MAA-201 VERSION 2.0

Catalyst Biosciences, Inc.

CLINICAL RESEARCH PROTOCOL

Phase 2 Study of Next-Generation Coagulation Factor VIIa, Marzeptacog Alfa (Activated) in Adult Subjects with Hemophilia A and B

Protocol Identifying Number:	MAA-201
Official Title:	Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B subjects with an inhibitor
IND/IDE Sponsor:	Catalyst Biosciences, Inc. 611 Gateway Blvd., Suite 710 South San Francisco, CA 94080
IND Number:	14789
Investigational Product:	Factor VIIa, Marzeptacog Alfa (activated) [MarzAA]
Development Phase:	2
Version Number:	2.0 Amendment 1
Effective Date:	25 August 2018
Sponsor Contact:	Name: Howard Levy, MD, PhD, MMM CMO, Catalyst Biosciences, Inc. Telephone: +1.650.266.8671 Fax: +1.650.871.2475 E-mail: hlevy@catbio.com

Prepared by:	Catalyst Biosciences, Inc.

Confidentiality Statement

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Compliance Statement: This study will be conducted in accordance with the clinical research guidelines established by the U.S. Code of Federal Regulations (Title 21, Parts 50 [including Subpart D], 54, 56 and 312), the regulations and guidelines of the Therapeutic Goods Administration, and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice. Study documents will be maintained in accordance with applicable regulations.

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B subjects with an inhibitor

PROTOCOL No.: MAA-201

VERSION NUMBER: 2.0, Amendment 1

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the Sponsor with complete and timely information, as outlined in the protocol.

Furthermore, on behalf of the study staff and myself, I agree to conduct the study as outlined in the protocol in accordance with the guidelines outlined in the study protocol and all applicable government regulations. In addition, I agree to provide all the information requested in the CRFs presented to me by the Sponsor in a manner that assures legibility and accuracy. I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, CRFs, verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the IRB/IEC. In addition, no reports or information about the study or its progress will be provided to anyone who is not involved in the study, other than Sponsor or designee, the IRB/IEC, or the appropriate regulatory agencies.

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR) (Title 21, Parts 50 [including Subpart D], 54, 56 and 312), the regulations and guidelines of the Therapeutic Goods Administration. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training. Study documents will be maintained in accordance with applicable regulations.

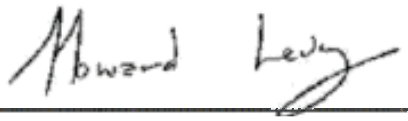
I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator Signature _____ Date _____

Print Name and Title _____

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B with an inhibitor
Protocol Number:	MAA-201
Version Number:	2.0 (Amendment 1), dated 25 August 2018



25 August 2018

Howard Levy, MD, PhD, MMM — Date

Chief Medical Officer, Catalyst Biosciences, Inc.

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DETAILED SUMMARY OF PROTOCOL CHANGES

Protocol Number: MAA-201

Protocol Title: Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B subjects with an inhibitor

	Version Number	Version Date
Current Approved Protocol	1.0	6 June 2017
Amended Protocol	2.0, Amendment 1	25 August 2018

Description of Changes:

Section	Update	Details
Title Page	Addition	**Amendment 1 Date: 11 April 2018**
Investigator Signature Page	Replacement	**VERSION NUMBER:** 1.0 With: **VERSION NUMBER:** 2.0, Amendment 1
Sponsor Signature Page	Replacement	Version Number: 1.0, dated xx June 2017 With: **Version Number: 2.0 (Amendment 1), dated 25 August 2018**
Sponsor Signature Page	Deletion	Jamie Siegel, MD Senior Medical Lead, Catalyst Biosciences, Inc.
Abbreviations	Updated	

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1.1 Synopsis; Trial Population; Exclusion Criteria	Replacement	2. Previous participation in a clinical trial evaluating a modified rFVIIa agent (including rFVIIa biosimilars, SC rFVIIa, PEGylated rFVIIa, NN1731, BAY86-6150, LR769, rVIIa-FP (CSL689), MOD-5014). Note: IV use of NovoSeven® is not an exclusion criteria. With: **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.**
1.3 Schedule of Activities (SOA)	Deletion	Diary entry of PRO scales at Part 1a Pre-dose
1.3 Schedule of Activities (SOA)	Deletion	Immunogenicity assay at Part 1a Pre-dose
5.2 Exclusion Criteria	Replacement	2. Previous participation in a clinical trial evaluating a modified rFVIIa agent (including rFVIIa biosimilars, SC rFVIIa, PEGylated rFVIIa, NN1731, BAY86-6150, LR769, rVIIa-FP (CSL689), MOD-5014). Note: IV use of NovoSeven® is not an exclusion criteria. With: **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.**
8.2 Study Procedures	Deletion	Diary entry of PRO scales at Part 1a Pre-dose
8.2 Study Procedures	Deletion	7 hr post-specimen draws at Day 3 and 5: 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~~

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		~~Hour 7~~), Day 5 (Pre-dose and ~~Post-dose Hour 7~~), Day 7 (Pre-dose and Post-dose Hour 7).
8.2.2.1 Pre-dose evaluations	Deletion	Immunogenicity assays to FVII, FVIIa, and MarzAA at Part 1a Pre-dose
8.2.2.1 Pre-dose evaluations	Deletion	Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
APPENDIX B	Updating	Link to HAEM A QoL
APPENDIX C	Deletion	Diary entry of PRO scales at Pre-dose at Part 1a Pre-dose
APPENDIX C	Deletion	Immunogenicity assays to FVII, FVIIa, and MarzAA at Part 1a Pre-dose

Administrative changes: Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.

ABBREVIATIONS

ABR	Annualized bleeding rate
ADL	Activities of daily living
AE	Adverse event
AICC	Anti-inhibitor coagulant complex
ALT	Alanine aminotransferase
APCC	Activated prothrombin complex concentrates
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BU	Bethesda Units
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CBC	Complete blood count
CD4	Cluster of differentiation 4
CFR	Code of Federal Regulations
ClinRO	Clinician reported outcomes
Cmax	Concentration maximum
CMP	Clinical Monitoring Plan
CNS	Central nervous system
Cr	Creatinine
CRF	Case report form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture

EQAS	External quality assessment scheme
eCRF	Electronic Case Report Forms
EQ-5D	European Quality of Life-5 Dimensions
F1+2	Prothrombin fragment 1+2
FVII	Factor VII
FVIIa	Factor VII activated
FVIII	Factor VIII
FIX	Factor IX
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIT	Gastrointestinal Tract
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GS	Gilbert's syndrome
GWAS	Genome-Wide Association Studies
H0	Null hypothesis
H1	Alternative hypothesis
Haem-A-QoL	Hemophilia A quality of life questionnaire
HAL	Hemophilia Activities List
HIPAA	U.S. Health Insurance Portability and Accountability Act
Hr	Hour
HTC	Hemophilia Treatment Centre
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMT	Immunomodulatory therapy
IND	Investigational New Drug Application
IP	Investigational product
IRB	Institutional Review Board

ITI	Immune tolerance induction IV intravenous
ITT	Intention-To-Treat
IV	Intravenous
LDL	Low-density lipoprotein
LLN	Lower limit of normal
MarzAA	Marzeptacog alpha (activated)
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
MOP	Manual of Procedures
NCT	National Clinical Trial
NDA	New Drug Application
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OTC	Over-the-counter
PC	Peak concentration
PCC	Prothrombin complex concentrates
PD	Pharmacodynamics
PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
r	Recombinant
rFIX	Recombinant factor IX
rFVIIa	Recombinant activated factor VIIa
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SNP	Single nucleotide polymorphisms

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TAT	Thrombin-antithrombin complexes
TBIL	Total bilirubin level
TE	Thromboembolic event
TGA	Therapeutic Goods Administration
TGT	Thrombin generation time
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
VAS	Visual analogue scale
VOD	Volume of distribution
VTE	Venous thromboembolic event
WFH	World Federation of Hemophilia
wt	Wild-type

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1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title of Study: Phase 2 study to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, efficacy and safety of a daily subcutaneous treatment regimen with marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B with an inhibitor
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.
Secondary Objectives: • 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.
Study Population: Twelve male subjects, aged 18 or older, with confirmed diagnosis of severe congenital hemophilia A or B with an inhibitor and history of frequent spontaneous bleeding episodes (historical annualized bleeding rate [ABR] of ≥12).
Phase of Development: Phase 2
Description of Sites: Multinational study conducted at up to approximately 10 centers.
Study Duration: Approximately 1 year
Participant Duration: The minimum duration of treatment for each subject is approximately 2 months (if no dose escalation is required) and the maximum duration is approximately 7 months (if three dose escalations are required). **Screening:** Up to 4 weeks **Part 1a:** 24 hours (single IV dosing and PK/PD/Safety testing) **Part 1b:** 48 hours (single SC dosing and PK/PD/safety testing) **Part 2:** Up to 197 days of daily SC dosing Note: Where interruptions to study drug dosing days are observed, study duration may be extended to incorporate full dosing schedule. **Follow-up:** Two weeks after last dose for PK/PD/safety follow-up and then approximately and additional 2 weeks follow-up to study completion.

Subjects must have no spontaneous bleeding for 50 days at any dose level and at least 50 exposure days and 30 days post-treatment follow-up to complete the study. Subjects escalating to 120 µg/kg will continue treatment for 50 exposure days to determine the bleed rate.

Study Methodology

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.

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.

Study Treatment and Assessments:

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.

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), Day 5 (Pre-dose), Day 7 (Pre-dose and Post-dose 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.

Number of planned subjects: 12

Trial population:

***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.

***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 (IMT). 11. Compromised hepatic or renal function: o Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal (ULN) o Total bilirubin level (TBIL) ≥2 mg/dL (>35 µmol/L) unless there is a known history of Gilbert's syndrome (GS) o Serum albumin ≤ the lower limit of normal (LLN) o Serum creatinine (Cr) level >1.25 x ULN 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.
Investigational product, dose, and mode of administration: ***Investigational Product:*** Recombinant Factor VII variant, Marzeptacog alfa (activated) [MarzAA] ***Dosage and mode of administration:*** Single IV dose at 18 µg/kg and then an initial SC doses at 30 µg/kg. Dose levels may increase to 60, 90, or 120 µg/kg, as required
Reference therapy: None
Concomitant Medications: In the event of spontaneous or traumatic bleeding, treatment for a bleeding episode will be permitted using the subject's current treatment regimen which could be FEIBA® (anti-inhibitor coagulant complex [AICC]), NovoSeven® (recombinant wild-type factor VII activated [wt-rFVIIa]), or a high dose regimen utilizing a FVIII or FIX product.
Efficacy and Safety Evaluations
Primary endpoints: • Annualized bleed (spontaneous and total) rate (ABR) during Part 2 when on final MarzAA dose level versus recorded historical ABR.
Secondary endpoints: • 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 time [TGT]) from pre-dose. • Occurrence of an antibody response to MarzAA and whether it is inhibitory and cross-reactive to wild-type recombinant FVIIa (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 subject as measured by compliance with treatment.

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.
- 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)

Statistics

Primary Analysis Plan:

Standard pharmacokinetic parameters, such as terminal half-life, AUC0-t, clearance, mean residence time and volume of distribution will be calculated. In addition, the bioavailability of the SC administration will be computed. Descriptive statistics for these parameters will be reported. The number of subjects requiring dose escalation will be reported.

The analysis of the primary endpoint (ABR) of the final dose used to treat a subject will be based on the evaluation of the ABR of MarzAA compared to a rate for on-demand therapy. The latter is assumed to be 12, ie, 1 bleed per month, as our null hypothesis (H0). The comparison of the actual ABR for MarzAA either pooled across all doses used or evaluated at the highest dose for an individual will be compared to this null hypothesized value using the one-sample test for a Poisson rate (using an exact calculation of the p-value). Because this will be a one-tailed test (the alternative hypothesis [H1] is the ABR for MarzAA will be < 12), a one-tailed 2.5% significance level will be used.

Rationale for Number of Subjects:

With a total of 12 subjects and assuming a null hypothesis of an ABR of 12, then the demonstration of a reduction to an ABR of 6 or less with a one-tailed 2.5% significance level would be accomplished with near 100% power 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%.

Name of sponsor: Catalyst Biosciences

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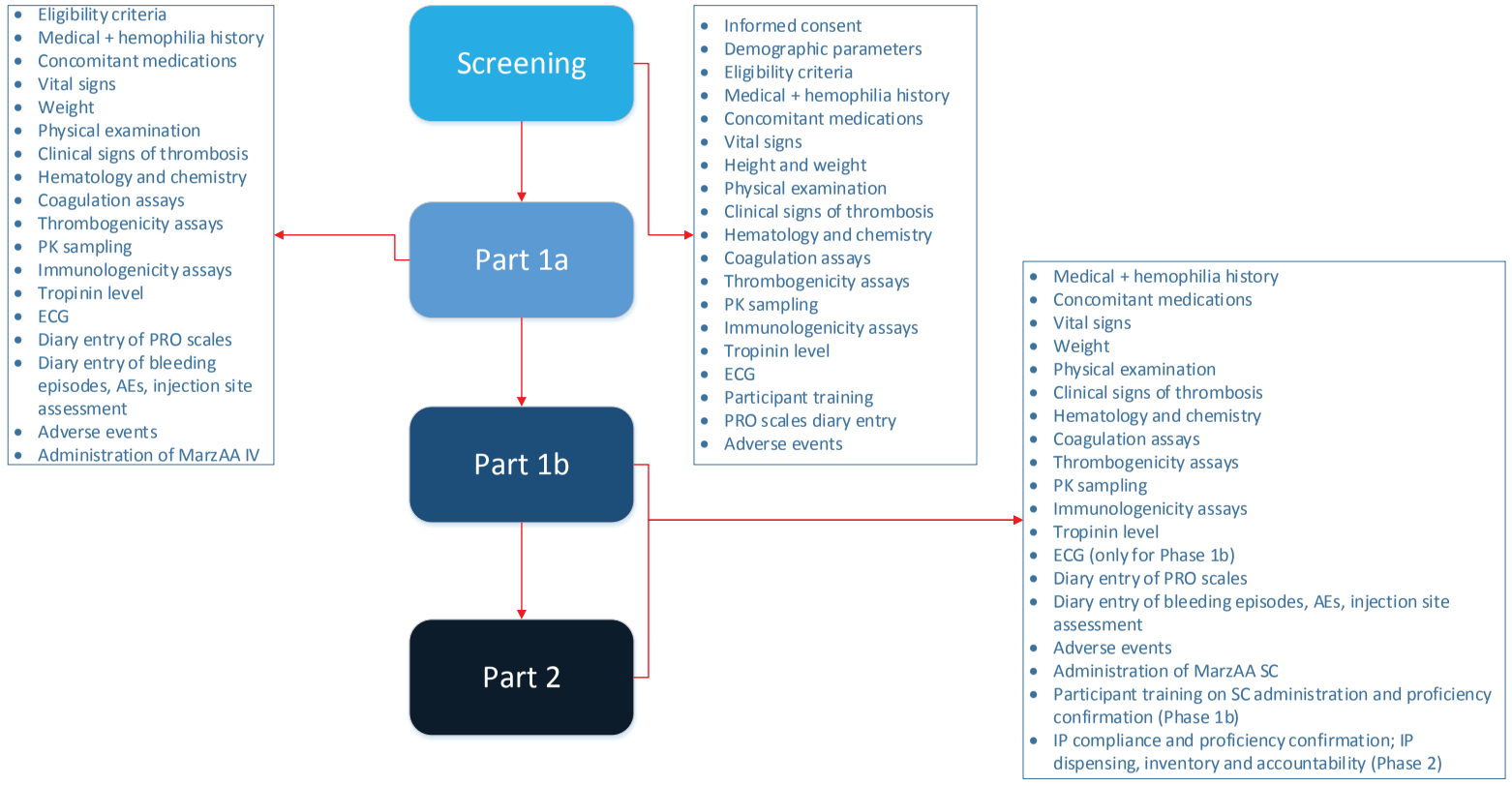
1.2 SCHEMA

Figure 1. Schematic of Study Design (see Appendix D for a more detailed schema)



1.3 SCHEDULE OF ACTIVITIES (SOA)

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.

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.

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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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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2. INTRODUCTION

2.1 STUDY RATIONALE

A significant number of patients with hemophilia A develop neutralizing antibodies ("inhibitors") against factor VIII and become refractory to standard factor replacement treatment.[1-4] Hemophilia A is four times as common as hemophilia B.[5] Patients with Hemophilia B can also develop neutralizing antibodies and become refractory to factor replacement therapy.[6-8] Currently, available treatment for patients with hemophilia A and B with inhibitors is with rFVIIa or with APCCs. The prevention of bleeding episodes, referred to as prophylaxis, requires frequent intravenous dosing.[9] Catalyst Biosciences has created a FVIIa variant with pre-clinical properties that suggest increased potency and duration and the ability to be administered subcutaneously for daily use as prophylaxis.

2.2 BACKGROUND

Hemophilia A and B are X-linked, recessive, hereditary bleeding disorders caused by an impaired deficiency of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B).[10] The prevalence of Hemophilia A is 1 in 5000 live male births and hemophilia B is 1 in 30,000 (hemophilia A is four times as common as hemophilia B).[5] Disease classification of mild (>5 and <40%), moderate (1 to 5%) or severe (<1%) is based on plasma FVIII and FIX levels.[11] Bleeding is the main clinical manifestation, which can occur spontaneously, especially in severe hemophilia. Bleeding most often affects the joints, causing arthropathy with significant impairment of mobility and quality of life. Other sites can include the soft tissue, gastrointestinal tract (GIT) and central nervous system (CNS).[12,13] Treatment of hemophilia A or hemophilia B typically involves factor replacement therapy by IV injection of FVIII or FIX concentrate respectively to treat or provide prophylaxis against bleeding episodes.[10] Factor replacement therapy is also used for surgical hemostasis and to maintain hemostasis during the post-operative wound healing period. Neutralizing antibodies (inhibitors) to the injected FVIII or FIX are a complication of factor replacement therapy that develops in approximately one-third of hemophilia A patients and in up to 5% of hemophilia B patients[14-17] Inhibitors can occur at high or low titer (quantitated in Bethesda Units [BU]), can neutralize the activity of the replacement therapy, and can make treatment of bleeding episodes unsuccessful, resulting in potentially catastrophic clinical consequences for the patient, including an increased morbidity and mortality risk.[10,17]

For hemophilia patients with high titer inhibitors to FVIII or FIX and for hemophilia patients with low titer inhibitors in whom it is not possible to achieve hemostasis

using FVIII or FIX replacement therapy, respectively, the current standard of care includes treatment with wt-rFVIIa (NovoSeven® or NovoSeven® RT, Novo Nordisk) or activated prothrombin complex concentrates (APCCs), including AICC, (FEIBA®, Baxalta Incorporated).[4,18-22] These agents fall in the category of bypass agents and effect hemostasis by achieving conversion of prothrombin to thrombin via the tissue factor pathway (extrinsic pathway) of coagulation or via a combination of the tissue factor pathway and the final common pathway of coagulation respectively.[23] NovoSeven®, a wt-rFVIIa, was approved by the Food and Drug Administration (FDA) in March 1999, for the treatment of bleeding episodes in hemophilia A (FVIII-deficient) or hemophilia B (FIX-deficient) patients with inhibitors, and in patients with congenital FVII deficiency. It is also approved for prevention of bleeding prior to surgery or invasive procedures in these patients with inhibitors or FVII deficiency. Based on its very short (2.3 hours) half-life, administration of NovoSeven® is repeated approximately every 2 hours to control hemorrhage in patients with hemophilia A or B with inhibitors.[4,18-22] Often, multiple doses (3 or more) are required to complete treatment of a bleeding episode.[9] Activated prothrombin complex concentrates (APCCs) were introduced for treatment of inhibitors in patients with hemophilia in the 1970s.[24] The only APCC currently available on a commercial basis is FEIBA® which was first marketed in 1977 and was first licensed in the US as FEIBA VH® (vapor heat-treated FEIBA). FEIBA VH® was manufactured via vapor heat treatment to inactivate lipid-enveloped RNA and DNA viruses and non-enveloped RNA viruses. In 2006 Baxter introduced nanofiltration to the manufacturing process of FEIBA VH® to create FEIBA NF®. During 2010, FEIBA VH® was completely replaced by FEIBA NF® on a worldwide basis.[24] FEIBA VH® and FEIBA NF® and is now available as FEIBA®. FEIBA® and FEIBA NF® are identical in formulation to FEIBA VH®.[24-26] FEIBA® is indicated for the control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes and to cover surgical interventions in hemophilia A and hemophilia B patients with inhibitors. For treatment of bleeding episodes in hemophilia patients with inhibitors, FEIBA® is typically administered in doses of 50 to 100 units/kg, determined by the type of bleeding episode. Repeat administration, if required, is typically administered at 6-12-hour intervals until resolution of bleed or alleviation of symptoms. For prophylaxis, the approved dose of FEIBA® is 85 units/kg administered every other day.[25]

Treatment of inhibitor patients with wt-rFVIIa or with APCCs has limitations with regard to efficacy, safety, and/or convenience[27-29], and therefore presents opportunities for development of improved or alternative biotherapeutics to satisfy an unmet medical need in this patient population. Efficacy of wt-rFVIIa or APCCs in patients with inhibitors is suboptimal in terms of ability to control bleeds and with regard to duration of action. These therapies fall short of the efficacy achieved with conventional factor replacement therapies in patients without inhibitors.[10,30,31] Because efficacy is suboptimal with either of the currently licensed products, elective surgical procedures may be deferred for patients with inhibitors who may need such procedures.[32] Pathogen transmission, thromboembolic

events, hypersensitivity and anamnestic response resulting in an increase in inhibitory antibody titers have been the main safety concerns when treating patients with hemophilia with inhibitors.[20,25] Thrombotic events in association with NovoSeven® treatment in hemophilia patients with inhibitors have been reported in up to 4% of patients.[20,33-35] Reported incidence of thrombotic events in association with FEIBA® use ranges from 4-8.24/100,000 infusions.[25,36-38] NovoSeven® is not approved for prophylaxis and its use for that purpose is not generally feasible for many reasons, including short duration of action that precludes administration schedules practical for routine use.[20,39] The percent reduction in annual bleed rate during prophylaxis of hemophilia patients with inhibitors with FEIBA®[40] is less than that reported for factor replacement therapy in hemophilia patients without inhibitors.[41] FEIBA® also contains small amounts of FVIII and has the potential to boost inhibitor titers in hemophilia A patients with inhibitors.[4]

2.2.1 Rationale for Prophylaxis with SC Administration of FVIIa

There is currently no cure for hemophilia.[42] The prevention of bleeding episodes in hemophilia patients requires life-long prophylaxis.[42,43] Due to the short half-life of wt-rFVIIa and APCC products, prophylaxis and treatment for bleeding episodes requires frequent IV dosing (daily for wt-rFVIIa or every other day for APCCs).[20,25] IV dosing often requires a medical professional or family member to perform the venipuncture, making home prophylaxis cumbersome, particularly for pediatric patients.[43,44] Other challenges include patient adherence, and reliable IV access.[45,45] IV administration requires direct venipuncture or sterile entry into a central venous access device on a regular basis, which makes it time-consuming and negatively influences adherence.[45]

SC administration presents a major advantage over IV administration because it enables at-home injection, improves quality of life, and reduces health care costs.[46] While home IV administration has been essential to the provision of comprehensive hemophilia care, it nonetheless remains a significant barrier.[45] SC dosing allows improved ease of self-administration and obviates the need for home nursing or a visit to a hemophilia center to provide an IV infusion when a patient or a family member has not been able to do so.[46] Compared with the IV route, SC administration of wt-rFVIIa has been shown to extend half-life (12.4 hours *vs* 2.7 hours) and significantly reduces the large daily fluctuations of systemic drug concentrations, though with a reduced bioavailability (21-30% *vs* 100%).[47] Consequently, there is a clear need for the development of rFVIIa variants with greater bioavailability and extended effect for SC administration to facilitate effective bleeding prophylaxis in hemophilia patients with inhibitors.

MarzAA, a novel rFVIIa variant, is being developed by Catalyst Biosciences (the Sponsor) to address the unmet need for medical management of hemophilia A and B patients with inhibitors. MarzAA was developed using a structure-based rational protein design approach intended to enhance the biological properties of wt-rFVIIa and contains a total of 4 amino acid substitutions. The 2 amino acid substitutions in the protease domain (Q286R and M298Q) increase catalytic activity for factor X activation in both a tissue factor dependent and tissue factor independent manner. The 2 others are in the light chain (T128N and P129A) and yield an additional N-linked glycosylation site designed to provide an extended duration of effect. These qualities are expected to prolong the interval between doses, improve convenience of treatment, and facilitate use of the product for bleeding prophylaxis.

2.2.2 Experience with MarzAA in the Clinic

To date, the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MarzAA IV administration has been evaluated in one clinical study (B3051001) which recruited 25 adult subjects with hemophilia A or B (all male) with or without inhibitors, with 1 subject in the 0.5 µg/kg dose group and 6 subjects in each of the 4.5, 9, 18, and 30 µg/kg dose groups.[48] Cmax was reached at 5-15 minutes after IV bolus administration. Both clearance and volume of distribution (VOD) were similar at 18 to 30 µg/kg dose level but decreased across the 3 lower doses (4.5 to 18 µg/kg). MarzAA terminal half-life (~3.5 hours) was similar across all doses. The MarzAA PK profile observed in study B3051001 was consistent with projections based on preclinical data. All hemophilia and non-hemophilia AEs were mild or moderate in severity; there were no severe treatment-emergent adverse events (TEAEs), no serious adverse events (SAEs) and no AEs leading to treatment discontinuation. Overall, the most common non-hemophilia-related AEs were dizziness, headache, and oropharyngeal pain (2 subjects each). Hemophilia-related AEs consisted of 3 AEs of arthralgia, and 1 AE each of flank pain, hemarthrosis, joint swelling, muscle swelling, and limb injury. MarzAA demonstrated good PD effects, with treatment-related (most often dose-related) changes observed for a variety of coagulation parameters. Thus, MarzAA showed an acceptable safety profile and promising PD effects in the phase 1 study.

3. OBJECTIVES AND ENDPOINTS

3.1 PRIMARY

- To evaluate the efficacy and safety of marzeptacog alfa (activated) for bleeding prophylaxis in adult subjects with hemophilia A and B with an inhibitor
    - To evaluate the ABR (spontaneous and total) during Part 2 when on final MarzAA dose level versus recorded historical ABR
    - To evaluate spontaneous bleeding requiring escalation to higher dose level
    - Note: A spontaneous bleeding episode is defined as one that is precipitated by normal ADL.

3.2 SECONDARY

- To determine the PK and PD, of SC administration of MarzAA in patients with hemophilia with inhibitors and compare IV versus SC administration of MarzAA regarding PK, PD, and safety parameters.
- To find the optimal dose of MarzAA for each subject, ie, the dose that prevents spontaneous bleeding*; and determine the PK, PD, and safety of daily SC administration of MarzAA at the optimal dose for each subject for an extended duration, mimicking the intended SC prophylactic use of MarzAA in patients with hemophilia.
- To determine occurrence of and categorize breakthrough bleeds requiring escalation to higher dose level as follows:
    - Number of bleeds that are life threatening
    - Number that require hospitalization and/or blood transfusion
    - Number of muscle bleeds
    - Median time to resolution (and interquartile range) of bleeds

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

3.3 EXPLORATORY

- To identify potential biomarkers and determine the effect of SC administration of MarzAA of the quality of life of patients with hemophilia with inhibitors
    - 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.
    - 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)

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2 study designed to evaluate the pharmacokinetics, bioavailability, pharmacodynamics, 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. It is an open-label study, so subjects and members of the clinical study team will not be blinded to treatment. It is estimated that it will take approximately one year from when the study opens enrollment until completion of data analyses. The study will enroll a total of 12 adult male subjects with severe congenital hemophilia A or B with an inhibitor, and history of frequent spontaneous bleeding episodes (historical annualized bleeding rate [ABR] of ≥12)., as per the individual's bleeding and treatment records. Participants will be given a single IV administration of MarzAA at 18 µg/kg followed by single daily SC administration of MarzAA at 30 µg/kg. Dose levels may increase to 60, 90, or 120 µg/kg as required. The H0 is that the ABR (for MarzAA) = 12 versus H1: ABR (for MarzAA) < 12.

Each subject will participate in all three phases (occurring consecutively):

Part 1a (24 hours) is intended to compare IV versus SC administration of MarzAA regarding PK, PD, and safety parameters. Each subject will receive a single 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 Hour 1, 3, 6, 9, 12, and 24.

Part 1b (48 hours) is intended to compare IV versus SC administration of MarzAA regarding PK, PD, and safety parameters. After the initial 24 hours, subjects will receive a single 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. During this period, subjects will be trained by appropriate study staff to self-administer a SC injection.

Part 2 is intended to (i) find the optimal dose of MarzAA for each subject, ie, the dose that prevents spontaneous bleeding; and (ii) determine the PK, PD, and safety of daily SC administration of MarzAA at the optimal dose for each subject for an extended duration, mimicking the intended SC prophylactic use of MarzAA in patients with hemophilia.

Subjects will sign an informed consent form (ICF) at the Screening Visit, prior to any study procedures. Eligibility to participate in the study will be determined by inclusion and exclusion criteria from medical history, hemophilia history, laboratory investigations and ECG. At screening, subjects will receive training

and diary entry of investigational drug administration & injection site assessment, bleeding episodes & treatment, evaluation & entry of AEs & entry of PRO scales. The screening period duration may be up to 4 weeks.

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 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, he 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.

The participation of each subject to all three phases is intended to reduce the number of subjects enrolled in this study.

Treatment of a spontaneous or traumatic 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 spontaneous or traumatic 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 whether to arrange for a blood specimen to be drawn (if feasible) before further administration of either study drug or the bypassing agent used for treatment. Decision whether to continue daily study drug administration will also be determined by the clinical study team after discussion with the Sponsor. See **Section 6.1.2, Dosing and Administration**, for details on dose escalation, dose de-escalation, and treatment interruption. This information will also be recorded in the subjects' diary.

Dose interruption and surgery: Daily SC study injections will be interrupted 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 and coagulation parameters will be measured at Day 1 (Pre-dose and Post-dose Hour 7), Day 3 (Pre-dose), Day 5 (Pre-dose), Day 7 (Pre-dose and Post-dose Hour 7).

If no spontaneous bleeding occurs at the first dose level in Part 2 of the study, trough antigen and activity and 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 on a 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- and 7 hours 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 and PD. MarzAA antigen and activity levels and 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.

4.2 END OF STUDY DEFINITION

The minimum duration of treatment for each subject is approximately 2 months (if no dose escalation is required) and the maximum duration is approximately 7 months (if three dose escalations are required).

Up to 4 weeks for screening period; 24 hours for the part 1a (single IV dosing and PK/PD/Safety testing); 48 hours for the Part 1b (single SC dosing and PK/PD/safety testing); and up to 197 days of daily SC dosing and a PK/PD/safety follow-up assessment 30 days after last dose. Subjects must have no spontaneous bleeding for 50 days if on the first three dose levels or complete 50 days of treatment on the fourth dose level. The end of study visit will be 30 days after the last dose of study drug treatment in Part 2.

A participant is considered to have completed the study if he has completed all phases of the study, including treatment at the same dose level for 50 days, and returned for procedures listed under end of study visit as shown in the SOA.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

An individual must meet all of the following criteria to be eligible to participate in this study:

1. Confirmed diagnosis of severe congenital hemophilia A or B with an inhibitor.
2. History of frequent spontaneous bleeding episodes (historical ABR ≥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.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

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 CAD, ischemic stroke, etc.), or known DVT or considered to be at a high risk of VTE as judged by the Investigator.
8. Known or suspected allergy to trial product or related products.
9. Absolute CD4 count <200 cells/µL.

10. Receiving IMT.
11. Compromised hepatic or renal function:
    a. ALT and AST levels ≥5 times ULN
    b. TBIL level ≥2 mg/dL (>35 µmol/L) unless there is a known history of GS
    c. Serum albumin ≤ LLN
    d. Serum Cr level >1.25 x ULN
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.

5.3 LIFESTYLE CONSIDERATIONS

There are no specific lifestyle considerations.

5.4 SCREEN FAILURES

An individual who does not meet the criteria for participation in this trial (screen failure) because of an out of range laboratory parameter may be rescreened.

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6. STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 Study Intervention Description

Description and Composition of the Drug Product

MarzAA will be provided as a powder for injection, at a 4.62 mg/vial dosage strength. The drug product is supplied in a 5-mL vial that is sealed with a 20mm lyophile stopper and 20mm aluminum over-seal. To manufacture the drug product, 2.2 ml of formulated bulk drug product is filled in each vial and lyophilized. The lyophilized drug product will be reconstituted for IV and SC injection.

6.1.2 Dosing and Administration

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

- 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.

6.1.2.1 Guidelines for Dose Escalation

An escalation to the next dose level is required if a spontaneous bleeding event occurs after the fifth daily dose on a dose level. A dose escalation will not occur if the subject is on the maximum dose level of 120 µg/kg. A spontaneous bleeding episode is defined as one that is precipitated by normal activities of daily living (ADL). Subjects will use their current bypass regimen for any spontaneous or traumatic bleed that occurs while on study drug.

Three dose escalations are allowed during Part 2: 60, 90, and 120 µg/kg (maximum dose).

Safety parameters and PK/PD assessments at each dose level will be monitored to ensure that dose escalation to a higher dose level is appropriate.

The spontaneous bleeding episode must be reported to the clinical team immediately and determination of a dose escalation will be made on review of available clinical information related to the spontaneous bleeding episode and may require subsequent treatment and laboratory data, including available results from the PK/PD/safety assessments.

A decision to proceed with dose escalation will be made by the principal investigator in agreement with personnel who have Sponsor, or designee, medical oversight responsibility.

If there is disagreement amongst any of those individuals, the decision will be reviewed on an urgent basis by an independent Medical Consultant for Safety Oversight.

6.1.2.2 Guidelines for Dose De-escalation

While it is not expected that there will be a need for dose de-escalation in this trial, if there is evidence of drug accumulation based on rising peak and trough levels of MarzAA or other laboratory parameters, then the subject's dose level will be reviewed by the PI and Sponsor, or designee, and a determination to hold treatment at the current dose level or decrease to the lower dose level will be made. This determination will be made in conjunction with the independent Medical Consultant for Safety Oversight.

6.1.2.3 Guidelines for Treatment Interruption

Daily SC study injections will be interrupted, as needed, when:

- A surgical procedure is needed
- There is a medical event requiring extended (>48 hours) hospitalization
- If there is a thrombotic event
- If there is clinical evidence of inhibitor formation
- If there are laboratory results suggesting an antibody may be developing

Daily SC study injections may be interrupted, as needed, when:

- A spontaneous bleeding event occurs
- A traumatic bleeding event occurs

Subjects will use their current treatment regimen for any spontaneous or traumatic bleed that occurs while on study. If treatment for a spontaneous or traumatic 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.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and Accountability

Upon receipt of the MarzAA shipment, the pharmacist, or a designee, will conduct an inventory and return an acknowledgement that all IP was received frozen and undamaged, thereby maintaining the Good Manufacturing Practice (GMP) status of the product during shipment.

All used and unused investigational product must be returned by the subject to the study site. Subjects must return all investigational product packages and vials (including used, empty, and unused vials) for reconciliation of IP.

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. The sponsor will supply drug accountability forms to be used in this study.

The sponsor or designee will arrange for the return of unused investigational product. The IP destruction procedure for used vials is to be decided locally to comply with local regulations and procedures.

Drug accountability will be reviewed by the monitor during routine monitoring visits. No IP can be destroyed or returned until the study monitor has reconciled all vials of IP.

6.2.2 Product Storage and Stability

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements. The IP and its storage and preparation requirements will be provided by the Sponsor, or designee.

Investigational product should be stored in its original container and in accordance with the drug label. The Sponsor will provide the Investigator with packaged IP in accordance with specific country label requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to appropriate storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor, or designee.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor, or designee, provides documentation of

permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. Site staff will instruct subjects on the storage requirements for take home medications including how to report temperature excursions.

6.2.3 Preparation

MarzAA will be provided as a powder for injection, at a 4.62 mg/vial dosage strength, and is supplied in a 5-mL vial. The lyophilized drug product will be reconstituted for IV and SC injection.

Details regarding the dosing administration, both at the study site and in the homecare setting, will be provided by the Sponsor, or designee.

At the study site, both the MarzAA IV dose and SC dose will be prepared and administered by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

In the homecare setting, the MarzAA SC dose will be prepared and administered by the study subject or subject caregiver/guardian.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The study is an open-label study; subjects and members of the clinical study team will not be blinded to treatment.

6.4 STUDY INTERVENTION COMPLIANCE

Reasonable efforts should be made to ensure that study drug administration is administered daily in the morning. However, if an unavoidable disruption of the daily administration occurs and a dose is not administered then the subject should be instructed to continue beginning the following day in the morning.

If the subject misses two or more daily doses, then a spontaneous bleeding event will result in a dose escalation only if it occurs 4 days or longer after resumption of the daily administration.

6.5 CONCOMITANT THERAPY

Enrolled subjects will record all concomitant medications administered from the Screening Visit to Study termination (including the date and time of administration) in their diary.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the electronic Case Report Form (eCRF) are concomitant prescription medications, over-the-counter (OTC) medications and supplements.]

There are no concomitant medication restrictions. However, individuals are excluded if they have been on a prophylactic treatment regimen with a FVIII or FIX replacement factor or a bypassing agent prior to enrollment.

If an individual has previously been enrolled on a clinical trial evaluating a treatment for prophylaxis other than a modified rFVIIa (as specified in exclusion criteria #2) or Emicizumab (ACE910)[49], Fitusiran (ALN-AT3SC)[50,51], or one of the anti-TFPI agents (Concizumab [mAb2021][52], BAY1093884[53], PF-06741086[54]) in clinical investigation he will be permitted to enroll onto this study, provided it is greater than 30 days since exposure to that study drug.

The following medications will be permitted during the study:

- In the event of spontaneous or traumatic bleeding, treatment for a spontaneous or traumatic bleeding episode will be permitted using the subject's current treatment regimen which could be FEIBA®, NovoSeven®, or a high dose regimen utilizing a FVIII or FIX product.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

Any new clinically relevant finding will be reported as an AE.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets a criterion (either newly developed or not previously recognized) that precludes further study participation
- Decision by Investigator or Sponsor

The reason for participant discontinuation or withdrawal from the study and the date will be recorded on the electronic case report form (eCRF).

Replacement of a subject occurs for the following reason:

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

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he fails to return for two consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, *request the subject to return all used and unused investigational product(s)*, request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

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8. STUDY ASSESSMENTAND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Subjects will be asked to record all spontaneous or traumatic bleeding episodes and concomitant medications administered into the eDiary, including (but not limited to) the following:

- Bleeding episode (date/time of onset and date/time of resolution)
- Cause of bleeding (spontaneous or traumatic)
- Bleeding site: joint (ankle, knee, elbow, other [right or left]); muscle (iliopsoas, calf, forearm, other [right or left]); mucous membranes (mouth, gums, nose, genitourinary tract); gastrointestinal (gastric ulcer, fissure, other [requiring transfusion – yes, no]), neck/throat, intracranial.
- Hemostatic drugs used for treatment of bleeding episodes (time/date of administration, type, amount [international units or mg and/or number of infusions])

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

Investigators will document:

- Subject demographics (sex, age, race and ethnicity) will be recorded at the screening visit.
- All ongoing conditions and relevant medical history (including all major hospitalizations and surgeries) as well as the subject's current medical status will be recorded at the screening visit.
- Diagnosis of severe congenital hemophilia A or B with an inhibitor will be documented including the frequency of spontaneous or traumatic bleeding episodes in the past 6 months.
- Notation will be made regarding history of orthopedic procedures including joint aspiration, synovectomy, fusion, or joint replacements or other complications of hemophilia including pseudotumors.
- Concomitant medication use including treatment used for control of spontaneous or traumatic bleeding events (infusion therapies, anti-fibrinolytic agents, local agents) and for management of pain and other complications related to hemophilia.
- Vital signs, height, weight, general physical examination will be performed at screening.

Evaluations related to PK and PD will include:

- MarzAA antigen and activity levels over time post-dose and calculation of standard PK parameters and bioavailability. These evaluations will be performed at a central laboratory.
- Coagulation parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, FVII, FVIIa activity, and thrombin generation time (TGT). These evaluations will be performed at a central laboratory.
- Thrombogenicity markers: D-dimer, F1+2, and thrombin-antithrombin complexes (TAT). These evaluations will be performed at a central laboratory.

8.2 STUDY PROCEDURES

Study procedures and evaluations to be done as part of the study. Please refer to **Section 1.3, Schedule of Activities (SOA)** for the sequence of events.

8.2.1 Screening

Please refer to **Section 1.3, Schedule of Activities (SOA)** and specifically Table 1 for the sequence of events that should occur during the screening process. Screening should occur within 4 weeks prior to enrollment.

- Informed consent
- Demographic parameters
- Inclusion and Exclusion Criteria review
- Medical and hemophilia history
- Concomitant medications
- Vital signs
- Height and weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry: (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- Immunogenicity assays: to FVII, FVIIa, and MarzAA

- Troponin level
- ECG
- Study Subject training on drug administration and injection site assessment; evaluation and diary entry of AEs, spontaneous or traumatic bleeding episodes and treatment, and PRO scales
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Adverse events

8.2.2 Part 1a (Duration 24 Hours)

Please refer to **Section 1.3, Schedule of Activities (SOA)** and specifically Table 1 for the sequence of events that should occur during the Part 1a process.

8.2.2.1 Pre-dose evaluations

- Inclusion and Exclusion Criteria review
- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Troponin level
- Adverse events

8.2.2.2 MarzAA administration (Hr 0)

- Subjects will receive a bolus IV dose of MarzAA at 18 µg/kg

8.2.2.3 Post-dose evaluations

Blood will be collected at 5 and 30 minutes and 1, 3, 6, 9, and 12 hours (on Day 1) post-dose for the following evaluations:

- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity

8.2.2.4 Post-dose evaluations (24 hours)

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Troponin level
- ECG
- Adverse events (from Hr 0 to 24 hours)

8.2.3 Part 1b (Duration: 48 Hours)

Please refer to **Section 1.3, Schedule of Activities (SOA)** and specifically Table 2 for the sequence of events that should occur during the Part 1b process.

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 done within 2 days).

8.2.3.1 Pre-dose evaluations

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Troponin level
- Adverse events

8.2.3.2 MarzAA administration (Hr 0)

- Subjects will receive a SC dose of MarzAA at 30 µg/kg.
- SC administration training and proficiency confirmation

8.2.3.3 Post-dose evaluations

Blood will be collected at 3, 5, 7, 9, and 12 hours post-dose for the following evaluations:

- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity

8.2.3.4 Post-dose evaluations (24 hours)

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Troponin level
- ECG

- SC administration training and proficiency confirmation
- Adverse events (Hr 0 to Hr 24)

8.2.3.5 Post-dose evaluations (30 hours)

- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity

8.2.3.6 Post-dose evaluations (48 hours)

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- SC administration training and proficiency confirmation
- Adverse events (Hr 24 to Hr 48)

8.2.4 Part 2 (Duration: ⩾50 Days)

Please refer to **Section 1.3, Schedule of Activities (SOA)** and specifically Table 3 and 4 for the sequence of events that should occur during the Part 2 process.

Part 2 procedures will be the same for all subjects; there are modifications in the schedule of follow-up visits and assays drawn for those subjects who have no spontaneous bleeding occurrence after the fifth daily dose, as shown in **Section 1.3, Schedule of Activities** and specifically **Table 3** and for those who have an interim spontaneous bleeding event requiring dose escalation as shown in **Section 1.3, Schedule of Activities** and specifically **Table 4**.

Day 1 of Part 2 will start the next morning right after Part 1b is completed. During Part 2, subjects will self-administer MarzAA SC daily in the morning at 30 µg/kg. Subjects will record daily in their diary: the injection day/time, dose, spontaneous or traumatic bleeding episodes that may occur and whether bypassing treatment is administered, which agent, and what dose, AEs that may occur, and injection site assessment.

Subjects will return to the clinic the day after Part 1b for the Part 2, Day 1 assessments.

8.2.4.1 Day 1 Visit

The following procedures will be performed.

Assessments required on Part 2, Day 1 that have been completed at Part 1b, do not have to be repeated (if done within 2 days).

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity

- Immunogenicity assays to FVII, FVIIa, and MarzAA
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.4.2 Day 3 and Day 5 Visits

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Injection compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.4.3 Day 7 Visit

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Troponin level
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.5 Part 2 – If No Spontaneous Bleeding Occurs after the fifth daily dose, (Duration: ⩾50 Days)

If No Spontaneous Bleeding Occurs after the fifth daily dose, the following procedures will be performed on the Days 14, 21, and 28 Visits:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight

- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.5.1 Day 42 Visit

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.5.2 Day 50 Visit

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.6 Part 2 – If Spontaneous Bleeding Occurs after the fifth daily dose (Duration: ⩾50 Days)

If a spontaneous bleeding episode occurs in Part 2 after the fifth daily dose, necessitating a dose escalation, the "day count" will be reset to zero. The day a spontaneous bleeding event occurs (and subsequent days until the event is resolved) is considered Day 0. Dose escalation starts on the next day (Day 1).

8.2.6.1 Day 0 Visit

If a breakthrough bleed event occurs, subjects are instructed to use their current bypass regimen for treatment and to then immediately contact the clinical investigative team to report the event, what treatment and dose was utilized, arrange for immediate follow-up, if feasible and determine follow-up plans for that event. The Day 0 Visit begins when a breakthrough bleed event occurs and includes the subsequent time until treatment resolution.

The following procedures will be performed on the Day 0 Visit:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Troponin level
- Study drug dispensing, inventory and accountability
- Dispense study drug at the escalated dose to the subject to use once the spontaneous bleeding episode has resolved. Reschedule subjects' visits for Days 7, 14, 21, 28, and 50 after dose escalation.
- Adverse events

Once the spontaneous bleeding episode has resolved, the subject will be instructed to inject MarzAA at the next dose level (60, 90, or 120 µg/mL) beginning in the morning on Day 1.

8.2.6.2 Day 7 Visit After Spontaneous Bleeding Event Reset and Day 0 evaluations

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Troponin level
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.6.3 Day 14, 21, 28 Visits After Spontaneous Bleeding Event Reset and Day 0 evaluations

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs

- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA (**Day 14** and **28** only)
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.3.6.4 Day 42 Visit After Spontaneous Bleeding Event Reset and Day 0 evaluations

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.6.5 Day 50 Visit After Spontaneous Bleeding Event Reset and Day 0 evaluations

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.7 Unscheduled Visit

Should a subject need to be seen at any time while enrolled onto the trial, and not on a study scheduled visit, the following assessments may need to be conducted based on the judgement of the clinical study team.

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Weight
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)

- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Troponin level
- IP compliance and proficiency confirmation
- Study drug dispensing, inventory and accountability
- Adverse events

8.2.8 End-of-Study Visit (30 Days after Last Dose)

The following procedures will be performed:

- Medical and Hemophilia History (including that obtained from review of diary entries of bleeding episodes and treatment, AEs, and PRO scales)
- Concomitant medications
- Vital signs
- Diary entry of PRO scales (see **Appendix B** – EQ-5D, VAS; Haem-A-QoL; HAL)
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT
- Thrombogenicity markers: D-dimer, F1+2, and TAT
- PK: MarzAA antigen and activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA
- Study drug dispensing, inventory and accountability
- Adverse events

8.3 STUDY ASSESSMENTS

8.3.1 Physical Examination

A full physical assessment of the major body systems will be recorded.

8.3.2 Vital signs

One measurement of blood pressure, heart rate, respiratory rate, and body temperature will be taken after the subject has been sitting quietly for at least 5 minutes.

8.3.3 Hematology

Complete blood cell count (CBC), platelet counts, and CD4 count will be will be measured using standard laboratory testing methods at a local laboratory.

8.3.4 Chemistry

Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT and AST), bilirubin, albumin, blood urea nitrogen (BUN), and Cr will be measured using standard laboratory testing methods at a local laboratory.

8.3.5 Coagulation assays

PT, aPTT, fibrinogen, FVII, FVIIa activity, and TGT. These evaluations will be performed at a central laboratory.

8.3.6 Thrombogenicity markers

D-dimer, F1+2, and thrombin-antithrombin complexes (TAT). These evaluations will be performed at a central laboratory.

8.3.7 Antibody response and neutralizing antibodies to MarzAA

These evaluations will be performed and tested at a central laboratory.

8.3.8 Clinical signs of thrombosis (Appendix A)

This assessment will be included as part of the study subject training, provided as a reference on the eDiary device, and will be a scheduled evaluation at clinical study visits.

8.3.9 Concomitant medications

Subjects will record concomitant medications (including name of medication, dose taken, day and time) they may be taking in their daily diaries. Diaries will be reviewed by the clinical staff at each visit.

8.3.10 ECG

A12-lead ECG will be performed using local standard methods.

8.3.11 Troponin levels

Blood troponin levels will be measured using standard laboratory testing methods at a local laboratory.

For participants that may discontinue or withdraw early, it is important to capture the rationale during the final visit. See **Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawa**l, for details.

8.4 SAFETY AND OTHER ASSESSMENTS

Evaluations related to safety will include:

8.4.1 AEs and SAEs

Subjects will record any AEs that occur during the study in their daily diaries. Diaries will be reviewed by the clinical staff at each visit.

8.4.2 Injection site reactions

Subjects will record site injection reactions in their daily diaries. Diaries will be reviewed by the clinical staff at each visit.

Evaluations that are related to the exploratory endpoints will include the following PRO and clinician reported outcomes (ClinRO) measures:

PRO:

- Health status with the use of the EQ-5D questionnaire.[55] This is a health utility measure that includes assessment of 5 dimensions of health (mobility, self-

care, usual activities, pain/discomfort, anxiety/depression) along with a 0-100 VAS.

- Haem-A-QoL, which measures the quality of life in patients with hemophilia.[56]
- Hemophilia Activities List (HAL), a self-assessment which measures the perceived functional status of patients with hemophilia.[57]

8.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.5.1 Definition of Adverse Events (AE)

Definition of an AE: An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that may not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Pre-existing conditions, diseases or disorders are not considered AEs unless there is a change in the intensity, frequency or quality.

8.5.2 Definition of Serious Adverse Events (SAE)

Definition of a SAE: Definition of a SAE: An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.5.3 Classification of an Adverse Event

8.5.3.1 Severity of Event

All AEs will be assessed by the study clinician using the CTCAE v4.0 where applicable.[59]

For those AEs that are not included under the CTCAE v4.0, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual ADL and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.5.3.2 Relationship to Study Drug

All AEs must have their relationship to study drug assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.5.3.3 Action Taken

None: No changes were made to Study Drug administration and dose

Permanently discontinued: Study drug was discontinued and not restarted

Temporarily interrupted, restarted same dose: Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose without unblinding to treatment group

8.5.3.4 Expectedness

The Principle Investigator (or Co-PI) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.5.4 Time Period and Frequency for Event Assessment and Follow-Up

Subjects will be instructed regarding direct reporting and diary entries of AEs; diaries will be reviewed at each visit and subjects queried if evidence of an AE recorded.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Subject Withdrawal from the Study Due to an Adverse Event:

Every reasonable effort should be made to maintain subject compliance and participation in the study. All enrolled subjects who received the study drug must

be followed through the Follow-Up visit, regardless of the reason for withdrawal. If a subject who has a clinically significant laboratory abnormality or AE withdraws from the study, every effort must be made to follow these events until satisfactory resolution.

8.5.5 Adverse Event Reporting

Members of the study team will record all reportable events with start dates occurring any time after informed consent is obtained until study completion, or discharge, for non-serious AEs. At each study visit, the investigator will inquire about the occurrence of AE since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will categorize the **outcome** of each AE according to the definitions below:

Resolved: The subject recovered from the AE.

Ongoing: At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death. No AE stop date should be recorded with an AE that is ongoing.

Chronic/Stable: At the time of the last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated.

Unknown: There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up).

All protocol-defined adverse events will be reported from the time a patient is enrolled in the study until the end of study visit.

Spontaneous or traumatic bleeding events will not be reported as an AE unless considered serious and should then be reported per the standard process for reporting.

All bleeds should be reported via the ePRO device including spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery (see Section 7.4). Only bleeds (spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery) that are considered serious as per definition (see Section 9.1.2) should be reported as *an* SAE in the CRF. Non-serious bleeds *are not considered adverse events for the purpose of this protocol and* should not be reported as adverse event in the eCRF.

The study drug has the potential risk of causing the following AEs based on information associated with other drugs in the same category, ie, bypassing agents for treatment of hemophilia; these are:

Thrombotic events (see Appendix A)

The study drug has the potential risk of causing thrombotic events based on information associated with other drugs for treatment of hemophilia. See Appendix A for signs and symptoms listed for the subjects and the study team personnel as those requiring urgent reporting and attention.

Development of Drug Antibodies and Inhibitors

There is a risk with the study drug of developing an immune response resulting in antibody formation and potentially an inhibitory antibody response. This will also be monitored for throughout the study.

Skin injection site may become reddened or painful.

Risks associated with blood collection:

A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

8.5.6 Serious Adverse Event Reporting

Members of the study team will record all reportable events within 24 hours of knowledge of the SAE with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will categorize the **outcome** of each SAE according to the definitions below:

Resolved:	The subject recovered from the AE.
Ongoing:	At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death. No AE stop date should be recorded with an AE that is ongoing.

Chronic/Stable: At the time of the last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated.

Death: The AE directly caused death.

Unknown: There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up).

Definitions:

Death: Any event resulting in a subject's death must be reported as an SAE. However, death, in and of itself, is not an AE; it is only an outcome. The cause of death is the AE. Therefore, the investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE should be documented as an "unspecified fatal event".

Life threatening AE: Any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (*i.e.,* it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Hospitalization: It should be noted that hospitalization, in and of itself, does not represent an SAE. It is the AE leading to the subject's hospitalization that becomes "serious" when it requires inpatient care. Consequently, an SAE should not be reported in the case of pre-planned hospitalizations for pre-existing conditions that did not worsen during the study.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

8.5.7 Adverse Events of Special Interest (AESIs)

The study drug has the potential risk of causing the following AESIs based on information associated with other drugs in the same category. These are:

1. Thromboembolic events (TEs) based on information associated with other drugs for treatment of hemophilia. TEs include myocardial infarction (MI); venous thrombosis, and pulmonary embolism (PE); and stroke. See **Appendix A** for signs and symptoms listed for the subjects and the study team personnel as those requiring urgent reporting and attention.

2. Immune response resulting in antibody formation and potentially an inhibitory antibody response. This will also be monitored for throughout the study.

8.5.8 Reporting of Pregnancy

Although pregnancy itself is not considered an adverse event or a serious adverse event, the partner of a male participant should be followed until termination or to term to ensure absence of congenital anomaly or birth defect that may have resulted from maternal exposure or transmission of the study drug via semen following paternal exposure.

Please advise all participants to use a highly effective method of birth control from the first dose of study drug through 28 days after dosing to protect the health and safety of the mother and/or child. Despite the warnings provided and precautions taken, pregnancy may occur during research participation. Investigators must be aware of the requirements related to reporting and follow-up in the event a research participant's partner becomes pregnant.

If a participant's partner becomes pregnant during this study, please provide an authorization form to present to the partner. If she is in agreement, that authorization will function as consent to approve the study doctor's access to medical information to allow the regulatory required monitoring of the pregnancy, and the birth and the health of the child.

Please report the pregnancy of a participant's partner to Catalyst Biosciences, or it's designee, and the IRB, and include the following information: expected date of delivery, last menstruation, estimated conception date and pregnancy result (if known).

Pregnancy should be reported as "Information" (not as an "Adverse Event" or "Other Problem or Event").

- Pregnancy does NOT have to be reported to the IRB if the subject is receiving follow-up only, and conception occurred outside of the time period that the study protocol requires contraception (ie, 28 days after the last dose of the study drug and the pregnancy occurred after that time).
- Subsequent reports containing follow-up information regarding a pregnancy is not required unless the pregnancy results in a congenital anomaly. The congenital anomaly should be promptly reported.
- NOTE: If you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child, it must be reported to the FDA.

9. STATISTICAL CONSIDERATIONS

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.

9.1 STUDY HYPOTHESIS

The null hypothesis (H0) is that the ABR in all subjects treated with daily SC administration of MarzAA will result in an ABR of 12 as compared to the historical control rate of 12, i.e. H0: ABR (for MarzAA) = 12. The alternative hypothesis (H1): ABR (for MarzAA) < 12.

Primary Endpoint

The primary endpoint will include:

- 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 vs Traumatic

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

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 (PT, aPTT, fibrinogen, MarzAA antigen and activity levels, and 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
    - Median time to resolution (and interquartile range) of bleeds

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.
- PRO measures: EQ-5D, VAS; Haem-A-QoL; Hemophilia Activities List (HAL)

9.2 SAMPLE SIZE DETERMINATION

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.

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

9.3 POPULATIONS FOR ANALYSES

Safety population: any patient who receives at least one dose

Efficacy/PD ITT population: any patient who receives at least one dose

Efficacy/PD modified ITT population: any patient who receives at least 7 SC doses at 30 µg/kg

Efficacy/PD per protocol population: any patient who completes at least 50 exposure days (SC product)

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.

9.4 STATISTICAL ANALYSIS

9.4.1 General Approach

Standard PK parameters such as terminal half-life, AUC0-t and AUC0-inf, clearance, volume of distribution, mean residence time and bioavailability (of the subcutaneous versus the intravenous administration) will be calculated. A semi-parametric model described by Lee et all (1990, 1997) will be used to calculate the terminal half-life. A noncompartmental approach based on the trapezoidal rule will be used to compute the AUCs and the parameters derived from them. Descriptive statistics will be reported for each parameter and will include mean ± standard deviation and median ± interquartile range. The number of subjects requiring dose escalation will be reported.

The analysis of the primary endpoint (annualized bleeding rate) of the final dose used to treat a subject will be based on the evaluation of the ABR of MarzAA compared to a rate seen with on-demand therapy. The latter is assumed to be 12 (or one bleed per month) as our null hypothesis (H0). The comparison of the actual ABR for MarzAA either pooled across all doses used or evaluated at the highest dose for an individual will be compared to this null hypothesized value using the one-sample test for a Poisson rate (using an exact calculation of the p-value based on the program StatXact 11, Cytel, Inc., 2015). Because this will be a one-tailed test (the alternative hypothesis is the ABR for MarzAA will be < 12), a one-tailed 2.5% significance level will be used.

All other statistical tests will be performed at the 0.05 significance level using two-sided tests.

There will be a formal Statistical Analysis Plan (SAP) completed prior to database lock and unblinding of the study data.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The analysis of the primary endpoint (annualized bleeding rate) of the final dose used to treat a subject will be based on the evaluation of the ABR of MarzAA compared to a rate seen with on-demand therapy. The latter is assumed to be 12 (or one bleed per month) as our null hypothesis (H0). The comparison of the actual ABR for MarzAA either pooled across all doses used or evaluated at the highest dose for an individual will be compared to this null hypothesized value using the one-sample test for a Poisson rate (using an exact calculation of the p-value based on the program StatXact 11, Cytel, Inc., 2015). Because this will be a one-tailed test (the alternative hypothesis is the ABR for MarzAA will be < 12), a one-tailed 2.5% significance level will be used.

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

9.4.3 Analysis of the Secondary Endpoint(s)

Study drug exposure and compliance will be provided for both phases, and by treatment group for the Treatment Phase.

The following parameters will be documented:

- 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 (PT, aPTT, fibrinogen, MarzAA antigen and activity levels, and 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

The frequencies of these events will be summarized as proportions and counts.

Protocol deviations will be listed. All major protocol deviations (in particular those regarding entry criteria) will be summarized in the study report.

9.4.4 Safety Analysis

Adverse Events

All AEs will be listed, documenting the course, outcome, severity, and causality to study drug. Verbatim terms on CRFs will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA).

Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown for. Incidence rates will also be displayed based on severity and relationship to study drug. AEs with a relationship of "possibly" or "probably" related will be considered by the Sponsor as "related" to the study drug. Events assessed as "unrelated", "unlikely" related, or where the relationship was not reported will be considered by the Sponsor as "not related" to the study drug. The incidence of SAEs will be provided for each phase. All incidence rates will be categorized and displayed by system organ class and preferred term.

Vital Signs

Safety analyses will include descriptive statistical summaries of shifts in vital signs (blood pressure, heart rate, respiratory rate) and in laboratory values for each phase.

9.4.5 Baseline Descriptive Statistics

Demographic and baseline measurement variables will be summarized using descriptive statistics.

9.4.6 Planned Interim Analyses

Not applicable to this study.

9.4.7 Sub-Group Analyses

Not applicable to this study.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

9.4.9 Exploratory Analyses

The following will be documented:

- 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.
- 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.
- 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.
- PRO measures: EQ-5D, VAS; Haem-A-QoL; Hemophilia Activities List (HAL)

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

The written informed consent documents will be prepared in the language(s) of the potential subject population, based on an English version provided by the Sponsor and should be easy to understand.

Before a subject's participation in the trial, the investigator is responsible for obtaining written information consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any study drugs are administered. Sufficient time must be given to consider whether to participate in the study.

The informed consent form should be signed and personally dated by the subject and by the study person who conducted the informed consent discussion. The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the subject.

10.1.2 Institutional Review Board/Independent Ethics Committee

Before initiation of the study, the investigator must submit for approval the protocol, ICF, Investigator's Brochure, and any advertisements to an IRB/IEC for written approval. The Investigator must ensure IRB/IEC compliance with the applicable regulations. A copy of written IRB/IEC approval of the protocol, ICF, and all advertisements must be provided to Sponsor or designee prior to initiation of the study and shipment of study drug. The Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding one year or at more frequent intervals if specified by the IRB/IEC. The Investigator must supply Sponsor or designee with written documentation of continued review of the clinical research.

The Investigator is responsible for reporting the following to the IRB/IEC:

- All SAEs (including deaths) regardless of cause and whether anticipated or unanticipated (reported immediately)
- Significant findings that become known in the course of the study that might affect the willingness of subjects to continue to participate
- Protocol, or consent amendments prior to the implementation of the change
- Study progress reports at least once a year, if applicable

- Notification of study completion or termination.

Sponsor may amend the protocol as needed to ensure that the clinical investigation is being conducted as intended. Sponsor will initiate protocol amendments in writing if any change significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Protocol changes must be submitted to the IRB/IEC as a protocol amendment. If necessary, the ICF will be revised to reflect the changes in the amendment and will be submitted to the IRB/IEC for review and approval. A copy of the amendment must be signed by the Investigator and returned to Sponsor or designee. Written documentation of IRB/IEC approval is required before the amendment is implemented. Investigators may not perform study-specific assessments that are not included in the protocol unless agreed to by Sponsor.

10.1.3 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB/IEC, and sponsor and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

When a study is prematurely terminated, refer to **Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**, for handling of enrolled study participants.

10.1.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor, or designee. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not

limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or sponsor requirements.

10.1.5 Future Use of Stored Specimens and Data

There is no genetic testing performed in relation to this study.

10.1.6 Safety Oversight

There will be an Independent Safety Consultant for review of dose escalation and dose de-escalation decisions as outlined in **Section 6.1.2.1, Guidelines for Dose Escalation** and **Section 6.1.2.2 Guidelines for Dose De-escalation**.

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Sponsor, or its designee, and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that subject confidentiality is respected. The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

To ensure the quality of clinical data a clinical data management review will be performed on subject data received by the Sponsor. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP.

Independent audits may be conducted by the Sponsor, or designee, or regulatory authority inspectors to inspection the Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

10.1.8 Quality Assurance and Quality Control

The Sponsor, or designee, will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the electronic data capture (EDC) system (eCRFs). In the event of data discrepancy, the Sponsor, or designee, will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The eCRFs and correction documentation will be maintained in the EDC system audit trail.

The ePRO data will be collected with the use of an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA and European regulations for electronic records (21 CFR, Part 11). The ePRO device data are available for view access only via secure access to a Web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Medidata Rave EDC, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.]

10.1.9.2 Study Records Retention

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained

10.1.10 Protocol Amendments

Sponsor may amend the protocol as needed to ensure that the clinical investigation is being conducted as intended. Sponsor will initiate protocol amendments in writing if any change significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Protocol changes must be submitted to the IRB/IEC as a protocol amendment. If necessary, the ICF and assent form will be revised to reflect the changes in the amendment and will be submitted to the IRB/IEC for review and approval. A copy of the amendment must be signed by the Investigator and returned to Sponsor or designee. Written documentation of IRB/IEC approval is required before the amendment is implemented. Investigators may not perform study-specific assessments that are not included in the protocol unless agreed to by Sponsor. Additionally, a site-specific amendment and revised ICF and assent form must be generated and submitted for approval to the IRB/IEC.

10.1.11 Publication and Data Sharing Policy

The final clinical study report is also intended to form the basis for a manuscript intended for publication in a peer-reviewed scientific journal. The authorship, timetable and any arrangements for review by the participating investigators will be coordinated by Catalyst Biosciences. No partial subset of data from individual investigational sites can be presented or published until after the primary manuscript for the entire study has been accepted for publication in a peer reviewed scientific journal.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	June 2017		
2.0	25 August 2018	Outlined in Detailed Summary of Protocol Changes	

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APPENDICES

APPENDIX A – CLINICAL SIGNS OF THROMBOSIS

Symptoms and Diagnosis of Venous Thromboembolism (VTE)

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VTE includes deep vein thrombosis (DVT), when a blood clot forms in a deep vein, usually in the leg. And it includes pulmonary embolism (PE), when the clot breaks off and travels from the leg up to the lungs. DVT and PE are serious, life-threatening conditions that require immediate medical attention.

What are the warning signs?
DVT mainly affects the large veins in the lower leg and thigh, almost always on one side of the body at a time. The clot can block blood flow and cause:

- Leg pain or tenderness of the thigh or calf
- Leg swelling (edema)
- Skin that feels warm to the touch
- Reddish discoloration or red streaks

PE, or pulmonary embolism, can be fatal and occurs when the DVT breaks free from a vein wall and blocks some or all of the blood supply to the lungs, causing:

- Unexplained shortness of breath
- Rapid breathing
- Chest pain anywhere under the rib cage (may be worse with deep breathing)
- Fast heart rate
- Light headedness or passing out

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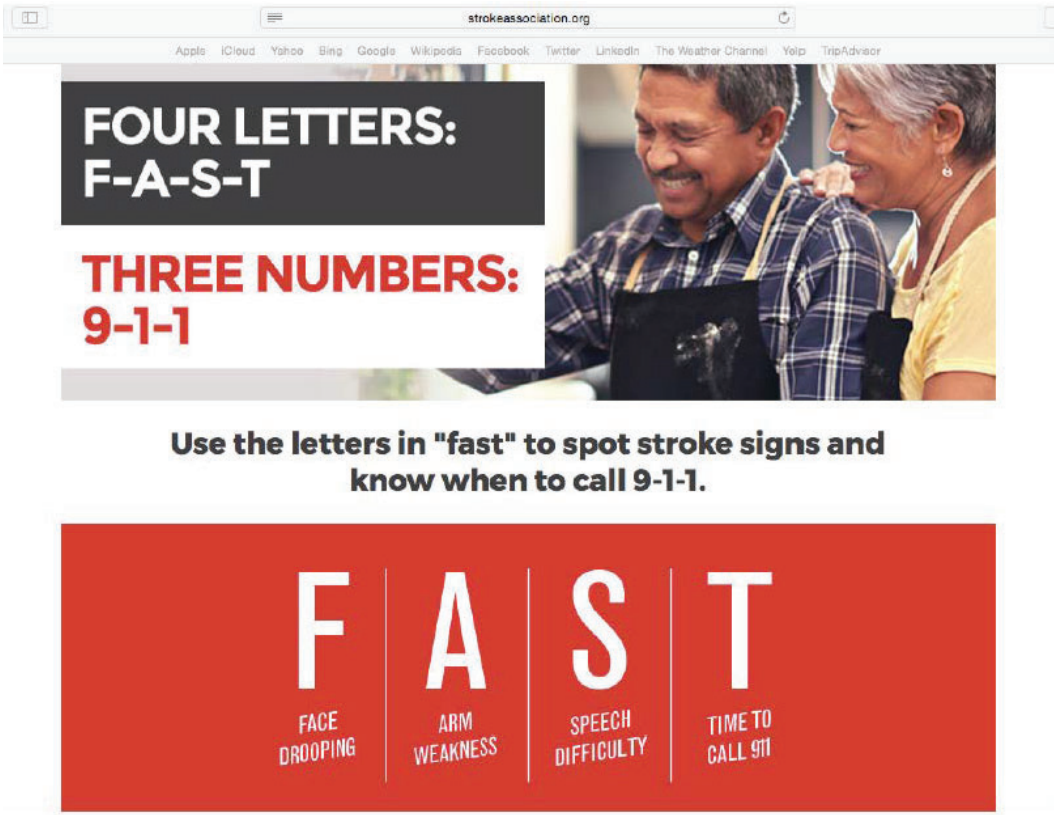

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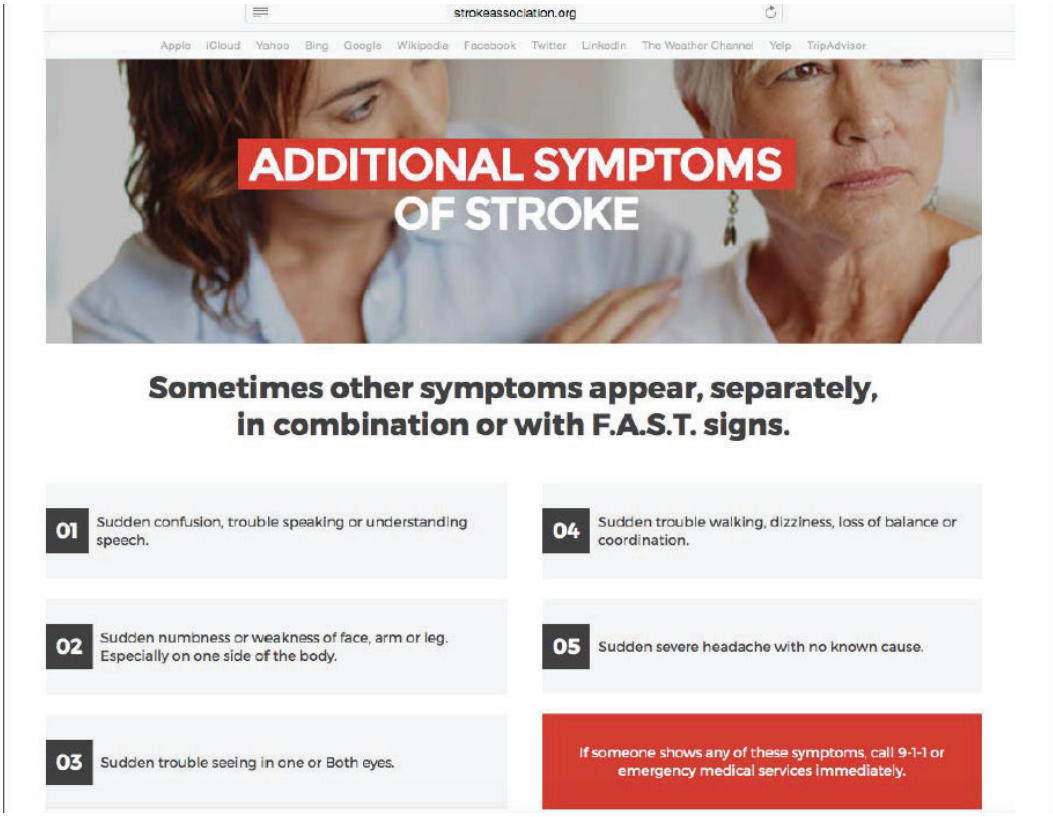

Symptoms and Signs of Venous Thromboembolism – Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):

Leg pain or tenderness of the thigh or calf

Leg swelling (edema)

Skin that feels warm to the touch

Reddish discoloration or red streaks

Unexplained shortness of breath

Rapid breathing

Chest pain anywhere under the rib cage (may be worse with deep breathing)

Fast heart rate

Light headedness or passing out

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Common Heart Attack Warning Signs

Pain or discomfort in the chest

Lightheadedness, nausea, or vomiting

Jaw, neck, or back pain

Discomfort or pain in arm or shoulder

Shortness of breath

Stroke Signs

Face Drooping

Arm Weakness

Speech Difficulty

Sudden confusion, trouble speaking or understanding speech

Sudden numbness or weakness of face, arm or leg. Especially on one side of the body.

Sudden trouble seeing in one or both eyes.

Sudden trouble walking, dizziness, loss of balance or coordination.

Sudden severe headache with no known cause.

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Signs and Symptoms of Thrombosis

The clinical spectrum of venous thromboembolism (VTE) ranges from deep vein thrombosis (DVT) to pulmonary embolism (PE). The symptoms of VTE depend on the location of the affected vessel and whether the vessel is totally or partially occluded by the clot.

Table. Clinical Spectrum of VTE

Type	Signs and Symptoms	Physical Examination
Deep vein thrombosis (DVT) •Blood clots may form in the deep blood vessels, most commonly in the legs and groin, and can block normal blood flow returning from the legs to the heart. •Venous clots that form in regions of slow to moderate flow are composed of a mixture of red cells, platelets, and fibrin and are known as mixed platelet fibrin thrombi. •Partially occlusive venous thrombosis of the deep veins in the legs or abdomen may present with subtle symptoms and sometimes may not present until significant collateral circulation* has developed.	• Pain • Swelling of the affected extremity/area with erythema and warmth over the vicinity of the clot • Discoloration including a bluish or suffused color	• Positive Homan's sign: pain with dorsiflexion of the foot • Swelling • Pain on palpation • Presence of a palpable cord • Evidence of collateral circulation, usually manifested by increased prominence of superficial veins • Some people with a DVT may be asymptomatic

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Pulmonary Embolism (PE) •PE results from a piece or all of a blood clot that breaks off and is carried by the blood stream to the lung where it obstructs the blood vessel. •The size of the clot and the site of the obstruction of blood flow in the vessel determine the extent and severity of the pulmonary embolus. •Proximal vein thrombosis is more likely to lead to fatal PE as compared to calf vein thrombosis. •The incidence of fatal PE can be markedly reduced if DVT is treated with anticoagulant therapy.	Pulmonary emboli may present subtly with the following complaints listed in order of frequency: • Dyspnea • Rapid breathing, fast heartbeat and chest pain especially with inhalation • Pleural pain: Some patients notice only a dull ache in their chest • Apprehension, anxiety • Cough • Hemoptysis • Sweats • Syncope • Fatigue	• Tachypnea • Tachycardia • Rales • Fever • Sweating • Thrombophlebitis • Accentuation of the pulmonary closure sound • Gallop heart sound • Cyanosis • Some people with a PE may be asymptomatic
Superficial Thrombophlebitis •Superficial thrombophlebitis is due to blood clots that form in veins that are closer to the surface of the skin and are associated with inflammation.	• These clots often partially block blood flow in affected veins and may cause pain and irritation. • Redness and inflammation along the vein may occur; if hard and erythematous, the affected vein is often visible and most commonly occurs in the legs or arms.	

•Superficial thrombophlebitis is often observed in individuals who are heterozygous or homozygous for the factor V Leiden mutation.	• Other associated symptoms include warmth and tenderness, surrounding purities and swelling. • Pain along the vein: patients may report a throbbing or burning sensation beneath the skin's surface; these symptoms may interfere with sleep as they progress. Fever: Patients with venous inflammation may develop an elevated temperature associated with an episode of thrombophlebitis.

Adapted from IHTC. Signs and Symptoms of Thrombosis. Available at http://www.ihtc.org/payors/conditions-we-treat/clotting-disorders/signs-and-symptoms-of-thrombosis.

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APPENDIX B – PATIENT REPORTED OUTCOME (PRO) SCALES

EQ-5D: http://www.euroqol.org/eq-5d-products/how-to-obtain-eq-5d.html

EQ-5D Health Questionnaire

Client ID ☐ New User ☐ Existing User ☐

Date ☐

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☐
- I have some problems with 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 with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain / Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety / Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

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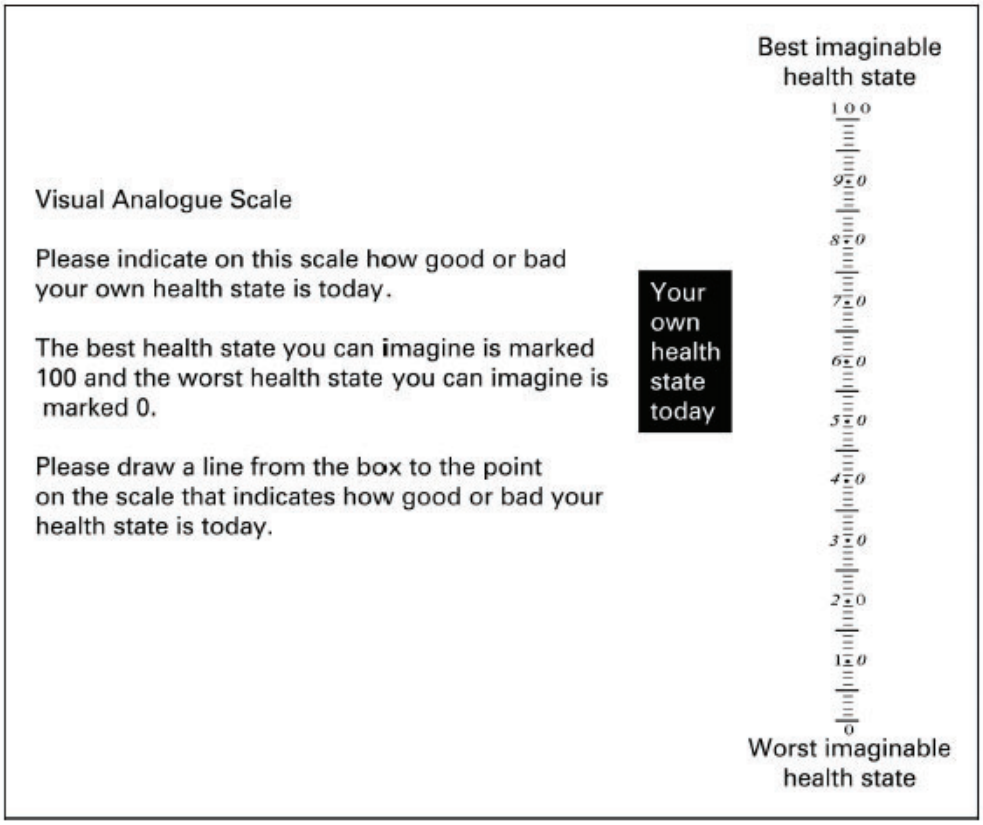

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

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HAEM-A-QoL: https://eprovide.mapi-trust.org/instruments/haemophilia-quality-of-life-questionnaire-for-adults **HAL:** http://elearning.wfh.org/resource/hemophilia-activities-list-hal/

Haemophilia Activities List

Introduction

This is the Hemophilia Activities List, or HAL. In this questionnaire several activities are listed that could be difficult for people with hemophilia. The aim of this questionnaire is to see how easy it is for you to do these activities

General comments

When answering the questions, it is only **your own** experience that counts. You should tick the box behind the question that best reflects your own situation.
For every activity, you are asked whether you had any difficulty in performing that activity **due to hemophilia**. There are six different response options. Answer each question by ticking the box that describes your situation.

Example:

In the past month, did you have any difficulty **due to hemophilia** with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Using public transportation (bus, train, subway)	❑8	❑1	❑2	❑3	❑4	❑5	❑6

For every question you are required to tick one box. The "n/a" response option ("not applicable") can be used if you never (have to) perform that specific activity. The "n/a" option is only available for some activities. The difference between the "Impossible" and "Always" response option, is that with "Always" you are in fact able to perform that activity, but with problems and with "Impossible" you are unable to perform that activity. It is very important that you answer all questions. Even when a question seems irrelevant to you, or when you have no opinion relating to the question, please tick the box that describes your situation most closely.

It will take 5-10 minutes to finish this questionnaire.

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Haemophilia Activities List

Lying down/ sitting / kneeling / standing

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Sitting down (e.g. on a chair or couch)	❑1	❑2	❑3	❑4	❑5	❑6
Rising from a chair with armrests	❑1	❑2	❑3	❑4	❑5	❑6
Rising from a chair without armrests	❑1	❑2	❑3	❑4	❑5	❑6
Kneeling / squatting	❑1	❑2	❑3	❑4	❑5	❑6
Bending forward	❑1	❑2	❑3	❑4	❑5	❑6
Kneeling for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6
Squatting for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6
Standing for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6

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UMC Utrecht

Functions of the legs

In the previous month, did you have any difficulty, due to hemophilia, with:

	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
Running (e.g. in order to catch the bus)	❑1	❑2	❑3	❑4	❑5	❑6
Jumping	❑1	❑2	❑3	❑4	❑5	❑6

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Haemophilia Activities List

Functions of the arms

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Lifting heavy objects	❑1	❑2	❑3	❑4	❑5	❑6
Carrying heavy objects in the arms	❑1	❑2	❑3	❑4	❑5	❑6
Fine hand movements (e.g. closing buttons)	❑1	❑2	❑3	❑4	❑5	❑6
Reaching above your head (to pick something up from a high shelf)	❑1	❑2	❑3	❑4	❑5	❑6

Use of transportation

In the previous month, did you have any difficulty due to hemophilia with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Riding a bicycle	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Getting in and out of a car	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Using public transportation (bus, train, subway)	❑8	❑1	❑2	❑3	❑4	❑5	❑6

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Self care

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Drying your whole body	❑1	❑2	❑3	❑4	❑5	❑6
Putting on a shirt, sweater etc.	❑1	❑2	❑3	❑4	❑5	❑6
Putting on sock and shoes	❑1	❑2	❑3	❑4	❑5	❑6
Putting on a tie or closing the top button of a shirt	❑1	❑2	❑3	❑4	❑5	❑6
Going to the toilet	❑1	❑2	❑3	❑4	❑5	❑6

Household tasks

In the previous month, did you have any difficulty, due to hemophilia, with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Going out shopping (for food, drink etc.)	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Washing the dishes, cleaning the sink	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Cleaning the house	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Other household tasks (ironing, making the beds)	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Doing odd jobs (both in and around the house)	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Gardening	❑8	❑1	❑2	❑3	❑4	❑5	❑6

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Leisure activities and sports

In the previous month, did you have any difficulty, due to hemophilia, with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Playing games (outdoors, e.g. with your children)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Sports	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going out (theatre / museum / movie theatre / bar)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Hobbies	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Dancing	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going on a holiday (active)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going on a holiday ("passive"; beach-/hotel holiday)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Adaptations and using an aid

To do some activities, you might need some adaptations or an aid. This does not apply to acute bleeding episodes, when you or more or less forced to use crutches to be able to walk. In the following questions we ask you some things regarding those adaptations or aids.

Do you own a car with adaptations?

- ❑ No, I don't have a car
- ❑ No, I don't have adaptations in my car

Yes, I own a car with (multiple responses are allowed):

- ❑ Electronic windows
- ❑ Power steering

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- ❑ Automatic gearbox
- ❑ The ability to sit in a wheelchair inside your car
- ❑ Brake and/or accelerator on the steering column
- ❑ Other, namely: .....
- ❑ Other, namely: .....
- ❑ Other, namely: .....

Do you use aids when performing certain activities?

- ❑ No, I don't use any aids

Yes, I use (multiple responses are allowed):

- ❑ A crutch (1 crutch / cane)
- ❑ Crutches (two)
- ❑ Wheelchair
- ❑ Rollator
- ❑ Other, namely: .....
- ❑ Other, namely: .....
- ❑ Other, namely: .....

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Thank you for completing the questions on activities. To finish this questionnaire, please provide us with some personal information in the box below. The information you provide will be handled strictly confidentially.

Today's date : .....

Your date of birth : .....

What type of haemophilia do you have?

Haemophilia type* ❑1 Haemophilia A
❑2 Haemophilia B

Severity* ❑1 Mild
❑2 Moderate
❑3 Severe

* Please tick the appropriate box

Thank you very much for your cooperation

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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

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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)

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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APPENDIX C – DETAILED STUDY SCHEMA

SCREENING	
Up to 4 weeks prior	Screening

- Obtain informed consent
- Review demographic parameters
- Screen potential subjects by inclusion and exclusion criteria
- Obtain medical and haemophilia history, document
- Evaluate concomitant medications, check vital signs, height and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, immunogenicity assay, troponin level, ECG
- Conduct study subject training
- Diary entry of PRO scales
- Adverse Events

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Part 1a – 24 hours	
Pre-Dose – 5 min	**Part 1a**
• Review inclusion and exclusion criteria • Obtain medical and haemophilia history, document • Evaluate concomitant medications, check vital signs, height and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, troponin level • Check for AEs	
Dose Hr 0	**Part 1a**
• Administer single IV 18 µg/kg dose of MarzAA	
Post-Dose at 5 and 30 min [± 2 min]; at Hr 1, 3, 6 [± 10 min]; at Hr 9, 12 [± 30 min]	**Part 1a**
• Conduct testing for coagulation assay, thrombogenicity markers, PK sampling	
Post-Dose at Hr 24 [± 1.5 Hr]	**Part 1a**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, weight • Diary entry of PRO scales, • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, troponin level, ECG • AEs (Hr 0 to Hr 24)	

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Part 1b – 48 hours	
Pre-Dose	**Part 1b**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay, troponin level • AEs	
Dose Hr 0	**Part 1b**
• Administer single SC 30 µg/kg dose of MarzAA • Conduct training for SC administration and proficiency confirmation	
Post-Dose at Hr 3, 5, 7 (± 10 min); at Hr 9, 12 (± 30 min)	**Part 1b**
• Conduct testing for coagulation assay, thrombogenicity markers, PK sampling	
Post-Dose at Hr 24 (± 1.5 Hr)	**Part 1b**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, troponin level, ECG • Conduct training for SC administration and proficiency confirmation • AEs (Hr 0 to Hr 24)	
Post-Dose at Hr 30 (± 1.5 Hr)	**Part 1b**
• Conduct testing for coagulation assay, thrombogenicity markers, PK sampling	
Post-Dose at Hr 48 (± 1.5 Hr)	**Part 1b**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling • Conduct training for SC administration and proficiency confirmation • AEs (Hr 24 to Hr 48)	

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Part 2	
Day 1	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability • AEs	
Day 3 and 5 (+ 1 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct coagulation assay, thrombogenicity markers, PK sampling • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability • AEs	
Day 7 (+ 1 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay, troponin level • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability	

If no spontaneous bleed occurs after the fifth daily dose

If spontaneous bleed occurs after the fifth daily dose

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Part 2 (If no spontaneous bleed occurs after the fifth daily dose)	
Day 14 , 21 and 28 (± 2 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability • AEs	
Day 42 (± 3 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for immunogenicity assay • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability • AEs	
Day 50 (+ 3 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling • IP compliance and proficiency confirmation • IP dispensing, inventory and accountability • AEs	

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Part 2 (If spontaneous bleed occurs after the fifth daily dose)	
Day 0*	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for coagulation assay, PK sampling, immunogenicity assay, troponin level • Dispense study drug at escalated dose, reschedule subjects' visits for days 7, 14, 21, 28 and 50 • AEs	
Day 7 (± 2 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay, troponin level • IP compliance and proficiency confirmation; IP dispensing, inventory and accountability • AEs	
Day 14, 21 and 28 (± 2 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay (Day 14 and 28 only) • IP compliance and proficiency confirmation; IP dispensing, inventory and accountability • AEs	
Day 42 (± 3 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications, check vital signs, and weight • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for immunogenicity assay • IP compliance and proficiency confirmation; IP dispensing, inventory and accountability • AEs	
Day 50 (+ 3 day)	**Part 2**
• Obtain medical and haemophilia history, document (including review of diary entries) • Evaluate concomitant medications and check vital signs • Diary entry of PRO scales • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling • IP compliance and proficiency confirmation; IP dispensing, inventory and accountability • AEs	

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Unscheduled **Part 2**

- Obtain medical and haemophilia history, document (including review of diary entries)
- Evaluate concomitant medications, check vital signs, and weight
- Diary entry of PRO scales
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay, troponin level
- IP compliance and proficiency confirmation; IP dispensing, inventory and accountability
- AEs

End of study **Part 2**

- Obtain medical and haemophilia history, document (including review of diary entries)
- Evaluate concomitant medications and check vital signs
- Diary entry of PRO scales
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assay
- IP compliance and proficiency confirmation; IP dispensing, inventory and accountability
- AEs