Statistical Analysis Plan

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Protocol Number and Title:	MAA-201 Phase 2 Study of Next-Generation Coagulation Factor VIIa, Marzeptacog Alfa (Activated) in Adult Subjects with Hemophilia A and B
Protocol Version and Date:	2.0, 25 August 2018
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Statistical Analysis Plan Catalyst Biosciences, Inc. **Protocol #** MAA-201

Version 2.0 **Syneos Health #**1009647

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2.0	05Nov2018	Tina Yan	Version 2.0 Final Release

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Statistical Analysis Plan Catalyst Biosciences, Inc. **Protocol # MAA-201**

Version 2.0 **Syneos Health #1009647**

I confirm that I have reviewed this document and agree with the content.

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Statistical Analysis Plan

Version 2.0

Catalyst Biosciences, Inc. **Protocol #** MAA-201

Syneos Health #1009647

TABLE OF CONTENTS

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualized bleeding rate
AE	Adverse Event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC_{inf}	Area under curve for PK vs time concentration profile from time 0 extrapolated to infinity
AUC_t	Area under curve for PK vs time concentration profile from time 0 to the last measured concentration
AUE	Area under curve effect for PD actual measured values vs time profile from time 0 to the last measured concentration
AUE_{CFB}	Area under curve effect for PD change from baseline vs time profile from time 0 to the last measured concentration
AUCextrap%	Area under curve % extrapolation to infinity
$CFB_{max/min}$	Max (or minimal) observed value of the change in baseline for PD biomarker depending on the direction of the change
C_{max}	Max observed PK concentration
C_{min}	Min observed trough PK concentration
CL	Plasma clearance of the drug for intravascular route
C_{last}	Last observed PK concentration
CL/F	Apparent plasma clearance of the drug for extravascular route
BMI	Body Mass index
ECG	Electrocardiogram
$E_{max/min}$	Max (or minimal) observed value of PD biomarker depending on the direction of the change
EQ-5D	European Quality of Life-5 Dimensions
Haem-A-QoL	Hemophilia A quality of life questionnaire
HAL	Hemophilia Activities List
GMR	Geometric mean ratio
ICH	International Conference on Harmonization
ICF	Informed consent form

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Abbreviation	Description
ITT	Intent to treat
IV	Intravenous
λz	First order terminal elimination rate constant
MarzAA	Marzeptacog alfa (activated)
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
R2adj	Adjusted square coefficient for linear regression of terminal elimination
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
T1/2	Terminal elimination half-life
TA_AUE	Time adjusted area under curve effect for PD actual measured values vs time profile from time 0 to the last measured concentration
TA_AUECFB	Time adjusted area under curve effect for PD change from baseline in values vs time profile from time 0 to the last measured concentration
TEAE	Treatment Emergent Adverse Event
TEmax	Time to max PD effect
Tlast	Time for the last measurable PK concentration

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Abbreviation	Description
TLF	Table, Listing and Figure
Tmax	Time to max PK concentration
VAS	Visual analogue scale
Vz	Volume of distribution for intravascular injection
Vz/F	Apparent volume of distribution for extravascular injection
WHO	World Health Organization

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2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1 RESPONSIBILITIES

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2 TIMINGS OF ANALYSES

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study.

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3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To evaluate the efficacy and safety of a daily subcutaneous (SC) treatment regimen with MarzAA for bleeding prophylaxis in adult subjects with Hemophilia A and B with an inhibitor.

3.2 SECONDARY OBJECTIVE(S)

- To determine the pharmacokinetics (PK) of SC MarzAA
- To determine the bioavailability of MarzAA when given via SC
- To determine the pharmacodynamics (PD) of SC MarzAA
- To evaluate and compare the levels of thrombogenicity markers following administration of a SC dose of 30 µg /kg MarzAA with the IV dose of 18 µg/kg MarzAA
- To evaluate for evidence of the development of antibodies to MarzAA, wild type recombinant factor VIIa (wt-rFVIIa), and/or wt-FVII, and to determine if these are neutralizing antibodies
- To determine the annualized bleeding rate (ABR) during MarzAA treatment compared to the rate of historic on-demand treatments

3.3 BRIEF DESCRIPTION

This multi-center, open-label Phase 2 study will evaluate the PK, bioavailability, PD, efficacy and safety of a daily SC treatment regimen with MarzAA for bleeding prophylaxis in adult subjects with hemophilia A and B with an inhibitor. The study will enroll and dose, both intravenously and subcutaneously, a total of 12 adult male subjects with severe congenital hemophilia A or B with an inhibitor, and history of frequent bleeding episodes during the 6 months prior to enrollment, as per the individual's bleeding and treatment records.

At the screening visit and prior to any study procedures, subjects will sign an informed consent form (ICF). Eligibility to participate in the study will be determined by inclusion and exclusion criteria elicited from medical history, hemophilia history, physical examination, laboratory assessments and an electrocardiogram (ECG). At screening, subjects will be provided with a diary in which they will be instructed to record any adverse events (AEs) and concomitant medication. The screening period duration may be up to 4 weeks.

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After the first IV dose of MarzAA, subjects will record daily study drug administration (to assess compliance), injection site assessment, any AEs they may experience, and bleeding episodes (location, inciting event if not spontaneous, and treatment administered), and patient reported outcome (PRO) scales.

Once a subject is enrolled into the trial, the study will be conducted in two phases consisting of three parts (occurring consecutively):

Part 1: Single dose administration

Part 1a (24 hours): Single IV administration of MarzAA at 18 µg /kg with assessment of PK, PD, and safety for 24 hours post-dose.

Part 1b (48 hours): Single SC administration of MarzAA at 30 µg /kg with assessment of PK, PD, and safety for 48 hours post-dose

Part 2: Daily SC administration

Daily SC administration of MarzAA at 30 µg /kg with assessment of PK, PD, and safety at designated days for 50 treatment days.

If dose escalation is required because of a spontaneous bleeding episode, then assessments of PK, PD, and safety will be at designated days for an additional 50 treatment days.

3.4 SUBJECT SELECTION

3.4.1 Inclusion Criteria

1. Confirmed diagnosis of severe congenital hemophilia A or B with an inhibitor.

2. History of frequent spontaneous bleeding episodes (historical annualized bleeding rate [ABR] of ≥12).

3. Male, age 18 or older.

4. Agreement to use highly effective birth control throughout the study.

5. Affirmation of informed consent with signature confirmation before any trial-related activities. (Trial related activities are any procedure that would not have been performed during normal clinical management of the subject).

6. Stated willingness to comply with all study procedures and availability for the duration of the study.

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3.4.2 Exclusion Criteria

1. Receiving prophylaxis treatment.

2. Previous participation in a trial involving Subcutaneous Administration of rFVIIa (Novo Seven or MOD-5014) or any trial using a modified rFVIIa such as: NN1731 or BAY86-6150. Prior participation in a trial of LR769 or rFVIIa-FP (CSL689 is permissible.

3. Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 3-half-lives or absence of clinical effect, whichever is longer.

4. Known positive antibody to FVII or FVIIa detected by central laboratory at screening.

5. History of clinically relevant coagulation disorders other than congenital hemophilia A or B.

6. Platelet count <100,000 based on screening laboratory assessments.

7. Advanced atherosclerotic disease (i.e. known history of coronary artery disease (CAD), ischemic stroke, etc.), or known deep venous thrombosis (DVT) or considered to be at a high risk of venous thromboembolic event (VTE) as judged by the Investigator.

8. Known or suspected allergy to trial product or related products.

9. Absolute cluster of differentiation 4 (CD4) count <200 cells/μL.

10. Receiving immunomodulatory therapy.

11. Compromised hepatic or renal function:

- Alanine aminotransferase and aspartate aminotransferase levels ≥5 × the upper limit of normal
- Total bilirubin level ≥2 mg/dL (>35 μmol/L) unless there is a known history of Gilbert's syndrome
- Serum albumin ≤ the lower limit of normal
- Serum creatinine (Cr) level >1.25 x the upper limit of normal

12. Inability or medical, psychosocial, or familial issues that might prevent full participation and cooperation with the procedures and requirements of the clinical trial as determined by the potential subject and physician investigator.

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3.5 DETERMINATION OF SAMPLE SIZE

With a total of 12 subjects and assuming a null hypothesis of an ABR of 12, then if the true ABR for MarzAA is 6 or less, with a one-tailed 2.5% significance level there is near 100% power to demonstrate this using a one sample Poisson test of the null hypothesis. Even if only 6 subjects were available to be pooled for this analysis, the power would still be in excess of 99%. Thus, a sample of 12 subjects is expected to provide sufficient power for the primary endpoint analysis in this study.

Twelve subjects were chosen to increase the size of the safety data set.

If a subject does not complete the study as defined in the protocol (i.e., before receiving study drug for 50 days at the same dose level) another subject will need to be enrolled in replacement.

3.6 TREATMENT ASSIGNMENT & BLINDING

Part 1a: Single IV administration

Each subject will receive an IV dose of 18 µg/kg MarzAA. PK, PD, and safety assessments will be collected pre-dose and post-dose at 5 and 30 minutes and at Hour 1, 3, 6, 9, 12, and 24.

Part 1b: Single SC administration

After the initial 24 hours, the same subject will receive a SC dose of 30 µg/kg MarzAA. PK, PD, and safety assessments will be done at pre-dose and repeated at Hour 3, 5, 7, 9, 12, 24, 30, and 48. At any time during this period, subjects will be trained by appropriate study staff to self-administer a SC injection.

Part 2: Daily SC administration

At Day 1 of daily SC dosing, subjects will begin their self-administered dosing regimen. MarzAA will be self-administered by subjects daily (at approximately the same time every day), starting with a SC dose of 30 µg/kg MarzAA. At each dose, subjects will record the day and time of the SC injections in their diary. If a spontaneous bleeding episode (defined as one that is precipitated by normal activities of daily living [ADL]) occurs before the fifth daily dose, subjects will continue at the current dosing level. If a spontaneous bleeding episode occurs after the fifth daily dose, the MarzAA dose will be escalated to the next dose level. Three dose escalations are allowed during part 2: 60, 90, and 120 µg/kg (maximum dose). At each dose level escalation, safety and PK/PD will be monitored to ensure that dose escalation to a higher dose level is appropriate. If a subject requires a third dose escalation to the fourth dose level, then they will continue treatment with that dose for 50 days and complete the study, regardless if a spontaneous bleeding episode occurs during the highest treatment dose level.

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Treatment of a spontaneous bleeding episode: Subjects will use their current bypass regimen for any spontaneous or traumatic bleed that occurs while on study drug. If treatment for a breakthrough bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event; treatment dose administered; and determine follow-up plans for that event, including to arrange for a blood specimen to be drawn (if feasible) before further administration of either study drug or bypassing agent used for treatment. This information will also be recorded in the subjects' diary.

Dose interruption and surgery: Daily SC study injections will be interrupted, as needed, if there is a need for a surgical procedure; an event requiring extended (>48 hours) hospitalization; a thrombotic event; clinical evidence of inhibitor formation; or laboratory results suggesting an antibody may be developing.

Measurements:

MarzAA antigen and activity levels, as well as coagulation parameters, will be measured during Part 2 of the study at Day 1 (At pre-dose and Hour 7 post-dose, Day 3 (Pre-dose and Post-dose Hour 7), Day 5 (Pre-dose and Post-dose Hour 7), Day 7 (Pre-dose and Postdose Hour 7).

If no spontaneous bleeding occurs at the first dose level in part 2 of the study, trough antigen and activity, as well as coagulation parameters, will be measured on days 14, 21, 28, and 50 after starting their dosing regimen.

If spontaneous bleeding occurs after the fifth daily dose at any dose level, MarzAA antigen and activity levels will be measured within 6 hours of the spontaneous bleed (if feasible). Specimens for coagulation and immunogenicity testing will also be drawn.

Once it is determined to escalate to the next dose level, a pre-dose and Hour 7 post dose specimen, will be drawn for PK, coagulation, and thrombogenicity markers on Day 7 after the dose has been escalated to estimate the new trough and peak concentrations (PCs) and PD. MarzAA antigen and activity levels, as well as coagulation parameters, will then be measured (pre-dose) at Day 14, 21, 28, and 50 after dose escalation.

Immunogenicity assays: Specimens for immunogenicity testing (antibody to MarzAA, neutralizing activity, cross reactivity) will be drawn at screening, Part 1a pre-dose, Part 1b pre-dose, and during part 2 pre-dose on Day 1, 7, 14, 21, 28, and 42, and then every two weeks until end of study.

3.7 DOSING AND ADMINISTRATION

This is an open-label study. Each subject will receive the study drug according to three phases occurring consecutively:

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- In Part 1a (24 hours), subjects will receive a single IV administration of MarzAA at 18 µg /kg with assessment of PK, PD, and safety for 24 hours post-dose.
- In Part 1b (48 hours), subjects will receive a single SC administration of MarzAA at 30 µg /kg with assessment of PK, PD, and safety for 48 hours post-dose
- In Part 2, subjects will receive daily SC administration of MarzAA at 30 µg/kg with assessment of PK, PD, and safety at designated days for 50 treatment days. During Part 2, dose may be escalated to 60, 90, or 120 µg/kg, if required because of spontaneous bleeding, with assessment of PK, PD, and safety at designated days for an additional 50 treatment days.

Each subject will participate in each phase of the study.

For Part 1a and 1b, investigational product will be administered at the study site by qualified study personnel.

During Part 1b, subjects will be trained to reconstitute and self-administer the study drug. Once proficiency in drug reconstitution and SC administration has been confirmed the subject can then proceed with home administration of study treatment.

On Day 1 of Part 2 daily SC dosing, subjects will begin their self-administered dosing regimen. MarzAA will be self-administered in the morning by the subjects daily (at approximately the same time), starting with a SC dose of 30 µg/kg MarzAA. Subjects will record the day and time of the SC injections in their diary.

If a spontaneous bleeding episode (defined as one that is precipitated by normal ADL) occurs before the fifth daily dose, the subject will continue at the current dosing level.

If a spontaneous bleeding episode occurs after the fifth daily dose, the MarzAA dose will be escalated to the next dose level. Three dose escalations are allowed during Part 2: 60, 90, and 120 µg/kg (maximum dose).

On those days that the subject is required to present for a study visit during which laboratory evaluations are scheduled, he will bring his study drug for self-administration of his daily dose under observation by study team staff after pre-dose assessments are completed.

3.8 STUDY PROCEDURES AND FLOWCHART

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Statistical Analysis Plan Catalyst Biosciences, Inc. **Protocol #** MAA-201

Version 2.0 **Syneos Health #1009647**

Table 1. Part 1a: Single dose administration of MarzAA 18 µg/kg IV

Study Period	Screening	Treatment								
Study Day/Hour	(Up to 4 weeks prior)	Pre-dose (- 5 min)	Dosing (Hr 0)	Post-dose (at 5 and 30 min) (± 2 m)	Hr 1 (± 10 m)	Hr 3 (± 10 m)	Hr 6 (± 10 m)	Hr 9 (± 30 m)	Hr 12 (± 30 m)	Hr 24 (± 1.5 hr)
Informed Consent	X									
Demographic Parameters	X									
Inclusion and Exclusion Criteria review	X	X								
Medical and Hemophilia History[1]	X	X								X
Concomitant Medications[1]	X	X								X
Vital Signs	X	X								X
Height (screening only) & Weight	X	X								X
Physical Examination[1]	X	X								X
Clinical Signs of Thrombosis[2]	X	X								X
Hematology and Chemistry[3]	X	X								X
Coagulation Assays[4]	X	X		X	X	X	X	X	X	X
Thrombogenicity markers[4]	X	X		X	X	X	X	X	X	X
Pharmacokinetic (PK) sampling[4]		X		X	X	X	X	X	X	X
Immunogenicity assays[4]	X									
Troponin level[3]	X	X								X
ECG	X									X
Study Subject Training[5]	X									
Diary entry of PRO scales[6]	X									X
Diary entry of bleeding episodes, AEs, injection site assessment	X	X								X
Adverse Events	X	X	X	X	X	X	X	X	X	X
MarzAA administration			X							

1. Complete evaluation at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit and review of diary entries (including PRO scales).
2. **Clinical Signs of Thrombosis – See Appendix A.**
3. Local Laboratory: **Hematology** - CBC and platelet count, CD4. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, BUN, creatinine. **Troponin Level.**
4. Central Laboratory: **Coagulation assays** – PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT. **Thrombogenicity markers** – D-dimer, F1+2, and TAT. **Pharmacokinetics** – MarzAA antigen and activity. **Immunogenicity assays** – to FVII, FVIIa, and MarzAA.
5. Training of investigational drug administration & injection site assessment, spontaneous or traumatic bleeding episodes & treatment, evaluation & diary entry of AEs, & patient reported outcome (PRO) scales.
6. PRO scales (**Appendix B**): EQ-5D, VAS; Haem-A-QoL; HAL.

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Table 2. Part 1b: Single dose administration of MarzAA 30 µg/kg SC (immediately following Part 1a)

Study Period	**Treatment**									
Study Day/Hour	**Pre-dose*** (- 5 min)	**Dosing (Hr 0)**	**Hr 3** (± 10 m)	**Hr 5** (± 10 m)	**Hr 7** (± 10 m)	**Hr 9** (± 30 m)	**Hr 12** (± 30 m)	**Hr 24** (± 1.5 hr)	**Hr 30** (± 1.5 hr)	**Hr 48** (± 1.5 hr)
Medical and Hemophilia History[1]	X							X		X
Concomitant Medications[1]	X							X		X
Vital Signs	X							X		X
Weight	X							X		X
Physical Examination[1]	X							X		X
Clinical Signs of Thrombosis[2]	X							X		X
Hematology and Chemistry[3]	X							X		X
Coagulation Assays[4]	X		X	X	X	X	X	X	X	X
Thrombogenicity markers[4]	X		X	X	X	X	X	X	X	X
Pharmacokinetic (PK) sampling[4]	X		X	X	X	X	X	X	X	X
Immunogenicity assays[4]	X									
Troponin level[3]	X							X		
ECG								X		
Diary entry of PRO scales[5]	X							X		X
Diary entry of bleeding episodes, AEs, injection site assessment	X							X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X
MarzAA administration		X								
SC administration training & proficiency confirmation		X						X		X

***NOTE:** Assessments required for Pre-dose in Part 1b that have been completed at Hour 24 in Part 1a do not have to be repeated if within 2 days.

1. Complete evaluation at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit and review of diary entries (including PRO scales).
2. **Clinical Signs of Thrombosis – See Appendix A.**
3. Local Laboratory: **Hematology** - CBC and platelet count, CD4. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, BUN, creatinine. **Troponin Level.**
4. Central Laboratory: **Coagulation assays** – PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT. **Thrombogenicity markers** – D-dimer, F1+2, and TAT. **Pharmacokinetics** – MarzAA antigen and activity. **Immunogenicity assays** – to FVII, FVIIa, and MarzAA.
5. PRO scales (**Appendix B**): EQ-5D, VAS; Haem-A-QoL; HAL.

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Statistical Analysis Plan Catalyst Biosciences, Inc. **Protocol #** MAA-201

Version 2.0 **Syneos Health #1009647**

Table 3. Part 2: Daily SC administration of MarzAA 30 µg/kg SC (following Part 1b), no spontaneous bleeding occurs after the fifth daily dose.

Study Period	**Treatment**										
Study Day/Hour	**Day 1***	**Day 3 (+1d)**	**Day 5 (+1d)**	**Day 7 (+1d)**	**Day 14 (±2d)**	**Day 21 (±2d)**	**Day 28 (±2d)**	**Day 42 (±3d)**	**Day 50 (+3d)**	**Un-sched-uled[9]**	**End of Study[10]**
Medical and Hemophilia History[1]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X		X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Clinical Signs of Thrombosis[2]	X	X	X	X	X	X	X	X	X	X	X
Hematology and Chemistry[3]	X			X	X	X	X		X	X	X
Coagulation Assays[4,5]	X	X	X	X	X	X	X		X	X	X
Thrombogenicity markers[4,5]	X	X	X	X	X	X	X		X	X	X
Pharmacokinetic (PK) sampling[4,5]	X	X	X	X	X	X	X		X	X	X
Immunogenicity assays[4,6]	X			X	X	X	X	X[6]		X[6]	X
Troponin level[3]				X						X	
Diary entry of PRO scales[7]	X			X	X	X	X	X	X	X	X
Diary entry of IP, bleeding episodes and treatment, AEs, injection site assessment	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
SC Daily MarzAA administration[8]	◄						►				
IP compliance & proficiency confirmation	X	X	X	X	X	X	X	X	X	X	
IP dispensing, inventory and accountability	X	X	X	X	X	X	X	X	X	X	X

***NOTE:** Assessments required for Day 1 that have been completed at Hour 48 in Part 1b do not have to be repeated if within 2 days.

** Assessments performed on Day 3, 5, 7, 14, 21, 28, 42, and 50 will be done pre-dose, unless otherwise specified.

1. Interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit and review of diary entries (including PRO scales).
2. **Clinical Signs of Thrombosis – See Appendix A.**
3. Local Laboratory: **Hematology** - CBC and platelet count, CD4. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, BUN, creatinine. **Troponin Level.**
4. Central Laboratory: **Coagulation assays** – PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT. **Thrombogenicity markers** – D-dimer, F1+2, and TAT. **Pharmacokinetics** – MarzAA antigen and activity. **Immunogenicity assays** – to FVII, FVIIa, and MarzAA.
5. Days 1, 3, 5, 7, 14, 21, 28, 50: Sampling is done predose and predose at 7 hours. MarzAA antigen and activity levels, as well as coagulation parameters, will be measured during Part 2 of the study at Day 1 (at predose and Hour 7 predose; Day 3 (Predose only), Day 5 (Predose only), and Day 7 (Predose only)
6. After Day 42, sampling will be done every two (2) weeks until the End of Study visit.
7. PRO scales (**Appendix B**): EQ-5D, VAS; Ham-A-QoL; HAL.
8. Subjects must have been at the same dose level for 50 days to complete the study.
9. At an Unscheduled Visit, perform only the assessments as appropriate to the reason for the visit.
10. End of Study Visit will occur 30 days after the last dose.

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Statistical Analysis Plan Catalyst Biosciences, Inc. **Protocol #** MAA-201

Version 2.0 **Syneos Health #1009647**

Table 4. Part 2: If spontaneous bleeding occurs after the fifth daily dose (only if necessary)

Study Period	**Treatment**								
Study Day/Hour	**Day 0***	**Day 7 (+1d)**	**Day 14 (± 2d)**	**Day 21 (± 2d)**	**Day 28 (± 2d)**	**Day 42 (± 3d)**	**Day 50 (+3d)**	**Un-scheduled[10]**	**End of Study[11]**
Medical and Hemophilia History[1]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X		X	
Physical Examination	X	X	X	X	X	X	X	X	X
Clinical Signs of Thrombosis[2]	X	X	X	X	X	X	X	X	X
Hematology and Chemistry[3]		X	X	X	X		X	X	X
Coagulation Assays[4,6]	X[5]	X	X	X	X		X	X	X
Thrombogenicity markers[4,6]		X	X	X	X		X	X	X
Pharmacokinetic (PK) sampling[4,6]	X[5]	X	X	X	X		X	X	X
Immunogenicity assays[4,7]	X[5]		X		X	X[7]		X[7]	X
Troponin level[3]	X	X						X	
Diary entry of PRO scales[8]		X	X	X	X	X	X	X	X
Diary entry of IP, bleeding episodes and treatment, AEs, injection site assessment	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
SC Daily MarzAA administration[9]		←	—	—	—	—	→		
IP compliance & proficiency confirmation		X	X	X	X	X	X	X	
IP dispensing, inventory and accountability	X	X	X	X	X	X	X	X	X

*** NOTE**: When a spontaneous bleeding episode and dose escalation occurs, the "day count" is reset to zero. The day the spontaneous bleeding episode occurs and subsequent time until treatment resolution is considered Day 0. Dose escalation starts the next day (Day 1).

**Assessments performed on Day 7, 14, 21, 28, 42, and 50 will be done pre-dose, unless otherwise specified.

1. Interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit and review of diary entries (including PRO scales).
2. **Clinical Signs of Thrombosis – See Appendix A.**
3. Local Laboratory: **Hematology** - CBC and platelet count, CD4. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, BUN, creatinine. **Troponin Level**.
4. Central Laboratory: **Coagulation assays** – PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT. **Thrombogenicity markers** – D-dimer, F1+2, and TAT. **Pharmacokinetics** – MarzAA antigen and activity. **Immunogenicity assays** – to FVII, FVIIa, and MarzAA.
5. Day 0 PK sampling should occur within 6 hours of spontaneous bleed, if feasible.
6. Days 7, 14, 21, 28, 50: Sampling will be done Pre- and Post-dose at 7 hours.
7. After Day 42, sampling will be done every two (2) weeks until the End of Study visit.
8. PRO scales (**Appendix B**): EQ-5D, VAS; Haem-A-QoL; HAL.
9. Subjects must have been at the same dose level for 50 days to complete the study.
10. At an Unscheduled Visit, perform only the assessments as appropriate to the reason for the visit.
11. End of Study Visit will occur 30 days after the last dose.

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4. ENDPOINTS

4.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is:

- ABR (spontaneous and total) during Part 2 when on final MarzAA dose level versus recorded historical ABR

Bleeding events will be evaluated as follows:

- Spontaneous versus traumatictraumatic

A spontaneous bleeding episode is defined as one that is precipitated by normal ADL.

4.2 SECONDARY ENDPOINTS

The secondary endpoints will include:

- Occurrence of breakthrough bleeds requiring escalation to higher dose level.
- Safety parameters: Occurrence of clinical thrombotic event not attributable to another cause, and occurrence of antibody formation resulting in a decreased endogenous level of FVII or FVIIa.
- Change in coagulation parameters (prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, MarzAA antigen and activity levels, and thrombin generation test (TGT)) from pre-dose.
- Occurrence of an antibody response to MarzAA and whether it is inhibitory and cross-reactive to wt-rFVIIa or wt-FVII.
- Clinically significant levels of thrombogenicity markers resulting from daily SC administration of MarzAA
- Feasibility and ease of use of daily SC self-administration by patient as measured by compliance with treatment
- Breakthrough bleeding events will be categorized as follows:
    - Number of bleeds that are life threatening
    - Number that require hospitalization and/or blood transfusion
    - Number of muscle bleeds

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4.3 EXPLORATORY ENDPOINTS

- Identification of biomarker(s) such as antigen levels, activity levels, or global thrombosis assay evaluation that can be used to predict or correlate with a subject's lack of spontaneous bleeding.

- Identification of biomarker(s) such as D-dimer, F1+2, or a functional assay of the FVIIa activity that will identify or predict clinical thrombogenicity with the daily SC administration of MarzAA.

- Identification of biomarker(s) such as D-dimer, F1+2, or a functional assay of the FVIIa activity that will identify or predict clinical thrombogenicity of daily SC administration of MarzAA when use of rescue medication is required.

- Patient-reported outcome (PRO) measures: European Quality of Life-5 Dimensions (EQ-5D), Visual analogue scale (VAS); Hemophilia A quality of life questionnaire (Haem-A-QoL); Hemophilia Activities List (HAL)

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5. ANALYSIS SETS

5.1 SCREENED/ENROLLED SUBJECTS

- Screened Subject: Any subject who signed the study-specific informed consent
- Screen Failures: Any subject who signed the study-specific informed consent but failed to meet study requirements (inclusion/exclusion criteria) during screening
- Enrolled Subject: Any subject who was successfully screened

5.2 SAFETY POPULATION

Safety population is defined as any patient who receives at least one dose.

5.3 INTENT-TO-TREAT (ITT) POPULATION

ITT population is defined as any patient who receives at least one dose.

5.4 MODIFIED ITT POPULATION

Modified ITT population is defined as any patient who receives at least 7 SC doses at 30 µg/kg.

5.5 PER PROTOCOL POPULATION

Per protocol population is defined as any patient who completes at least 50 exposure days at the highest dose level(SC product). Any protocol deviations which will have impact on the primary endpoint will be determined before database lock, based on a review of all protocol deviations.

5.6 PHARMACOKINETIC (PK) POPULATION

PK population is defined as any patient who has received one dose and has at least one measured PK concentration post-dose. The PK data will be listed for this population and used in all PK analyses. The PK data for subjects with protocol deviations affecting the results may be excluded from summaries and analyses. Any Protocol deviations pertaining to the validity of PK analyses (and thus inclusion in the PK population) will be determined before the database lock (and receipt of PK data), based on a review of all protocol deviations.

5.7 PHARMACODYNAMIC (PD) POPULATION

PD population is defined as any patient who has received one dose and who has PD data pre-dose or post-dose. The PD data will be listed for this population and used in all PD and PK/PD analyses. The PD data for subjects with protocol deviations affecting the

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results may be excluded from summaries and analyses. This will be determined before the database lock based on review of all protocol deviations.

5.8 PROTOCOL DEVIATIONS

Protocol deviations will be listed. All major protocol deviations will be summarized in the study report for the following deviation category:

- Inclusion criteria
- Exclusion criteria
- Treatment deviation (incorrect or missed doses)
- Improper informed consent procedure
- Noncompliance (SAE not reported)
- Visit schedule (out of window)
- Procedure not per protocol, or visit not done
- Concomitant medication
- Laboratory sample (not done or results not available)
- Other

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6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 KEY DEFINITIONS

6.1.1 Baseline

Baseline is defined as the last assessment (pre-dose) prior to the first administration of the study drug in Part 1a. This baseline will be used for both part 1a and part 1b, and will be used in all efficacy and safety analyses in section 12

For the baselines for PK and PD analyses, they will be defined separately in Section 9 and Section 10.

6.2 MISSING DATA

Missing data will not be imputed in this study. All analyses will be based on available data.

6.3 VISIT WINDOWS

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, if the scheduled visit is not available in the dataset, unscheduled visit will be mapped to a scheduled visit for analysis using the date and/or time of collection/assessment to mapped to the intended visit using the visit window specified below. If more than one record occurs within the same visit window where only one assessment is expected, then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Study Part	Visit in Protocol	Analyses Visit	Visit Window
Part 1a	Hr 0	Part 1a, Hr 0	-
	5 min	Part 1a, 5 min	3 - 7 min
	30 min	Part 1a, 30 min	28 - 32 min
	Hr 1	Part 1a, Hr 1	50 - 70 min
	Hr 3	Part 1a, Hr 3	170 - 190 min
	Hr 6	Part 1a, Hr 6	350 - 370 min
	Hr 9	Part 1a, Hr 9	510 - 570 min
	Hr 12	Part 1a, Hr 12	690 - 750 min
	Hr 24	Part 1a, Hr 24	1350 - 1530 min
Part 1b	Hr 3	Part 1b, Hr 27	1610 - 1630 min
	Hr 5	Part 1b, Hr 29	1730 - 1750 min
	Hr 7	Part 1b, Hr 31	1850 - 1870 min
	Hr 9	Part 1b, Hr 33	1950 - 2010 min

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	Hr 12	Part 1b, Hr 36	2130 – 2190 min
	Hr 24	Part 1b, Hr 48	2790 – 2970 min
	Hr 30	Part 1b, Hr 54	3150 – 3330 min
	Hr 48	Part 1b, Hr 72	4230 – 4410 min
Part 2	Day 3	Part 2, Day 6	6 – 7 days
	Day 5	Part 2, Day 8	8 - 9 days
	Day 7	Part 2, Day 10	10 – 11 days
	Day 14	Part 2, Day 17	15 – 19 days
	Day 21	Part 2, Day 24	22 – 26 days
	Day 28	Part 2, Day 31	29 – 33 days
	Day 42	Part 2, Day 45	42 – 48 days
	Day 50	Part 2, Day 53	53 – 56 days

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7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized overall and presented for the number and percentage of subjects for the following (a consort diagram can be found in Appendix V):

- Screened subject (only number of subjects will be presented)
- Screen failure
- Enrolled subjects
- Safety population
- ITT population
- Modified ITT population
- Per protocol population
- Subjects who completed the treatment
- Subjects who discontinued the treatment and the reason for discontinuation
- Subjects who completed for each study part (Part 1a, Part 1b, and Part 2)
- Subjects who discontinued for each study part (Part 1a, Part 1b and Part 2)
- Subjects who completed the study
- Subjects who discontinued the study and the reason for discontinuations

7.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be presented for demographic and baseline characteristics using the safety populations. Demographic and baseline characteristics, including age, gender, race, ethnicity, height, weight, and body mass index (BMI), will be summarized overall and listed.

The below conversions will be used to calculate BMI:
Height (in cm) = height (in inches) * 2.54
Weight (in kg) = weight (in lbs) * 0.4536

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BMI (kg/m^2) = Weight (kg)/[Height $(m)^2$]

7.3 MEDICAL HISTORY

The medical history of subjects will be coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. The number and percentage of subjects with medical history will be summarized overall presenting the number and percentage of subjects with a history in each SOC and in each preferred term (PT) for the safety population.

7.4 HEMOPHILIA HISTORY

Hemophilia history will be summarized overall for the categories below:

- Number and percentage of hemophilia type (Hemophilia A and Hemophilia B)
- Age at diagnosis
- Number and percentage of clinical setting of hemophilia diagnosis (Prenatal, at birth and unanticipated/unexpected bleeding)
- Factor VIII level
- Factor IX level
- Number and percentage of clinical setting of diagnosis of inhibitor (Incidental laboratory finding, non-responsiveness to factor infusion and other)
- Number and percentage of history of orthopedic procedure (Yes and No)
- Number and percentage of types of orthopedic procedure (Joint aspiration, synovectomy, fusion, joint replacements and other)

7.5 HEMOPHILIA BLEED HISTORY

The frequency of hemophilia bleed history will be summarized descriptively for the prior 6 months and the prior 50 days respectively.

Individual plot to show the bleeding pattern will be presented for each subject by the time the bleeding starts and ends.

Hemophilia bleed history and other hemophilia history will be listed.

7.6 CONCOMITANT MEDICATION

The number and percentage of subjects using each concomitant medication will be summarized overall according to the World Health Organization Drug Dictionary

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(WHODRUG) Global B3 Sept 2017 for the safety population. Anatomical Therapeutic Chemical (ATC) level III and PT will be used. Subjects with multiple uses of a concomitant medication will be counted only once for a given PT in a given ATC level III term and only once within a given ATC level III term.

The number and percentage of subjects using each hemophilia specific medication will be summarized separately.

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8. EFFICACY

Efficacy analyses will be based on the ITT, modified ITT and per-protocol population and summarized by study part, final dose level and overall.

The primary efficacy endpoint will be tested inferentially using a one-sided test with 2.5% significance level. All other statistical tests will be performed at the 0.05 significance level using two-sided tests (i.e. two-sided 95% CIs).

8.1 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1 Primary Efficacy Endpoint

The analysis of the primary endpoint (annualized bleeding rate (ABR) for spontaneous and traumatic bleeds) under the final treated dose of MarzAA for each subject will be based on the one sample test compared to a pre-defined rate assumed for the on-demand therapy. The pre-defined rate is assumed to be 12 bleeds in total (i.e. one bleed per month), defined as the minimum ABR for each subject according to inclusion criterion 2 (defined as the null hypothesis (H0)). The comparison of the actual ABR for MarzAA at the highest dose for an individual will be performed using the one-sample test for a Poisson rate versus the pre-defined margin of 12 (using an exact Poisson regression model in SAS 9.4). A one-tailed 2.5% significance level will be used For the following hypothesis test:

$$H_0: ABR_{MarzAA} >= 12 \text{ versus } H_1: ABR_{MarzAA} < 12.$$

The ITT population will be used for the statistical analysis of the primary efficacy endpoint.

In order to calculate the ABR for subjects who do not have a total of 12 months of follow up, the ABR will be calculated as:

(Number of bleeds/number of months on study) x 12

Note: number of months is calculated as the exposure (in days) at each dose level / 30.5.

Formally, assume that the hypothesis is: H_0: $\lambda=\lambda_0$ vs Ha: $\lambda<\lambda_0$. Let n be the number of subjects, we can calculate the critical point N_{crit} which is the largest integer meeting

$$\sum_0^{Ncrit} e^{-n\lambda 0} \frac{(n\lambda 0)^k}{k!} \leq \alpha \qquad (1)$$

If the total number of bleeds during the final MarzAA dose for all subjects is less than N_{crit}, then the null hypothesis is rejected.

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In order to compare ABR (spontaneous and total) during part 2 when on final MarzAA dose level with the actually recorded historical data, a Poisson regression model using PROC GENMOD procedure will be used with the ABR as the dependent variable, intercept as the independent variable and log e transformed of 12 will be used as offset variable. An example SAS code has been provided in Appendix I.

8.1.2 Sensitivity Analyses

The analysis in Section 8.1 will also be performed using the modified ITT population and per-protocol population.

8.2 SECONDARY ENDPOINTS AND ANALYSES

8.2.1 Analysis of Occurrence of Breakthrough Bleeds and Proportion of Bleeding Days

A breakthrough bleed is any spontaneous or traumatic bleed. Subjects who had breakthrough bleeds out of total bleedings will be summarized separately as spontaneous and traumatic as well as combined and listed using ITT, modified ITT population and per-protocol population.

Breakthrough bleeding events will be categorized and summarized as follows:

- Number and percentage of bleeds that are life threatening for each dose level within each study part
- Number and percentage that require hospitalization and/or blood transfusion for each dose level within each study part
- Number and percentage of muscle bleeds for each dose level within each study part

A listing of breakthrough bleeding events will be provided, including start and end date of bleeding.

Mean pre-treatment between bleeding intervals for all subjects will be compared with post-treatment between bleeding intervals for each dose level in Part 2 using paired t-test. This analysis will only be performed if there are at least 6 data points at pre- or post treatment. The analysis will be performed using ITT, modified ITT and per-protocol population.

The proportion of bleeding days pre-treatment by subject will be compared with the proportion of bleeding days post-treatment for each dose level in Part 2 using paired t-test after transforming the individual proportions by an arcsin transformation ($2*\arcsin(\sqrt{p})$). This analysis will only be performed if there are at least 6 data points at pre- or post treatment. The proportion of bleeding days pre-treatment will be

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calculated as (cumulative number of bleeding days recorded in bleed history / 180). The proportion of bleeding days post-treatment will be calculated as (cumulative number of bleeding days from the first SC dose to last dose in eDiary in Part 2 / cumulative number of actual treatment days for each dose level in Part 2). The analysis will be performed using ITT, modified ITT and per-protocol population.

Graphic presentation will also be provided for the interval of each bleeding event and each subject.

8.2.2 Analysis of Occurrence of Clinical Thrombotic Event

The following categories will be summarized using ITT and modified ITT population:

- the number and percentage of subjects with thrombotic event (1 or more events)
- the number and percentage of subjects with one thrombotic event
- the number and percentage of subjects with two thrombotic events
- the number and percentage of subjects with three thrombotic events

The data will be listed.

8.2.3 Analysis of Coagulation

Actual and change from baseline values will be summarized for the following coagulation parameters:

- PT
- aPTT
- fibrinogen
- MarzAA antigen activity level
- TGT

8.3 EXPLORATORY ENDPOINTS AND ANALYSES

8.3.1 Analysis of European Quality of Life-5 Dimensions (EQ-5D)

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and unable to

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perform. Score 1, 2, 3, 4 and 5 will be assigned to each level: level 1 = 1, level 2 = 2, level 3=3, level 4=4 and level 5=5.

The health state index score will be calculated based on EQ-5D-5L Index Value Calculator - EuroQol, assessing the dimension scores from the 5 dimensions using the UK version, ranging between 1.0 (best imaginable health) and -0.594 (worst imaginable health).

Descriptive analysis for actual and change from baseline scores for health state index score will be provided by study part, dose level and visit.

The one sample Wilcoxon signed rank test for a single group will be used to compare the baseline health state index score vs. the last post-baseline assessment at the final treatment dose health state index score, independently for each dose level in Part 2. A 95% Confidence interval for the median change from baseline value at the last post-baseline assessment at the final treatment dose will also be obtained. Sample SAS code can be found in Appendix I.

8.3.2 Analysis of EQ-Visual Analogue Scale (VAS)

Descriptive analysis for actual and change from baseline scores for VAS will be provided by study part, dose level and visit.

The one sample Wilcoxon signed rank test for a single group will be used to compare the baseline VAS result vs the last post-baseline assessment at the final treatment dose VAS result, independently for each dose level in Part 2. A 95% Confidence interval for the median change from baseline value at the last post-baseline assessment at the final treatment dose will also be obtained. Sample SAS code can be found in Appendix I.

8.3.3 Analysis of Hemophilia A quality of life questionnaire (Haem-A-QoL)

Haem-A-QoL comprises of 10 scales and one total Haem-A-QOL transformed score (HAEMA_Z):

- Physical health (PHYS) – 5 items
- Feelings (FEEL) – 4 items
- View of yourself (VIEW) – 5 items
- Sports and Leisure (SPORT) – 5 items
- Work and school (WORK) – 4 items
- Dealing with Haemophilia (DEAL) – 3 items
- Treatment (TREAT) – 8 items
- Future (FUTURE) – 5 items
- Family planning (FAMPL) – 4 items
- Partnership and sexuality (SEXUAL) – 3 items

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For the detailed scoring method, please see Appendix III.

Descriptive analyses for the actual and change from baseline scores for Haem-A-QoL will be provided for each of the dimensions by study part, dose level and visit.

The one sample Wilcoxon signed rank test for a single group will be used to compare the baseline Haem-A-QoL result vs. the last post-baseline assessment at the final treatment dose Haem-A-QoL result per subject, independently for each dose level in Part 2. A 95% Confidence interval for the median change from baseline value at the last post-baseline assessment at the final treatment dose will also be obtained. Sample SAS code can be found in Appendix I.

8.3.4 Analysis of Hemophilia Activities List (HAL)

HAL contains 7 domains: Lying/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks and leisure activities and sports. Additionally, three component scores can be calculated (upper extremity activities, basic lower extremity activities and complex lower extremity activities) as well as an overall score. Normalized score will be calculated for each of the 7 domains, 3 component scores and total score. For detailed scoring method, please see Appendix IV.

Descriptive analyses for normalized score and change from baseline normalized scores for HAL will be provided by study part for each of the dimensions by study part, dose level and visit.

The one sample Wilcoxon signed rank test for a single group data will be used to compare the baseline HAL result vs the last post-baseline assessment at the final treatment dose HAL result, independently for each dose level in Part 2. A 95% Confidence interval for the median change from baseline value at the last post-baseline assessment at the final treatment dose will also be obtained. Sample SAS code can be found in Appendix I.

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9. ANALYSIS OF PHARMACOKINETICS

PK analysis will be performed using non-compartmental analysis in professional PK software Phoenix WinNonLin 6.4 or higher (Certara, Princeton, NJ, USA). The PK TLFs will be produced using SAS statistical package version 9.3 or higher. PK analysis will be performed for PK population as defined in the Section 5.6 of the SAP.

9.1 PK SAMPLING SCHEDULE

PK sampling schedule will be specific to each part and dose administration. The PK data will be measured as MarzAA antigen concentration and activity levels. Additional PK data will include FVII, FVIIa activity.

Part 1a – single IV dose of 18 µg/kg MarzAA. PK sampling – predose, and post-dose at 5 and 30 minutes and Hour 1, 3, 6, 9, 12, and 24.

Part 1 b – single SC dose of 30 µg/kg MarzAA. PK sampling - pre-dose and Hour 3, 5, 7, 9, 12, 24, 30, and 48 post-dose.

Part 2 – daily SC dosing with variable dose to be determined.

PK sampling - Day 1 (Pre-dose and Post-dose Hour 7), Day 3 (Pre-dose), Day 5 (Pre-dose), Day 7 (Pre-dose). In the absence of spontaneous bleeding for the first dose level in Part 2 of the study, trough antigen and activity will be measured on days 14, 21, 28, and 50.

In case of spontaneous bleeding the PK samples will be taken within 6 hours of the spontaneous bleed and a pre- and 7 hours post-dose on Day 7, 14, 21, 28, and 50 after dose escalation.

9.2 PLASMA PK ENDPOINT

PK parameters will be derived by non-compartmental analysis using intravascular or extravascular trapezoidal log-linear rule for MarzAA antigen concentration and activity *and for FVII concentration and FVIIa activity where possible*.

Following PK parameters will be derived for Parts 1a and 1b of the study:

C_{max}, T_{max}, AUC_t, AUC_{inf} (MarzAA only), MRT (MarzAA only), Vz (MarzAA only)and CL (MarzAA only)for intravenous injection, Vz/F (MarzAA only)and CL/F (MarzAA only) for subcutaneous injection, F (MarzAA only) – absolute bioavailability for the subcutaneous injection relative to intravenous bioavailability and other parameters are relevant.

The PK parameters will be estimated as follows:

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The apparent C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data, not predicted data by the program);

AUCs will be calculated using the linear-log trapezoidal rule:

The terminal elimination rate constant (λ_z) if data allow will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}. The adjusted square of the correlation coefficient (R-square adjusted) for the goodness of fit of the regression line through the data points must be at least 0.85 for the λ_z value to be considered acceptable;

$t_{1/2}$ is calculated by the program as $\ln(2)/\lambda_z$;

If the time interval between the lower and upper time points used for the regression spans less than the derived half-life itself, then λ_z and the associated $t_{1/2}$ will be considered unreliable;

The AUC from 0 to infinity is calculated by the program as:

AUC_{inf} = AUC_{last} + $AUC_{last\text{-}inf}$ where last is the sampling time point of the last measurable concentration (t_{last}). $AUC_{last\text{-}inf}$ is calculated by the program as: C_{last}/λ_z, where C_{last} is the observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase; AUC_{inf} will only be presented for subjects with a reliable λ_z;

The AUC extrapolation to infinity must be ≤25% of the total area for AUC_{inf} to be considered reliable;

CL and CL/F is calculated by program as (dose/AUC_{inf})

V_z and V_z/F is calculated by the program as (dose/AUC_{inf})/ λ_z.

For subjects with unreliable λ_z (i.e., R-square adjusted <0.85, interval for λ_z calculation shorter than $t_{1/2}$, number of points to calculate λ_z <3), λ_z, $t_{1/2}$, AUC_{inf}, CL or CL/F and V_z or V_z/F will be flagged in the individual data.

For subjects with unreliable AUC_{inf} (because of extrapolation >25%), AUC_{inf}, CL or CL/F and V_z or V_z/F will be flagged in the individual data.

Flagged PK parameters will be excluded from summarization and statistical analyses.

Absolute bioavailability F for MarzAA antigen concentration and activity for SC injection vs intravascular route will be calculated using the formula:

$$F = \frac{AUC_{inf}^{SC} \times Dose^{IV}}{AUC_{inf}^{IV} \times Dose^{SC}}$$

Where $Dose^{IV}$ and $Dose^{SC}$ are respective doses for both route of administration

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Following PK parameters will be derived for Part 2 of the study:

C_{min} (trough concentrations) and expected C_{max} (at 7 hrs post-dose), accumulation ratio R_{Cmax} estimated for all days with PK sampling vs Day 1 where possible. For C_{min} the ratio R_{Cmin} will be estimated for each PK sampling day trough concentrations relative to Day 3.

9.3 PRESENTATION OF CONCENTRATION DATA

9.3.1 Handling of missing data

Missing concentration and activity data for all subjects who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of PK parameters, the following rules will apply:

Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;

The sampling time of pre-dose samples relative to dosing will also be treated as zero;

Post-dose BLQ values after the first quantifiable time point will be set to missing.

If the actual time of sampling is missing, the planned time may be used.

Samples taken outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to database lock.

For PK concentration and activity summary, individual concentration versus time curves and mean concentration versus time graphs, the following rules will apply:

PK concentrations BLQ in pre-dose samples and in samples taken before the time of the first quantifiable value will be set to zero;

The PK concentrations BLQ after quantifiable concentration will be set to zero.

No further imputation will be applied to any missing values.

9.3.2 Listing and Presentation of individual PK data

The actual sampling time of PK blood sample collection will be listed for each subject in both parts of the study and will include the deviation in time from the protocol scheduled time, if applicable. Both MarzAA antigen concentration and activity as well as FVII, FVIIa activity will be presented. Subjects with protocol deviations affecting PK may be flagged and excluded from summaries.

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Individual PK concentrations and activity data for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be listed by subject, time point and treatment (in relevant concentration units) separately for Parts 1 and 2. For Part 2 the time from start of 1st dose level and time elapsed from dose escalation as well as actual dose used will be presented in the listing of antigen concentration and activity.

The PK concentration and activity data for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be summarized at each time point by actual treatment. For the Part 2 of the study this summary will be grouped by actual dose level administered taking into account dose escalation history.

Individual subject intense PK parameters for Parts 1a and 1b will be listed for the PK population and will be summarized by treatment. Trough and C_{max} PK parameters such as C_{min} for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be listed for Part 2 PK population. Unreliable PK parameters will be listed but flagged and excluded from summary.

PK parameters of secondary interest for MarzAA antigen concentration and activity levels only, namely R-square adjusted, the number of data points used for estimating λ_z, the upper and lower time point used for estimation of λ_z, and the % AUC extrapolation from t_{last} to infinity in Parts 1a and 1b of the study will be listed by subject and treatment to enable verification of the exclusions, if any, of data from the summary statistics of the PK parameters of primary interest.

The following figures will be produced for MarzAA:

Individual intense PK concentration-time profiles for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be presented for Parts 1a and 1b separately with all subjects within the same treatment in the same figure on linear and log-linear scales. The profiles can be stratified by subject ID in blocks of 6 to reduce number of curves per plot.

Mean ± SD intense PK concentration-time profiles for MarzAA antigen concentration and activity levels, FVII, FVIIa activity for Parts 1a and 1b will be presented combining the curves for both IV and SC treatments within the same figure, on linear and log-linear scales. Box plots comparison of PK parameters C_{max}, AUC_t, AUC_{inf} between IV and SC routes.

For Part 2 individual trough and max concentrations for MarzAA antigen concentration and activity levels, FVII, FVIIa activity for all subjects vs dose day of treatment will be presented combined for all subjects within the same dose level. For the subjects requiring dose escalation the individual plots will be produced taking into account the day of the dose escalation.

Mean ± SD trough and max PK concentration-time profiles for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be presented for all subjects,

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combining the curves for different dose levels relative to the day of dose initiation or escalation within the same figure, on linear and log-linear scales

9.3.3 Summary of PK concentrations and parameters in plasma

The PK concentrations and activities for MarzAA antigen concentration and activity levels, FVII, FVIIa activity for Part 1 will be summarized by the treatment IV or SC administration of MarzAA.

For Part 2 the summary of results for MarzAA antigen concentration and activity levels, FVII, FVIIa activity will be based on actual dose administered and will be presented relative to the start of dosing for the 1st dose level or day of dose escalation for all subsequent dose levels. The history of dose escalation i.e. the day of bleeding which required dose escalation will be taken into account for the summaries.

PK parameters and concentrations will be summarized by treatment and time point using the following descriptive statistics:

Variable	**Summarized with:**
PK concentration and activities at each nominal time point	n, number and % BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
AUC, C_{max}, CL or CL/F and Vz or V_z/F, R_{Cmin}, R_{Cmax}, etc.	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
$t_{1/2}$, and λ_Z	n, arithmetic mean, SD, CV%, minimum, median, maximum
T_{max}, T_{last} (actual time)	n, minimum,Q1, median, Q3 and maximum

Note: CV% = SD/mean in %.
%BLQ = 100 * (total number of subjects who have BLQ values/total number of subjects within each treatment at each time point)

Mean concentrations will not be presented if 70% or more of the actual values for PK population at any one time point in the terminal phase are BLQ or missing.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and concentrations:

PK Reporting Precision

Statistics	**Degree of Precision**

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Minimum, Maximum; Q1 (25%) and Q3 (75%)	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PK concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PK concentrations)

Additionally, the following inferential analyses will be performed as described below in Sections 9.4 and 9.5 of the SAP:

- Attainment of steady state by MarzAA
- Evaluation of dose effect on dose normalized PK parameters for MarzAA

9.4 ATTAINMENT OF STEADY STATE FOR FOR MARZAA ANTIGEN CONCENTRATION AND ACTIVITY LEVELS, FVII, FVIIA ACTIVITY

Attainment of steady state will be estimated for Part 2 data using aggregate assessment of trough concentrations if sufficient data will be available.

To assess whether steady state was achieved for for MarzAA antigen concentration and activity levels, FVII, FVIIa activity after multiple doses of MarzAA, the PK parameters will be summarized for each dosing interval. Aggregate assessment of trough concentrations by will be used to evaluate attainment of steady state[1]. The approach is based on the comparison of log-transformed normalized trough concentration values for each dose to the mean of the results for all the following doses.

The above analysis will be done using repeated measures analysis only if the data are sufficient to support. Alternatively, Analysis of variance (ANOVA) comparison will be carried out on log-transformed C_{min} (concentrations at the end of dosing interval) for Days 3, 5, 7, 14, 21, 28 and 50 for dosing level 1 (30 µg/mL). If data allow the same analysis may be repeated separately for dose levels 2 (60 µg/mL), 3 (90µg/mL) and 4(120µg/mL) using time relative to dose escalation day. The following example SAS code may be used to conduct the analysis:

```
PROC MIXED;
CLASS time patient;
```

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MODEL loge(pk) = time / DDFM = KR;

LSMEANS time;

RUN;

The DDFM = KR (KenwardRoger) option performs the degrees-of-freedom calculations detailed by Kenward and Roger (1997)[2].

Contrasts will be tested between a time point and the pooled mean over all remaining time points. For example, following contrasts will be tested as an example for dose level 1 without bleeding and thus without dose escalation:

- Day 3 vs Days 5, 7, 14, 21, 28 and 50
- Day 5 vs Days 7, 14, 21, 28 and 50
- etc.

The first non-significant comparison will be concluded to be the dosing interval at which steady state concentrations are attained. The p-value for difference of Least Square Means (LSM), Geometric Mean Ratio, and the 95% confidence interval for the contrasts will be provided.

The comparison will be also presented graphically as individual and mean plots for trough concentrations at the end of dosing intervals as described in the Section 9.3.2 of the SAP.

9.5 DOSE PROPORTIONALITY FOR MARZAA

Analysis of dose proportionality in Part 2 will be performed by a repeated measures ANOVA model using the SAS Proc Mixed procedure if sufficient number of data points for different dose levels for SC injection route only are available. The analysis will be performed using the $\log_e$-transformed, dose-normalized, C_{max}/D and C_{min}/D as dependent variable, visit (Days 7, 14, 21, 28, and 50 relative to start of dosing for dose level 1 or day of dose escalation) and treatment as fixed effect. VisitVisit will be specified as repeated measurement. Subject as random effect.

The comparison will be performed for at least 2 dose levels with at least 6 subjects of PK data available (C_{min} or C_{max} values for each time point). Pair-wise comparisons will be made between test dose levels of 60, 90 and 120 µg/kg and the reference dose group of 30 µg/kg.

95% CIs for the geometric mean ratios (GMRs) will be obtained from the mixed-effects model. The formula for the calculation of the estimated ratio between the test and reference and the (1-2*α)*100 % CI of the ratio is given below.

- Difference = Estimate of difference between test and reference LSMs

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- Ratio = $100 \times e^{Difference}$
- (1-2*α)*100% CIs for the Ratio:
  - Lower = $100 \times e^{(Lower\ Bound\ (1-2*\alpha)\%\ CIs\ for\ the\ Difference)}$
  - Upper = $100 \times e^{(Upper\ Bound\ (1-2*\alpha)\%\ CIs\ for\ the\ Difference)}$

Dose proportionality will also be explored graphically:

Box and whiskers plots of dose normalized PK parameters with treatments on X axisaxis. If simultaneous comparison of multiple dose numbers is required, the treatment and dose number combination may be presented on X axes

9.6 DEVIATION FROM ANALYSES PLANNED IN PROTOCOL

The PK population was added to the analysis populations.

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10. ANALYSIS OF PHARMACODYNAMICS

PD analysis will be performed using SAS statistical packaged version 9.3 or higher. PD analysis will be performed for PD population as defined in the Section 5.6 of the SAP. PD parameters may be derived using Phoenix WinNonLin or SAS software packages.

10.1 PD SAMPLING SCHEDULE

PD analysis includes following assessments

Coagulation assays	Thrombogenicity biomarkers
PT, aPTT, fibrinogen, and TGT	D-dimer, F1+2, and thrombin-antithrombin complexes (TAT)

PD sampling schedule will be specific to each part and dose administration.

Part 1a – single IV dose of 18 µg/kg MarzAA. PD sampling – predose, and post-dose at 5 and 30 minutes and Hour 1, 3, 6, 9, 12, and 24.

Part 1 b – single SC dose of 30 µg/kg MarzAA. PD sampling - pre-dose and Hour 3, 5, 7, 9, 12, 24, 30, and 48 post-dose.

Part 2 – daily SC dosing with variable dose to be determined.

PD sampling and assessments - Day 1 (Pre-dose and Post-dose Hour 7), Day 3 (Pre-dose), Day 5 (Pre-dose), Day 7 (Pre-dose). In the absence of spontaneous bleeding for the first dose level in Part 2 of the study, trough antigen and activity will be measured on days 14, 21, 28, and 50.

In case of spontaneous bleeding the PD samples will be taken within 6 hours of the spontaneous bleed and a pre- and 7 hours post-dose on Day 7, 14, 21, 28, and 50 after dose escalation.

10.2 PLASMA PD ENDPOINT

PD parameters will be derived by non-compartmental analysis using intravascular or extravascular trapezoidal log-linear rule.

The following PD parameters will be derived for Parts 1a, 1b and 2 of the study:

E_{max} or E_{min}	Maximum or minimum effect depending on the direction of change in PD result
CFB_{max} or CFB_{min}	Maximum or minimum change in baseline for the effect depending on the direction of change in PD result
$TE_{max/min}$	Time to max or min value of the effect

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AUE and AUE_{CFB}	Area under curve effect vs time profile for actual measurements and change from baseline
TA_AUE and TA_AUE_{CFB}	Time adjusted area under curve effect vs time profile for actual measurements and change from baseline

The PD parameters will be estimated as follows:

The apparent E_{max} and the corresponding CFB_{max} and T_{max} will be read directly from the PD value-time plot (observed data, not predicted data by the program);

AUEs will be calculated using the linear-log trapezoidal rule both for measured data and change from baseline;

TA_AUE will be estimated as AUE divided by the time elapsed from assessment.

The parameters will be derived for the complete duration of treatment starting from the dose in Parts 1a and 1 b and from the fist injection for each dose level in Part 2 of the study.

10.3 PRESENTATION OF PD DATA

10.3.1 Handling of missing data

Missing concentration data for all subjects who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of PD parameters and presentation of individual and summary PD data, the following rules will apply:

Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;

The sampling time of pre-dose samples relative to dosing including 1st dosing in Part 2 for each dose level will also be treated as zero;

Post-dose BLQ values after the first quantifiable time point will be set to 0.

If the actual time of sampling is missing, the planned time may be used.

Assessments done outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to database lock.

No further imputation will be applied to any missing values.

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10.3.2 Listing and Presentation of Individual PD Results

The actual assessment time or sampling for PD biomarkers will be listed for each subject in both parts of the study and will include the deviation in time from the protocol scheduled time, if applicable. Both actual measurements and change from baseline for each parameter will be presented. Baseline value will be defined as the last available value of PD biomarker before the 1st dose of the drug for part 1a, part 1b and part 2 separately.

Subjects with protocol deviations affecting PK may be flagged and excluded from summaries.

Individual PD actual measured and change from baseline data will be listed by subject, time point and treatment (in relevant concentration units) separately for Parts 1 and 2. For Part 2 the time from start of 1st dose level and time elapsed from dose escalation as well as actual dose used will be presented in the listing.

The PD results and change from baseline will be summarized at each time point by actual treatment. For the Part 2 of the study this summary will be grouped by actual dose level administered taking into account dose escalation history.

Individual PD parameters for Parts 1a and 1b will be listed for the PD population and will be summarized by treatment. Individual PD parameters for Part 2 will be listed separately for each dose level.

The following figures will be produced for PD results:

Individual PD data-time profiles for actual measurement and change from baseline results will be presented for Parts 1a, 1b and 2 separately with all subjects within the same treatment in the same figure on linear and log-linear scales. The profiles can be stratified by subject ID in blocks of 6 to reduce number of curves per plot.

Mean ± SD PD data-time profiles for actual measurement and change from baseline results profiles for Parts 1a and 1b will be presented combining the curves for both IV and SC treatments within the same figure, on linear and log-linear scales.

For Part 2 PD data-time profiles for actual measurement and change from baseline results for all subjects vs dose day of treatment will be presented combined for all subjects within the same dose level. For the subjects requiring dose escalation the individual plots will be produced taking into account the day of the dose escalation.

10.3.3 Summary of PD concentrations and parameters in plasma

The PD results for Part 1a will be summarized by the treatment IV or SC administration of MarzAA.

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For Part 2 the summary of PD results will be based on actual dose administered and will be presented relative to the start of dosing for the 1st dose level or day of dose escalation for all subsequent dose levels. The history of dose escalation i.e. the day of bleeding which required dose escalation will be taken into account for the summaries.

PD parameters and results will be summarized by treatment and time point using the following descriptive statistics:

Variable	Summarized with:
PD data at each nominal time point	n, number and % BLQ, arithmetic mean, SD, coefficient of variance (CV) %, minimum, median and maximum
AUE, Emax, CFB_{max}, TA_AUE	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
TE_{max} (actual time)	n, minimum,Q1, median, Q3 and maximum

Note: CV% = SD/mean in %.
%BLQ = 100 * (total number of subjects who have BLQ values/total number of subjects within each treatment at each time point)

Mean concentrations will not be presented if 50% or more of the actual values for PD population at any one time point in the terminal phase are BLQ or missing.

Samples taken outside the allowed time windows may be excluded from summarization. This will be determined prior to database lock.

The following conventions will be used for the presentation of the descriptive statistics of PD results and parameters:

PD Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum; Q1 (25%) and Q3 (75%)	3 significant digits or as needed based on actual measured values (for example PD concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PD concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PD concentrations)

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CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PD concentrations)

Additionally, the following inferential analyses will be performed as described below in Sections 10.4 and 10.5 of the SAP:

10.4 COMPARISON OF PD DATA TO BASELINE

PD data at different time points in Part 2 of the study will be compared to baseline values using a repeated measures ANOVA model in the SAS Proc Mixed procedure including log e transformed PD actual measured data as dependent variable and visit as independent variable. The model will conducted on the data including baseline and post-baseline visits (Days 7, 14, 21, 28 and 50). If data allow the same analysis may be repeated separately for dose levels 2 (60 µg/mL), 3 (90 µg/mL) and 4(120 µg/mL) using time relative to dose escalation day. The baseline will be considered as pre-dose value before the first dose at the 1st dose level.

The comparison will be performed for the dose level with at least 6 subjects of PD data available. Pair-wise comparisons will be made between PD values on Day 7 vs reference at baseline, Day 14 vs baseline and so on.

95% CIs for the geometric mean ratios (GMRs) will be obtained from the mixed-effects model. The formula for the calculation of the estimated ratio between the test and reference and the (1-2*α)*100 % CI of the ratio is given below.

Difference = Estimate of difference between test and reference LSMs

- Ratio = $100 \times e^{\text{Difference}}$
- (1-2*α)*100% CIs for the Ratio:
  - Lower = $100 \times e^{(\text{Lower Bound (1-2*α)\% CIs for the Difference})}$
  - Upper = $100 \times e^{(\text{Upper Bound (1-2*α)\% CIs for the Difference})}$

The post-baseline visit where it shows statistically significant difference with baseline ($p < 0.05$) will be considered to represent the drug effect on PD results. Kenward-Rogers procedure will be used to resolve the issue of the small sample size. The confidence interval of the difference between each post- baseline visit vs. baseline visit will be also be presented conclude the significance of the difference.

The PD results with statistically significant difference with baseline will be considered for biomarkers of clinical outcome and will be advanced to further comparisons.

The comparison of PD values to baseline will also be explored graphically:

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Box and whiskers plots of PD actual measured data with Days on X iaxis. Multiple days including baseline will be presented on the same plot.

10.5 EVALUATION OF THE RELATIONSHIP BETWEEN BLEEDING EVENTS AND PD DATA.

Each PD actual measured data in Part 2 will be grouped into bleeding and non-bleeding groups depending on if the subject at each PD visit is experiencing bleeding across all dose levels. The following ANOVA models will be conducted:

- log(e) transformed PD actual measured values as dependent variable and bleeding group based on PD actual measured data as independent variable

- change from baseline PD actual measured values as dependent variable and bleeding group based on PD actual measured data as independent variable

PD parameter data will also be grouped into bleeding and non-bleeding groups depending on if the subject is experiencing bleeding during the period for each dose level. The following ANCOVA model will be conducted:

- PD parameter ($E_{max/min}$, $CFB_{max/min}$, TA_AUE and TA-AUE_{CFB}) values as dependent variable, bleeding group based on PD parameter data as independent variable and baseline at each dose level of each subject will be used as covariate. The same model will be used separately for each dose level. Note that log e transformation will be done when the appropriate PD parameters is used.

The model will only be performed for the bleeding/non-bleeding groups for each dose level with at least 6 observations available.

Patients with dose escalation may contribute more than one observation to this comparison. The same subject data will be used in both groups with PD data for dose levels with bleeding event and PD data for the escalated doses resulting in stopping of bleeding events.

Contrasts for bleeding and non-bleeding groups will be evaluated. Multiple models may be explored and the model meeting the convergence criteria will be presented with the effects of all used covariates included in the table.

The results with statistically significant difference between groups ($p < 0.05$) will be considered for biomarkers of clinical outcome. Kenward-Rogers method will be used to allow for robust convergence[2]. Due to small sample size, the findings of the study will be considered exploratory and will require additional validation.

Graphic presentation for the comparison analysis will include box and scatter plots for the relevant PD concentration and parameter data for the two categories based on bleeding events.

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10.6 INTERIM ANALYSES

No formal interim PK analysis is planned for the study

10.7 DEVIATION FROM ANALYSES PLANNED IN PROTOCOL

The PD population was added to the analysis populations.

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11 ANALYSIS OF IMMUNOGENICITY

11.1 IMMUNOGENICITY SAMPLING SCHEDULE

Antibody response and neutralizing antibodies to MarzAA to FVII, FVIIa, and MarzAA will be measured. The schedule of assessments of immunogenicity will be defined by study part as follows:

Part 1a – screening and pre-dose

Part 1b – pre-dose

Part 2 - Pre-dose on Day 1, 7, 14, 21, 28, and 42, and then every 2 weeks until end of study; 30 days after last dose (end of study) at the 1st dose level in the absence of bleeding events.

Bleeding event - within 6 hours of the spontaneous bleed

Dose escalation post-bleeding - days 14, 28, 42; 30 days after last dose (end of study).

11.2 IMMUNOGENICITY ENDPOINTS

Occurrence of antibody formation resulting in a decreased endogenous level of FVII or FVIIa

Occurrence of antibody response to MarzAA

The number and percentage antibody formation resulting in a decreased endogenous level of FVII or FVIIa will be presented using safety population.

11.3 PRESENTATION OF IMMUNOGENICITY DATA

The sampling for immunogenicity results will be listed combining all time points throughout the study starting from Screening, Parts 1a and 1b and Part 2 with the results from screening and confirmation assay in binary form (Positive/Negative) with the value of titer for Positive immune response.

The immunogenicity results will be summarized by frequency of ADA positive subjects at each time point for all parts of the study. For the Part 2 of the study the summary will take into account the actual dose level and subject with dose escalation will be summarized separately from the subjects who did not experience bleeding event at the starting dose. The frequency of subjects with dose escalation will be summarized by actual dose and time elapsed from the start of each dose escalation.

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12 SAFETY

Safety analyses will be based on the safety population. No inferential statistics will be performed; only summary statistics will be provided. Missing safety data will not be imputed.

12.1 EXTENT OF EXPOSURE

Exposure to study drug (in days) will be calculated for part 2 for each dose level and overall for all dose levels.

Exposure is calculated as below:

Exposure in part 2 for each dose level = cumulative number of actual treatment days for each dose level

Exposure overall in part 2 = cumulative number of actual treatment days of the dosing

12.2 TREATMENT COMPLIANCE

Study drug compliance (%) is calculated as 100 x (total number of days subject report to take study drug in study part 2 /exposure of study drug (in days) in study part 2.

Compliance will be summarized for each dose level in part 2.

12.3 ADVERSE EVENTS / ADVERSE DRUG REACTIONS

Adverse events will be coded using MedDRA Version 20.1 to classify events under primary SOC and PT.

A treatment emergent adverse event (TEAE) is defined as an AE that either begins after the first dose of study drug in this study or worsens after the first dose of study drug in this study but not later than the date of last dose + 30 days.

TEAEs will be assigned to each study part (part 1 or part 2) if the start date of the TEAE is after the first dosing date/time in part 1 or first date of dosing in part 2 for each dose level. TEAEs will be summarized for part 1 and 2 and different dose levels in part 2.

Number of subjects per TEAE and number of events per TEAE below will be summarized by SOC, PT and by study part/dose level. Multiple occurrences of an AE are counted only once per subject per SOC and PT for summary tables:

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (in the following order: severe, moderate and mild). Missing severity will be considered as severe.

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- Incidence of TEAE by relationship to study drug (related, not related). Missing relationship will be considered as related.
- Incidence of serious TEAEs
- Incidence of serious TEAEs related to study drug
- Incidence of TEAEs leading to study drug withdrawn

All AEs will be listed.

12.4 LABORATORY EVALUATIONS

All clinical laboratory parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and abnormal results will be used in the summary of laboratory data. Data will be flagged according to the reference limits (high or low) if applicable.

Descriptive statistics will be calculated for each numeric laboratory test parameter by study part / visit and dose level for actual values and changes from baseline. In addition, change from baseline to the last assessment of the final dose level will be summarized. For chemistry and hematology lab tests, shift tables showing baseline and post-baseline visit will be performed for the categories low, normal, and high. Additionally, the shift from the study baseline to the final value in each dose level will be provided.

12.5 VITAL SIGNS

Descriptive summaries of actual values and changes from study baseline will be calculated for vital signs by study part, dose level and each visit, which includes blood pressure (BP), heart rate (HR), respiration rate (RR), body temperature, weight and BMI. In addition, change from baseline to the last assessment of the final dose level will be summarized.

Vital sign results for each parameter will then be tabulated for actual and change from period baseline values by study part, dose level and each visit.

The same method of calculating BMI in section 7.2 will be used;

All vital sign data will be listed by subject and time of measurement.

12.6 ELECTROCARDIOGRAM (ECG)

A standard 12-lead ECG will be performed at the visits outlined in section 3.8. All ECGs should be assessed by the Investigator and deemed “Normal”, “Abnormal, not clinically significant” and “Abnormal, clinically significant”. A shift table showing baseline to

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post-baseline by study part and visits /dose level will be performed for the above categories. Additionally, the shift from the study baseline to the final value in each dose level will be provided. The ECG variables that will be analyzed are PR interval, QRS interval, and QT corrected with Fridericia's formula (QTcF). The actual value and change from study baseline of ECG measurements will be summarized by study part and visits. In addition, change from baseline to the last assessment of the final dose level will be summarized.

All-important abnormalities from the ECG readings that, in the opinion of the Investigator are deemed clinically significant should be reported as AEs and will be listed in the AE listing.

All ECG data will be listed by subject and time of measurement.

12.7 PHYSICAL EXAMINATION

All physical examination data will be listed by subject and time of measurement.

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13 INTERIM ANALYSES

No interim analyses are conducted during the study.

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14 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

1. Protocol primary efficacy endpoint stated the Poisson analysis will be performed using StatXact 11. However, SAS 9.4 will be used for the exact analyses as specified in this SAP.

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15 REFERENCE LIST

1. Maganti L, Panebianco DL, Maes AL. Evaluation of methods for estimating time to steady state with examples from phase 1 studies. The AAPS Journal. 2008; 10(1):141-147

2. Kenward, M. G. and J. H. Roger. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics, 1997, 53(3), 983–997.

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16 PROGRAMMING CONSIDERATIONS

15.1 GENERAL CONSIDERATIONS

- One SAS program can create several outputs. / A separate SAS program will be created for each output.
- One output file can contain several outputs. / Each output will be stored in a separate file.
- Output files will be delivered in Word format / pdf format.
- Numbering of TFLs will follow ICH E3 guidance

15.2 TABLE, LISTING, AND FIGURE FORMAT

15.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2 Headers

- All output should have the following header at the top left of each page:
  <Sponsor Name> Protocol XXX (Syneos Health study number xxx)
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

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- The date output was generated should appear along with the program name as a footer on each page.

15.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

15.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

15.2.5 Body of the Data Display

15.2.5.1 General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

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15.2.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

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- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC3 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000).
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

15.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.

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- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source.

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17 QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

SAS programming and quality control plan will be created.

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APPENDIX I EXAMPLE SAS CODE

Poisson regression model for primary efficacy endpoint:

```
PROC GENMOD DATA = bleed;
MODEL abr = / DIST = poi LINK = log PRED OFFSET = <ln (12)>;
EXACT intercept/ESTIMATE = parm ONESIDED ALPHA = 0.025;
RUN;
```

Poisson regression model for primary sensitivity analysis:

```
PROC GENMOD DATA = bleed;
CLASS subjid time
MODEL abr = time / DIST = poi LINK = log PRED;
REPEATED SUBJECT = subjid/ CORRW TYPE = un;
LSMEANS time/DIFF CL;
RUN;
```

Wilcoxon Signed Rank test with 95% CI for Median:

```
proc univariate data=bleedtp cipctldf;
var chg;
run;
```

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APPENDIX II SCORING FOR EQ-5D-5L DESCRIPTIVE SYSTEM AND VAS

The EQ-5D-5L descriptive system should be scored, for example, as follows:

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

MOBILITY
- ☑ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

SELF-CARE
- ☐ I have no problems washing or dressing myself
- ☑ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☑ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

PAIN / DISCOMFORT
- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☑ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

ANXIETY / DEPRESSION
- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☑ I am extremely anxious or depressed

Levels of perceived problems are coded as follows:

- ☑ Level 1 is coded as a '1'
- ☑ Level 2 is coded as a '2'
- ☑ Level 3 is coded as a '3'
- ☑ Level 4 is coded as a '4'
- ☑ Level 5 is coded as a '5'

This example identifies the health state '12345'.

NB: *There should be only ONE response for each dimension*

NB: Missing values *can be coded as '9'.*

NB: Ambiguous values *(e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.*

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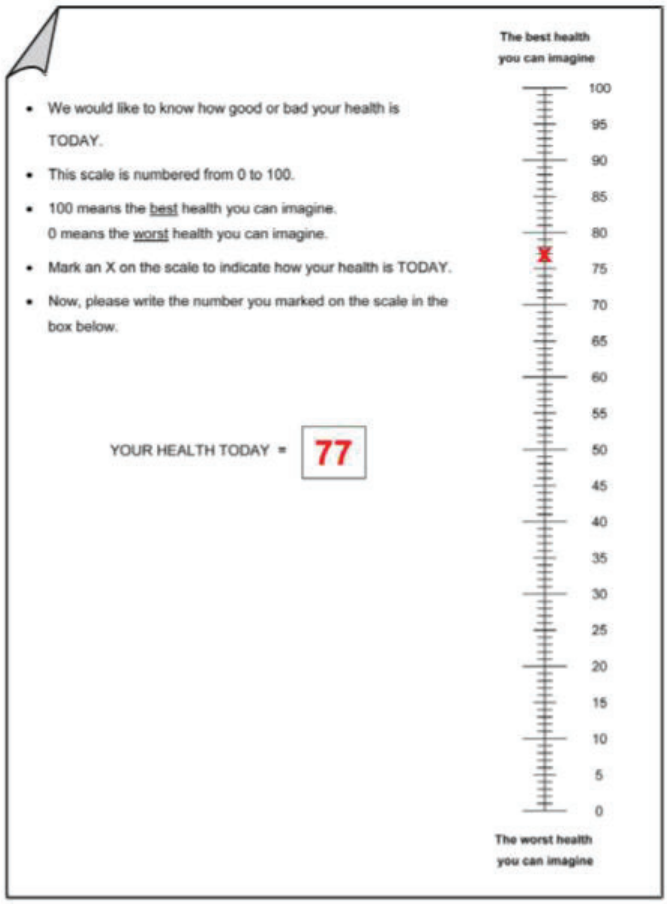
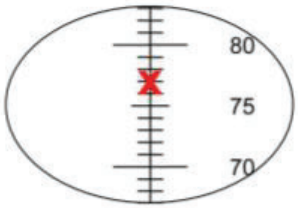
The EQ VAS should be scored, for example, as follows:





For example this response should be coded as 77

***NB: Missing values** should be coded as '999'.*

***NB:** If there is a discrepancy between where the respondent has placed the X and the number he/she has written in the box, administrators should use the number in the box.*

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APPENDIX III SCORING METHOD FOR HEMOPHILIA A QUALITY OF LIFE QUESTIONNAIRE

The 46-items of the Haem-A-QoL are scored into 10 scales:

- Physical health (PHYS) – 5 items
- Feelings (FEEL) – 4 items
- View of yourself (VIEW) – 5 items
- Sports and Leisure (SPORT) – 5 items
- Work and school (WORK) – 4 items
- Dealing with Haemophilia (DEAL) – 3 items
- Treatment (TREAT) – 8 items
- Future (FUTURE) – 5 items
- Family planning (FAMPL) – 4 items
- Partnership and sexuality (SEXUAL) – 3 items

Responses range from 'Never' (1) to 'All of the time' (5), with several items having a 'Not applicable' option that is scored as a (0).Higher scores are reflective of greater impairment or poorer health-related quality of life.

In order to have all of the responses scored in the same direction, several items will have to be reverse-scored. The following items should be reverse scored:

- VIEW – 2nd item
- VIEW – 5th item
- SPORT – 3rd item
- WORK – 1st item
- WORK – 2nd item
- DEAL – 1st item
- DEAL – 2nd item
- DEAL – 3rd item
- TREAT – 8th item
- FUTURE – 2nd item

The reverse scoring for those items is as follows: (1=5), (2=4), (3=3), (4=2), and (5=1). Any (0) will be recoded as missing data for the purposes of scale scoring. In listings of frequencies, the number of patients reporting 'Not applicable' can also be displayed.

These reverse scored items will be given a new label (e.g., view2x) and used instead of the original items when calculating the scale score.

Several additional items are recoded into the same scores but will be given a different label for future use. These are:

- SPORT – 1st item
- SPORT – 2nd item

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- SPORT – 4th item
- SPORT – 5th item
- WORK – 3rd item
- WORK – 4th item
- FAMPL – 1st item
- FAMPL – 2nd item
- FAMPL – 3rd item
- FAMPL – 4th item

The recoding for these items is: (1=1) (2=2) (3=3) (4=4) and (5=5).
The recoded items will be given a new label (e.g., sport1m) and used in future analyses.

Scales can be calculated if ≥ 50% of items have been answered. As the questionnaire is being administered electronically and patients are not able to skip items, there should not be any missing items. As patients can answer "Not applicable", however, to questions in the SPORT, WORK, and FAMPL domains, items could be treated as missing. In this case, the minimum number of items that needs to be completed and not responded to as "Not applicable" is:

- SPORT: 3
- WORK: 2
- FAMPL: 2

Following the recoding, the sum of each scale should be computed. The computation of these scales is as follows:

- PHYS is the sum of the 5 items from the scale (phys1, phys2, phys3, phys4, phys5).
- FEEL is the sum of the 4 items from the scale (feel1, feel2, feel3, feel4).
- VIEW is the sum of items 1, 3, and 4 and reverse-scored items 2 and 5 from the scale (view1, view2x, view3, view4, view5x).
- SPORT is the sum of items 1, 2, 4, 5 and reverse-scored item 3 from the scale (sport1, sport2, sport3x, sport4, sport5).
- WORK is the sum of items 3, 4 and reverse-scored items 1 and 2 from the scale (work1x, work2x, work3, work4).
- DEAL is the sum of reverse-scored items 1, 2, and 3 from the scale (deal1x, deal2x, deal3x).
- TREAT is the sum of items 1 through 7 and reverse-scored item 8 from the scale (treat1, treat2, treat3, treat4, treat5, treat6, treat7, treat8x).
- FUTURE is the sum of items 1, 3, 4, 5 and reverse-scored item 2 from the scale (future1, future2x, future3, future4, future5).
- FAMPL is the sum of items 1 through 4 from the scale (fampl1, fampl2, fampl3, fampl4).

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- SEXUAL is the sum of items 1, 2, and 3 from the scale (sexual1, sexual2, sexual3).

A Total Haem QOL score (HAETOTAL) is calculated by summing all of the previously mentioned raw and reverse coded items in the scales above (phys1, phys2, phys3, phys4, phys5, feel1, feel2, feel3, feel4, view1, view2x, view3, view4, view5x, sport1, sport2, sport3x, sport4, sport5, work1x, work2x, work3, work4, deal1x, deal2x, deal3x, treat1, treat2, treat3, treat4, treat5, treat6, treat7, treat8x, future1, future2x, future3, future4, future5, fampl1, fampl2, fampl3, fampl4, sexual1, sexual2, sexual3).

The scores for each scale should then be standardized onto a 100-point scale. This can be done as follows:

- PHYS_Z = summing the raw score of the items in the PHYS scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. As an example, PHYS_Z = (MEAN (phys1, phys2, phys3, phys4, phys5)-1)/4)*100.
- FEEL_Z = summing the raw score of the items in the FEEL scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (feel1, feel2, feel3, feel4)-1)/4)*100.
- VIEW_Z = summing the raw and reverse score of the items in the VIEW scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (view1, view2x, view3, view4, view5x)-1)/4)*100.
- SPORT_Z = summing the raw and reverse scores of the items in the SPORT scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (sport1m, sport2m, sport3x, sport4m, sport5m)-1)/4)*100.
- WORK_Z = summing the raw and reverse scores of the items in the WORK scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (work1x, work2x, work3m, work4m)-1)/4)*100.
- DEAL_Z = summing the raw and reverse scores of the items in the DEAL scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (deal1x, deal2x, deal3x)-1)/4)*100.
- TREAT_Z = summing the raw and reverse scores of the items in the TREAT scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (treat1, treat2, treat3, treat4, treat5, treat6, treat7,

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treat8x)-1)/4)*100.

- FUTURE_Z = summing the raw and reverse scores of the items in the FUTURE scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (future1, future2x, future3, future4, future5)-1)/4)*100.
- FAMILY_Z = summing the raw score of the items in the FAMILY scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100. (MEAN (fampl1m, fampl2m, fampl3m, fampl4m)-1)/4)*100.
- RELAT_Z = summing the raw score of the items in the RELAT scale and taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100 (MEAN (sexual1, sexual2, sexual3)-1)/4)*100.

Finally, a Total Haem-A-QOL transformed score (HAEMA_Z) should be computed by summing the raw and reverse scores of all of the items, taking the mean of those items, subtracting one (1) from that number and dividing by four (4) which is the range for the scale. This number is then multiplied by 100

HAEMA_Z = (MEAN (phys1, phys2, phys3, phys4, phys5, feel1, feel2, feel3, feel4, view1, view2x, view3, view4, view5x, sport1m, sport2m, sport3x, sport4m, sport5m, work1x, work2x, work3m, work4m, deal1x, deal2x, deal3x, treat1, treat2, treat3, treat4, treat5, treat6, treat7, treat8x, future1, future2x, future3, future4, future5, fampl1m, fampl2m, fampl3m, fampl4m, sexual1, sexual2, sexual3)-1)/4)*100.

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APPENDIX IV SCORING METHOD FOR HAL QUESTIONNAIRE

Scoring system

Scores can be calculated for each of the seven domains of the HAL. Additionally, three component scores can be calculated (Activities involving the Upper Extremities, Basic activities involving the Lower Extremities and Complex activities involving the Lower Extremities) as well as an overall score. Before summarizing the individual item scores, recoding is required (see Table 1); a higher raw score represents more functional limitations; possible scoring ranges are given (Table 2).

Normalized scores for the domains, components, and the full questionnaire can also be obtained. Missing values are controlled for and the possible scores range from 0 to 100, where 0 represents the worst possible functional status and 100 the best possible functional status (Table 3).

Tabel 1: Recoding

Score	Recode	Meaning
8	0	N/A
1	6	Impossible
2	5	Always problems
3	4	Mostly problems
4	3	Sometimes problems
5	2	Rarely problems
6	1	Never problems

Table 2: Scores

Score		**Items**	**Score range**
Lying / sitting / kneeling / standing	LSKS	1-8 (8)	8 - 48
Functions of the legs	LEGS	9-17 (9)	9 - 54
Functions of the arms	ARMS	18-21 (4)	4 - 24
Use of transportation	TRANS	22-24 (3)	3 - 18
Self care	SELFC	25-29 (5)	5 - 30
Household tasks	HOUSEH	30-35 (6)	6 - 36
Leisure activities and sports	LEISPO	36-42 (7)	7 - 42
Upper Extremity Activities	UPPER	* (9)	9 - 54
Basic Lower Extremity Activities	LOWBAS	** (6)	6 -36
Complex Lower Extremity Activities	LOWCOM	*** (9)	9 - 54
Sum score	SUM	1-42 (42)	42 - 252

* Items for UPPER-component: 18, 19, 20, 21, 25, 26, 27, 28, 29. (9 items)
** Items for LOWBAS-component: 8, 9, 10, 11, 12, 13. (6 items)
*** Items for LOWCOM-component: 3, 4, 6, 7, 14, 15, 16, 17, 22. (9 items)

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Table 3: Normalization

Score	Normalisatie
LSKS	100 - ((Σ_{1-8} - valid) * (100/(5 * valid)))
LEGS	100 - ((Σ_{9-17} - valid) * (100/(5 * valid)))
ARMS	100 - ((Σ_{18-21} - valid) * (100/(5 * valid)))
TRANS	100 - ((Σ_{22-24} - valid) * (100/(5 * valid)))
SELFC	100 - ((Σ_{25-29} - valid) * (100/(5 * valid)))
HOUSEH	100 - ((Σ_{30-35} - valid) * (100/(5 * valid)))
LEISPO	100 - ((Σ_{36-42} - valid) * (100/(5 * valid)))
UPPER	100 - (($\Sigma_{18-21;25-29}$ - valid) * (100/(5 * valid)))
LOWBAS	100 - ((Σ_{8-13} - valid) * (100/(5 * valid)))
LOWCOM	100 - (($\Sigma_{3-7;14-17;22}$ - valid) * (100/(5 * valid)))
SUM	100 - ((Σ_{1-42} - valid) * (100/(5 * valid)))

"valid" = number of items scored within the specific domain/component.
Items with "n/a"-response are to be considered ***NOT*** valid

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Example:

A patient completed the domain of Leg Functions as follows:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Walking short distances (less than 1 kilometer / 15 minutes)	☐ 1	☐ 2	☐ 3	☒ 4	☐ 5	☐ 6
Walking long distances (more than 1 kilometer / 15 minutes)	☐ 1	☐ 2	☒ 3	☐ 4	☐ 5	☐ 6
Walking on a soft surface (e.g. on the beach or through the woods)	☐ 1	☐ 2	☐ 3	☐ 4	☒ 5	☐ 6
Walking on an uneven surface (e.g. cobblestones, high sidewalks)	☐ 1	☐ 2	☐ 3	☒ 4	☐ 5	☐ 6
Strolling / (window-)shopping	☐ 1	☐ 2	☐ 3	☒ 4	☐ 5	☐ 6
Climbing up the stairs	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
Climbing down the stairs	☐ 1	☐ 2	☐ 3	☒ 4	☐ 5	☐ 6
Running (e.g. in order to catch the bus)	☒ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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Jumping

☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Item	Score	Recode
Item 9	4	3
Item 10	3	4
Item 11	5	2
Item 12	4	3
Item 13	4	3
Item 14	Invalid	Invalid
Item 15	4	3
Item 16	1	6
Item 17	1	6

Based on the recoded scores, the raw domain score for the LEGS domain is 30 points.

The LOWBAS component encompasses the items 8-13. Item 8 scored 6 points (i.e. "Impossible"), which results in a raw component score of 6+3+4+2+3+3 = 21 points.

To normalize the scores (both domain and component scores), the formulas presented in Table 3 are used. This results in the following:

LEGS Normalized: Within the domain, 1 item is invalid, resulting in 8 valid responses out of a possible 9. This results in the following formula:

$100-((\Sigma_{9-17}\text{-valid})*(100/(5*\text{valid}))) = 100-((30-8)*(100/(5*8))) = 100-55 =$ **45 points**

LOWBAS Normalized: Within the component, no items are invalid, resulting in 6 valid responses out of a possible 6. This results in the following formula:

$100-((\Sigma_{8-13}\text{-valid})*(100/(5*\text{valid}))) = 100-((21-6)*(100/(5*6))) = 100 - 50 =$ **50 points**

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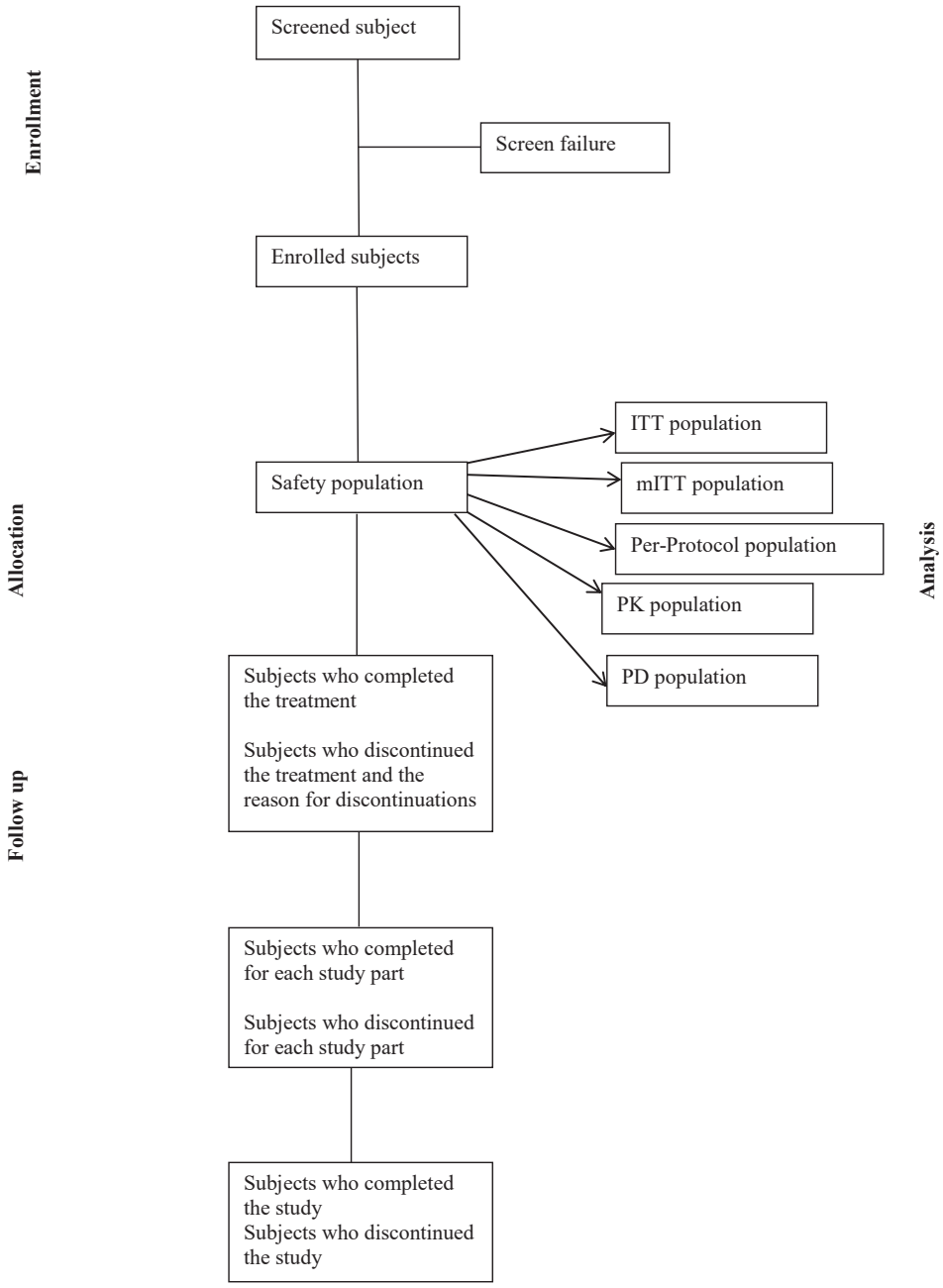
APPENDIX V DISPOSITION CONSORT DIAGRAM

FLOW DIAGRAM FOR PARTICIPANTS



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16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures if Used

The central laboratory used in the study is listed below. Local laboratory information (for investigators who did not use the central laboratory) and normal laboratory ranges (if applicable) are available on request.

Haemtech Biopharma Services
57 River Road, Unit 1010
Essex Junction, Vermont 05452
United States

16.1.11 Publications Based on the Study

There are no publications based on the study.

16.1.12 Important Publications Referenced in the Report

The complete list of references is available in Section 15 of the clinical study report. Copies of these references are available on request.