CLINICAL STUDY PROTOCOL

Study Title:	Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia	
Investigational Product:	Factor VIIa, marzeptacog alfa (activated) [MarzAA]	
Protocol Number:	MAA-102	
Developmental Phase:	1	
US IND Number:	14789	
Study Sponsor:	Catalyst Biosciences, Inc. 611 Gateway Blvd., Suite 710 South San Francisco, CA 94080	
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Protocol Version History:	Original Protocol:	17 Jan 2018
	Amendment 1.0:	11 Mar 2019
	Amendment 2.0	25 Nov 2019

Compliance Statement

This study will be conducted in accordance with the clinical research guidelines established by the 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, and the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH GCP). Study documents will be maintained in accordance with applicable regulations.

INVESTIGATOR SIGNATURE PAGE

Study Title: Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia

Protocol No.: MAA-102

Version: Amendment 2.0

Investigator Statement

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 preclinical 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 Institutional Review Board (IRB)/ Independent Ethics Committee (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 ICH GCP, applicable United States (US) 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 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 Name (Printed)	Institution
Investigator Signature	Date

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia
Protocol Number:	MAA-102
Version:	Amendment 2.0

Linda Neuman, MD, MBA
Vice President Clinical Development, Catalyst Biosciences, Inc.

Date

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrates
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time 0 to infinity
BsMAb	bispecific monoclonal antibody
BU	Bethesda units
CAD	coronary artery disease
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	maximum plasma drug concentration
CNS	central nervous system
Cr	creatinine
CRF	case report form
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report forms
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
ICF	informed consent form
ICH	International Conference on Harmonisation
IDE	investigational device exemption
IEC	Independent Ethics Committee
IMT	immunomodulatory therapy
IND	investigational new drug

IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LLN	lower limit of normal
MarzAA	marzeptacog alfa (activated)
MedDRA	Medical Dictionary for Regulatory Activities
OHRP	Office for Human Research Protections
OTC	over-the-counter
PC	peak concentration
PCC	prothrombin complex concentrates
PD	pharmacodynamic
PE	pulmonary embolism
PI	principal investigator
PK	pharmacokinetic
PRO	patient-reported outcome
PT	prothrombin time
QA	quality assurance
QC	quality control
rFIX	recombinant Factor IX
rFVIIa	recombinant activated Factor VIIa
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOA	schedule of activities
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TAT	thrombin-antithrombin complexes
TBIL	total bilirubin level
TE	thromboembolic event
TGT	thrombin generation time
ULN	upper limit of normal
VOD	volume of distribution
VTE	venous thromboembolic event
Wt	wild-type

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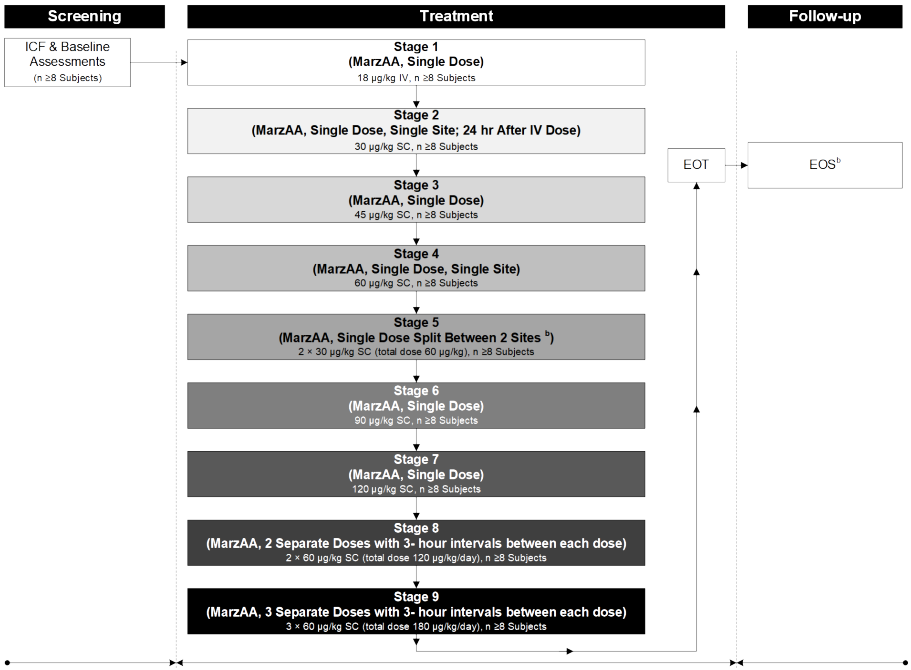
PROTOCOL SYNOPSIS

Study Title:	Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia
Protocol Number:	MAA-102
Investigational Product:	marzeptacog alpha (activated) (MarzAA)
Target Population:	Males ≥18 years of age with confirmed diagnosis of Hemophilia A or B with or without an inhibitor.
IND Number:	14789
Study Phase:	1
Study Centers Planned:	Approximately 10 Global Sites
Number of Subjects Planned:	A total of at least 8 male subjects ≥18 years of age are planned within each dosing Stage (Stages 1 to 9). If a subject cannot participate in all 9 dosing stages of the study, the subject will be replaced so that at least 8 subjects participate in each stage of the study with adequate pharmacokinetic (PK) sampling for analysis.
Estimated Study Duration:	18 months
Estimated Participant Duration:	The maximum study duration for each study subject participating in all nine (9) stages will be approximately 3 months if done consecutively. The dosing period for each stage will be approximately 3 days, with approximately 10 weeks of study dosing, depending on participation in all 9 stages and time elapsed between each study stage. Following the end of SC dosing with MarzAA and completion of assessments for follow-up a 30-day visit will be performed.
Primary Objective(s):	• To evaluate the pharmacokinetics of ascending subcutaneous (SC) doses of MarzAA
Secondary Objectives:	• To determine the pharmacokinetics of single dose IV and SC MarzAA • To determine if pharmacokinetics behave in a dose proportional manner • To determine whether a split injection provides the same pharmacokinetics as a single injection • To determine the pharmacodynamics of IV and SC 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 evaluate the safety of IV and SC MarzAA
Study Design Overview:	This multi-center, open label Phase 1 study will evaluate the pharmacokinetics, pharmacodynamics, and safety of a single IV dose of MarzAA followed by ascending SC doses of MarzAA in adult subjects with moderate or severe Hemophilia A or B, with or without an inhibitor. The study will enroll at least 8 adult male subjects with moderate or severe Hemophilia A or B with or without an inhibitor.

Each subject will receive escalating doses of MarzAA for each stage of the study (except for Stage 5, where subjects receive the same dose as in Stage 4 split between two sites) as detailed in Figure S-1.

Figure S-1 Study Schema



Abbreviations: EOS=end of study; EOT=end of treatment; ICF=informed consent form; IV=intravenous; MarzAA=marzeptacog alfa (activated); n=number of subjects; SC=subcutaneous.

Notes: Stages 2 through 9 occur consecutively and immediately after the 48 hour specimen is collected; however, if a subject completed Stages 1 to 7 prior to Amendment 2 there is no time limit on when they may enter Stage 8.

a. EOT + 30 days
b. Dose in Stage 4 is split between 2 different anatomical sites which drain into separate lymphatic tributary areas (eg, left and right thigh, or different sides of abdomen, or abdomen and thigh)

For Stage 1, specimens will be obtained for pharmacokinetics (MarzAA activity levels) at predose and then at 5, and 60 minutes ±5 minutes; 2, 6, 9 hours ±15 minutes; 12 and 24 hours ±2 hours after dosing with MarzAA. For Stages 2 to 7 specimens will be obtained for pharmacokinetics (MarzAA activity levels) at predose and then at 30, 60, and 90 minutes ±5 minutes; 2, 6, 9 hours ±15 minutes; 24 and 48 hours ±2 hours after dosing with MarzAA. For stages 8 and 9, PK parameters will be obtained hourly starting at 2 through 9 hours, then at 12, 24,48 and 72 hours.

For Stage 1 coagulation and thrombogenicity parameters will be obtained at predose and then at 5 minutes ±5 minutes; 2 and 6 hours ±15 minutes; and 24 hours ±2 hours. For Stages 2 to 9, coagulation and thrombogenicity parameters will be obtained at predose and then at 2 and 6 hours ±15 minutes; and 24 and 48 hours ±2 hours. For stages 8 and 9, coagulation and thrombogenicity parameters will also be obtained at 72 hours.

For Stage 1 (IV), Stage 2 (SC) may be initiated immediately after the 24-hour specimens have been obtained. If Stage 2 is initiated immediately after Stage 1, then the 48-hour specimens can be used as the predose specimens for the next Stage (Stage 2).

For Stages 2 to 9, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If the stage is initiated immediately after the previous stage, then the 48-hour specimens can be used as the predose specimens for the next stage. For Stages 1 to 9, a maximum of 7 days may elapse between the

	48-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol). For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, no additional screening parameters will be required and the 7-day maximum between Stage 7 and 8 does not apply.All predose assessment will be required. If a new subject is enrolled in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to Stages 2 to 9. Investigators will record study drug administration, route of administration (IV or SC), anatomical location of administration, injection site assessment, any adverse events (AEs) the subject may experience, and any bleeding episodes (location, inciting event if not spontaneous), and concomitant treatment administered.
Inclusion Criteria:	Study candidates must meet all the following inclusion criteria to be eligible for participation in this study: 1) Confirmed diagnosis of moderate or severe congenital Hemophilia A or B, with or without an inhibitor 2) Male, age ≥18 years 3) Agreement to use highly effective birth control throughout the study 4) Affirmation of informed consent with signature confirmation before any trial-related activities Note: trial related activities are any procedure that would not have been performed during normal clinical management of the subject 5) Stated willingness to comply with all study procedures and availability for the duration of the study
Exclusion Criteria:	Study candidates who meet any of the following criteria will not be eligible for participation in this study: 1) Inability to discontinue and washout prophylaxis treatment 72 hours prior to dosing 2) Previous participation in a trial involving SC administration of rFVIIa (NovoSeven or MOD-5014) or any trial using a modified amino-acid sequence FVIIa such as: NN1731 or BAY86-6150. Prior participation in a trial of intravenous (IV) LR769 or rFVIIa-FP (CSL689) is permissible. 3) Previous participation in a clinical trial with subsequent treatment within the previous 30 days or 5-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, with or without an inhibitor 6) Platelet count <100,000 /µL based on screening laboratory assessments 7) Advanced atherosclerotic disease (ie, 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) Receiving immunomodulatory therapy (IMT). 10) Compromised hepatic or renal function:

<table>
<tr><td></td><td>
a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥5 x the upper limit of normal (ULN)
b. Total bilirubin (TBIL) level ≥2 mg/dL (>35 µmol/L) unless there is a known history of Gilbert's syndrome (GS)
c. Serum albumin (ALB) level ≤1 × the lower limit of normal (LLN)
d. Serum creatinine (Cr) level >1.25 × ULN.
11) 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
</td></tr>
<tr><td>Study Procedures:</td><td>See Schedule of Study Assessments (Table 17-1, Table 17-2, Table 17-3)</td></tr>
<tr><td>Investigational Product</td><td>
Recombinant FVII variant, MarzAA
Dose and Route of Administration:
Dosing, route, and frequency of administration are provided in Table S-1.
Table S-1 MarzAA Dose & Mode of Administration by Dosing Stage
<table>
<tr><th>Stage</th><th>Dose [a]</th><th>Route</th><th>Number of Doses</th><th>Timing [b]</th></tr>
<tr><td>1</td><td>18 µg/kg</td><td>IV</td><td>1</td><td>NA</td></tr>
<tr><td>2</td><td>30 µg/kg</td><td>SC</td><td>1</td><td>24 hours after Stage 1</td></tr>
<tr><td>3</td><td>45 µg/kg</td><td>SC</td><td>1</td><td>48 hours after Stage 2</td></tr>
<tr><td>4</td><td>60 µg/kg</td><td>SC</td><td>1</td><td>48 hours after Stage 3</td></tr>
<tr><td>5</td><td>2 × 30 µg/kg [c]</td><td>2 × SC</td><td>1</td><td>48 hours after Stage 4, 2 sites [c]</td></tr>
<tr><td>6</td><td>2 × 45 µg/kg [d]</td><td>2 × SC</td><td>1</td><td>48 hours after Stage 5, 2 sites [d]</td></tr>
<tr><td>7</td><td>2 × 60 µg/kg [e]</td><td>2 × SC</td><td>1</td><td>48 hours after Stage 6, 2 sites [e]</td></tr>
<tr><td>8</td><td>2 × 60 µg/kg [f]
(120 µg/kg/day)</td><td>SC</td><td>2</td><td>48 hours after Stage 7, unless subjects were enrolled in the study prior to Amendment 2 [b], 2 doses at 3-hour intervals [f]</td></tr>
<tr><td>9</td><td>3 × 60 µg/kg [g]
(180 µg/kg/day)</td><td>SC</td><td>3</td><td>72 hours after Stage 8, 3 doses at 3-hour intervals [g]</td></tr>
</table>
Abbreviations: IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.
a For subjects requiring more than 2 vials of supplied study drug, the number of SC injections should be commensurate with the number of vials needed. Injection sites should be different for each injection but should be at the same anatomic location.
b Timing provided is minimum time after dosing. Maximum time after dosing should not exceed 7 days if a subject continues to the next stage of the study except for subjects completing their EOS visit prior to Amendment 2.
c 2 × 30 µg/kg MarzAA (total dose 60 µg/kg) injected at two different anatomic locations (which must drain into separate lymphatic tributary areas [eg, left and right thigh, or different sides of abdomen, or abdomen and thigh])
d 2 × 45 µg/kg MarzAA (total dose 90 µg/kg) injected at two different sites at the same anatomic location
e 2 × 60 µg/kg MarzAA (total dose 120 µg/kg) injected at two different sites at the same anatomic location and timepoint
f 60 µg/kg MarzAA (total dose 120 µg/kg/day) administered at two separate timepoints with 3-hour intervals between each dose and in the same anatomic location
g 60 µg/kg MarzAA (total dose 180 µg/kg/day) administered at three separate timepoints with 3-hour intervals between each dose and in the same anatomic location
</td></tr>
</table>

	Dose **Adjustments and Dosing Stage Interruption:** No dose adjustments are planned for this study. Advancing to the next dosing stage is stopped 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 to MarzAA may be developing. The subject may continue to the next dosing stage once the bleeding event is resolved and the subject has stopped treatment for the bleed for at least 72 hours prior to dosing. A study stage may be repeated in a subject if PK assessments are interrupted by treatment of a bleed or inadequate PK samples for analysis.
Reference Therapy:	Not applicable
Rescue Therapy or Emergency Procedures (if applicable):	**Treatment of spontaneous or traumatic bleeding:** Subjects with spontaneous or traumatic bleeds can use their current treatment regimen. A washout period of 72 hours after the subject is stablized must be completed before the subject continues to the next stage of the study.
Concomitant Medication:	There are no concomitant medication restrictions unless otherwise noted (in exclusion criteria and prohibited medications) or required.
Prohibited Medication:	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 and cannot discontinue and washout this therapy prior to dosing.
Efficacy Endpoints:	**Primary:** • Comparative pharmacokinetics of MarzAA by dose level/stage **Secondary:** • Comparative pharmacokinetics of IV and SC MarzAA • Effect of split injections on pharmacokinetics • Change in coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen, MarzAA activity levels, and thrombin generation time [TGT]) from predose • Occurrence of an antibody response to MarzAA and whether it is inhibitory and cross-reactive to wt-rFVIIa or wt-FVII
Safety Endpoints:	• 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 • Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
Statistical Methods:	**Primary Analysis Plan:** • PK analysis by route of administration, dose level/ stage • Analysis for dose proportionality • Appropriate statistics of all recorded, measured and calculated parameters will be reported, including 95% confidence intervals, n, mean, standard deviation, median, minimum and maximum

	Safety Analysis Plan: • Subject disposition (ie, number of subjects treated, subjects who completed the study, subjects who discontinued and the primary reasons for discontinuation) will be tabulated • All AEs will be listed by preferred term and system organ class as classified by using Medical Dictionary for Regulatory Activities (MedDRA) and type, frequency, course, outcome, severity, and causality to study drug will be documented. Verbatim terms on CRFs will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). • Vital signs (blood pressure, heart rate, termperature, respiratory rate) and laboratory values with descriptive statistical summaries of shifts for each stage **Sample size justification:** The sample size estimate is based on PK guidance for the development of hemophilia factors published by regulatory agencies. **Analysis Sets** Safety: any subject who receives at least one dose of study drug. The Safety population will be used for safety analysis PK Population: any subject who completes an entire stage including the PK assessments and has adequate samples for analyses. **Safety:** The safety of MarzAA will be monitored closely by a medical monitor and the Sponsor on aongoing basis. All SAEs will be reported to the medical monitor and Sponsor.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents.

1.0 INTRODUCTION

1.1 Study Rationale

A significant number of patients with Hemophilia A develop neutralizing antibodies ("inhibitors") against FVIII and become refractory to standard factor replacement treatment (Kempton, 2009; Ma, 2006; Peyvandi, Mannucci, , 2016; Walsh, 2015). Hemophilia A is four times as common as Hemophilia B (National Hemophilia Foundation, 2019). Patients with Hemophilia B can also develop neutralizing antibodies and become refractory to factor replacement therapy (Martensson, 2016; Wieland, 2011; Zhou, 2015). Currently, available treatment for patients with Hemophilia A or B with inhibitors, is with rFVIIa, activated prothrombin complex concentrates (APCCs), or with bispecific monoclonal antibody (BsMAb). The prevention of bleeding episodes, referred to as prophylaxis, requires frequent IV dosing (NovoSeven RT US Package Insert, 2019). Catalyst Biosciences has created a FVIIa variant, marzeptacog alfa (activated) (MarzAA), with preclinical properties that suggest increased potency and duration, as well as the ability to be administered subcutaneously for daily use as prophylaxis and potentially, for the SC treatment of bleeding.

1.2 Background

Hemophilia

Hemophilia A and B are X-linked, recessive, hereditary bleeding disorders caused by an impaired deficiency of coagulation FVIII (Hemophilia A) or FIX (Hemophilia B) (Mannucci, 2001). 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) (National Hemophilia Foundation, 2019). Disease classification of mild (>5 and <40% of normal levels of active clotting factor), moderate (1 to 5%) or severe (<1%) is based on plasma FVIII and FIX levels (White, 2001). 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) (Franchini, 2013; Manco-Johnson, 2007). 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 (Mannucci, 2001). Factor replacement therapy is also used for surgical hemostasis and to maintain hemostasis during the postoperative 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 patients with Hemophilia A and in up to 5% of patients with Hemophilia B (Astermark, 2010; Franchini, 2011; Sultan, 1992; Wight, 2003). 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 (Astermark, 2010; Mannucci, 2001).

Current Therapies

For hemophilia patients with high titer inhibitors to FVIII or FIX and for those hemophilia patients with low titer inhibitors for 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 RT) or APCCs, including AICC, (FEIBA) (FEIBA US Package Insert, 2018; Kempton, 2014; Kempton, 2009; NovoSeven RT US Package Insert, 2019; World Federation of Hemophilia, 2012). 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 (Franchini, 2013). NovoSeven, a wt-rFVIIa, was approved by the 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 (Kempton, 2014; Kempton, 2009; NovoSeven RT US Package Insert, 2019; World Federation of Hemophilia, 2012). Often, multiple doses (3 or more) are required to complete treatment of a bleeding episode (NovoSeven RT US Package Insert, 2019).

Activated prothrombin complex concentrates were introduced for treatment of inhibitors in patients with hemophilia in the 1970s (FEIBA US Package Insert, 2018). The only activated prothrombin complex concentrates (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 ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses and nonenveloped 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. FEIBA was previously licensed in the United States as FEIBA VH and FEIBA NF and is now available as FEIBA. FEIBA, and FEIBA NF are identical in formulation to FEIBA VH (FEIBA US Package Insert, 2018). 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 (FEIBA US Package Insert, 2018).

Treatment of inhibitor patients with wt-rFVIIa or with APCCs has limitations with regard to efficacy, safety, and/or convenience (Abshire, 2004; Lusher, 1998; Pipe, 2005), 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, route of administration, and

regarding duration of action. These therapies fall short of the efficacy achieved with conventional factor replacement therapies in patients without inhibitors (Mannucci, 2001; Santagostino, 1999; Santagostino, 2006). Because efficacy is suboptimal with these agents, elective surgical procedures may be deferred for patients with inhibitors who may need such procedures (Rodriguez-Merchan, 2010). 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 (FEIBA US Package Insert, 2018; NovoSeven RT US Package Insert, 2019). Thrombotic events in association with NovoSeven treatment in hemophilia patients with inhibitors have been reported in up to 4% of patients (Abshire, 2008; Neufeld, 2011; NovoSeven RT US Package Insert, 2019; O'Connell, 2006). Reported incidence of thrombotic events in association with FEIBA use ranges from 4 to 8.24/100,000 infusions (Aledort, 2008; FEIBA US Package Insert, 2018; Gomperts, 2006; Luu, 2004). 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 (NovoSeven RT US Package Insert, 2019; Young, 2011). The percent reduction in annual bleed rate during prophylaxis of hemophilia patients with inhibitors with FEIBA (Antunes, 2014) is less than that reported for factor replacement therapy in hemophilia patients without inhibitors (Tagliaferri, 2008). FEIBA also contains small amounts of FVIII and has the potential to boost inhibitor titers in Hemophilia A patients with inhibitors (Kempton, 2009).

Once-weekly emicizumab-kxwh (HEMLIBRA), a BsMAb, was approved by the FDA in November 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with Hemophilia A with FVIII inhibitors and in October 2018 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children, ages newborn and older, with Hemophilia A without FVIII inhibitors (HEMLIBRA US Package Insert, 2018).

1.2.1 Rationale for Prophylaxis with SC Administration of FVIIa

Intravenous dosing often requires a medical professional or family member to achieve venous access making home prophylaxis cumbersome, particularly for pediatric patients (Hartmann, 2016; Peyvandi, Garagiola, , 2016). Other challenges include patient adherence, and reliable IV access (Hacker, 2001; Stoner, 2014). 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 (Hacker, 2001; Stoner, 2014).

SC administration presents a major advantage over IV administration because it enables at-home injection, improves quality of life, and reduces health care costs (Stoner, 2014). While home IV administration has been essential to the provision of comprehensive hemophilia care, it nonetheless remains a significant barrier (Hacker, 2001). 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 (Stoner, 2014). 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 to 30% vs 100%) (Tiede, 2011). 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. Furthermore, the ability to treat bleeding episodes by SC administration would be ideal.

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, and potentially for treating breakthrough bleeding.

1.2.2 Experience with MarzAA in the Clinic

To date, the safety, pharmacokinetics, and pharmacodynamics 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. C_{max} was reached at 5 to 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 pharmacokinetic (PK) profile observed in clinical study B3051001 was consistent with projections based on preclinical data. All hemophilia and nonhemophilia AEs were mild or moderate in severity; there were no severe TEAEs, no SAEs and no AEs leading to treatment discontinuation. Overall, the most common nonhemophilia-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 pharmacodynamic (PD) effects, with drug-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.

A Phase 2 study is currently being conducted 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.

2.0 OBJECTIVES

2.1 Primary Objectives

- To evaluate the pharmacokinetics of ascending SC doses of MarzAA

2.2 Secondary Objectives

- To determine the pharmacokinetics of single dose IV and SC MarzAA
- To determine if pharmacokinetics behave in a dose proportional manner
- To determine whether a split injection provides the same pharmacokinetics as a single injection
- To determine the pharmacodynamics of IV and SC MarzAA
- To evaluate for evidence of the development of antibodies to MarzAA, wild-type recombinant FVIIa (wt-rFVIIa), and/or wt-FVII, and to determine if these are neutralizing antibodies
- To evaluate the safety of IV and SC MarzAA

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

- Comparative pharmacokinetics of MarzAA by dose level/stage

3.2 Secondary Endpoints

The secondary endpoints are as follows:

- Comparative pharmacokinetics of IV and SC MarzAA
- Effect of split injections on pharmacokinetics
- Change in coagulation parameters (PT, activated prothrombin complex concentrates [aPTT], fibrinogen, MarzAA activity levels, and thrombin generation time [TGT]) from predose
- Occurrence of an antibody response to MarzAA and whether it is inhibitory and cross-reactive to wt-rFVIIa or wt-FVII

3.3 Safety Endpoints

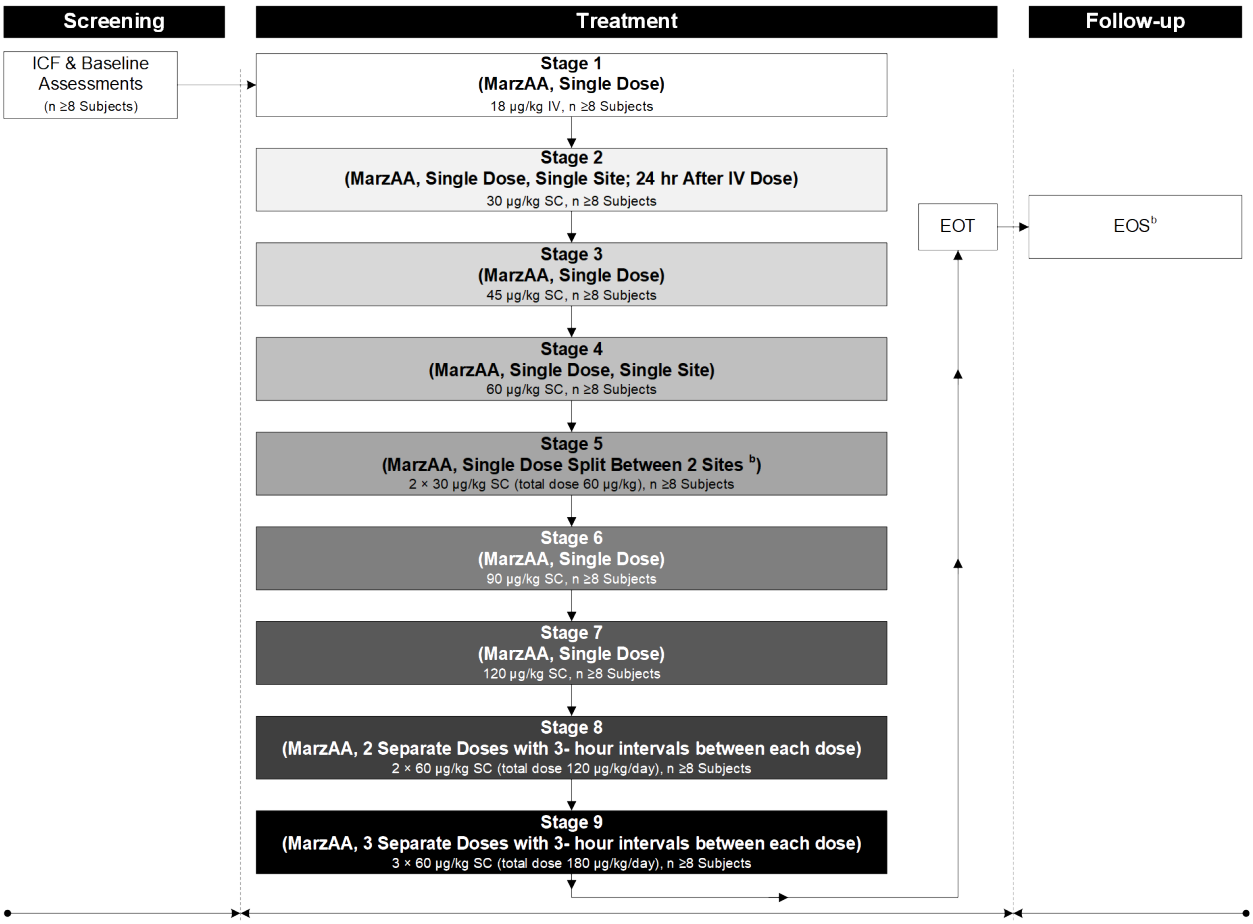
- Occurrence of clinical thrombotic event not attributable to another cause, and occurrence of antibody formation resulting in a decreased endogenous level of FVII or FVIIa
- Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 1 study designed to evaluate the pharmacokinetics, pharmacodynamics, and safety of a single IV dose and ascending doses of SC MarzAA in adult subjects with Hemophilia A or B, with or without an inhibitor. It is an open-label study, so subjects and members of the clinical study team will not be blinded to treatment. The study is summarized in the study schema (Figure 4-1).

Figure 4-1 Study Schema



Abbreviations: EOS=end of study; EOT=end of treatment; ICF=informed consent form; IV=intravenous; MarzAA=marzeptacog alfa (activated); n=number of subjects; SC=subcutaneous.

Notes: Stages 2 through 9 occur consecutively and immediately after the 48 hour specimen is collected; however, if a subject completed Stages 1 to 7 prior to Amendment 2 there is no time limit on when they may enter Stage 8.

a. EOT + 30 days

b. Dose in Stage 4 is split between 2 different anatomical sites which drain into separate lymphatic tributary areas (eg, left and right thigh, or different sides of abdomen, or abdomen and thigh)

The study will be completed in approximately 18 months (from when the study opens enrollment until completion of data analyses). The study will enroll at least 8 adult male subjects with moderate or severe Hemophilia A or B with or without an inhibitor in each dosing stage.

Each subject may continue on to the next stage of MarzAA dosing if they wish to continue the study provided they do so no more than 7 days after the end of the previous stage and that any

spontaneous or traumatic bleeds have been resolved and that the subject has undergone a 72-hour washout period of the treatment used for the spontaneous or traumatic bleed. If any subject completes the EOS assessments prior to Amendment 2 and wishes to participatein Stages 8 and/or 9, the 7-day requirement does not apply, and no screening assessment will need to be repeated. All predose assessments will be required. If a new subject is enrolled in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to Stages 2 to 9.

Each subject may receive the study drug in nine (9) dosing stages (Stage 1 to 9) as detailed in Section 6.1.1.

Study endpoints are provided in Section 3.0. Investigators will record study drug administration, route of administration, anatomical location, injection site assessment, any AEs the subject may experience, and any bleeding episodes (location, inciting event if not spontaneous), and concomitant treatment administered.

Subjects will sign an informed consent form (ICF) at screening and prior to any study procedures. Eligibility to participate in the study will be determined by inclusion and exclusion criteria elicited from medical history, physical examination, laboratory assessments and an ECG. The screening period may be up to 4 weeks prior to dosing.

Additional details on study assessments and procedures are provided in Section 7.0.

No dose adjustments are planned for this study. Guidelines for the interruption of dose escalation are provided in Section 6.1.1.1.

4.2 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.

4.3 End of Study Definition

The maximum study duration for each study subject participating in all nine (9) stages will be approximately 4 months. The dosing period for each stage will be approximately 3 days, with a maximum of approximately 8 weeks of dosing, depending on participation in all 9 stages and time elapsed between each study stage. Following the end of dosing with MarzAA and completion of assessments, then a 30-day visit will be performed for safety and follow-up.

The end-of-study visit will be 30 days after the last dose of study drug. For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes (, EOS assessments should be repeated (ie, after Stage 8 and/or 9).

A participant is considered to have completed the study if he has completed all assessments in a stage of the study and returned for procedures listed under end of study visit, as shown in the SOA (Table 17-1, Table 17-2, and Table 17-3).

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

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

1) Confirmed diagnosis of moderate or severe congenital Hemophilia A or B, with or without an inhibitor
2) Male, age 18 or older
3) Agreement to use highly effective birth control throughout the study
4) Affirmation of informed consent with signature confirmation before any trial-related activities

   NOTE: Trial related activities are any procedure that would not have been performed during normal clinical management of the subject.

5) 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) Inability to discontinue and washout prophylaxis treatment 72 hours prior to dosing.
2) Previous participation in a trial involving SC Administration of rFVIIa (Novo Seven or MOD-5014) or any trial using a modified amino-acid sequence FVIIa such as: NN1731 or BAY86-6150. Prior participation in a trial of IV LR769 or rFVIIa-FP (CSL689) is permissible.
3) Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 5-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, with or without an inhibitor.
6) Platelet count <100,000 /μL based on screening laboratory assessments.
7) Advanced atherosclerotic disease (ie, 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) Receiving IMT.
10) Compromised hepatic or renal function:
    a) Alanine amino transferase (ALT) and aspartate aminotransferase (AST) levels ≥5 × ULN

b) TBIL ≥2 mg/dL (>35 µmol/L) unless there is a known history of GS

c) Serum albumin <1 × LLN

d) Serum Cr level >1.25 × ULN

11) 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 Subject Withdrawal Criteria and Procedures; Subjects Lost to Follow-Up; and Subject Replacement

5.3.1 Subject Withdrawal Criteria and Procedures

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 noncompliance
- 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 must be recorded on the eCRF.

Any remaining study procedures should be completed as indicated by the study protocol. Any new clinically relevant finding will be reported as an AE.

If the subject withdraws from the study and 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.

5.3.2 Subjects 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 for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

5.3.3 Subject Replacement

If a subject does not complete a stage of the study or withdraws from the study, a replacement subject will be added for that stage. If a replacement subject is enrolled in the study on Amendment 2, the subject will need to complete Stage 1 (IV) dosing and assessments prior to advancing to Stages 2 to 9.

Study stages are detailed in Section 6.1.1. All replacement subjects completingat the lowest incomplete stage of the study for all stages except for Stage 5. If subject does not complete Stage 5, the replacement subject will complete Stage 1 (IV) dosing and assessments and then start at Stage 4 (duplicating Stage 4) and then complete Stage 5 to have the same subject complete Stage 4 and 5.

For all other stages when the completion of a stage has occurred, the replacement subject complete Stage 1 (IV) dosing and assessments before advancing to the next incomplete stage.

6.0 STUDY DRUG

6.1 Investigational Product

All study subjects will be treated with MarzAA. MarzAA will be provided as a powder for injection, at a 4.62 mg/vial dosage strength. The drug product will be supplied in a 5-mL vial that is sealed with a 20 mm lyophile stopper and 20 mm aluminum over-seal. The lyophilized drug product must be reconstituted for SC injection or IV use.

6.1.1 Dosing and Administration

This is an open-label study. Each subject may receive the study drug in nine (9) dosing stages (Stage 1 to 9). Detailed dosing, route of administration, and timing of each dose is provided in Table 6-1.

Table 6-1 MarzAA Dose & Mode of Administration by Dosing Stage

Stage	Dose [a]	Route	Number of Doses	Frequency, Timing [b]
1	18 µg/kg	IV	1	NA
2	30 µg/kg	SC	1	24 Hours after Stage 1
3	45 µg/kg	SC	1	48 hours after Stage 2
4	60 µg/kg	SC	1	48 hours after Stage 3
5	2 × 30 µg/kg [c]	2 × SC	1	48 hours after Stage 4, 2 sites [c]
6	2 × 45 µg/kg [d]	2 × SC	1	48 hours after Stage 5, 2 sites [d]
7	2 × 60 µg/kg [e]	2 × SC	1	48 hours after Stage 6, 2 sites [e]
8	2 × 60 µg/kg [f] (120 µg/kg/day)	SC	2	48 hours after Stage 7, unless subjects were enrolled in the study prior to Amendment 2 [b], 2 doses at 3-hour intervals [f]
9	3 × 60 µg/kg [g] (180 µg/kg/day)	SC	3	72 hours after Stage 8, 3 doses at 3-hour intervals [g]

Abbreviations: IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.

a. For subjects requiring more than 2 vials of supplied study drug, the number of SC injections should be commensurate with the number of vials needed. Injection sites should be different for each injection but should be at the same anatomic location.

b. Timing provided is minimum time after dosing. Maximum time after dosing should not exceed 7 days if a subject continues to the next stage of the study except for subjects completing their EOS visit prior to Amendment 2.

c. 2 × 30 µg/kg MarzAA (total dose 60 µg/kg) injected at two different anatomic locations (which must drain into separate lymphatic tributary areas [eg, left and right thigh, or different sides of abdomen, or abdomen and thigh])

d. 2 × 45 µg/kg MarzAA (total dose 90 µg/kg) injected at two different sites at the same anatomic location

e. 2 × 60 µg/kg MarzAA (total dose 120 µg/kg) injected at two different sites at the same anatomic location at the same timepoint

f. 60 µg/kg MarzAA (total dose 120 µg/kg/day) administered at two separate timepoints with 3-hour intervals between each dose and in the same anatomic location

g. 60 µg/kg MarzAA (total dose 180 µg/kg/day) administered at three separate timepoints with 3-hour intervals between each dose and in the same anatomic location

NOTE: All subjects enrolled in Stage 4, who will receive a SC dose of 60 µg/kg MarzAA injected at a single anatomic location, must also continue to Stage 5 to receive an equal split SC dose of 60 µg/kg MarzAA injected at two different anatomic locations

(2 × 30 µg/kg) for an accurate comparison, so it is possible that more than 8 subjects will be dosed in Stage 4.

If a subject moves on to another dosing stage, each subsequent injection site must be different from all prior injection sites. There is no efficacy-based dose escalation in this study.

6.1.1.1 Guidelines for Interruption of Dose Escalation

Dose escalataion will be interrupted 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
- 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. There is a 72-hour washout period after subjects are stabilized on their treatment.

A study stage may be repeated in a subject if PK assessments are interrupted by treatment of a bleed or if PK samples are inadequate for analysis.

6.2 Preparation, Handling, Storage, and Acountability

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 investigational product (IP) was received frozen and undamaged, thereby maintaining the Good Manufacturing Practice (GMP) status of the product during shipment.

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

The sponsor or designee will arrange for the return of unused IP. 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 IP 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 (eg, 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 IP 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 (eg, 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 IP must be quarantined and not used until the Sponsor, or designee, provides documentation of permission to use the IP. 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.

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 administration or SC injection.

Details regarding the dosing administration, will be provided by the Sponsor, or designee.

MarzAA 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.

6.3 Monitoring Compliance

The study drug is administered at the study site and will be reported in the eCRF.

6.4 Concomitant Therapy

Enrolled subjects will inform the study investigator about all prior and concomitant medications administered from the Screening Visit to Study termination (including the date and time of administration).

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 or requirements. 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 and cannot discontinue and washout this therapy for 72 hours prior to dosing.

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-kxwh, fitusiran, or one of the anti-TFPI agents (eg, concizumab, BAY1093884, or PF-06741086) in clinical investigation, he will be permitted to enroll onto this study, provided 30 days since exposure to that study drug have passed.

6.5 Rescue Therapy

In the event of spontaneous or traumatic bleeding in subjects with inhibitors, treatment for a spontaneous or traumatic bleeding episode will be permitted using the subject's current treatment regimen which could be FEIBA, NovoSeven, HEMLIBRA, or a FVIII or FIX product. A washout period of 72 hours after the subject is stablized is required before the subject continues to the next stage of the study.

6.6 Meals and Dietary Restrictions

Five days prior to dosing through 48 hours postdosing in each stage, subjects should be advised to refrain from food and drinks that may influence blood clotting. Food and drink that may influence blood clotting are high in "salicylates." Examples of these include, but is not limited to, some herbs and spices (ginkgo, garlic, ginger, ginseng, horse chestnut, turmeric, and white willow) and some fruits (raisins, prunes, cherries, cranberries, blueberries, grapes, strawberries, tangerines, and oranges). Furthermore, advise subjects that grapefruit or grapefruit related juices may not be consumed from 7 days prior to the first dose of study medication until the final sample collections are done 48 hours after dosing in Stage 9.

7.0 STUDY ASSESSMENT AND PROCEDURES

Study endpoints are detailed in Section 3.0. A schedule of assessments and procedures is provided in Appendix A.

7.1 Study Procedures and General Assessments

General Assessments are summarized in Table 17-1.

Investigators will document:

- Subject demographics (sex, age, race and ethnicity) 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 at the screening visit
- Diagnosis of moderate or severe congenital Hemophilia A or B with or without an inhibitor
- Prior medications and any nondrug treatments
- 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, and general physical examination will be performed at screening
- Administration of study drug (MarzAA) for each stage (route [IV or SC], anatomical location of administration, inject site assessment)

7.2 Pharmacokinetics and Pharmacodynamics Assessments

For Stage 1, specimens will be obtained for pharmacokinetics (MarzAA activity levels) at predose and then at 5, and 60 minutes ±5 minutes; 2, 6, 9 hours ±15 mins; 12 and 24 hours ±2 hours after dosing with MarzAA. For Stages 2 to 7 specimens will be obtained for pharmacokinetics (MarzAA activity levels) at predose and then at 30, 60, and 90 minutes ±5 mins; 2, 6, 9 hours ±15 mins; 24 and 48 hours ±2 hours after dosing with MarzAA. For stage 8 and 9, specimens for PK parameters will be obtained hourly starting at 2 through 9 hours, then at 12, 24, 48 and 72 hours

For Stage 1 coagulation and thrombogenicity parameters will be obtained at predose and then at 5 minutes ±5 minutes; 2 and 6 hours ±15 minutes; and 24 hours ±2 hours. For Stages 2 to 9 coagulation and thrombogenicity parameters will be obtained at predose and then at 2 and 6 hours ±15 minutes; and 24 and 48 hours ±2 hours. For stage 8 and 9, coagulation and thrombogenicity assessments will also be obtained at 72 hours.

For Stage 1 (IV), Stage 2 (SC) may be initiated immediately after the 24-hour specimens have been obtained. If Stage 2 is initiated immediately after Stage 1, then the 48-hour specimens can be used as the predose specimens for the next Stage 2.

For Stages 2 to 9, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If the stage is initiated immediately after the previous stage, then the 48-hour specimens can be used as the predose specimens for the next stage. A maximum of 7 days may elapse between the 48-hour blood draw and when the next stage commences (unless

delayed because of dose interruption as specified in the protocol). For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, there are no additional screening parameters required and the 7-day maximum between Stage 7 and 8 does not apply. All predose assessment will be required. If a new subject is enrolled in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to Stages 2 to 9.

Pharmacokinetic and PD assessments are detailed in Appendix A, Table 17-2, Table 17-3 and include:

- MarzAA activity levels at various timepoints throughout the study. Calculation of standard PK parameters and bioavailability will be performed at a central laboratory.
- Coagulation parameters including PT, aPTT, and TGT (performed at a central laboratory)
- Thrombogenicity markers including fibrinogen, D-dimer, F1+2, and TAT (performed at a central laboratory)

Subjects will need to inform the study investigator about all spontaneous or traumatic bleeding episodes and concomitant medications administered, 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 activities of daily living.

7.3 Safety Assessments

Safety will be evaluated by assessment of AEs including SAEs as described in Section 8.4.5. Additional safety evaluations include the following parameters:

- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (chemistry and hematology)
- Use of concomitant medications

7.3.1 AEs and SAEs

Subjects will inform study investigator/nurse about any AEs that occur during the study.

7.3.2 Injection site reactions

Subjects will inform study investigator/nurse about any injection site reactions. Photographic documentation is desirable and should include a coin as a size marker.

7.3.3 Adverse Events and Serious Adverse Events

7.3.3.1 Definition of Adverse Events (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 the study drug. 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, irrespective of the relationship 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.

Note: Bleeding events **should not be recorded as an adverse event unless considered serious** and then the reporting process for a serious adverse event should be followed.

7.3.3.2 Definition of Serious Adverse Events (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.

7.3.3.3 Classification of an Adverse Event

7.3.3.3.1 Severity of Event

All AEs will be assessed by the study clinician using the CTCAE v4.0 where applicable.57

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 activities of daily living 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".

7.3.3.4 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. During the assessment of causality, the most plausible etiology should be considered. The degree of certainty about causality will be graded using the categories below:

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.

7.3.3.5 Action Taken

None:	no changes were made to study drug administration and dose.
Permanently discontinued:	study drug was discontinued and not restarted.
Next dosing (stage) temporarily delayed:	advancement to the next study drug dosing stage was delayed due to an AE and restarted at the next stage (if AE occurs during Stage 4 subject would repeat Stage 4 as noted in Section 6.1.1).

7.3.3.6 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 drug in the Investigator's Brochure.

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

Subjects will be instructed regarding direct reporting of AEs 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.

7.3.5 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 nonserious 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 (ie, subject withdraws consent or is lost to follow-up).

All protocol-defined AEs will be reported from the time a subject is enrolled in the study until the end of study visit with the exception of nonserious spontaneous or traumatic bleeding events.

Nonserious spontaneous or traumatic bleeds are not considered adverse events for the purpose of this protocol and should not be reported as adverse event in the eCRF; however, all nonserious bleeds should continue to be logged in the eCRFs, including spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery. A separate log line in the eCRF will be provided to record nonserious bleeds.

NOTE: **Bleeds considered serious** should be reported per the standard process for SAE reporting.

7.3.6 Potential Risks

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 (The study drug has the potential risk of causing thrombotic events based on information associated with other drugs for treatment of hemophilia. A list of signs and symptoms of thrombotic events requiring urgent reporting attention is provided in Appendix B.
- Development of anti-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 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.
  - Fasting could cause dizziness, headache, stomach discomfort, or fainting

7.3.7 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 (ie, subject withdraws consent or is lost to follow-up).

7.3.7.1 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 (ie, 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 preplanned 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.

7.3.8 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:

- 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. Signs and symptoms of TEs requiring urgent reporting and attention are listed in Appendix B.
- Immune response resulting in antibody formation and potentially an inhibitory antibody response. This will also be monitored for throughout the study.

7.3.9 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 a consent authorization form to present to the partner. If she agrees, 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.

7.4 Unscheduled Visit Procedures and Withrawals

If during the duration of the trial, a subject requires medical attention from the study team, the following should be recorded. If a subject requires medical attention, not previously planned, from another medical practitioner or team, this should be considered an indication of an adverse event unless demonstrated otherwise. At the unscheduled visit, the following assessments may need to be conducted based on the judgement of the clinical study team.

- Vital signs
- Weight
- Physical examination
- Concomitant medications
- Adverse events
- Clinical signs of thrombosis (Appendix B)
- Hematology and chemistry (Appendix A, Table 17-1, Footnote F)
- Coagulation assays: PT, aPTT, and TGT
- Thrombogenicity markers: fibrinogen, D-dimer, F1+2, and TAT
- Pharmacokinetics: MarzAA activity
- Immunogenicity assays to FVII, FVIIa, and MarzAA

If a subject discontinues or withdraws early, it is essential to capture the rationale for withdrawal during the final visit. Criteria for study withdrawal and discontinuation are provided in Section 5.3.

7.5 End-of-Study Assessments/Follow-up

Following the end of dosing with MarzAA and the completion of all assessments, then a 30-day visit will be performed for safety and follow-up.

The end of study visit will be 30 days after completing the last stage possible in the study. For example, if a subject completes Stage 6 but withdraws then the subject will have their end-of-study assessment 30 days after dosing for Stage 6.

A participant is considered to have completed the study if he has completed all assessments in a stage of the study and returned for procedures listed under end of study visit, as detailed Appendix A.

8.0 STATISTICAL CONSIDERATIONS

8.1 Primary Analysis Plan

- PK analysis by route of administration, dose level/stage of the study
- Analysis for dose proportionality
- Appropriate statistics of all recorded, measured and calculated parameters will be reported, including 95% confidence intervals, n, mean, standard deviation, median, minimum and maximum
- Safety results will be tabulated. The numbers of subjects who were treated, who completed the study, who discontinued and the primary reasons for discontinuation will be tabulated.

8.2 Sample Size Determination

The sample size estimate is based on PK guidance for the development of hemophilia factors published by regulatory agencies.

8.3 Populations for Analyses

Intent to Treat (ITT) population:	any subject who receives at least one dose of study drug. The ITT population will be used for all safety analyses.
PK population:	any subject who completes an entire dosing stage including the PK assessments and has adequate samples for analysis.

8.4 Statistical Analysis

8.4.1 Subject Disposition

A disposition listing of all enrolled subjects will be generated for each stage of the study to describe study center, subject number, first study drug dosing date, dose stage, total duration of study drug dosing, the reason for discontinuing study drug dosing, and reason for discontinuing the study.

8.4.2 General Approach

Standard PK parameters such as terminal half-life, area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}t}$) and area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration ($AUC_{0\text{-}inf}$), clearance, volume of distribution, mean residence time and bioavailability (of the subcutaneous administration) will be calculated. A semi-parametric model described by Lee et al (Lee, 1990; Lee, 1997) will be used to calculate the terminal half-life. A noncompartmental approach based on the trapezoidal rule will be used to compute the area under curve (AUC) and the parameters derived from them. Descriptive statistics will be reported for each parameter and will include mean ± standard deviation and median ± interquartile range.

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

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

8.4.3 Analysis of the Primary Pharmacokinetic Endpoint(s)

The analysis of the primary endpoint (comparative pharmacokinetics of MarzAA by dose level) will be based on the examination of the AUC_{0-t}/dose for each of the six dose groups. Under the hypothesis of dose proportionality, a mixed linear model will be used (accounting for patient effect) to test for the equality of the mean ratio across dose group. A similar model will be used to compare the results for the split dose with the same dose (60 µg/kg) given at a single location.

The comparison of the dose means for the other PK parameters calculated will also be evaluated with a mixed linear model with dose being the primary main effect.

In addition, all PK parameters will be summarized at each of the dosing levels using means and standard deviations.

8.4.4 Analysis of the Secondary Endpoint(s)

Study drug exposure of IV and SC dosing will be provided for all stages.

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 activity levels, and TGT) from predose
- 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 administration of MarzAA

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

8.4.5 Safety Analysis

8.4.5.1 Adverse Events

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

Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be provided for all stages. Incidence rates will also be displayed based on severity and relationship to study drug as determined by the clinician who examines and evaluates the study subject (Section 7.3.3.4). AEs with a relationship of “possibly” or “probably” related will be considered as “related” to the study drug. Events assessed as “unrelated”, “unlikely” related, or will be considered 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.

8.4.5.2 Vital Signs

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

8.4.6 Baseline Descriptive Statistics

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

8.4.7 Planned Interim Analyses

Not applicable to this study.

8.4.8 Sub-Group Analyses

Not applicable to this study.

8.4.9 Tabulation of Individual Participant Data

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

8.5 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures that is under the PI's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of study drug dosing, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if necessary for the safety or clinical management of study subjects and must immediately be reported to Catalyst Biosciences, Inc. or its designee.

Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.

9.0 DIRECT ACCESS TO SOURCE DOCUMENTS: AUDIT AND INSPECTION

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The investigator will allow the sponsor auditor, regulatory authority or ethics committee (EC) representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 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).

Independent audits may be conducted by the Sponsor, or designee, or regulatory authority inspectors to inspection the Study Center facilities (eg, 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.

10.2 Quality Control

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by Catalyst Biosciences, Inc. or its designee. As noted in Section 9.0, the Investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, eCRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the ICH E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to the sponsor or designee, including unscheduled and missed assessments

10.3 Quality Assurance

The following steps will be taken to assure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements.

- Investigator meeting and/or Investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents
- As needed, local laboratory normal ranges will be collected from each local laboratory at the onset of the study and throughout the study whenever there are changes to the normal ranges

11.0 ETHICS

11.1 Compliance with Ethical and Regulatory Guidelines

The investigator will ensure that this study is conducted in accordance with the protocol and in accordance to the ICH GCP E6 guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection for the rights, safety and well-being of the study subjects. For studies conducted under a US investigational new drug application (IND), the investigator will ensure adherence to the basic principles of GCP as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

11.2 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

The 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.

11.3 Informed Consent

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.

Each subject must provide his or her consent in compliance with all applicable laws for the region.

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 ICF should be signed and personally dated by the subject and by the study person who conducted the informed consent discussion. The original signed ICF 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.

11.4 Subject Confidentiality

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.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 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.]

12.2 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

13.0 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

14.0 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 5.3 for handling of enrolled study participants.

15.0 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.

16.0 REFERENCES

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17.0 APPENDICES

APPENDIX A SCHEDULE OF ASSESSMENTS (SOA)

Table 17-1 Overview of Protocol Visits and Procedures

Study Period	Screening [a]	Enrollment (prior to 1st dose)	Stages 1 to 9 [b]			Stages 2 to 9	Stages 8 to 9	Unscheduled [c]	EOS d
			Predose (−15 min)	Day 1	Day 2	Day 3	Day 4		
				Hours					
Study Day/Hour	Day −28 to −1			0	24	48	72		
Informed consent	X								
Demographic parameters	X	X							
Inclusion & exclusion review	X	X							
Medical & hemophilia History	X	X							
Enrollment confirmation		X [a]							
Prior medications & nondrug treatment	X								
Vital signs	X	X		X	X	X	X	X	X
Height (screening only) & weight	X	X		X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X
ECG	X								
Clinical signs of thrombosis [e]	X	X		X	X	X	X	X	X
Hematology & chemistry [f]	X		X		X	X	X	X	X
Coagulation assays [g]	X		X	X	X	X	X	X	X
Thrombogenicity markers [g]	X		X	X	X	X	X	X	X
PK sampling [g]			X	X	X	X	X	X	X
Immunogenicity assays [g]	X		X			X	X	X	X
AEs & ConMeds	X	X	X	X	X	X	X	X	X
MarzAA administration [h]				X					
Study drug accountability				X					

Abbreviations: AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ConMeds=concomictant medications; ECG=electrocardiogram; MarzAA=marzeptacog alfa (activated); PK=pharmacokinetic; PD= pharmacodynamic.

Footnotes Provided on Next Page

Table 17-1 Footnotes

a. All Screening procedures must be completed and reviewed prior to enrollment. Sample collection and shipment to the Central Laboratory should take place at least 2 weeks prior to scheduled enrollment. For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, there are no additional screening parameters required.

b. For PK/PD assessments for Stages 1 to 7, refer to Table 17-2 and Stages 8 and 9, refer to Table 17-3. Pharmacokinetic assessments should be performed before all other assessments for each time point. If a new subject is enrolled in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to Stages 2 to 9.

c. At an Unscheduled Visit, perform only the assessments that are appropriate for the reason of the visit.

d. End of Study visit will occur 30 days after the last stage has been completed by the subject ±5 days. For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, EOS assessments should be repeated.

e. Clinical signs of thrombosis per protocol.

f. Local Laboratory: **Hematology** – CBC and platelet count. **Chemistry** – Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine. For each stage, blood will be collected at Predose (−5 minutes), 24 and 48 hours postdose. For Stages 8 to 9, blood will also be collected at 72 hours postdose.

g. Central laboratory: **Coagulation assays** – PT, aPTT and TGT. **Thrombogenicity markers** – Fibrinogen, D-dimer, F1+2, and TAT. **Pharmacokinetics** – MarzAA activity. Immunogenicity assays – to FVII, FVIIa, and MarzAA. For PK/PD assessments for Stages 1 to 7, refer to Table 17-2 and Stages 8 to 9, refer to Table 17-3.

h. At Hour 0 of each Stage, an IV or SC dose of MarzAA will be given.

Table 17-2 PK/PD Schedule of Assessments for Each Study Stage (Stage 1 to 7)

Study Day/Hour	Predose (−15 min)	IV/SC Admin	Stage 1							Stages 2 to 7							
										Day 1						Day 2	Day 3
			Minutes		Hours					Minutes			Hours				
			5	60	2	6	9	12	24	30	60	90	2	6	9	24	48
			±5 minutes		±15 minutes			±2 hours		±5 minutes			±15 minutes			±2 hours	
Vital Signs [a]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam																X	X
Clinical Signs of Thrombosis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry	X															X	X
Coagulation	X		X		X	X			X				X	X		X	X
Thrombogenicity	X		X		X	X			X				X	X		X	X
Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity [b]	X																
MarzAA administration [c]		X															
AEs & ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; ConMeds=concomitant medications; IV=intravenous; MarzAA=marzeptacog alfa (activated); min=minutes; PD=pharmacodynamics; PK=pharmacokinetics; SC=subcutaneous.

NOTE: After Stage 1, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If a stage is initiated immediately after, then the 48-hour specimens can be used as the predose specimens for the next stage. A maximum of 7 days may elapse between the 48-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol).

a. Pharmacokinetic assessments should be performed before all other assessments for each time point. Vital signs performed include measure supine blood pressure, pulse, temperature and respiratory rate

b. For subjects who complete all stages, starting at an initial dose of 18 µg/kg, immunogenicity will be done at predose for Stage 3 and Stage 6 only, and end of study. For replacement subjects starting at a higher dose level, specimens will be drawn at screening and at the end of the study

c. After the IV dose of 18 µg/kg, the initial SC dose at 30 µg/kg, followed by an increase to 45, 60, 90, and 120 µg/kg if the subject continues enrollment in the study. If a subject does not proceed through all stages, then a replacement subject will be added at the missing stage to achieve 8 subjects. If a replacement subject is enrolled in the study in Amendment 2, subject will need to complete Stage 1 (IV) dosing and assessments prior to advancing to Stages 2 to 9. If asubject discontinues Stage 5the replacement subject will complete Stage 1 (IV) dosing and assessments and then repeat Stage 4 and then continue with the remaining doses such that the same subject completes Stages 4 and 5. For all other stages when the completion of a dose level has occurred, the replacement subject will complete Stage 1 (IV) dosing and assessments and then will start at the next incomplete dose level. There are two doses at 60 µg/kg: Stage 4 injected at a single anatomic location and Stage 5 an equal split SC dose injected at two different anatomic locations, which drain into separate lymphatic tributary areas (eg, left and right thigh, or different sites of abdomen, or abdomen and thigh).

Table 17-3 PK/PD Schedule of Assessments for Each Study Stage (Stage 8 and 9)

Study Day/Hour	Predose (−15 min)	SC Admin	Stages 8 to 9											
			Day 1									Day 2	Day 3	Day 4
			Hour											
			2	3	4	5	6	7	8	9	12	24	48	72
			±15 minutes								±2 hours			
Vital Signs [a]			X	X	X	X	X	X	X		X	X	X	X
Physical Exam												X	X	X
Clinical Signs of Thrombosis	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry	X											X	X	X
Coagulation	X						X	X		X	X	X	X	X
Thrombogenicity	X						X	X		X	X	X	X	X
Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity [b]	X													
MarzAA administration [a, c]		X		X			X							
AEs & ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; ConMeds=concomitant medications; IV=intravenous; MarzAA=marzeptacog alfa (activated); min=minutes; PD=pharmacodynamics; PK=pharmacokinetics; SC=subcutaneous.

NOTE: After Stage 1, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If a stage is initiated immediately after, then the 48-hour specimens can be used as the predose specimens for the next stage. A maximum of 7 days may elapse between the 48-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol or had previously completed dosing prior to Amendment 2).

a. Pharmacokinetic assessments should be performed before all other assessments for each time point.Vital signs performed include measure supine blood pressure, pulse, temperature and respiratory rate

b. For subjects who complete all stages, starting at an initial dose of 18 µg/kg, immunogenicity will be done at predose for Stage 3 and Stage 6 only, and end of study. For replacement subjects starting at a higher dose level, specimens will be drawn at screening and at the end of the study

c. Stage 8 will give 2 separate doses of 60 µg/kg dosed at 3-hour intervals, and Stage 9 will give 3 separate doses of 60 µg/kg, dosed at 3-hour intervals If a subject does not proceed to Stage 9, then a replacement subject will be added at the missing stage to achieve 8 subjects in each stage. The replacement subject will need to complete Stage 1 (IV) dosing and assessments prior to advancing to Stage 8 to 9

APPENDIX B CLINICAL SIGNS OF THROMBOSIS

Common signs and symptoms of thrombosis are provided in Table 17-4. 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 and described in Table 17-5.

Table 17-4 Common Signs and Symptoms of Thrombosis

Symptoms and Signs of Venous Thromboembolism –DVT and PE:	Common Heart Attack Warning Signs	Stroke Signs
• Leg pain or tenderness of 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	• 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	• 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

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism.

Source: American Heart Association (http://www.ihtc.org/payors/conditions-we-treat/clotting-disorders/signs-and-symptoms-of-thrombosis); Accessed on 9 Mar 2017).

Table 17-5 Clinical Spectrum of Venous Thromboembolism (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	• 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

Type	Signs and Symptoms	Physical Examination
may not present until significant collateral circulation has developed		prominence of superficial veins • Some people with a DVT may be asymptomatic
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 • Superficial thrombophlebitis is often observed in individuals who are heterozygous or homozygous for the Factor V Leiden mutation	• 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 • 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	

Abbreviations: DVT=deep vein thrombosis; IHTC=Indiana Hemophilia and Thrombosis Center, Inc.; PE=pulmonary thrombosis; VTE=venous thromboembolism.

Source: Adapted from IHTC. Signs and Symptoms of Thrombosis (http://www.ihtc.org/payors/conditions-we-treat/clotting-disorders/signs-and-symptoms-of-thrombosis); Accessed on 9 Mar 2017).

Catalyst Biosciences, INC

STATISTICAL ANALYSIS PLAN

PROTOCOL *MAA-102*

Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia

Protocol Code:	MAA-102
SAP Version:	Final
SAP Date:	16-JUN-2020
Author:	Tina Dube, Senior Statistician, PSI

DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
NA	Initial release

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
	N/A	Initial release	N/A

APPROVAL SIGNATURES

STUDY TITLE: Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia

PROTOCOL NUMBER: *MAA-102*

SAP *Final, 16-JUN-2020*

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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Description
Mg	Microgram
ƒ	Bioavailability
AE	Adverse event
aPTT	Activated prothrombin complex concentrates
ATC	Anatomical therapeutic chemical (class)
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration
CL	Clearance
CV%	Percent coefficient of variation
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of study
F1+2	Prothrombin fragment 1+2
FVII	Factor VII
FVIIa	Factor VII activated
IRF	Immune response/antibody formation
IV	Intravenous
Kg	Kilogram
MarzAA	Marzeptacog alfa (activated)
MRT	Mean residence time
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PT	Preferred term
rFVIIa	Recombinant activated Factor VII
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
$t_{1/2}$	Terminal half-life
TAT	Thrombin-antithrombin complexes
TE	Thromboembolic event
TEAE	Treatment-emergent adverse event
TGT	Thrombin generation time
V_d	Volume of distribution
WHO-DDE	World Health Organization Drug Dictionary Enhanced
Wt	Wild-type

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol MAA-102 final version 1.0 (Amendment 1.0) dated 11 March 2019, and electronic case report form (eCRF) production version of 05 August 2019.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

To evaluate the pharmacokinetics of ascending subcutaneous (SC) doses of marzeptacog alfa (activated) (MarzAA).

3.2 SECONDARY OBJECTIVES

- To determine the pharmacokinetics of single dose intravenous (IV) and SC MarzAA.
- To determine if the pharmacokinetics of increasing SC doses behave in a dose proportional manner.
- To determine whether a split injection provides the same pharmacokinetics as a single injection.
- To determine the pharmacodynamics of IV and SC MarzAA.
- To evaluate for evidence of the development of antibodies to MarzAA, wild-type (wt) recombinant activated Factor VII (rFVIIa), and/or wt-FVII, and~~v~~ to determine if these are neutralizing antibodies.
- To evaluate the safety of IV and SC MarzAA.

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

This is a Phase 1 study designed to evaluate the pharmacokinetics, pharmacodynamics, and safety of a single IV dose and ascending doses of SC MarzAA in adult subjects with hemophilia A or B, with or without an inhibitor. It is an open-label study, so subjects and members of the clinical study team will not be blinded to treatment.

The study will be completed in approximately 18 months (from when the study opens enrollment until completion of data analyses). The study will enroll at least 8 adult male subjects with moderate or severe Hemophilia A or B with or without an inhibitor in each dosing stage.

Each subject may continue on to the next stage of MarzAA dosing if they wish to continue the study provided they do so no more than 7 days after the end of the previous stage, and that any spontaneous or traumatic bleeds have been resolved, and that the subject has undergone a 72-hour washout period of the treatment used for the spontaneous or traumatic bleed.

If any subject completes the EOS assessments prior to Amendment 2 and wishes to participate in Stages 8 and/or 9, the 7-day requirement will not apply, and no screening assessment will need to be repeated. All predose assessments will be required. If a new subject enrolls in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to Stages 2 to 9.

4.2 STUDY TREATMENT

All study subjects will be treated with MarzAA. Each subject may receive the study drug in nine dosing stages (Stage 1 to 9). Detailed dosing, route of administration, and timing of each dose are provided in Table 4-1~~Table 4-1~~.

Table 4-1 MarzAA Dose and Mode of Administration by Dosing Stage

Stage	Dose [a]	Route	Frequency, Timing [b]
1	18 µg/kg	IV	Once
2	30 µg/kg	SC	Once 24 Hours after Stage 1
3	45 µg/kg	SC	Once, 48 hours after Stage 2
4	60 µg/kg	SC	Once, 48 hours after Stage 3
5	2 × 30 µg/kg [c]	2 × SC	Once, 48 hours after Stage 4, 2 sites [c]
6	~~2 × 45~~90 µg/kg [d]	~~2 ×~~ SC	Once, 48 hours after Stage 5, ~~2 sites~~ [d]
7	~~2 × 60~~120 µg/kg [e]	~~2 ×~~ SC	Once, 48 hours after Stage 6, ~~2 sites~~ [e]
8	2 × 60 µg/kg [d]	2 × SC	48 hours after Stage 7, unless subjects were enrolled in the study prior to Amendment 2 b, 2 doses at 3-hour intervals [f]
9	3 × 60 µg/kg [e]	~~3~~2 × SC	72 hours after Stage 8, 3 doses at 3-hour intervals [g]

Abbreviations: IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.
[a] For subjects requiring more than 2 vials of supplied study drug, the number of SC injections should be commensurate with the number of vials needed. Injection sites should be different for each injection but should be at the same anatomic location.
[b] Timing provided is minimum time after dosing. Maximum time after dosing should not exceed 7 days if a subject continues to the next stage of the study
[c] 2 × 30 µg/kg MarzAA (total dose 60 µg/kg) injected at two different anatomic locations (which must drain into separate lymphatic tributary areas [eg, left and right thigh, or different sides of abdomen, or abdomen and thigh])
[d] 2 × 45 µg/kg MarzAA (total dose 90 µg/kg) injected at two different sites at the same anatomic location
[e] 2 × 60 µg/kg MarzAA (total dose 120 µg/kg) injected at two different sites at the same anatomic location
[f] 60 µg/kg MarzAA (total dose 120 µg/kg/day) administered at two separate timepoints with 3-hour intervals between eachdose and in the same anatomic location
[g] 60 µg/kg MarzAA (total dose 180 µg/kg/day) administered at three separate timepoints with 3-hour intervals between each dose and in the same anatomic location

Commented [SD1]: In the protocol it is single dose of 90ug not 2 x 45 ug for this stage

Commented [SD2]: As such, don't think this footnote is needed

Commented [SD3]: In the protocol it is single dose of 1200ug not 2 x 60 ug for this stage

Commented [SD4]: As such, don't think this footnote is needed

4.3 DATA AND SAFETY MONITORING BOARD

There is no Data and Safety Monitoring Board in this study.

5. RANDOMIZATION AND BLINDING

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

6. SAMPLE SIZE AND POWER CALCULATION

No formal sample size calculation was performed. The sample size estimate is based on pharmacokinetic (PK) guidance for the development of hemophilia factors published by regulatory agencies.

7. ANALYSIS ENDPOINTS

7.1 PRIMARY ENDPOINT

Comparative pharmacokinetics of MarzAA by dose level/stage.

7.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

- Comparative pharmacokinetics of IV and SC MarzAA.
- Comparative pharmacokinetics of split injections versus single injection (60 µg/kg)
- Change in coagulation parameters (prothrombin time, activated prothrombin complex concentrates [aPTT], fibrinogen, MarzAA 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 wt-rFVIIa or wt-FVII.
- Clinically significant levels of thrombogenicity markers resulting from administration of MarzAA.

7.3 SAFETY ENDPOINTS

- 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.
- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

8. ANALYSIS POPULATIONS

Screened population: all screened subjects.

Safety population: any subject who receives at least one dose of study drug. The Safety population will be used for subject disposition, protocol deviations, subject characteristics, secondary endpoints, and safety analyses.

PK population: any subject who receives the full planned dose and completes an entire PK assessment for the stage and has adequate samples for analysis. The PK population will be used for all PK and secondary endpoints analyses.

9. ANALYTICAL PLAN AND STATISTICAL METHODS

9.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed and data appendices will be created using the SAS system version 9.4 or higher.

Data collected in this study will be presented in summary tables and subject data listings.

Descriptive statistics (number of non-missing values, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and percentages) will be presented for categorical variables. If not

specified otherwise, the number of observations with non-missing values will be the denominator for percentage calculation.

Data on screening and demographic characteristics, medical and disease history will be summarized by dosing stage. A subject is included in the summary for a certain stage, if he/she was enrolled under that stage.

All data collected will be presented in the data listings.

9.2 Definition of Baseline, Study Visits, and Visit Windows

Results obtained at pre-dose of each stage will be considered baseline. For hematology and chemistry the pre-dose results are collected under eCRF visit Day 1 for each stage. For vital signs, coagulation, and thrombogenicity marker, the results obtained at the pre-dose timepoint will be used as baseline, unless “pre-dose sample equivalent to post dose sample from previous study stage” is selected on the eCRF, and then results from the 48-hours post dose sample from the previous study stage will be used as baseline.

The data will be analyzed according to the visits and timepoints recorded in the eCRF.

9.3 Handling of Missing Data

Partial or missing start and end dates of adverse events (AEs) and concomitant medications, as well as missing attributes of AEs will not be imputed. All data will be analyzed as collected.

9.4 Patient Disposition

The number of subjects screened and the reasons for screen failure, including exclusion criteria met and inclusion criteria not met, will be summarized in the Screened population.

The number and percentage of subjects who enrolled in the study will be summarized by dosing stage subject entered the study and overall in the Safety population. The number and percentage of subjects discontinued from the study and the reasons for study discontinuation will be summarized by stage subject discontinued and overall in the Safety population. The number and percentage of subjects who completed the study will be summarized for the overall Safety population.

The number and percentage of subjects included in the Safety and PK populations will also be summarized by stage and overall.

A consort diagram with subject disposition will be created.

A listing with all enrolled subjects will be generated for each dosing stage, including country/study center, subject number, first and last study drug dosing date, dose stage, total duration of study drug dosing, end of study date, and reason for discontinuation from the study.

9.5 Protocol Deviations

The number and percentage of subjects with at least one major protocol deviation and the categories of the major protocol deviations will be summarized in the overall Safety population.

Protocol deviations will be classified as major and minor as specified in the Protocol Deviations

Management Plan.

All protocol deviations will be provided in a listing.

9.6 PATIENT CHARACTERISTICS

9.6.1 SCREENING AND DEMOGRAPHIC CHARACTERISTICS

Descriptive statistics for continuous variables (age at screening, height, weight, and body mass index) and frequency counts and percentages for categorical demographic variables (ethnicity and race) will be summarized in the Safety population and tabulated by dosing stage.

Screening and demographic characteristics will be provided in a listing.

9.6.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Disease characteristics will be summarized by dosing stage in the Safety population using descriptive statistics for age at diagnosis and Factor VIII/IX level at screening; and using frequency counts and percentages for the type of hemophilia, severity, history of inhibitors, and prescribed hemophilia treatment.

Medical history will be coded using the version 22.0 of Medical Dictionary for Regulatory Activities (MedDRA) classification and summarized by System Organ Class (SOC) and preferred term (PT), by dosing stage and overall in the Safety population. Subjects having the same medical condition (based on SOC and PT) more than once will be counted only once for a particular SOC and PT.

Disease characteristics and medical history will be listed.

9.6.3 PRIOR AND CONCOMITANT MEDICATIONS

All prior and concomitant medications will be coded using March 2019 Format Global B3 version of World Health Organization Drug Dictionary Enhanced (WHO-DDE).

The number and percentages of subjects with at least one prior or concomitant medication will be summarized by anatomical therapeutic chemical class (ATC) level 4 and ATC level 2 class in the PK and Safety populations. Prior and concomitant non-hemophilia medications and prior hemophilia specific medications will be summarized in overall.

Concomitant hemophilia-specific medications will be tabulated by dosing stage and overall. Concomitant hemophilia-specific medication is considered taken at a certain stage, if administered on or after the date of study drug administration for that stage, and before the date of study drug administration for the next stage, or until the end of study for the last stage the subject participated in. One medication can be considered concomitant for multiple stages.

A medication is considered prior if the end date of the medication is prior to the first study drug dose date. A medication is considered concomitant if it is administered after the first study drug dose date.

Medications having both start and end dates missing will be considered concomitant; in the case of a missing start date and not a missing end date, the medication will be considered concomitant, unless the end date is prior to the date of the first dose. In such case, the

medication will be reported in the overall summary only.

Subjects receiving the same medication more than once will be counted only once for a particular medication class and stage, where applicable.

All prior and concomitant medications will be provided in a listing.

9.7 PK ENDPOINTS AND ANALYSIS

PK parameters derivation will be performed by Catalyst and described in a separate PK SAP.

The following PK parameters will be calculated:

- terminal half-life ($t_{1/2}$);
- area under the plasma concentration-time curve from time 0 to infinity (AUC_{0-inf});
- area under the plasma concentration-time curve from time 0 to the time of the last measurable plasma concentration (AUC_{0-t});
- clearance (CL);
- volume of distribution (V_d);
- mean residence time (MRT);
- bioavailability (f) (of the SC administration).

A semi-parametric model described by Lee et al (Lee, 1990; Lee, 1997) will be used to calculate the terminal half-life. A noncompartmental approach based on the trapezoidal rule will be used to compute the AUC and the parameters derived from them. These include:

- AUC_{0-inf};
- AUC_{0-t};
- CL;
- V_d;
- MRT;
- f (of the SC administration).

PK data will be analyzed for the PK population defined in section 8.

9.7.1 ANALYSIS OF PRIMARY PHARMACOKINETIC ENDPOINT

The analysis of the primary endpoint (comparative pharmacokinetics of MarzAA by dose level) will be based on the examination of the AUC_{0-t}/dose for each dose group. Under the hypothesis of dose proportionality, a mixed linear model will be used (accounting for subject effect) to test for the equality of the mean ratio across dose groups.

The sample code for mixed linear model, assuming dose level as categorical fixed effect and subject as random effect, is provided below:

```
proc mixed data=sample;
class DOSE_LEVEL;
model AUC0-t_dose_ratio= DOSE_LEVEL/cl;
random intercept/Subject=SUBJID;
run;
```

In the tables, parameter estimates with standard errors, significance of parameter estimates (95% confidence intervals and type III hypothesis test) will be provided.

9.7.2 ANALYSES OF SECONDARY PHARMACOKINETIC ENDPOINTS

Mean ratio of the AUC_{0-t}/dose for the split dose (2*30 µg/kg) with the same dose (60 µg/kg) given at a single location will be compared using mixed linear model as defined in section 9.7.1.

The analysis of the primary endpoint will be repeated for each PK parameter listed in section 9.7 of the SAP.

Descriptive statistics will be reported for each parameter by dosing stage. PK parameter results will be listed.

9.8 ANALYSES OF SECONDARY ENDPOINTS

Secondary endpoints will be analyzed in the PK and Safety populations.

MarzAA activity levels will be summarized by dosing stage using descriptive statistics, including percent coefficient of variation (CV%), geometric mean, and geometric SD.

Results of thrombogenicity markers (fibrinogen, D-dimer, prothrombin fragment 1+2 [F1+2] and thrombin-antithrombin complexes [TAT]), coagulation tests (prothrombin time, aPTT and TGT values) results and changes from pre-dose will be tabulated by timepoint and stage~~,~~ and summarized using descriptive statistics. Immunogenicity assay result will be tabulated by stage and visit. For coagulation tests descriptive statistics will include CV%, geometric mean and geometric SD, calculated as: geo SD= exp (SQRT(v)) where v is the squared standard deviation of the log-transformed values.

The number and percentage of subjects with clinical signs of thrombosis will be tabulated by timepoint, stage, and overall.

If a subject is unable to complete all of the PK assessments and repeats a stage, MarzAA activity levels, thrombogenicity markers, coagulation tests, and immunogenicity assay results obtained during the original stage will not be included in the tables and analyzed, as this patient will not be included in the PK population for the original stage.

For analysis of all secondary endpoints in the Safety population, if a subject is unable to complete all of the PK assessments and repeats a stage, all data collected will be included in the analysis. The subject will be counted twice for that stage and at each repeated timepoint.

MarzAA activity levels, thrombogenicity markers, immunogenicity assay, and coagulation test results will be listed.

9.9 SAFETY ENDPOINTS AND ANALYSIS

All safety outcomes will be analyzed in the Safety population.

Safety will be evaluated by presenting summaries of exposure to study treatment, AEs, vital signs, and laboratory evaluations (hematology and chemistry).

9.9.1 EXPOSURE TO STUDY TREATMENT

The actual dose received in micrograms (µg) and the extent of exposure, calculated as last dose date – first dose date +1, will be summarized using descriptive statistics by dosing stage and overall.

If a subject is unable to complete all of PK assessments and repeats a stage, each actual dose received by the subject will be counted separately for that stage.

Data on exposure will be listed.

9.9.2 ADVERSE EVENTS

AEs will be coded using the version 22.0 of MedDRA and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE).

Injection site reactions will be summarized separately~~,~~ and will not be included in AE summaries described below.

A TEAE is defined as an AE that occurs or worsens after the first study drug administration. AEs having both onset and end dates missing will be considered as TEAEs. AEs having a missing onset date and not missing an end date will be considered as TEAEs unless the end date is prior to the date of the first dose.

Each summary table with AEs will be presented by dosing stage and overall. An AE is reported under the stage specified if it occurs or worsens on or after the date of study drug administration during the stage, and before the date of study drug administration in the next stage, or until the end of study for the last stage the subject participated in.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any TEAE, any SAE, any thromboembolic event (TE), any immune response/antibody formation (IRF), any drug-related TEAE, any TEAE leading to premature discontinuation from study, and any TEAE leading to death.

The incidence of TEAEs will be summarized by SOC and PT; by SOC, PT and severity; and by SOC, PT and relatedness. If the same AE (based on SOC, PT, and stage) is reported for the same subject more than once, the AE is counted only once for that SOC, PT, and stage, if applicable, and at the highest severity or relatedness, respectively.

In addition, the incidence of SAEs, TEs, IRFs, and TEAEs leading to discontinuation from study will be presented by SOC and PT and will be tabulated by dosing stage and overall. If the same AE (based on SOC, PT, and stage) is reported for the same subject more than once, the AE is counted only once for that SOC, PT, and stage, if applicable.

Number of subjects with injection site reactions will be tabulated by type of injection site reaction and severity in the Safety population by dosing stage and overall. Injection site reaction will be reported under a stage if occurs on or after the date of study drug administration during the stage and before the date of study drug administration in the next stage, or until the end of study for the last stage the subject participated in.

Separate listings will be prepared for all AEs, SAEs, TEs, IRFs, AEs leading to discontinuation from the study, AEs leading to death, and injection site reactions.

9.9.3 LABORATORY DATA

Pre-dose results, maximum results, and change from pre-dose to maximum results for hematology and clinical chemistry data, collected by local laboratories, will be summarized by dosing stage using descriptive statistics. In addition, maximum change from pre-dose across all stages will be calculated and summarized.

Shift tables classified by reference range indicator (low [<lower limit of normal], normal [within normal limits], and high [>upper limit of normal]) from pre-dose to maximum result per stage will be presented separately by laboratory test, where applicable. In addition, shift tables from maximum pre-dose result to maximum result across all stages, classified as low, normal, and high, will be presented by laboratory test.

If a subject is unable to complete all of PK assessments and repeats a stage, the subject will be counted twice for that stage, i.e., two pre-dose results, two maximum values and two maximum changes from pre-dose will be analyzed.

For laboratory results reported with a prefix, i.e., “<”, “<=”, “=>” or “>”, the value derived from reported results without a prefix will be analyzed.

Data listings will be produced for all collected laboratory data.

9.9.4 VITAL SIGNS AND OTHER SAFETY PARAMETERS

9.9.4.1 VITAL SIGNS

Pre-dose results, maximum results and change from pre-dose to maximum results of vital signs (temperature [degree C], systolic and diastolic blood pressure [mmHg], heart rate [bpm], and respiratory rate [breaths/min]) will be summarized by stage using descriptive statistics. In addition, maximum change from pre-dose across all stages will be calculated and summarized.

If a subject is unable to complete all of PK assessments and repeats a stage, the subject will be counted twice for that stage, i.e., two pre-dose results, two maximum values and two maximum changes from pre-dose will be analyzed.

9.9.4.2 12-LEAD ELECTROCARDIOGRAM (ECG) AND PHYSICAL EXAMINATION

Data listings of ECG and physical examination data collected at screening will be provided.

9.9.4.3 BLEEDING EPISODES

Descriptive statistics for number of bleeding episodes per subject and overall number of bleeding episodes will be tabulated by stage and overall. Frequency counts and percentages for cause of bleeding, bleeding site, whether the subject required transfusion (yes/no), and use of hemostatic drugs for treatment (yes/no) will be summarized on bleeding level and tabulated by stage and overall. Bleeding episodes will be analyzed under a certain stage if they occur on or after the date of study drug administration during the stage and before the date of study drug administration in the next stage, or until the end of study for the last stage the subject participated in. Medications used to treat the bleeding episode will also be summarized and tabulated by ATC 4 and ATC 2 level, and by dosing stage during which the bleeding episode occurred and overall.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Section 8: The safety population will be used in the safety analysis, not the intent-to-treat (ITT) population.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each output, the protocol number will be presented. On the next line, a *table/listing number* followed by the *title* of the table/listing and p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* will appear on the bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear on the bottom left under the SAS program name line.

Example:

```
MAA-102

Table 14.x.x Title - Population

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Program:\\xxx\xxx\MAA-102_table XXX.sas                                      Source: Listing XXX
Created DDMMMYYYY at HH:MM                                                            Page 1 of x
```

Courier New 8-point font will be used for all tables and listings. Landscape layout will be used. Any date information in the listing will use the date9. format, for example, 25OCT2019.

Tables and listings will be produced in “rtf” format, each output in separate file and all tables, all figures and all listings in one file each.

Percentages for categorical data summaries will be displayed with 1 decimal point (e.g. 51.4), except for 100% which will be presented with no decimals (i.e. 100).

Use of decimal places in descriptive statistics:

- Min, Max: same as the actual data,
- Mean, Geometric mean, Median, 95% CI: actual data + 1 decimal,
- Standard deviation (SD), CV%: actual data + 2 decimals.

A maximum of 3 significant digits will be displayed.

All raw data will be presented to the original number of decimal places in the listings.

In case table break across multiple pages, the heading rows should be repeated.

In case there are no data to present in a table, listing or figure, the file will still be created,

containing only a short message to explain: e.g., the listing of SAEs will only show a message like 'No SAEs in the study' if there were no SAEs in the study.

For listings, if the answer to a question is "other", "other" should be displayed and then what the other represents should be specified in parentheses in the cell.

12. LIST OF TABLES, LISTINGS AND FIGURES

Shells for unique tables, listings and figures are provided in a separate Mock-Up TFLs document.

13. REFERENCES

Lee, M. L., Poon, W. Y., & Kingdon, H. S. (1990). A two-phase linear regression model for biologic half-life data. J Lab Clin Med, 115(6), 745-748.

Lee ML, Schroth P, Bray G, Gomperts ED. The use of robust regression techniques to obtain improved coagulation factor half-life estimates. XVIth Congress of the International Society for Thrombosis and Hemostasis, Florence, Italy, 1997.

APPENDIX I. SCHEDULE OF ASSESMENT

Table 0-1

Study Period	Screening [a]	Enrollment (prior to 1st dose)	Stages 1 to 9 [b]			Stages 2 to 9	Stages 8 to 9	Unscheduled [c]	EOS d
			Predose (−15 min)	Day 1	Day 2	Day 3	Day 4		
				Hours					
Study Day/Hour	Day −28 to −1			0	24	48	72		
Informed consent	X								
Demographic parameters	X	X							
Inclusion & exclusion review	X	X							
Medical & hemophilia History	X	X							
Enrollment confirmation		X [a]							
Prior medications & nondrug treatment	X								
Vital signs	X	X		X	X	X	X	X	X
Height (screening only) & weight	X	X		X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X
ECG	X								
Clinical signs of thrombosis [e]	X	X		X	X	X	X	X	X
Hematology & chemistry [f]	X		X		X	X	X	X	X
Coagulation assays [g]	X		X	X	X	X	X	X	X
Thrombogenicity markers [g]	X		X	X	X	X	X	X	X
PK sampling [g]			X	X	X	X	X	X	X
Immunogenicity assays [g]	X		X			X	X	X	X
AEs & ConMeds	X	X	X	X	X	X	X	X	X
MarzAA administration [h]				X					
Study drug accountability				X					

Abbreviations: AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ConMeds=concomitant medications; ECG=electrocardiogram; MarzAA=marzeptacog alfa (activated); PK=pharmacokinetic; PD= pharmacodynamic.

Footnotes Provided on Next Page

[a.] All Screening procedures must be completed and reviewed prior to enrollment. Sample collection and shipment to the Central Laboratory should take place at least 2 weeks prior to scheduled enrollment. For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, there are no additional screening parameters required.
[b.] For PK/PD assessments for Stages 1 to 7, refer to Table 14-2 and for Stages 8 and 9, refer to Tables 14-3. Pharmacokinetic assessments should be performed before all other assessments for each time point. If a new subject is enrolled in the study in Amendment 2, the subject will need to complete IV dosing and assessments (Stage 1) prior to advancing to stages 2 to 9.
[c.] At an Unscheduled Visit, perform only the assessments that are appropriate for the reason of the visit.
[d.] End of Study visit will occur 30 days after the last stage has been completed by the subject ±5 days. For subjects previously enrolled and completing the EOS visit prior to Amendment 2, if participation resumes, EOS assessments should be repeated.
[e.] Clinical signs of thrombosis per protocol.
[f.] Local Laboratory: Hematology – CBC and platelet count. Chemistry – Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine. For each stage, blood will be collected at Predose (−5 minutes), 24 and 48 hours postdose. For Stages 8 to 9, blood will also be collected at 72 hours postdose.
[g.] Central laboratory: Coagulation assays – prothrombin time, aPTT and TGT. Thrombogenicity markers – Fibrinogen, D-dimer, F1+2, and TAT. Pharmacokinetics – MarzAA activity. Immunogenicity assays – to FVII, FVIIa, and MarzAA. For PK/PD assessments for Stages 1 to 7, refer to **Error! Reference source not found.**~~Table 14-2~~ and Stages 8 to 9, refer to **Error! Reference source not found.**~~Table 14-3~~.
[h.] At Hour 0 of each Stage, an IV or SC dose of MarzAA will be given.

Table 0-2

			Stage 1							Stages 2 to 7							
										Day 1						Day 2	Day 3
			Minutes		Hours					Minutes			Hours				
	Predose (−15 min)	IV/SC Admin	5	60	2	6	9	12	24	30	60	90	2	6	9	24	48
Study Day/Hour			± 5 minutes		± 15 minutes		± 2 hours			± 5 minutes			± 15 minutes			± 2 hours	
Vital Signs [a]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam																X	X
Clinical Signs of Thrombosis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry	X															X	X
Coagulation	X		X		X	X			X				X	X		X	X
Thrombogenicity	X		X		X	X			X				X	X		X	X
Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity [b]	X																
MarzAA administration [c]		X															
AEs & ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; ConMeds=concomitant medications; IV=intravenous; MarzAA=marzeptacog alfa (activated); min=minutes; PD=pharmacodynamics; PK=pharmacokinetics; SC=subcutaneous.

NOTE: After Stage 1, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If a stage is initiated immediately after, then the 48-hour specimens can be used as the predose specimens for the next stage. A maximum of 7 days may elapse between the 48-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol).

[a.] Pharmacokinetic assessments should be performed before all other assessments for each time point. Vital signs performed include measure supine blood pressure, pulse, temperature and respiratory rate

[b.] For subjects who complete all stages, starting at an initial dose of 18 µg/kg, immunogenicity will be done at predose for Stage 3 and Stage 6 only, and end of study. For replacement subjects starting at a higher dose level, specimens will be drawn at screening and at the end of the study.

[c.] After the IV dose of 18 µg/kg, the initial SC dose at 30 µg/kg, followed by an increase to 45, 60, 90, and 120 µg/kg if the subject continues enrollment in the study. If a subject does not proceed through all stages, then a replacement subject will be added at the missing stage to achieve 8 subjects. If a replacement subject is enrolled in the study in Amendment 2, subject will need to complete Stage 1 (IV) dosing and assessments prior to advancing to Stages 2 to 9. If a subject discontinues Stage 5, the replacement subject will complete Stage 1 (IV) dosing and assessments and then repeat Stage 4 and then continue with the remaining doses such that the same subject completes Stages 4 and 5. For all other stages when the completion of a dose level has occurred, the replacement subject will complete Stage 1 (IV) dosing and assessments and then will start at the next incomplete dose level. There are two doses at 60 µg/kg: Stage 4 injected at a single anatomic location and Stage 5 an equal split SC dose injected at two different anatomic locations, which drain into separate lymphatic tributary areas (eg, left and right thigh, or different sites of abdomen, or abdomen and thigh).

Table 0-3

Study Day/Hour	Predose (−15 min)	SC Admin	Stages 8 to 9											
			Day 1									Day 2	Day 3	Day 4
			Hour											
			2	3	4	5	6	7	8	9	12	24	48	72
			±15 minutes								±2 hours			
Vital Signs [a]			X	X	X	X	X	X	X		X	X	X	X
Physical Exam												X	X	X
Clinical Signs of Thrombosis	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry	X											X	X	X
Coagulation	X						X	X		X	X	X	X	X
Thrombogenicity	X						X	X		X	X	X	X	X
Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity [b]	X													
MarzAA administration [a, c]		X		X			X							
AEs & ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse events; ConMeds=concomitant medications; IV=intravenous; MarzAA=marzeptacog alfa (activated); min=minutes; PD=pharmacodynamics; PK=pharmacokinetics; SC=subcutaneous.

NOTE: After Stage 1, each subsequent stage may be initiated immediately after the 48-hour specimens have been obtained. If a stage is initiated immediately after, then the 48-hour specimens can be used as the predose specimens for the next stage. A maximum of 7 days may elapse between the 48-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol or had previously completed dosing prior to Amendment 2).

[a.] Pharmacokinetic assessments should be performed before all other assessments for each time point. Vital signs performed include measure supine blood pressure, pulse, temperature and respiratory rate.

[b.] For subjects who complete all stages, starting at an initial dose of 18 µg/kg, immunogenicity will be done at predose for Stage 3 and Stage 6 only, and end of study. For replacement subjects starting at a higher dose level, specimens will be drawn at screening and at the end of the study.

[c.] Stage 8 will give 2 separate doses of 60 µg/kg dosed at 3-hour intervals, and Stage 9 will give 3 separate doses of 60 µg/kg, dosed at 3-hour intervals If a subject does not proceed to Stage 9, then a replacement subject will be added at the missing stage to achieve 8 subjects in each stage. The replacement subject will need to complete Stage 1 (IV) dosing and assessments prior to advancing to Stage 8 to 9.