug therapies:
  - Any non-drug therapy (e.g., physiotherapy) deemed necessary by the subject's physician to treat or prevent any medical condition

10.5 Subject Questionnaires

Two questionnaires will be administered to subjects within this study (TSQM [14] and a patient preference questionnaire). These questionnaires will be used to assess the subject's preferences on the IP, as well as their satisfaction with the IP, and will be collected in the CRF or on paper. Both questionnaires will be administered:

- After screening prior to Infusion 1
- After Infusion 3 prior to Infusion 4
- After Infusion 6 prior to Infusion 7
- After Infusion 9, prior to infusion 10
- After infusion 12 or up to the completion of the Study Completion/Termination Visit

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These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when the subject ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according to the protocol.

Reasons for completion/discontinuation will be reported on the Completion / Discontinuation CRF, including: completed, screen failure, AE (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, e.g., technical problems, and severe hypersensitivity reaction), ISMC recommends a subject should not continue. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the Study Completion/Termination Visit. If the Study Completion/Termination Visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the Study Completion/Termination Visit. If a subject terminates participation in the study and does not return for the Study Completion/Termination Visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.3 Schedule of Study Procedures and Assessments and Supplement 20.5 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

The sponsor may complete the study earlier once 24 evaluable patients complete the study (i.e., before 32 subjects are enrolled).

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10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF PHARMACOKINETICS

Pharmacokinetics will not be evaluated in this study.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay. Admittance for the purpose of PK blood draws will not be considered an SAE.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse

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Additional events which should be reported the same way as SAEs are as follows:

- Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, HCV, hepatitis E virus, or parvovirus B19
- Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE
- Any thromboembolic event (including thrombotic microangiopathy)
- Hypersensitivity reactions

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE. Any pregnancy occurring during the study following maternal or paternal exposure should be reported to the sponsor within 24 hours of the site learning about the pregnancy. The pregnancy should be followed until completion of the pregnancy and up to 1 year postdelivery, if feasible. A separate ICF will be used to cover partner consent for data collection in the event of a pregnancy. Pregnancies not considered an (S)AE as described above will be captured in the CRF.

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Voluntary overnight stays by subjects in hospital or hospital-affiliated facilities for the convenience/compliance with study procedures as described in Section 10.3.2 for reasons unrelated to AEs will not be considered as hospitalization for SAE reporting purposes unless the hospitalization is prolonged.

12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (e.g., IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.1.4 Pre-existing Diseases

Pre-existing diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE CRF.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study termination/completion will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

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For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, it is medically stabilized, or 30 days after the Study Completion/Termination Visit, whichever comes first, and the follow-up information is to be documented in the CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage including overdosing (20% higher than the highest permitted dose), underdosing (20% lower than the lowest permitted dose), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery and 1 year postdelivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject after study completion/termination, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

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These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility.

For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours after IP administration the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

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12.1.2.3 Safety Reporting

Adverse events/SAEs will be assessed at all study visits as outlined in the Schedule of Study Procedures and Assessments (see Table 3) and Section 12.1.

Adverse Events/SAEs are to be recorded on the AE page of the CRF. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the IP, must be reported immediately (within 24 hours of the study center's first knowledge of the event). All SAEs must be reported by completing the relevant CRF page(s) in English. Once the SAE has been recorded, SAEs must be reported to the sponsor to meet the 24-hour timeline requirement (contacts and instructions to be provided in separate documentation).

The initial SAE information reported on the applicable CRF pages (must at least include the following:

- Protocol Number
- Subject identification number and demographics (gender, age at onset of event and/or date of birth)
- Investigational product exposure
- Medical Term for Event (Diagnosis preferably)
- Description of the (S)AE, including:
  - Date of onset
  - (S)AE treatment (drug, dose, route of administration)
  - Causal relationship by the investigator
  - Measures taken (i.e., action taken regarding IP in direct relationship to the AE)
- Seriousness criteria (i.e., death, life-threatening, or other criterion)
- Cause of death
- Autopsy findings (if available)
- Name, address, fax number, email, and telephone number of the reporting investigator (for paper SAE Report Forms)

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12.1.3 Medical Device Safety Reporting

The IP kit contains the BaxJect II Hi-Flow needleless transfer device. All Serious Injuries (SI) and Unexpected Adverse Device Events (UADE) must be reported to the sponsor as an SAE in the same process as described above.

Serious injury is defined as:

- Life-threatening injury or illness results in permanent impairment/ damage to body function/ structure.
- Requires medical or surgical intervention to preclude permanent impairment/ damage to body function/ structure.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

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The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee (EC) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF . These events will be considered as SAEs but will not be included in the analysis of SAEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims
- Medication errors: an error (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication e.g., administration of incorrect dose

Any NMCs of the product will be documented on an NMC form and reported to the sponsor (or sponsor's representative) within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

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12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

General medical history will be collected for 4 weeks prior to screening. Any information on the subjects' hemophilia history will be collected a year prior to screening including documented history of hemophilia, confirmation of inhibitors, bleeding episodes history, and history of FEIBA or rFVIIa usage.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening (as described in Table 2 and Table 3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Section 12.1.1.4), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

Assessments will be performed at a central laboratory (see Section 15.7), according to the laboratory manual. Blood samples that remain after study testing is done may be stored and used for any additional testing as needed (see Section 12.7.6). Samples will be destroyed after a maximum of 2 years from the time the final study report has been completed.

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12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of 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.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, aspartate aminotransferase (AST), total protein, albumin, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening and at study completion/termination.

In addition, serum samples for pregnancy tests for females of childbearing potential will be collected at screening.

12.7.2 Activity of FII and Coagulation Testing

Blood samples for the determination of FEIBA components FII will be taken at screening, within 60 (±15) min before and at 30 (±10) min, after completion of each infusion. In addition, hours 1 (±15min), 2 (±30min), 6 (±1hour), 8 (±2hours) and 12 (±4hours) samples will be taken after infusion 1,3,4,6,9 and 12. The preinfusion FII can be considered as post infusion 48 hr timepoint sample for the prior infusion; therefore no additional blood sample will be required for this timepoint (see Section 20.6 for sampling time points and allowed sampling time windows). The date and time of each sample collections will be documented in the subject's CRF.

Blood will be obtained for the assessment of coagulation testing and consist of aPTT, PT, and thrombotic markers (D-Dimers, prothrombin fragment F 1+2, TAT, and fibrinopeptide A). Coagulation testing will be performed during the study and samples will be taken within 60 (±15) min before and at hours 1 (±15min), and 6 (±1) hour after infusion 1,3,4,6,9 and 12 (see Section 20.6 for sampling time points and allowed sampling time windows).

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12.7.3 Viral Serology

Viral serology testing will include HIV-1 and HIV-2 antibody, hepatitis A virus (HAV) antibody, hepatitis B surface antigen (HBsAg), HCV antibody, parvovirus B19 (immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG). The HCV titer will be confirmed by PCR for all subjects reported as HCV positive. All viral serology assessments will be performed at screening and at the Study Completion/Termination Visit.

12.7.4 CD4 Levels

At screening only, CD4 levels will be determined using flow cytometry in the case of a subject being HIV positive.

12.7.5 Assessment of Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.4), or is due to another issue that will be specified. If the abnormal value was not clinically

significant, the investigator will indicate the reason, i.e., because it is due to a pre-existing disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. Backup samples that remain after study testing is done may be stored and used for additional testing (e.g., further evaluation of an abnormal test or an AE. Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) measured once at screening and weight (lb or kg) measured at screening and completion/termination will also be collected.

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Vital signs will be measured at screening and within 30 minutes before and after (except weight) administration of IP, at each Infusion study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine position.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1 and record the medical diagnosis (preferably), symptom, or sign on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Karnofsky Performance Test

The Karnofsky Performance Test is a status scale (0-100) utilized to measure the level of activity and medical care requirements in subjects. It is an investigator based assessment of subject status which evaluates the subjects' ability to carry on normal life activities, as well as the symptoms of their disease. In this scale, a high number performance status represents high functionality, and a lower number represents low functionality and likely rapid progression of disease.[15] Subjects will be scored using this scale at screening.

12.10 Infusion Site Evaluations

The current site of IP infusion will be assessed for immediate local reactions at 30 minutes (±10 min) after infusion. In addition, infusion sites will be monitored by the subject for up to 12 hours after infusion, and will be discussed with the site staff during the next study visit.

Infusion sites will be monitored for pain, tenderness, erythema, and swelling. Infusion site evaluations will be made by clinical staff or by the subject or caregiver. If an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Infusion sites will continue to be reviewed at each study visit, and any infusion site reactions will be followed until resolution. Each infusion site reaction will be categorized using the intensity grading described for AEs in Section 12.1.2.1.

12.11 Special Treatment Considerations

Subjects will be screened for eligibility in the study as described in Section 9.1 and Section 8.7.3, and will be informed of the study specific restrictions and requirements of the study. Subjects who are not willing to comply with the study requirements and restrictions of the study will not be eligible for enrollment.

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All biological agents carry the risk of hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic reaction

Proteins may also cause redness, itching, swelling, or pain locally at the infusion site.

Thromboembolic events have been observed with bypassing agents including FEIBA. Clinical manifestations of these events may include, but not limited to:

- myocardial infarction
- deep vein thrombosis
- pulmonary embolism
- stroke and
- transitory ischemic attack

Sometimes, these reactions can be life-threatening. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a subject experiences an acute hypersensitivity reaction after an infusion of IP, the subject should be managed appropriately and given instruction to receive relevant supportive care.

Subjects who experience a potentially severe hypersensitivity reaction will be discontinued from IP. They will complete a Termination/Study Completion Visit, and will be monitored for stabilization or resolution of the AE. Premedication to prevent allergic reactions will not be permitted, as severe hypersensitivity reactions are an outcome measure for this study.

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13. STATISTICS

Data handling will be conducted by the contract research organization. The data will be inspected for inconsistencies by performing validation checks.

Statistical analysis for this study will be descriptive in nature. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the statistical analysis plan (SAP) prepared by the contract research organization and approved by the sponsor before database lock.

13.1 Sample Size and Power Calculations

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 patients 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.

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13.2 Datasets and Analysis Cohorts

Safety: The safety analysis set will include all subjects who received at least 1 dose of IP (FEIBA). All safety analyses will be performed on the safety analysis set. Subjects will be evaluated according to the treatment received.

13.3 Handling of Missing, Unused, and Spurious Data

All data will be evaluated as observed. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of withdrawal.

13.4 Methods of Analysis

13.4.1 Primary Outcome Measure

13.4.1.1 Analysis of the Primary Outcome Measure (Parts 1 and 2)

AEs, SAEs and AEs leading to discontinuation, thromboembolic events, hypersensitivity and infusion site reactions that occur during or after the IP infusion will be presented in summary tables. Summary tables shall indicate the number of subjects who experienced adverse events. Separate tables will be carried out for temporally associated adverse events; and for temporally associated or potentially related adverse events as assessed by the investigators. Temporally associated AEs 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.

In addition, tables will be prepared to list each AE, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s).

AEs will be grouped by system organ class. Each event will then be divided into defined severity grades (mild, moderate, severe). The tables will also divide the AEs into those considered related to the infusion and those considered unrelated. These tables will also be carried out for temporally associated adverse events; and for temporally associated or causally related adverse events.

AEs and SAEs for each subject, including the same event on several occasions, will be listed separately, giving both MedDRA preferred term and the original term used by the investigator, system organ class, severity grade, seriousness, relation to the treatment, onset date, and stop date.

AEs that occurred before first IP infusion will be listed separately.

Lab results and vital signs which are considered AEs will be listed.

13.4.2 Exploratory Outcome Measures

All exploratory outcome measures will be analyzed for descriptive purposes only.

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 48 hour time point, the pre-infusion value of the next infusion will be taken), and maximum standardized increase from the pre-dose level will be analyzed for descriptive purposes only.

The standardized increase from pre-dose levels will be calculated as (Ct – Cpre)/dose where Ct refers to the FII level at time point t in U/dL, Cpre is the corresponding pre-dose level in U/dL, and dose refers to the weight adjusted FEIBA dose administered in U/kg which will be summarized per subject and infusion as minimum, time-averaged up to 48 hours and maximum over the sampling period. The time-averaged standardized increase (TASI) will be calculated as a weighted average of the standardized increases with weights corresponding to linear interpolation between sampling time points.

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, period and volume as fixed effect and subject nested within sequence as random effect.

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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 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 described using point estimates for infusion volume and rates with corresponding two-sided 95% confidence intervals obtained from the models described above.

Full details of the statistical analysis will be specified in the SAP.

13.5 Planned Interim Analysis of the Study

There is no planned interim analysis other than a safety data review by the ISMC.

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14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP E6 R(2), and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

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15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

Primary objective of the study is to monitor safety parameters throughout the study with a special emphasis on hypersensitivity and thromboembolic events. Adverse event data will be collected at each visit assessed and documented on the CRFs as outlined in Section 12.1.2.3.

Serious adverse events are monitored and reported per the safety reporting guidelines as outlined in Section 12.1.2.3.

This study will be monitored by an ISMC. The ISMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from the ongoing clinical study. For this study, the ISMC will be composed by appropriate members of clinical, safety, and biostatistics division that are not involved in the active execution of the trial. The ISMC can stop a study if it finds toxicities or if treatment is proven to be not beneficial.

All SAEs will be reviewed within 24 hours by the Chair of the ISMC. There are 3 planned ISMC meetings:

1. Within 24 hours after 6 subjects in Part 1 (3 subjects in each group) have completed Infusion 5
2. Within 24 hours after 6 subjects have completed Infusion 7 (Part 2)
3. Within 24 hours after 6 subjects have completed Infusion 10 (Part 2)

ISMC preplanned meetings will be held concurrently with the ongoing study.

Subjects can continue with their scheduled therapy and assessments unless the ISMC warrants that the trial needs to be suspended due to safety concerns. Additional ad hoc meetings of the ISMC may be convened as appropriate per ongoing safety evaluations.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

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15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

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16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided to patients will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

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16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper/electronic format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

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The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper/electronic format, and this documentation will be considered source documentation. Changes to an CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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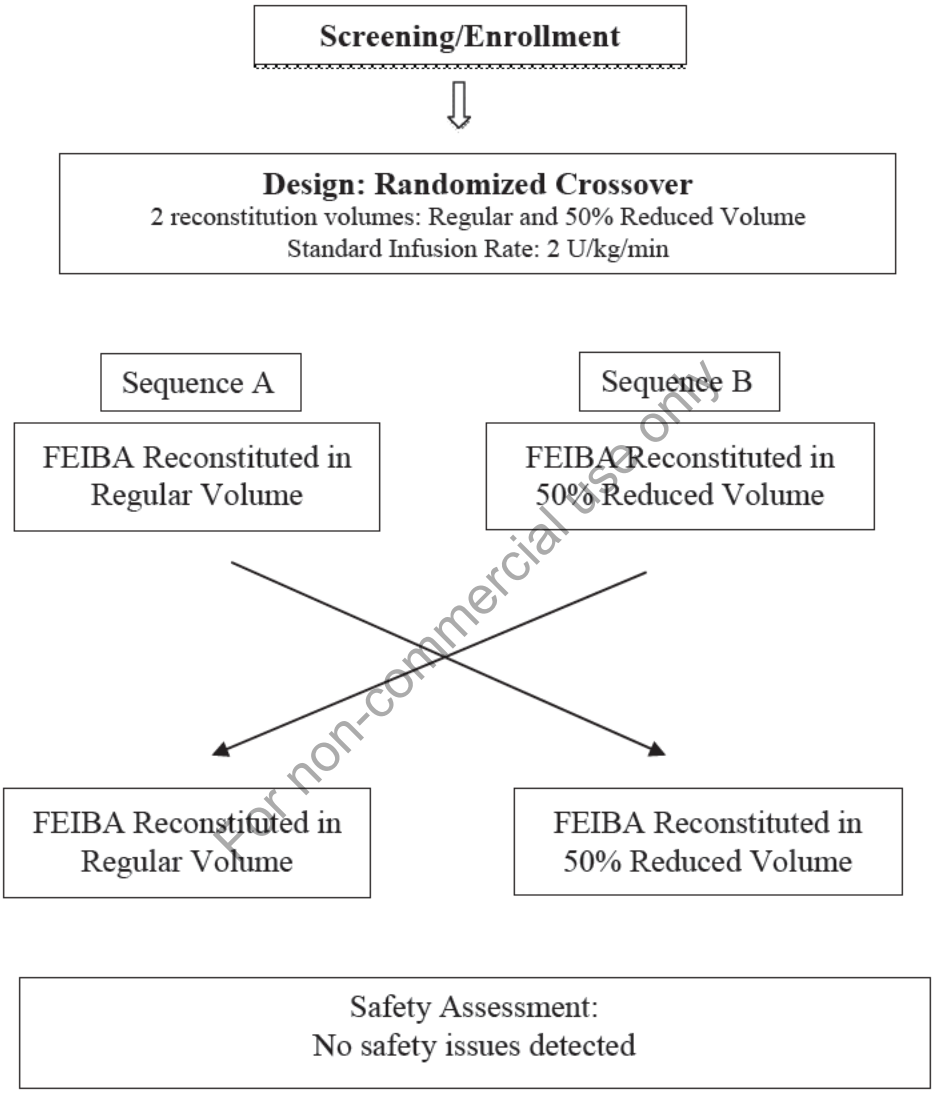
20. SUPPLEMENTS

20.1 Study Flow Chart Part 1

Figure 1
Study Design for Part 1 Baxalta Clinical Study 091501



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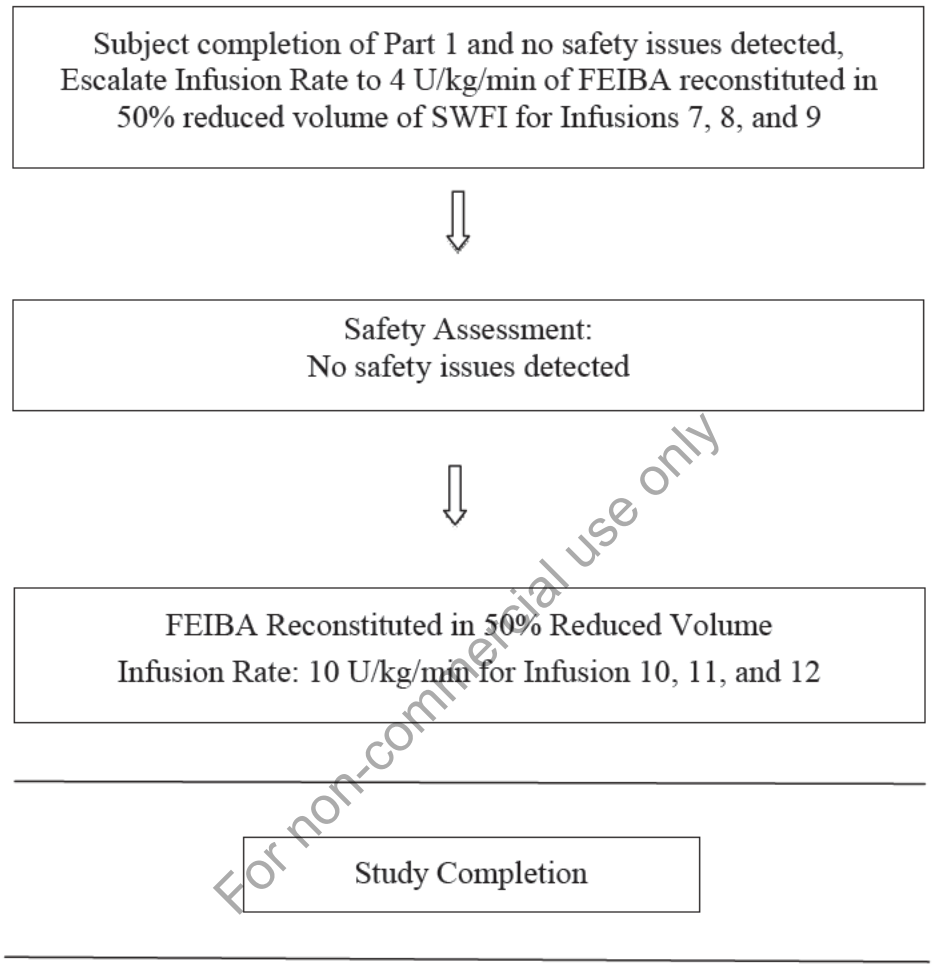
20.2 Study Flow Chart Part 2

Figure 2
Study Design for Part 2 Baxalta Clinical Study 091501



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20.3 Schedule of Study Procedures and Assessments (Part 1)

Table 2
Schedule of Study Procedures and Assessments (Part 1)

Procedures/ Assessments	Screening Assessments	Randomization	Study Visits[a]						
			Infusion #1	Infusion #2	Infusion #3		Infusion #4	Infusion #5	Infusion #6
Study Visit Windows[b]	A maximum of -35 days to 0		Day 1	within 48 hrs (-8/+24) from Infusion 1	48 hrs (-8/+24) from Infusion 2		48 hrs (-8/+24) from Infusion 3	48 hrs (-8/+24) from Infusion 4	48 hrs (-8/+24) from Infusion 5
Informed Consent[c]	X								
Eligibility Criteria	X								
Medical History	X								
Medication and Non-drug Therapies	X		X	X	X		X	X	X
Physical Examination	X								
Pregnancy Test	X								
Vital Signs[d]	X		X	X	X		X	X	X
Karnofsky Performance Test	X								
Laboratory Assessments[e]	X		X	X	X		X	X	X
Inhibitor level if no documentation	X								
Factor II levels[f, g]	X		X	X	X		X	X	X
Adverse Events, breakthrough bleeds, and infusion site reactions[h]			X	X	X		X	X	X
IP Treatment			X	X	X		X	X	X
TSQM and patient preference questionnaires[i]		X				X			
Coagulation testing[j]			X		X		X		X

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Abbreviations: ICF=informed consent form; IP=investigational product

[a] A Study Completion/Termination Visit is to be completed in Part 1 only for subjects who withdraw or discontinue prior to the end of the study. If a subject withdraws or discontinues, this visit should be completed within 7 days but no sooner than 72 hours from the last infusion that the subject received. Otherwise, the Study Completion/Termination Visit will occur at the end of Part 2 (see Table 3).

[b] Study Visit Windows:

Infusion 1 can be scheduled after screening assessments have been completed; all other infusions will occur within 48 hours (-8/+24hours) from the previous infusion.

[c] Occurs at enrollment (prior to any study-specific procedure).

[d] Vital signs will include body temperature, pulse rate, blood pressure, and respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[e] For laboratory assessments, see Section 20.5.

[f] FII levels within 60 minutes (±15min) before, and 30 mins (±10min) after infusions 2 and 5.

[g] FII levels within 60 min (±15 min) before, and at 30 min (±10 min) and hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour) and 12 (±4hours) after infusions 1, 3, 4 and 6.

[h] The infusion site will be monitored for AEs for 30 ±10 minutes after each study infusion. See Section 12.10 for details. SAEs occurring before IP exposure. See Section 12.3 for details.

[i] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit.. See Section 10.5 for details.

[j] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) pre-infusion within 60 min (±15 min), and post-infusion at 1 hr ± 15 min and 6 hr ± 1 hr (mentioned in Section 12.7.2).

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20.4 Schedule of Study Procedures and Assessments (Part 2)

Table 3
Schedule of Study Procedures and Assessments (Part 2)

Procedures/ Assessments	Study Visits									
		Infusions 7	**Infusion 8**	**Infusion 9**		**Infusion 10**	**Infusion 11**	**Infusions 12**		**Study Completion/ Termination Visit[a]**
Rate of Infusion		**Rate: 4 U/kg/min**				**Rate: 10 U/kg/min**				
Study Visit Windows[b]		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion	48 hours (-8/+24) from previous infusion		72 h to 7 days from Infusion 12 (or last infusion)
Medications and Non-drug Therapies		X	X	X		X	X	X		X
Vital Signs[c]		X	X	X		X	X	X		X
Laboratory Assessments[d]		X	X	X		X	X	X		X
Factor II levels[e, f]		X	X	X		X	X	X		
Adverse Events, breakthrough bleeds, and infusion site, infusion related reactions[g]		X	X	X		X	X	X		X
IP Treatment		X	X	X		X	X	X		
TSQM and patient preference questionnaires[h]	X				X				X	
Coagulation testing[i]				X				X		

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[a] The Study Completion/Termination Visit includes cases of withdrawal or discontinuation. This visit should be done within 7 days but no sooner than 72 hours after Infusion 12). If a subject withdraws or discontinues, this visit should be done within 7 days but no sooner than 72 hours after the last infusion that the subject receives.

[b] Infusions will occur within 48 hours (-8/+24hours) from the previous infusion.

[c] Vital signs will include body temperature, pulse rate, blood pressure, respiratory rate,. Blood pressure will be measured when subjects are in the supine position. On the day of IP administration, vital signs will be taken within 30 minutes prior to infusion and within at 30 minutes after completion of the infusion. Height, measured once at Screening, and weight measured at Screening and Completion/Termination will also be collected.

[d] For laboratory assessments, see Section 20.5.

[e] FII levels within 60 minutes (±15min) before, and 30 mins (±10min) after infusions 7, 8, 10 and 11.

[f] FII levels within 60 min (±15 min) before, and at 30 min (±10 min) and hours 1 (±15 min), 2 (±30 min), 6 (±1 hour), 8 (±2 hour) and 12 (±4hours) after infusions 9 and 12.

[g] The infusion site will be monitored for AEs for 30 ±10 minutes after the infusion. See Section 12.10 for details. SAEs **occurring before IP exposure** will not be included in the analysis of SAEs. See Section 12.3 for details.

[h] Questionnaires (TSQM and patient preference questionnaire) will be administered after screening prior to Infusion 1, after Infusion 3 prior to Infusion 4, after Infusion 6 prior to Infusion 7, after Infusion 9 prior to infusion 10, and after infusion 12 or up to the completion of the Study Completion/Termination Visit. These questionnaires can be completed between visits but should be completed prior to the start of the next infusion. The final questionnaire should be completed prior to or during the Study Completion/Termination Visit. See Section 10.5 for details.

[i] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A) pre-infusion within 60 min (±15 min), and post-infusion at 1 hr ± 15 min and 6 hr ± 1 hr (mentioned in Section 12.7.2).

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20.5 Clinical Laboratory Assessments

Table 4
Clinical Laboratory Assessments

Assessments	Screening Visit	Infusions 1, 3, 4, 6, 9, 12	Study Completion/ TerminationVisit[a]
Hematology[b]	X		X
Clinical Chemistry[c]	X		X
Coagulation Testing[d]		X	
Serological Testing[e] and CD4[f]	X		X
Pregnancy Test[g]	X		

[a] Includes cases of withdraw or discontinuation.
[b] Hematology assessments include: CBC (Hct, Hgb, RBC count, WBC count) with differential, MCV, MCHC, and platelet count.
[c] Clinical chemistry assessments include sodium, chloride, potassium, bicarbonate, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, GGT, 5'-nucleotidase.
[d] Coagulation testing will include: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A (mentioned in Section 12.7.2).
[e] Serological testing will include: HIV-1 and HIV-2 antibodies (HIV+, check CD4 count–screening visit only), HAV antibodies, , HBsAg, HCV antibody, parvovirus B19 (IgM and IgG), cytomegalovirus antibodies (IgM and IgG), and Epstein-Barr virus antibodies (IgM and IgG).
[f] CD4 at screening in case of positive HIV test results.
[g] A serum pregnancy test will be performed for females of childbearing potential.

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20.6 FII activity and Coagulation testing

Table 5
FII and Coagulation Testing Time Frame

Procedures/Assessments	**PART 1** **Infusions 1, 3, 4, 6**	**PART 2** **Infusions 9, 12**	**Infusions** **2, 5, 7, 8, 10, 11**
FII activity At screening	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min 1 hr ± 15 min 2 hr ± 30 min 6 hr ± 1 hr 8 hr ± 2 hr 12 hr ± 4 hr	Preinfusion: within 60 min (±15 min) Post infusion: 30 ± 10 min
Coagulation testing: aPTT, PT, thrombotic markers (D-Dimers, Prothrombin fragment F 1+2, TAT, fibrinopeptide A)	Infusions 1, 3, 4, 6, 9, and 12 Preinfusion: within 60 min (±15 min) Post infusion: 1 hr ± 15 min 6 hr ± 1 hr		

Abbreviations: FII=Factor II, h=hours; min=minutes

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22. SUMMARY OF CHANGES

Protocol 091501 AMENDMENT 4 (Global): 2018 MAR 07

Replaces: Protocol 091501 AMENDMENT 3 (Global): 2017 SEP 14

In this section, changes made in this amendment from the previous version of the protocol, dated **2017 SEP 14**, are described and their rationale is given.

1. **Throughout the document**
   Description of change: "concentration" of Factor II was changed to "activity" of Factor II throughout.
   Purpose of change: To provide clarification as the assay measures activity.

2. **Synopsis and Outcome Measures, Section 8.4.1**
   Description of Change: Primary outcome measure rephrased.
   Purpose of Change: To clarify facilitation of statistical analysis of the primary outcome measure after study completion.

3. **Synopsis, Targeted Accrual**
   Description of change: added "enroll 32 patients" to have 24 evaluable.
   Purpose of change: To provide clarity for study recruitment, that enrolling 32 subjects will provide the required 24 evaluable subjects by allowing a non-evaluable rate of 25%.

4. **Synopsis and Statistics, Section 13**
   Description of change: Added and rephrased: *Evaluable patients 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.*
   Purpose of change: Rephrased to clarify criteria for evaluable subjects. Added the non-evaluable rate to specify number of subjects to be enrolled, to achieve the required evaluable subjects.

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5. **Synopsis and Exclusion Criteria, Section 9.2**
   Description of Change: Exclusion criterion added: taking Emicizumab (Hemlibra) added as an exclusion criterion.
   Purpose of Change: As Emicizumab was recently licensed, there is a need to mention that administration of it concurrently with FEIBA during this study constitutes an exclusion criterion.

6. **Synopsis and Analysis of the Primary Outcome Measure (Parts 1 and 2), Section 13.4.1**
   Description of Change: Clarification that vital signs and lab results considered AEs will be listed in summary tables.
   Purpose of Change: To facilitate statistical analysis of the primary outcome measure after study completion.

7. **Synopsis and Analysis of the Exploratory Outcome Measure 1**
   Description of Change: Text added: 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 48 hour time point, the pre-infusion value of the next infusion will be taken), and maximum standardized increase from the pre-dose level will be analyzed for descriptive purposes only.

   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, period and volume as fixed effect and subject nested within sequence as random effect.

   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 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 described using point estimates for infusion volume and rates with corresponding two-sided 95% confidence intervals obtained from the models above.

   Purpose of Change: To facilitate statistical analysis of the exploratory outcome measure after study completion.

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8. **Synopsis and Study Design, Section 8.2**
   Description of change: The following text was added: Evaluable patients from Part 2 are all subjects who receive 4 of the 6 planned infusions, at least 2 infusions per infusion rate.
   Purpose of change: Rephrased to clarify criteria for evaluable subjects in part 2 of the study.

9. **Medications and Non-Drug Therapies, Section 10.4**
   Description of Change: Addition of Emicuzimab as a product not permitted as a concomitant therapy. Also, addition of rFVIIa as a product not permitted for concomitant/sequential therapy that should not be used unless FEIBA does not work to treat breakthrough bleeding.
   Purpose of Change: To provide clarity in terms of permissible study medication .

10. **Definitions, Section 12.1.1**
    Description of Change: Addition of the following text in italics: "Any pregnancy occurring during the study following maternal or paternal exposure should be reported to the sponsor within 24 hours."
    Purpose of Change: To provide clarity in terms of permissible study conduct.

11. **Activity of FII and Coagulation Testing , Section 12.7.2**
    Description of Change: Slight changes to timing of blood draws, specifically addition of a pre-infusion blood draw for coagulation parameters to add a control to compare to post-infusion blood draw findings, and removal of a blood draw at 12 hours to make the study less strenuous for the patient. Also added a blood draw for FII at screening.
    Purpose of Change: To provide clarity and include blood draws that are required for proper data analysis.

12. **Viral Serology, Section 12.7.3**
    Description of Change: Removal of hepatitis B virus antibody from testing.
    Purpose of Change: For HBV, antigen testing is included in the protocol so antibody testing is not needed.

13. **Schedule of Study Procedures and Assessments, Section 20.3 and Section 20.4**
    Description of Change: Addition of Xs to clarify when blood would be drawn to monitor FII levels, and to clarify that pre-infusion blood draws will be considered as 48 hour post-infusion time point for prior infusion.
    Purpose of Change: Clarification of study procedure.

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14. **Clinical Laboratory Assessments, Section 20.5**
    Description of Change: Removal of HBVantibody from the testing schedule.
    Purpose of Change: HBV antigen testing is included in the protocol so antibody testing is not needed.

15. **Activity of FII and Coagulation Testing, Section 20.6**
    Description of Change: Clarification of the FII blood draw schedule in Table 5 .
    Purpose of Change: Clarification of study procedures.

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INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 4 (Global): 2018 MAR 07

Replaces

AMENDMENT 3 (Global): 2017 SEP 14

OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

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By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: Anti-inhibitor Coagulant Complex Nanofiltered (activated prothrombin complex concentrate [APCC]) FEIBA NF

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

PROTOCOL IDENTIFIER: 091501

CLINICAL TRIAL PHASE 3b/4

AMENDMENT 4 (Global): 2018 MAR 07

Replaces

AMENDMENT 3 (Global): 2017 SEP 14

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OTHER ID(s)
NCT Number: to be determined
EudraCT Number: 2015-005781-39
IND NUMBER: 13715

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Coordinating Investigator Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative Date
[redacted] MD,
[redacted]
Global Clinical Development Operations