16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

The documents listed below are provided in this section.

Protocol DLZ-201 Version 1 dated 23-March-2018

Protocol DLZ-201 Amendment 1 Version 2 dated 17-October-2018

CB2679d DLZ-201 VERSION 1.0

Catalyst Biosciences, Inc.

CLINICAL RESEARCH PROTOCOL

Phase 2b Study of Next-Generation Recombinant Factor IX Variant, CB2679d, in Adult Subjects with Hemophilia B

Protocol Identifying Number:	DLZ-201
Official Title:	Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B.
IND/IDE Sponsor:	Catalyst Biosciences, Inc. 611 Gateway Blvd., Suite 710, South San Francisco, California, USA 94080
Investigational Product:	Recombinant Factor IX, CB2679d
Development Phase:	2b
Draft or Version Number:	v.1.0
Effective Date:	23 March 2018
Sponsor Contact:	Name: Howard Levy, MD, PhD, MMM CMO, Catalyst Biosciences, Inc. Telephone: +1.650.266.8671 Fax: +1.650.871.2475 E-mail: hlevy@catbio.com

Prepared by:	Catalyst Biosciences, Inc.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

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

CB2679d DLZ-201 VERSION 1.0

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B.

PROTOCOL No.: DLZ-201

VERSION NUMBER: *1.0*

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 case report forms (CRFs) presented to me by the Sponsor in a manner that assures legibility and accuracy. I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, CRFs, verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR) (Title 21, Parts 50 [including Subpart D], 54, 56 and 312), the regulations and guidelines of the Therapeutic Goods Administration (TGA). The Principal Investigator (PI) 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.

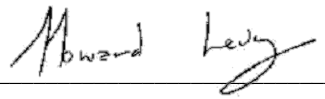
Investigator Signature *Date*

Print Name and Title

CB2679d DLZ-201 VERSION 1.0

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B.
Protocol Number:	DLZ-201
Version Number:	1.0, dated 23 March 2018



23rd March 2018

Howard Levy, MD, PhD, MMM — Date

Chief Medical Officer, Catalyst Biosciences, Inc.

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ABBREVIATIONS

%	Percent
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATIII	Anti-thrombin III
AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the curve from time 0 to the last measurable concentration
$AUC_{0\text{-}t}$	Area under the curve-time curve
CAD	Coronary artery disease
CB2679d	Recombinant Factor IX variant
CBC	Complete blood count
CD4	Cluster of differentiation 4
CFR	Code of Federal Regulations
C_{max}	Concentration maximum
CMO	Chief Medical Officer
Cr	Creatinine
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
F1+2	Prothrombin fragment 1+2
FDA	Food and Drug Administration
FVIII	Factor VIII

FVIIIa	Factor VIII activated
FIX	Factor IX
FIXa	Factor IX activated
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GS	Gilbert's syndrome
Hr	Hour
HTC	Hemophilia Treatment Centre
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMT	Immunomodulatory therapy
IND	Investigational New Drug Application
IP	Investigational product
IRB	Institutional Review Board
IU	International unit
IV	Intravenous
Kg	Kilogram
L	Liter
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
Min	Minute
NCT	National Clinical Trial
OTC	Over-the-counter
PD	Pharmacodynamics
pdFIX	Plasma-derived factor IX

PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QoL	Quality of life
r	Recombinant
rFIX	Recombinant factor IX
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SQ	Subcutaneous
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
$T_{1/2}$	Half-life
TAT	Thrombin-antithrombin complexes
TBIL	Total bilirubin level
TE	Thromboembolic event
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time that studied drug is present at the maximum concentration in serum
µmol	Micromole
ULN	Upper limit of normal
US	United States
VTE	Venous thromboembolic event
WFH	World Federation of Hemophilia

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CB2679d DLZ-201 VERSION 1.0

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title of Study: Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d in adult subjects with hemophilia B.

Primary Objective: To evaluate the dose required to achieve a steady-state of >12% factor IX (FIX) levels.

Secondary Objectives:

- To determine the pharmacokinetics (PK) of subcutaneous (SQ) regimens of CB 2679d.
- To determine the pharmacodynamics (PD) of SQ regimens of CB 2679d.
- To evaluate the levels of thrombogenicity markers of SQ regimens of CB 2679d.
- To evaluate for evidence of the development of antibodies to CB2679d and to determine if these are neutralizing antibodies.
- To monitor and evaluate safety parameters of SQ regimens of CB2679d.

Study Population: Five male subjects, aged 18 or older, with confirmed diagnosis of severe congenital hemophilia B (<2% FIX level).

Phase of Development: Phase 2b

Description of Sites: Single center study.

Study Duration: Approximately 6 months.

Participant Duration: The duration of treatment for each subject is approximately 6 weeks.

Screening: Up to 4 weeks.

Study Drug Administration: SQ prophylaxis treatment regimens over a 6-week period with the goal to achieve steady-state levels above 12% FIX activity when dosed daily, every second day or every third day.

Note: Where interruptions to study drug dosing days occur, study duration may be extended to incorporate full dosing schedule.

Follow-up: 30 days (± 2 days) after last dose for PK/PD/safety follow-up.

Study Methodology

This single-center, open-label Phase 2b study will evaluate the PK, PD, efficacy and safety parameters of SQ prophylaxis treatment regimens with CB2679d in adult subjects with hemophilia B. The study will enroll and dose subcutaneously, a total of 5 adult male subjects with severe congenital hemophilia B.

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

At enrollment, subjects will be provided with a diary in which they will be instructed to record any adverse events (AEs) and concomitant medication.

After the initial intravenous (IV) dose of CB2679d, and subsequent SQ doses, the following will be monitored daily: injection site reaction, any AEs the subject may experience, and any bleeding episodes (location, inciting event if not spontaneous, and treatment administered).

IV/SQ Study Drug Administration and Assessments:

Initial IV Load Dose Followed by Daily SQ study drug administration

Part 1; Weeks 1 and 2: The subject will receive an IV loading dose of 70 IU/kg followed 30 minutes later by a SQ dose of 140 IU/kg. Daily SQ doses of 140 IU/kg will be administered until Day 14 (14 total SQ doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 30 minutes later prior to the SQ dose. Subsequent PK, PD and safety assessments will be performed 7 hours post-SQ dose on Day 1, Day 2 at hour 24 post-SQ dose and pre-dose on days 5, 8, 11 and 14.

Every Second Day SQ study drug administration

Part 2; Week 3: The subject will receive a SQ dose every second day of 280 IU/kg, starting on Day 15 until Day 21 (total of 4 SQ doses). On Day 15 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD and safety assessments will be performed on Day 16 at hour 24 and pre-dose on days 17, 19 and 21.

Every Third Day SQ study drug administration

Part 3; Weeks 4 and 5: The subject will receive a SQ dose every third day of 420 IU/kg, starting on Day 23 until Day 32 (total of 4 SQ doses). On days 23 and 32 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD, and safety assessments will be performed at Day 24 at hour 24 and pre-dose on days 26, and 29.

Washout Period

PK, PD, and safety assessments will be done on Days 33, 34, 35, 37 and 38. Daily FIX activity levels will be measured, except on Day 36, unless FIX activity level is known to be < 5%, as measured by local laboratory.

An End of Study visit will occur 30 days (± 2 days) after the last dose of study drug.

Treatment of a bleeding episode: Subjects will self-administer their currently prescribed FIX replacement product for treatment of any spontaneous or traumatic bleed that occurs while on study drug. If treatment for a breakthrough spontaneous bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event; treatment dose administered; and arrange for an urgent follow-up visit to the study site for additional evaluation and laboratory testing, if needed.

Dose interruption: SQ study drug injections will be interrupted if any of the following occurs: a thrombotic event; clinical evidence of inhibitor formation; or laboratory results suggesting a high titer antibody may be developing; trough activity levels >80% or peak

levels >175%, where subsequent dosing will be determined in consultation with the sponsor.

Surgery: If there is an urgent need for a surgical procedure or an event requiring extended (>48 hours) hospitalization, a FIX activity level will be urgently obtained and measured prior to the event, and the PI will confer with the Sponsor Medical representative regarding the need for any additional treatment and whether study drug requires interruption.

***Measurements*:**

PK, PD, and safety assessments: CB2679d activity levels, as well as fibrinogen, D-dimer, prothrombin fragment 1+2 (F1+2), and thrombin-antithrombin complexes (TAT). PT and aPTT will be measured at screening and end of study visit only.

Immunogenicity assays: Specimens for immunogenicity testing (antibody to CB 2679d, wild-type FIX cross reactivity, and neutralizing activity) will be drawn at screening, on days 1, 8, 15, 23, 32, and end of study.

If the FIX activity level decreases unexpectedly by more than 25%, ie, IU/dL, as measured by the central or local lab, CB2679d activity levels will be drawn for analysis within 24 hours and immediately sent to the central laboratory. Specimens for fibrinogen, D-dimer, F1+2, and TAT and immunogenicity testing will also be drawn.

Number of planned subjects: 5

Trial population:

***Inclusion criteria*:**

1. Confirmed diagnosis of severe (<2%) congenital hemophilia B.
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. (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*:**

1. Patients with a history or a family history of FIX inhibitors.
2. Positive antibody to FIX detected by central laboratory at screening.
3. Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 3-half-lives, whichever is longer, or absence of clinical effect.
4. History of clinically relevant coagulation disorders other than congenital hemophilia B including Factor V Leiden or other identified activated Protein C resistance.
5. Platelet count <100,000 based on screening laboratory assessments.
6. 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.
7. Known or suspected allergy to trial product or related products.

8. Known absolute cluster of differentiation 4 (CD4) count <200 cells/µL.
9. Receiving immunomodulatory therapy (IMT).
10. Compromised hepatic or renal function:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal (ULN)
    - Total bilirubin level (TBIL) ≥2 mg/dL (>35 µmol /L) unless there is a known history of Gilbert's syndrome (GS)
    - Serum albumin ≤ the lower limit of normal (LLN)
    - Serum creatinine (Cr) level >1.25 x 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.

Investigational product, dose, and mode of administration:

Investigational Product: Recombinant FIX variant; CB2679d
Dosage and mode of administration:
Part 1: Weeks 1 and 2 (Days 1-14): IV loading dose of 70 IU/kg followed 30 minutes later with 140 IU/kg SQ administration daily x 14 (14 total doses).
Part 2: Week 3 (Days 15, 17, 19 and 21): 280 IU/kg, SQ administration every second day (4 total doses).
Part 3: Weeks 4 and 5 (Days 23, 26, 29, 32): 420 IU/kg SQ administration every third day (4 total doses)

Reference therapy: None

Concomitant Medications: In the event of spontaneous or traumatic bleeding, treatment for a bleeding episode will be permitted using the subject's current treatment regimen.

Efficacy and Safety Evaluations

Primary endpoints:

- Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing.

Secondary endpoints:

- Safety assessments: Occurrence of antibody formation resulting in a decreased endogenous level of FIX; occurrence of a clinical thrombotic event not attributable to another cause.
- Occurrence of a conformed antibody response with high titer to CB2679d and whether it is inhibitory and cross-reactive to wild-type FIX.
- Change in CB2679d activity levels, and from pre-dose.
- Clinically significant levels of thrombogenicity markers resulting from SQ administration of CB 2679d.
- Feasibility of using an adjusted-dose SQ prophylaxis treatment regimen clinically.

Statistics

Primary Analysis Plan:

Appropriate descriptive statistics of all measured parameters will be reported, including 95% confidence intervals.

The dose required to achieve steady-state levels >12%, >30% and >50% will be reported for daily, every second day or every third day dosing, including 95% confidence intervals.

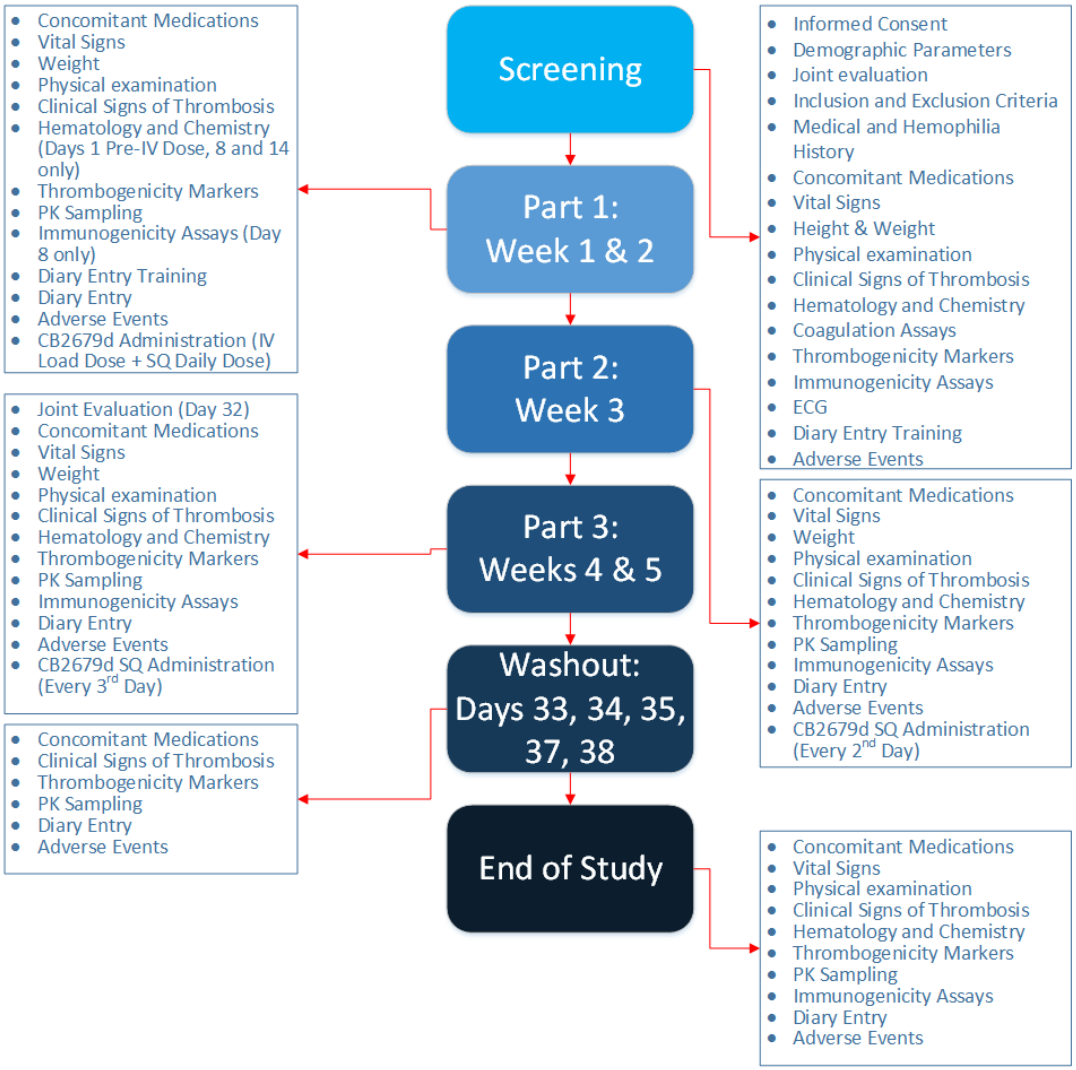
Rationale for Number of Subjects:

5 subjects will provide guidance on dose required to achieve steady-state activity >12%, 30% or 50% and starting SQ dose for subsequent studies.

Name of sponsor: Catalyst Biosciences

1.2 SCHEMA

Figure 1. Schematic of Study Design



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1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Part 1: Weeks 1 and 2

Study Period	**Screening**	**Weeks 1 and 2 (Days 1 – 14)**				
Study Day	Day -28 to -1	Day 1, IV Pre-dose (- 5 min)	Day 1, SQ dose 30 min Post IV	Day 1, Hour 7 (± 1 hour)	Day 2, Hour 24 (± 1 hour)	Days 5, 8, 11, 14[7] Pre-dose (- 5 min)
Informed Consent	X					
Demographic Parameters	X					
Joint Evaluation[1]	X					
Inclusion and Exclusion Criteria	X					
Medical and Hemophilia History[2]	X					
Concomitant Medications	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Height (screening only) & Weight	X	X				
Physical Examination[2]	X	X	X	X	X	X
Clinical Signs of Thrombosis[3]	X	X	X	X	X	X
Hematology and Chemistry[4]	X	X				X (Days 8 and 14 only)
Coagulation Assays[5]	X					
Thrombogenicity markers[5]	X	X	X	X	X	X
Pharmacokinetic (PK) sampling[5]		X	X	X	X	X
Immunogenicity assays[5]	X					X (Day 8 only)
ECG	X					
Diary entry training[6]		X				
Diary entry of any bleeding episodes, AEs, injection site		←----------	----------	----------	----------	----------→
Adverse Events	X	X	X	X	X	X
CB 2679d administration[7]				←----------	----------	----------→

1. As per Standard of Care at hemophilia treatment center.
2. Complete evaluation at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit.
3. **Clinical Signs of Thrombosis** per protocol
4. Local Laboratory: **Hematology** - CBC and platelet count. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine.
5. Central Laboratory: **Coagulation assays** – PT and aPTT. **Thrombogenicity markers** – Fibrinogen, D-dimer, F1.2, and TAT. **Pharmacokinetics** – CB 2679d activity. **Immunogenicity assays** – to BeneFIX and CB 2679d.
6. Diary entry training consists of investigational drug administration, injection site assessment, adverse events, any bleeding episodes & treatment.
7. IV load dose (70 IU/kg) followed by SQ dose (140 IU/kg) 30 minutes (+ 30 mins) after. **Daily SQ** (140 IU/kg) dosing until Day 14 (14 total SQ doses).
8. Post dose assessments performed 7 hours (± 1 hour) after SQ dose

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Part 2. Week 3

Study Period	**Week 3 (Days 15 – 21)**					
Study Day/Hour	Day 15, Pre-dose (- 5 min)	Day 15, Hour 7 (± 1 hour)	Day 16, Hour 24 (± 1 hour)	Day 17, Pre-dose (- 5 min)	Day 19, Pre-dose (- 5 min)	Day 21, Pre-dose (- 5 min)
Concomitant Medications	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Weight	X					X
Physical Examination[1]	X	X	X	X	X	X
Clinical Signs of Thrombosis[2]	X	X	X	X	X	X
Hematology and Chemistry[3]						X
Thrombogenicity markers[4]	X	X	X	X	X	X
Pharmacokinetic (PK) sampling[4]	X	X	X	X	X	X
Immunogenicity assays[4]	X					
Diary entry of any bleeding episodes, AEs, injection site assessment[5]	←----------					----------→
Adverse Events	X	X	X	X	X	X
CB2679d administration[6]		←----------				----------→

1. Targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit.
2. **Clinical Signs of Thrombosis:** per protocol
3. Local Laboratory: **Hematology** - CBC and platelet count. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine.
4. Central Laboratory: **Thrombogenicity markers** – Fibrinogen, D-dimer, F1.2, and TAT. **Pharmacokinetics** – CB 2679d activity. **Immunogenicity assays** – to BeneFIX and CB 2679d.
5. Diary entry consists of investigational drug administration, injection site assessment, adverse events, any bleeding episodes & treatment.
6. **Dosing every second day SQ (280 IU/kg) starting Day 15 until Day 21 (4 total doses).**

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Part 3. Weeks 4 and 5, Washout, Unscheduled and End of Study

Study Period	**Weeks 4 and 5 (Days 23-32)**							**WASH-OUT**	**Un-scheduled**	**End of Study[9]**
Study Day/Hour	Day 23, Pre-dose (- 5 min)	Day 23, Hour 7 (± 1 hr)	Day 24, Hour 24 (± 1 hr)	Day 26, Pre-dose (- 5 min)	Day 29, Pre-dose (- 5 min)	Day 32, Pre-dose (- 5 min)	Day 32, Hour 7 (± 1 hr)	Days 33, 34, 35, 37, 38[8]		
Joint evaluation[1]							X			
Medical and Hemophilia History[2]									X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X		X	X
Weight	X								X	
Physical Examination[2]	X		X	X	X	X	X		X	X
Clinical Signs of Thrombosis[3]	X	X	X	X	X	X	X	X	X	X
Hematology and Chemistry[4]	X						X		X	X
Coagulation Assays[5]										X
Thrombogenicity markers[5]	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic (PK) sampling[5]	X	X	X	X	X	X	X	X	X	X
Immunogenicity assays[5]	X					X			X	X
Diary entry of any bleeding episodes, AEs, injection site assessment[6]	←----------→									
Adverse Events	X	X	X	X	X	X	X	X	X	X
CB2679d administration[7]		←----------→								

1. As per Standard of Care at hemophilia treatment center.
2. Targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit.
3. **Clinical Signs of Thrombosis** per protocol
4. Local Laboratory: **Hematology** - CBC and platelet count. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine.
5. Central Laboratory: **Coagulation assays** – PT and aPTT. **Thrombogenicity markers** – Fibrinogen, D-dimer, F1.2, and TAT. **Pharmacokinetics** – CB 2679d activity. **Immunogenicity assays** – to BeneFIX and CB 2679d.
6. Diary entry training consists of investigational drug administration, injection site assessment, adverse events, any bleeding episodes & treatment.
7. **Dosing every third day SQ (420 IU/kg) starting Day 23 until Day 32 (4 total doses).**
8. Daily FIX activity levels needed (except Day 36), unless FIX activity level known to be < 5%, as per local lab.
9. End of Study Visit will occur 30 ± 2 days after the last dose.

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2. INTRODUCTION

2.1 STUDY RATIONALE

The rapid clearance of FIX necessitates frequent intravenous (IV) administrations to achieve effective prophylaxis for patients with hemophilia B. Subcutaneous (SQ) administration, a preferred administration route, has historically been limited by low bioavailability and potency. CB2679d, formerly known as ISU304, was developed using a rational design approach to be the next-generation SQ coagulation prophylactic FIX therapy.

2.2 BACKGROUND

Hemophilia B, or sometimes referred to as Christmas disease, is a hereditary X chromosomal-linked recessive bleeding disorder caused by Factor IX (FIX) deficiency.[1] Hemophilia B, especially in severe phenotypes, is characterized by frequent and spontaneous bleeding[1,2] into joints, muscles and body cavities, and can lead to arthropathy with progressive cartilage damage, chronic pain, disability, diminished quality of life (QoL) and ultimately joint destruction.[1] Disease classification of mild (factor activity >5 % and <40%), moderate (1 to 5%) or severe phenotype (<1%) is based on residual plasma FIX levels.[3,4] The number of patients with mild, moderate and severe phenotypes of hemophilia B is not well established, however community studies have estimated that 60–70% of patients with hemophilia B have a moderate or severe form.[5-7] Historically, treatment for hemophilia B has been on demand, that is, clotting FIX replacement therapy administered when a hemorrhage occurs or before a surgical procedure.[8] Currently, the standard of care treatment for hemophilia B is FIX replacement therapy administered prophylactically, at regular intervals to maintain FIX levels greater than 1%, to prevent the onset of bleeding episodes.[8-11] Routine prophylaxis therapy has been demonstrated to substantially reduce the frequency of bleeding episodes[11-13], prevent joint diseases[11,14] and even reduce the risk of death.[15,15] Treatment with FIX products, initially purified from plasma-derived factor IX product (pdFIX) and subsequently as recombinant human FIX (rFIX), require 2 or 3 IV infusions per week to achieve effective bleeding prevention due mostly to the half-life ($t_{1/2}$)[17-20], rFIX has a $t_{1/2}$ of approximately 18 hours.[21] High frequency of infusions can be a major barrier to adhering to the prescribed prophylactic regimen, especially in pediatric patients; in those with poor venous access[22-24]; and in those concerned about the associated complications of infection and thrombosis.[25-27] A FIX product with a longer $t_{1/2}$ to prolong the protective hemostatic effect, would potentially enable fewer injections, thereby reducing the need for repeated venous access. This could potentially improve the

acceptance of prophylactic regimens by patients with hemophilia. SQ administration is the preferred route of administration for convenience and less pain but has been limited historically by low bioavailability and potency of the marketed FIX products.[28]

2.2.1 Rationale for Prophylaxis with SQ Administration of FIX

There is currently no cure for hemophilia.[29] The prevention of bleeding episodes in hemophilia patients requires life-long prophylaxis.[29,30] Due to the short $t_{1/2}$ of rFIX, prophylaxis and treatment for bleeding episodes requires frequent IV dosing (2-3 IV infusions per week).[17-21] IV dosing often requires a medical professional or family member to perform the venipuncture, making home prophylaxis cumbersome, particularly for pediatric patients.[30,31] Other challenges include patient adherence, and reliable IV access.[32,33] 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.[32]

SQ administration presents a major advantage over IV administration because it enables at-home injection, improves quality of life, and reduces health care costs.[33] While home IV administration has been essential to the provision of comprehensive hemophilia care, it nonetheless remains a significant barrier.[32] SQ 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.[33]

CB2679d, a novel rFIX variant, is being developed by Catalyst Biosciences (the Sponsor) to address the unmet need for medical management of hemophilia B patients. CB2679d was developed using a rational design approach with three-point mutations in two loops within the FIX protein: (1) arginine-318 is transformed into tyrosine (Arg318Tyr) located in 'loop-150'(also known as the autolysis loop), can stabilize the activation structure of activated FIX (FIXa), as well as directly interact with factor X (FX), a substrate of FIX and anti-thrombin III (ATIII), a key inhibitor; (2) arginine-338 is transformed into glutamic acid (Arg338Glu); and (3) threonine-343 is transformed into arginine (Thr343Arg), both located in 'loop-170', can significantly enhance affinity to the cofactor VIII and stabilize FIXa. These mutations in the molecular structure enable CB2679d to increase catalytic activity (CB2679d has demonstrated 3 times the catalytic efficiency to factor X [substrate]); increase affinity for activated factor VIII (FVIIIa) (CB2679d has a 10 times higher affinity to cofactor FVIIIa) and improve resistance to inhibition by ATIII (CB2679d has 15 times the resistivity to inhibitor ATIII compared to wild-type FIX), with a resultant 20-fold enhanced potency in vitro (clotting activity) and in vivo (tail clip model) and 8-fold increased duration of aPTT activity in vivo compared

with recombinant wild-type FIX dosed at the same mass.[34-35] The SQ half-life in mini-pig studies was found to be 33 hours and the bioavailability was 20-42%.[36]

These qualities are expected to prolong the interval between doses, improve convenience of treatment, and facilitate use of the product for bleeding prophylaxis.

2.2.2 Experience with CB2679d in the Clinic

To date, the safety, PK, and PD of CB2679d, is being evaluated in an open-label IV to SQ cross-over clinical study (NCT03186677), which will recruit 12 adult subjects with hemophilia B (all male).[37,38] The trial design is provided below. IV PK (antigen and activity) was sampled at pre-dose, 0, 0.25, 0.5, 1, 3, 6, 9, 24, 48 and 72 hours. SQ PK was sampled at pre-dose, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours. Cohort 5 has PK sampled before each injection, 6 hours after first and 6th injection and 24 hours after 6th daily injection. Hematology, chemistry and coagulation was measured at Seoul Clinical Laboratories (Yongin-si, South Korea). FIX antigen and FIX activity, anti-drug antibody to BeneFIX® and CB2679d and neutralizing antibody were measured at Haematologic Technologies Inc (Essex Junction, VT). A safety follow-up was done 2 weeks after last visit. FIX antigen was measured using VisuLize™ Factor IX Antigen KitAG (Affinity Biologicals, Inc, Ancaster, ON, Canada) and FIX activity was measured using a one-stage clotting assay using ACL TOP 700 and Instrumentation Laboratories (Bedford, MA) reagents. The calculation of area under the curve (AUC) was based on the trapezoidal rule. To calculate the additional AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}inf}$), the log-linear regression line for the last three-time points was fit and extrapolated to the x-intercept. The calculation of $t_{1/2}$ was based on the use of Demitasse 2000 (version 1.1.3, M. Lee, 2000) which uses an iterative piecewise fitting algorithm based on a robust (M-regression) log-linear model. All activity data were adjusted for baseline before analysis, assuming exponential falloff after IV administration and a $t_{1/2}$ of 20 hours. Bioavailability was calculated from the AUC-time curve ($AUC_{0\text{-}t}$) for the IV and SQ data using FIX activity data.

Subject safety was reviewed by an external Data Safety Monitoring Board and also an internal Data Monitoring Committee.

Interim results showed PK and activity of CB2679d as 22-fold greater potency over BeneFIX® and longer mean residence time. Single-dose bioavailability was 18.2-23.6%, SQ beta $t_{1/2}$ was 66-103 hours and time that CD2679d is present at the maximum concentration in serum (T_{max}) was 6-24 hours. One subject reported transient fever and a mild SQ injection site reaction. Cohort 4 was omitted as sufficient data had been gained from single dosing SQ in Cohorts 2 and 3. The SQ dose in Cohort 5 was reduced from 300 IU/kg to 150 IU/kg daily. PK and activity

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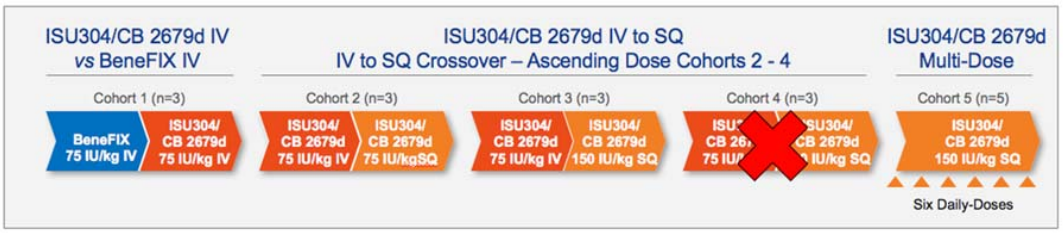
levels after 6 daily doses in 5 subjects reached a median of 15.7% [interquartile range 14.9% to 16.6%] Four of 5 subjects had levels above 12%. Half-life was 63.2 hours [interquartile range 60.2 to 64.0 hours]. The interim study results support the aim of achieving normal or high mild hemophilia FIX levels in individuals with hemophilia B with repeated SQ dosing. Mild pain, erythema and redness was reported at the injection site in initial injections and not a later injection. One subject reported these adverse events to be moderate for the first 2 injections and mild thereafter. An intravenous loading dose has been added in this study to see if it eliminates these local adverse events as they are believed to be due to low FIX levels because of washout of prior treatment.



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3. OBJECTIVES

3.1 PRIMARY

The primary objective is:

- To evaluate the dose required to achieve steady-state FIX levels >12% of SQ prophylaxis treatment regimens of CB2679d, in adult subjects with hemophilia B.

3.2 SECONDARY

The secondary objectives are:

- To determine the PK of SQ regimens of CB2679d.
- To determine the PD of SQ regimens of CB2679d.
- To evaluate the levels of thrombogenicity markers of SQ regimens of CB2679d.
- To evaluate for evidence of the development of antibodies to CB2679d and to determine if these are neutralizing antibodies.
- To monitor and evaluate safety parameters of SQ regimens of CB2679d.

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4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, open-label Phase 2b study designed to evaluate the PK, PD, efficacy and safety of SQ prophylaxis treatment regimens with CB2679d in adult subjects with hemophilia B. It is an open-label study, so subjects and members of the clinical study team will not be blinded to treatment. It is estimated that it will take approximately 6 months from when the study opens enrollment until completion of last patient last visit. The study will enroll a total of 5 adult male subjects with severe congenital hemophilia B. Participants will be given SQ prophylaxis CB2679d regimens over a 6-week period, with the goal to achieve steady-state levels above 12% FIX activity when dosed daily, every second day or every third day.

Each subject will participate for approximately 6-weeks of SQ CB2679d drug administrations:

Part 1; Weeks 1 and 2: Each participant will receive an IV loading dose of 70 IU/kg followed 30 minutes later by a SQ dose of 140 IU/kg. **Daily** SQ doses of 140 IU/kg will be administered until Day 14 (14 total SQ doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 30 minutes later prior to the SQ dose. Subsequent PK, PD and safety assessments will be performed 7 hours post-SQ dose on Day 1, Day 2 at hour 24 post-SQ dose and pre-dose on days 5, 8, 11 and 14.

Part 2; Week 3: Each participant will receive a SQ dose **every second day** of 280 IU/kg, starting on Day 15 until Day 21 (total of 4 SQ doses). On Day 15 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD and safety assessments will be performed on Day 16 at hour 24 and pre-dose on days 17, 19 and 21.

Part 3; Weeks 4 and 5: Each participant will receive a SQ dose **every third day** of 420 IU/kg, starting on Day 23 until Day 32 (total of 4 SQ doses). On days 23 and 32 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD, and safety assessments will be performed at Day 24 at hour 24 and pre-dose on days 26, and 29.

Washout Period

PK, PD, and safety assessments will be done on Days 33, 34, 35, 37 and 38. Daily FIX activity levels will be measured, except on Day 36, unless FIX activity level is known to be < 5%, as measured by local laboratory.

An End of Study visit will occur 30 days (± 2 days) after the last dose of study drug.

Subjects will sign an ICF at the Screening Visit, prior to any study procedures. Eligibility to participate in the study will be determined by inclusion and exclusion criteria from medical history, hemophilia history, laboratory investigations and ECG. The screening period duration may be up to 4 weeks.

At enrollment, subjects will receive training and diary entry of self-administered investigational drug administration & injection site assessment, bleeding episodes & treatment, evaluation & entry of AEs.

Treatment of a spontaneous or traumatic bleeding episode: Subjects will use their current prescribed treatment regimen for any spontaneous or traumatic bleed that occurs while on study drug. If treatment for a spontaneous or traumatic bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event, treatment dose administered, and determine follow-up plans for that event including whether to arrange for a blood specimen to be drawn (if feasible) before further administration of either study drug or the current prescribed treatment regimen used. Decision whether to continue daily study drug administration will also be determined by the clinical study team after discussion with the Sponsor.

Dose interruption: SQ study drug injections will be interrupted if any of the following occurs: a thrombotic event; clinical evidence of inhibitor formation; or laboratory results suggesting a high titer antibody may be developing; trough activity levels >80% or peak levels >175% where subsequent dosing will be determined in consultation with the sponsor.

Surgery: If there is an urgent need for a surgical procedure or an event requiring extended (>48 hours) hospitalization, a FIX activity level will be urgently obtained and measured prior to the event, and the PI will confer with the Sponsor Medical representative regarding the need for any additional treatment and whether study drug requires interruption.

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Measurements:

PK, PD, and safety assessments: CB2679d activity levels, as well as fibrinogen, D-dimer, F1+2, and TAT. PT and aPTT will be measured at screening and end of study visit only.

Immunogenicity assays: Specimens for immunogenicity testing (antibody to CB 2679d, wild-type FIX cross reactivity, and neutralizing activity) will be drawn at screening, pre-dose on days 1, 8, 15, 23, 32 and end of study.

If the FIX activity level decreases unexpectedly by more than 25%, ie, IU/dL, as measured by the central or local lab, CB2679d activity levels will be drawn for analysis within 24 hours and immediately sent to the central laboratory. Specimens for fibrinogen, D-dimer, F1+2, and TAT and immunogenicity testing will also be drawn.

4.2 END OF STUDY DEFINITION

The duration of treatment for each subject is approximately 6 weeks.

Up to 4 weeks for screening period; SQ prophylaxis treatment regimens over a 6-week period with the goal to achieve steady-state levels above 12% FIX activity when dosed daily, every second day or every third day.

Where interruptions to study drug dosing days occur, study duration may be extended to incorporate full dosing schedule.

The end of study visit will be 30 days ± 2 days after the last dose of study drug treatment.

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5. STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Confirmed diagnosis of severe (<2%) congenital hemophilia B.
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. (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. Patients with a history or a family history of FIX inhibitors.
2. Positive antibody to FIX detected by central laboratory at screening.
3. Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 3-half-lives, whichever is longer, or absence of clinical effect.
4. History of clinically relevant coagulation disorders other than congenital hemophilia B including Factor V Leiden or other identified activated Protein C resistance.
5. Platelet count <100,000 based on screening laboratory assessments.
6. 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.
7. Known or suspected allergy to trial product or related products.
8. Known absolute CD4 count <200 cells/µL.
9. Receiving IMT.
10. Compromised hepatic or renal function:
    - ALT and AST levels ≥5 x ULN
    - TBIL ≥2 mg/dL (>35 µmol /L) unless there is a known history of GS
    - Serum albumin ≤ LLN
    - Cr level >1.25 x 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 LIFESTYLE CONSIDERATIONS

There are no specific lifestyle considerations.

5.4 SCREEN FAILURES

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

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6. STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 Study Intervention Description

Description and Composition of the Drug Product

Recombinant Factor IX variant; CB2679d, formerly known as ISU304, will be provided as a powder for injection, at a 2.0 mg/vial dosage strength. The drug product is supplied in a 5-mL vial that is sealed with a 20mm lyophile stopper and 20mm aluminum over-seal. CB2679d is supplied in vials which contain excipients (stabilizer, buffer, etc.) and packaged in a lyophilized form. Before lyophilization, each vial contains 1.42 mg/mL of CB2679d drug substance is filled with 1.4 mL of formulation buffer. The lyophilized drug product will be reconstituted for SQ injection.

6.1.2 Dosing and Administration

This is an open-label study. Each subject will receive the study drug:

CB2679d loading dose of 70 IU/kg IV, followed 30 minutes later with a 140 IU/kg, SQ administration daily x 14 (total 1 IV dose and 14 SQ doses); then a 280 IU/kg, SQ administration every second day, starting on Day 15 until Day 21 (total 4 SQ doses); then a 420 IU/kg SQ every third day, starting on Day 23 until Day 32 (total of 4 SQ doses).

6.1.2.1 Guidelines for Treatment Interruption

CB2679d SQ study injections will be interrupted, as needed, when:

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

Cb2679d SQ study injections may be interrupted, as needed, when:

- A spontaneous bleeding event occurs

- A traumatic bleeding event occurs

Subjects will use their current treatment regimen for any spontaneous or traumatic bleed that occurs while on study. A spontaneous bleeding episode is defined as one that is precipitated by normal activities of daily living (ADL). If treatment for a spontaneous or traumatic bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event; treatment dose administered; and determine follow-up plans for that event, including to arrange for a blood specimen to be drawn (if feasible). This information will also be recorded in the subjects' diary.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and Accountability

Upon receipt of the CB2679d shipment, the pharmacist, or a designee, will conduct an inventory and return an acknowledgement that all IP was received refrigerated and undamaged, thereby maintaining the Good Manufacturing Practice (GMP) status of the product during shipment.

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

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of the 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 IPs 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.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of 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 (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the 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. Site staff will instruct subjects on the storage requirements for take home medications including how to report temperature excursions.

6.2.3 Preparation

CB2679d will be provided as a powder for injection, at a 2.0 mg/vial dosage strength, and is supplied in a 5-mL vial. The lyophilized drug product will be reconstituted with 1.4 mL sterile water for SQ injection.

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

At the study site, the CB2679d SQ dose will be prepared and administered by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

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6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

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

6.4 STUDY INTERVENTION COMPLIANCE

Reasonable efforts should be made to ensure that study drug administration is administered according to the schedule. However, if an unavoidable disruption of the administration occurs, and a dose is not administered on the assigned day then the subject should take the dose as soon as possible. In the event that the subject remembers more than 2 days late, then the subject must contact the research site for instructions on how to proceed.

6.5 CONCOMITANT THERAPY

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

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

There are no concomitant medication restrictions.

If an individual has previously been enrolled on a clinical trial evaluating a treatment (as specified in exclusion criteria #3) in clinical investigation he will be permitted to enroll onto this study, provided it is greater than 30 days since exposure to that study drug, or 3-half-lives, whichever is longer, or absence of clinical effect.

The following medications will be permitted during the study:

- In the event of spontaneous or traumatic bleeding, treatment for a spontaneous or traumatic bleeding episode will be permitted using the subject's current prescribed treatment regimen which could be BeneFIX® or Rixubis®.

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7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

The reason for participant discontinuation or withdrawal from the study and the date will be recorded on the eCRF.

Replacement of a subject occurs for the following reason:

- If a subject does not complete at least 2 doses of every third day SQ dosing as defined in the protocol, another subject may be enrolled.

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

7.2 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.

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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 will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

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

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8. STUDY ASSESSMENTAND PROCEDURES

8.1 STUDY PROCEDURES

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

8.1.1 Screening

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

- Informed consent
- Demographic parameters
- Joint evaluation (as per SOC at hemophilia treatment center)
- Inclusion and Exclusion Criteria review
- Medical and hemophilia history
- Concomitant medications
- Vital signs
- Height (screening only) and weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry: (see Footnote 4 for **Table 1** in **Section 1.3**, **Schedule of Activities**)
- Coagulation assays: PT and aPTT (both at screening and end of study visit only)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- Immunogenicity assays: antibody to CB 2679d and BeneFIX
- ECG
- Adverse events

8.1.2 Part 1, Weeks 1 and 2 (Duration 7 days)

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

8.1.2.1 Day 1 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 for **Table 1** in **Section 1.3**, **Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Study Subject training on drug administration and injection site assessment
- Review of diary entry of injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.2.2 CB2679d administration (Every day from Day 1 to Day 14)

- Subjects will receive a loading **IV dose of 70 IU/kg**, followed 30 minutes later with a **140 IU/kg SQ dose** of CB2679d
- Subjects will then administer a **140 IU/kg daily SQ dose** of CB2679d
- SQ CB2679d should be self-administered by subjects at approximately the same time every day.

8.1.2.3 Day 1 at SQ dose administration (30 minutes post-IV dose)

Blood will be collected at 30-minutes post-IV dose for the following evaluations:

- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity

Other evaluations will include:

- Concomitant medications
- Vital signs
- Physical examination
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.2.4 Day 1 Post-SQ dose (Hour 7) and Day 2 Post-SQ dose (Hour 24) evaluations

Blood will be collected at hour 7 post-dose on Day 1 and hour 24 post-dose on Day 2 for the following evaluations:

- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity

Other evaluations will include:

- Concomitant medications
- Vital sign
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events (from Hr 6 to 24 hours)

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8.1.2.5 Day 5, 8, 11 and 14 Pre-dose evaluations

Blood will be collected at -5 minutes pre-dose for the following evaluations:

- Days 8 and 14 only: Hematology and chemistry (see Footnote 4 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- On Day 8 only: Immunogenicity assays to BeneFIX and CB2679d

Other evaluations will include:

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3 Part 2, Week 3 (Duration: 7 days)

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

8.1.3.1 CB2679d administration (Day 15, Day 17, Day 19 and Day 21)

- Subjects will receive a 280 IU/kg SQ dose of CB2679d every second day, starting on Day 15 to Day 21 (total of 4 SQ doses).
- SQ CB2679d should be self-administered by subjects at approximately the same time every second day.

8.1.3.2 Day 15 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Immunogenicity assays to BeneFIX and CB2679d
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3.3 Day 15 Post-dose (Hour 7), Day 16 Post-dose (Hour 24), Day 17 and Day 19 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3.4 Day 21 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Weight

- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 2** in **Section 1.3, Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.4 Part 3, Weeks 4 and 5 (Duration: 14 days)

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

8.1.4.1 CB2679d administration (Day 23, Day 26, Day 29, and Day 32)

- Subjects will receive a **420 IU/kg SQ dose** of CB2679d **every third day**, starting on Day 23 until Day 32 (total of 4 SQ doses)
- SQ CB2679d should be self-administered by subjects at approximately the same time of day every third day.

8.1.4.2 Day 23 and Day 32 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Day 23 only: Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Day 23 only: Hematology and chemistry (see Footnote 4 for **Table 3** in **Section 1.3, Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity

- Immunogenicity assays to BeneFIX and CB2679d
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.4.3 Day 23 Post-dose evaluations (Hour 7)

- Concomitant medications
- Vital signs
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.4.4 Day 24 Post-dose (Hour 24) and Day 26 and Day 29 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.4.5 Day 32 Post-dose evaluations (Hour 7)

- Joint evaluation (as per SOC at hemophilia treatment center)
- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 for **Table 3** in **Section 1.3, Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.5 Washout Period, Unscheduled Visits and End of Study evaluations

Please refer to **Section 1.3**, **Schedule of Activities (SOA)** and specifically **Table 3** for the sequence of events that should occur during the washout period and end of study process.

8.1.5.1 Washout period evaluations (Day 33, 34, 35, 37 and 38)

- Concomitant medications
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

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8.1.5.2 Unscheduled visit evaluations

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

- Medical and Hemophilia History
- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 3 for **Table 1** in **Section 1.3, Schedule of Activities**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: CB2679d activity
- Immunogenicity assays to BeneFIX and CB2679d
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.5.2 End of Study visit evaluations (30 days after last dose)

The following procedures will be performed:

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 for **Table 3** in **Section 1.3, Schedule of Activities**)
- Coagulation assays: PT and aPTT (both at screening and end of study visit only)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT

- PK: CB2679d activity
- Immunogenicity assays to BeneFIX and CB2679d
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.2 STUDY ASSESSMENTS

8.2.1 Efficacy Assessments

Subjects will be asked to record daily SQ injections, any injection site reactions, any AEs experienced, and all spontaneous or traumatic bleeding episodes and concomitant medications administered into the Diary, including (but not limited to) the following:

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

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

Investigators will document:

- Subject demographics (sex, age, race and ethnicity) will be recorded at the screening visit.
- All ongoing conditions and relevant medical and hemophilia history (including all major hospitalizations and surgeries), as well as the subject's current medical status will be recorded at the screening visit.
- Diagnosis of severe congenital hemophilia B will be documented including the frequency of spontaneous or traumatic bleeding episodes in the past 6 months and in the past 50 days.

- Notation will be made regarding history of orthopedic procedures including joint aspiration, synovectomy, fusion, or joint replacements or other complications of hemophilia including pseudotumors.
- Concomitant medication use including treatment used for control of spontaneous or traumatic bleeding events (infusion therapies, anti-fibrinolytic agents, local agents) and for management of pain and other complications related to hemophilia.
- Vital signs, height, weight, general physical examination will be performed at screening.

Evaluations related to PK and PD will include:

- CB2679d activity levels over time post-dose and calculation of standard PK parameters. Study evaluations will be performed at a central laboratory. However, FIX activity levels may be performed at a local laboratory for safety.
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT. These evaluations will be performed at a central laboratory.

8.2.2 Physical Examination

A full physical assessment of the major body systems will be recorded at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit.

8.2.3 Vital signs

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

8.2.4 Hematology

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

8.2.5 Chemistry

Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST and GGT), TBIL, albumin, and creatinine (Cr) will be measured using standard laboratory testing methods at a local laboratory.

8.2.6 Coagulation assays

PT and aPTT (at screening and end of study ONLY) will be performed at a central laboratory.

8.2.7 Thrombogenicity markers

Fibrinogen, D-dimer, F1+2, and TAT. These evaluations will be performed at a central laboratory.

8.2.8 Antibody response and neutralizing antibodies to CB2679d

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

8.2.9 Clinical signs of thrombosis (**Appendix A**)

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

8.2.10 Concomitant medications

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

8.2.11 ECG

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

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

8.3 SAFETY AND OTHER ASSESSMENTS

Evaluations related to safety will include:

8.3.1 AEs and SAEs

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

8.3.2 Injection site reactions

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

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 Definition of Adverse Events (AE)

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

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

8.4.2 Definition of Serious Adverse Events (SAE)

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

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8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

All AEs will be assessed by the study clinician using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 where applicable.[39]

For those AEs that are not included under the CTCAE v5.0, the following guidelines will be used to describe severity.

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

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

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

8.4.3.2 Relationship to Study Drug

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

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

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

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8.4.3.3 Action Taken

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

Permanently discontinued: Study drug was discontinued and not restarted

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

8.4.3.4 Expectedness

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

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

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

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

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

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

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs

characterized as intermittent require documentation of onset and duration of each episode.

Subject Withdrawal from the Study Due to an Adverse Event:

Every reasonable effort should be made to maintain subject compliance and participation in the study. All enrolled subjects who received the study drug must be followed through the Follow-Up visit, regardless of the reason for withdrawal. If a subject who has a clinically significant laboratory abnormality or AE withdraws from the study, every effort must be made to follow these events until satisfactory resolution.

8.4.5 Adverse Event Reporting

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

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

Resolved:	The subject recovered from the AE.
Ongoing:	At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death. No AE stop date should be recorded with an AE that is ongoing.
Chronic/Stable:	At the time of the last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated.
Unknown:	There is an inability to access the subject or the subject's records to determine the outcome (ie, subject withdraws consent or is lost to follow-up).

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

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

All bleeds should be entered into the diary including spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery (see **Section 4.1**). Only

bleeds (spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery) that are considered serious as per definition (see **Section 8.4.6**) should be reported as *an* SAE in the CRF. Non-serious bleeds *are not considered adverse events for the purpose of this protocol and* should not be reported as adverse event in the eCRF.

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

Thrombotic events (see Appendix A)

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

Development of Drug Antibodies and Inhibitors

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

Skin injection site may become reddened or painful.

Risks associated with blood collection:

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

8.4.6 Serious Adverse Event Reporting

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

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

Resolved: The subject recovered from the AE.

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

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

Death: The AE directly caused death.

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

Definitions:

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

Life threatening AE: Any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (*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 pre-planned hospitalizations for pre-existing conditions that did not worsen during the study.

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

8.4.7 Adverse Events of Special Interest (AESIs)

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

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

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

8.4.8 Reporting of Pregnancy

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

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

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

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

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

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

9. STATISTICAL CONSIDERATIONS

9.1 STUDY HYPOTHESIS

Please note that there is no study hypothesis, as this study is not intended to be inferential.

Primary Analysis Plan:

Appropriate descriptive statistics of all measured parameters will be reported, including 95% confidence intervals.

The dose required to achieve steady-state levels >12%, >30% and >50% will be reported for daily, every second day and every third day dosing, including 95% confidence intervals.

Primary Endpoint

The primary endpoint will include:

- Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing.

Secondary Endpoints

The secondary endpoints will include:

- Safety assessments: Occurrence of antibody formation resulting in a decreased endogenous level of FIX; occurrence of a clinical thrombotic event not attributable to another cause.
- Occurrence of a conformed antibody response with high titer to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX.
- Change in CB2679d activity levels, and from pre-dose.
- Occurrence of clinically significant levels of thrombogenicity markers resulting from SQ administration of CB 2679d.
- Feasibility of using an adjusted-dose SQ prophylaxis treatment regimen clinically.

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9.2 SAMPLE SIZE DETERMINATION

5 subjects are sufficient to provide guidance on range of dose required to achieve steady-state activity 12%, >30% or >50% and starting SQ dose for subsequent studies. As this study is not inferential, no formal sample size calculation is required.

9.3 POPULATIONS FOR ANALYSES

Safety population: any patient who receives at least one dose

Efficacy/PD population: any patient who receives at least one week of dosing and PK specimens obtained

If a subject does not complete the study as defined in the protocol another subject will need to be enrolled in replacement.

9.4 STATISTICAL ANALYSIS

9.4.1 General Approach

Various pharmacokinetic parameters will be calculated, including area under the time curve (o-t and 0-infinity), clearance, volume of distribution at steady-state, T_{max} and C_{max}, and terminal (beta phase) $t_{1/2}$, will be calculated. A semi-parametric model described by Lee et al[40] will be used to calculate the terminal $t_{1/2}$. Other parameters will be calculated using a standard noncompartmental approach. Descriptive statistics will be reported for each parameter and will include mean ± standard deviation and median ± interquartile range. The dosing profile and adjustments made will be reported.

The evaluation of the primary endpoint is descriptive, but 95% confidence intervals will be calculated as appropriate.

There will be a formal Statistical Analysis Plan (SAP) completed prior to database lock.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The analysis of the primary endpoint will include:

- Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing.

9.4.3 Analysis of the Secondary Endpoint(s)

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

The following parameters will be documented:

- Occurrence of clinical thrombotic event not attributable to another cause, and occurrence of antibody formation resulting in a decreased endogenous level of FIX.
- Change in coagulation parameters (fibrinogen, and CB2679d activity levels) from pre-dose.
- Occurrence of an antibody response to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX.
- Clinically significant levels of thrombogenicity markers resulting from SQ administration of CB2679d

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

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

9.4.4 Safety Analysis

Adverse Events

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

Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown for. Incidence rates will also be displayed based on severity and relationship to study drug. AEs with a relationship of "possibly" or "probably" related will be considered by the Sponsor as "related"

to the study drug. Events assessed as "unrelated", "unlikely" related, or where the relationship was not reported will be considered by the Sponsor as "not related" to the study drug. The incidence of SAEs will be provided for each phase. All incidence rates will be categorized and displayed by system organ class and preferred term.

Vital Signs

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

9.4.5 Baseline Descriptive Statistics

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

9.4.6 Planned Interim Analyses

Not applicable to this study.

9.4.7 Sub-Group Analyses

Not applicable to this study.

9.4.8 Tabulation of Individual Participant Data

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

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

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

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

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

10.1.2 Institutional Review Board/Independent Ethics Committee

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

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

- All SAEs (including deaths) regardless of cause and whether anticipated or unanticipated (reported immediately)
- Significant findings that become known in the course of the study that might affect the willingness of subjects to continue to participate

- Protocol, or consent amendments prior to the implementation of the change
- Study progress reports at least once a year, if applicable
- Notification of study completion or termination.

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

10.1.3 Study Discontinuation and Closure

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

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

10.1.4 Confidentiality and Privacy

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

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

10.1.5 Future Use of Stored Specimens and Data

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

10.1.6 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 ICH GCP, and with applicable regulatory requirement(s).

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

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

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

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

10.1.7 Quality Assurance (QA) and Quality Control (QC)

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

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

Diary data will be entered into the eCRF.

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

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

10.1.8 Data Handling and Record Keeping

10.1.8.1 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.

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

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

10.1.8.2 Study Records Retention

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

10.1.9 Protocol Amendments

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

10.1.10 Publication and Data Sharing Policy

The final clinical study report is also intended to form the basis for a manuscript intended for publication in a peer-reviewed scientific journal. The authorship, timetable and any arrangements for review by the participating investigators will be coordinated by Catalyst Biosciences. No partial subset of data from

individual investigational sites can be presented or published until after the primary manuscript for the entire study has been accepted for publication in a peer reviewed scientific journal.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11. REFERENCES

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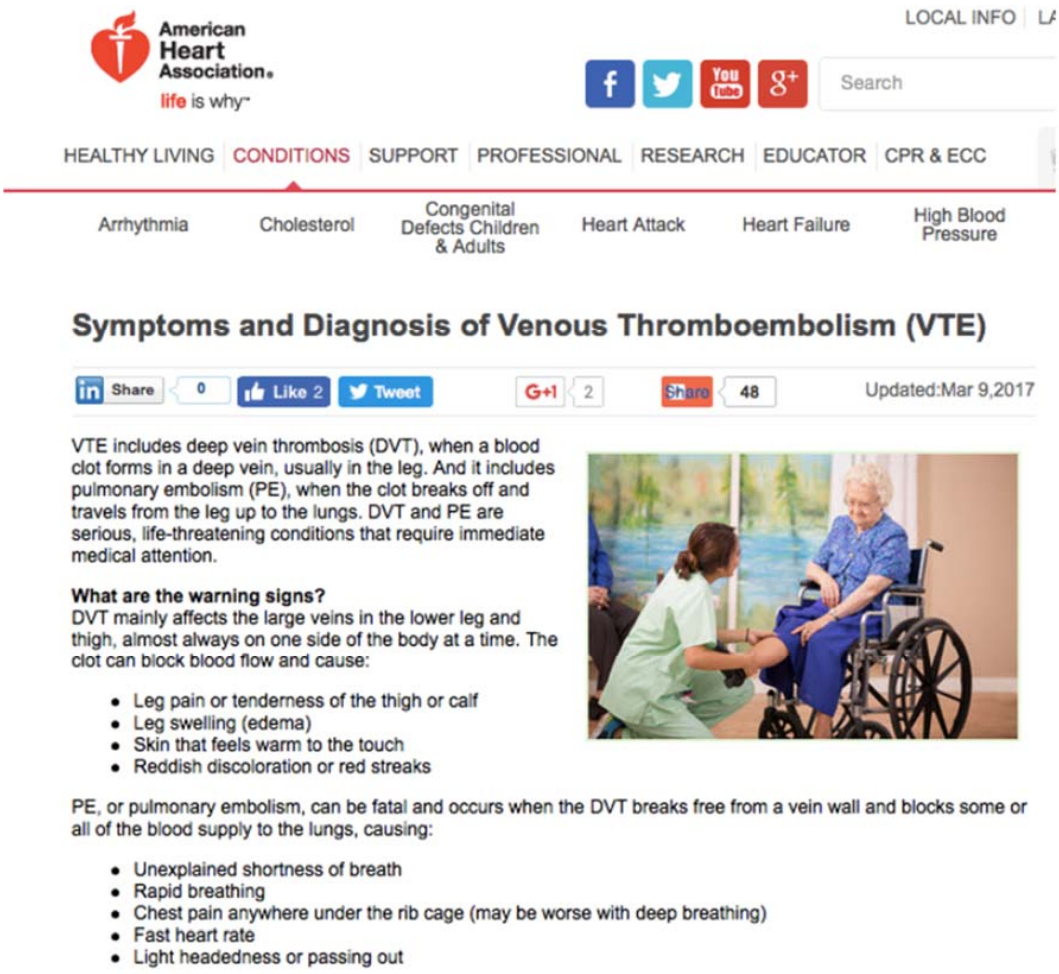
APPENDICES

APPENDIX A – CLINICAL SIGNS OF THROMBOSIS



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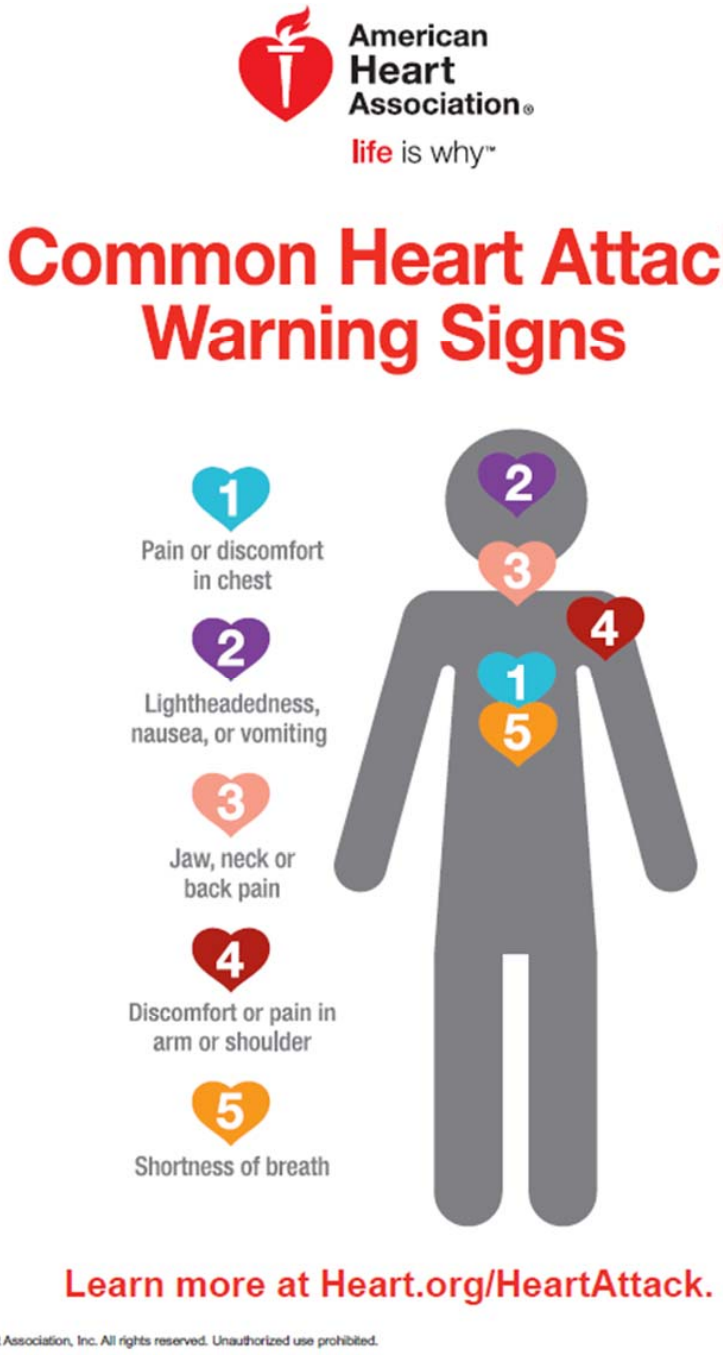

http://www.heart.org/HEARTORG/Conditions/HeartAttack/WarningSignsofaHeartAttack/Warning-Signs-of-a-Heart-Attack_UCM_002039_Article.jsp#.WkkEAWeYpfw

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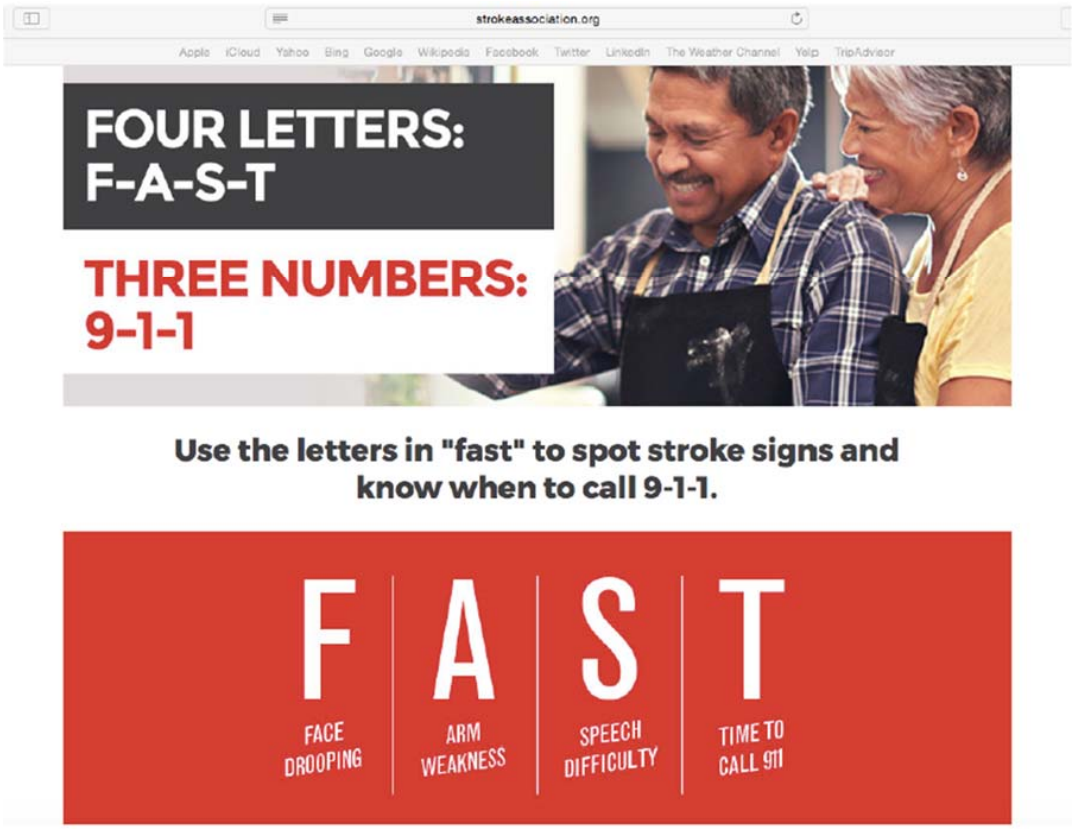

http://www.strokeassociation.org/STROKEORG/WarningSigns/Stroke-Warning-Signs-and-Symptoms_UCM_308528_SubHomePage.jsp

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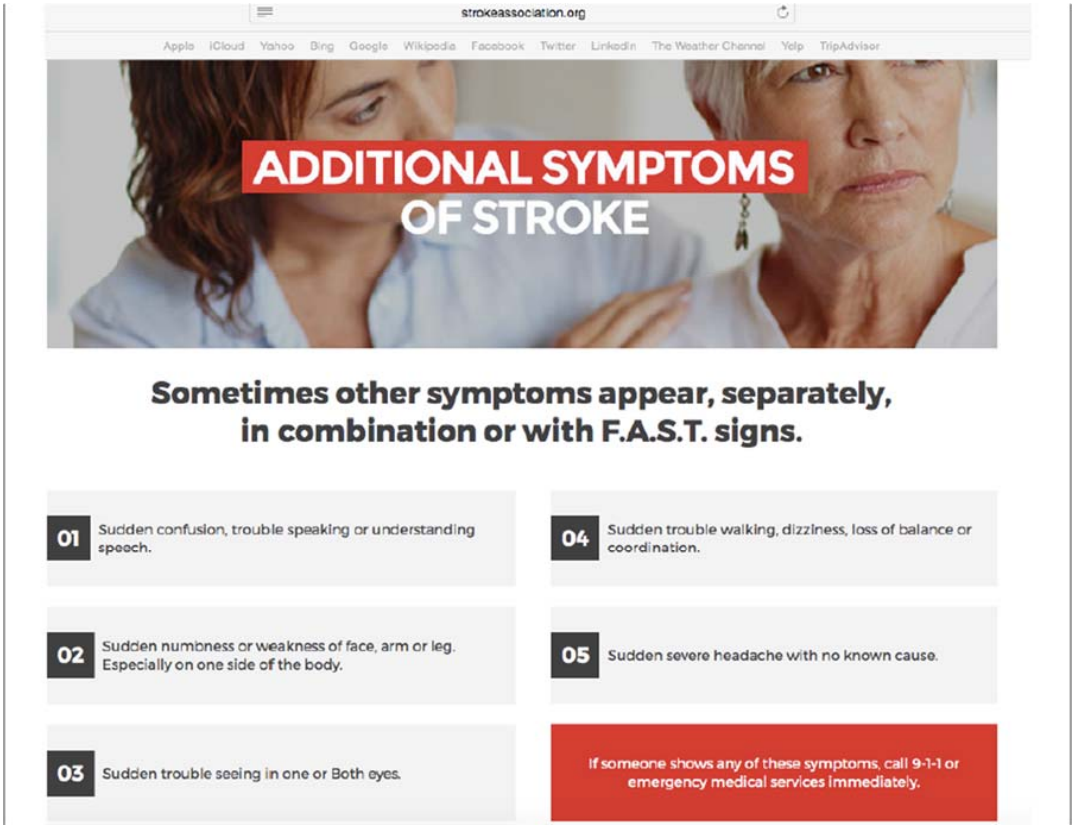

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Symptoms and Signs of Venous Thromboembolism – Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):

Leg pain or tenderness of the thigh or calf

Leg swelling (edema)

Skin that feels warm to the touch

Reddish discoloration or red streaks

Unexplained shortness of breath

Rapid breathing

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

Fast heart rate

Light headedness or passing out

Common Heart Attack Warning Signs

Pain or discomfort in the chest

Lightheadedness, nausea, or vomiting

Jaw, neck, or back pain

Discomfort or pain in arm or shoulder

Shortness of breath

Stroke Signs

Face Drooping

Arm Weakness

Speech Difficulty

Sudden confusion, trouble speaking or understanding speech

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

Sudden trouble seeing in one or both eyes.

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

Sudden severe headache with no known cause.

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Signs and Symptoms of Thrombosis

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

Table. Clinical Spectrum of VTE

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

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

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

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

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APPENDIX B – DETAILED STUDY SCHEMA

SCREENING	
Up to 4 weeks prior	Screening

- Obtain informed consent
- Review demographic parameters
- Conduct a joint evaluation as per the SOC at hemophilia treatment center
- Screen potential subjects by inclusion and exclusion criteria
- Obtain medical and hemophilia history, document
- Evaluate concomitant medications, check vital signs, height and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, immunogenicity assays, and ECG
- Adverse Events

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Part 1 – 14 days	
Day 1 Pre-IV Dose – 5 min	**Part 1**
• Evaluate concomitant medications, check vital signs, and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assays • Conduct study subject diary training • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs	
Day 1 IV Dose Followed by SQ Dose; Day 2 to Day 14 SQ Dose	**Part 1**
• Day 1: Administer single IV 70 IU/kg loading dose of CB2679d • Day 1: 30 minutes later administer SQ 140 IU/kg dose of CB2679d • Day 2 to 14: Administer SQ 140 IU/kg dose of CB2679d	
Day 1 Post-Dose SQ Dose – (30 min and Hr 7); Day 2 Post-Dose SQ Dose – Hr 24	**Part 1**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs	
Days 5, 8, 11 and 14 Pre Dose	**Part 1**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Day 8 and 14 only: Conduct testing for hematology and chemistry • Conduct testing for thrombogenicity markers, PK sampling • Day 8 only: Conduct testing for immunogenicity assays • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs	

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Part 2 – 7 days	
Dose Hr 0 on Day 15, Day 17, Day 19, and Day 21	**Part 2**
• Administer 280 IU/kg SQ dose of CB2679d (every second day)	
Day 15 Pre-Dose – 5 min	**Part 2**
• Evaluate concomitant medications, and check vital signs and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling, and immunogenicity assays • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	
Day 15 Post-Dose at Hour 7 [± 1 hour]; Day 16 Post-Dose at Hour 24 [± 1 hour]; Day 17 and Day 19 Pre-Dose - 5 min	**Part 2**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	
Day 21 Pre-Dose - 5 min	**Part 2**
• Evaluate concomitant medications, and check vital signs and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	

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Part 3 – 14 Days	
Dose Hr 0 on Day 23, Day 26, Day 29, and Day 32	**Part 3**
• Administer 420 IU/kg SQ dose of CB2679d (every third day)	
Day 23 and Day 32 Pre-Dose – 5 min	**Part 3**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Day 23 only: Check weight and conduct testing for hematology and chemistry • Conduct testing for thrombogenicity markers, PK sampling, immunogenicity assays • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	
Day 24 Post-Dose at Hour 24 [± 1 hr]; Day 26 and 29 Pre-Dose – 5 min	**Part 3**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	
Day 32 Post-Dose at Hour 7 [± 1 hour]	**Part 3**
• Conduct a joint evaluation as per the SOC at hemophilia treatment center • Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs	

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Washout Period - Days 33, 34, 35, 37, 38

- Evaluate concomitant medications, check for clinical signs of thrombosis
- Conduct testing for thrombogenicity markers, PK sampling
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs

Unscheduled

- Review medical and hemophilia history, document
- Evaluate concomitant medications, check vital signs, and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling, immunogenicity assays
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs

Unscheduled

- Review medical and hemophilia history, document
- Evaluate concomitant medications, check vital signs, and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling, immunogenicity assays
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs

Catalyst Biosciences, Inc.

CLINICAL RESEARCH PROTOCOL

Phase 2b Study of Next-Generation Recombinant Factor IX Variant, CB 2679d, in Adult Subjects with Hemophilia B

Protocol Identifying Number:	DLZ-201
Official Title:	Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B
IND/IDE Sponsor:	Catalyst Biosciences, Inc. 611 Gateway Blvd., Suite 710, South San Francisco, California, USA 94080
Investigational Product:	Recombinant Factor IX, CB 2679d (formerly ISU304)
Development Phase:	2b
Draft or Version Number:	v.2.0, Amendment 1
Effective Date:	17 October 2018
Sponsor Contact:	Name: Howard Levy, MD, PhD, MMM CMO, Catalyst Biosciences, Inc. Telephone: +1.650.266.8671 Fax: +1.650.871.2475 E-mail: hlevy@catbio.com

Prepared by:	Catalyst Biosciences, Inc.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

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

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B

PROTOCOL No.: DLZ-201

VERSION NUMBER: 2.0, Amendment 1

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

Furthermore, on behalf of the study staff and myself, I agree to conduct the study as outlined in the protocol in accordance with the guidelines outlined in the study protocol and all applicable government regulations. In addition, I agree to provide all the information requested in the case report forms (CRFs) presented to me by the Sponsor in a manner that assures legibility and accuracy. I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, CRFs, verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR) (Title 21, Parts 50 [including Subpart D], 54, 56 and 312), the regulations and guidelines of the Therapeutic Goods Administration (TGA). The Principal Investigator (PI) 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 Signature *Date*

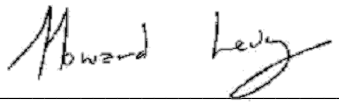
_____

Print Name and Title

Dalcinonacog alfa_DLZ-201 VERSION 2.0, Amendment 1

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B
Protocol Number:	DLZ-201
Version Number:	2.0, Amendment 1



17 October 2018

Howard Levy, MD, PhD, MMM — Date

Chief Medical Officer, Catalyst Biosciences, Inc.

Dalcinonacog alfa_DLZ-201 VERSION 2.0, Amendment 1

DETAILED SUMMARY OF PROTOCOL CHANGES

Protocol Number: DLZ-201

Protocol Title: Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B

	Version Number	**Version Date**
Current Approved Protocol	1.0	23 March 2018
Amended Protocol	2.0, Amendment 1	17 October 2018

Description of Changes:

Section	**Update**	**Details**
Title Page	Replacement	**VERSION NUMBER: 1.0** With: **VERSION NUMBER: 2.0, Amendment 1**
Title Page	Replacement	**Effective Date: 23 March 2018** With: **Effective Date: 17 October 2018**
Investigator Signature Page	Replacement	**VERSION NUMBER: 1.0** With: **VERSION NUMBER: 2.0, Amendment 1**
Sponsor Signature Page	Replacement	**Version Number: 1.0, dated 23 March 2018** With:

		Version Number: 2.0, Amendment 1
Abbreviations	Updated	**SQ** With: **SC**
1.1 Synopsis: Study Population:	Updated	**Five male subjects, aged 18 or older, with confirmed diagnosis of severe congenital hemophilia B (<2% FIX level).** With: **Six male subjects, aged 18 or older, with confirmed diagnosis of severe congenital hemophilia B (<2% FIX level).**
1.1 Synopsis: Participant Duration:	Updated	**The duration of treatment for each subject is approximately 6 weeks.** With: **The duration of treatment for each subject is approximately 4 weeks.**
1.1 Synopsis: IV/SQSC Study Drug Administration and Assessments	Updated	**Part 1; Weeks 1 and 2:** The subject will receive an IV loading dose of 70 IU/kg followed 30 minutes later by a SQ dose of 140 IU/kg. Daily SQ doses of 140 IU/kg will be administered until Day 14 (14 total SQ doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 30 minutes later prior to the SQ dose. Subsequent PK, PD and safety assessments will be performed 7 hours post-SQ dose on Day 1, Day 2 at hour 24 post-SQ dose and pre-dose on days 5, 8, 11 and 14. With: **Treatment: Day 1 to Day 28**: The subject will receive an IV loading dose of 50 IU/kg followed 35 ± 5 minutes later by a SC dose of 100 IU/kg. Daily SC doses of 100 IU/kg will be administered until Day 28 (28 total SC doses). On Day 1, PK, PD, and safety assessments will

		be done at pre-IV dose and repeated 35 (± 5) minutes later prior to the SC dose. Subsequent PK, PD and safety assessments will be performed pre-dose on days 2, 3, 7, 14, 21 and 28.
1.1 Synopsis: IV/SQSC Study Drug Administration and Assessments	Deletions	*Every Second Day SQ study drug administration* Part 2; Week 3: The subject will receive a SQ dose every second day of 280 IU/kg, starting on Day 15 until Day 21 (total of 4 SQ doses). On Day 15 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD and safety assessments will be performed on Day 16 at hour 24 and pre-dose on days 17, 19 and 21. *Every Third Day SQ study drug administration* Part 3; Weeks 4 and 5: The subject will receive a SQ dose every third day of 420 IU/kg, starting on Day 23 until Day 32 (total of 4 SQ doses). On days 23 and 32 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD, and safety assessments will be performed at Day 24 at hour 24 and pre-dose on days 26, and 29.
1.1 Synopsis: Washout Period	Updated	**Days 33, 34, 35, 37, and 38** With: **Days 29, 30, 31, 32, and 33**
1.1 Synopsis: Measurements: and Throughout	Updated	**CB2679d** activity levels With: **FIX** activity levels
1.1 Synopsis: Measurements:	Added	Genotype testing will be performed at screening.
1.1 Synopsis: Measurements: Immunogenicity assays	Updated	**Specimens for immunogenicity testing (antibody to CB2679d, wild-type FIX cross reactivity, and neutralizing activity) will be drawn at screening, on days 1, 8, 15, 23, 32, and end of study.**

		With: **Specimens for immunogenicity testing (antibody to CB2679d, BeneFIX®, and neutralizing activity) will be drawn at screening, on days 7, 14, 21, 28, and end of study.**
1.1 Synopsis: Measurements: Immunogenicity assays and Throughout	Updated	**Wild-type FIX** With: **BeneFIX®**
1.1 Synopsis: Number of planned subjects	Updated	**5** With: **6**
1.1 Synopsis: Exclusion Criteria:	Added	12. Factor IX gene mutation 128G>A.
1.1 Synopsis: Dosage and mode of administration:	Updated	**Part 1: Weeks 1 and 2 (Days 1-14): IV loading dose of 70 IU/kg followed 30 minutes later with 140 IU/kg SQ administration daily x 14 (14 total doses).** **Part 2: Week 3 (Days 15, 17, 19 and 21): 280 IU/kg, SQ administration every second day (4 total doses).** **Part 3: Weeks 4 and 5 (Days 23, 26, 29, 32): 420 IU/kg SQ administration every third day (4 total doses)** With: **IV loading dose of 50 IU/kg, followed 35 ± 5 minutes later with 100 IU/kg SC administration, then daily SC administration until Day 28 (28 total SC doses).**
1.1 Synopsis: Primary Endpoints	Updated	**Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing.** With:

		Number of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.
1.1 Synopsis: Secondary Endpoints	Deletion	Feasibility of using an adjusted-dose SQ prophylaxis treatment regimen clinically.
1.1 Synopsis: Primary Analysis Plan	Updated	**The dose required to achieve steady-state levels >12%, >30% and >50% will be reported for daily, every second day or every third day dosing, including 95% confidence intervals.** With: **The dose required to achieve steady-state levels >12% will be reported for daily dosing, including 95% confidence intervals.**
1.1 Synopsis: Rationale for Number of Subjects	Updated	**5 subjects will provide guidance on dose required to achieve steady-state activity >12%, 30% or 50% and starting SQ dose for subsequent studies.** With: **6 subjects will provide guidance on dose required to achieve steady-state activity >12% and starting SC dose for subsequent studies.**
1.2 Schema	Updated	**Figure 1. Schematic of Study Design**
1.3 Schedule of Activities (SOA)	Updated and Deletions	**Updated Table.** **Deleted Tables for Parts 2 and 3.**
2.2.2 Experience with CB2679d in the Clinic	Updated and Addition	**An intravenous loading dose has been added in this study to see if it eliminates these local adverse events as they are believed to be due to low FIX levels because of washout of prior treatment.** With:

		An IV loading dose has been added to cohort 6 in this study to see if it eliminates injection site adverse events as they are believed to be due to low FIX levels because of washout of prior treatment (Figure 2). **ADDED:** The nadir activity after IV plus SC dosing was 20% in both subjects in cohort 6 and thereafter levels increased to >30%. It is clear that the IV loading dose increased the bioavailability of SC CB2679d by increasing the saturation of the extravascular compartment and resulted in greater activity levels than simple addition of SC to IV activity. Neutralizing antibodies developed in both subjects, (transiently in one subject). A root cause analysis determined that the most likely cause was a 3-month gap between dosing in cohort 5 and cohort 6 in these 2 participants (**Figure 3**). FIGURE 2. CB2679D PHASE 1/2 OPEN LABEL STUDY DESIGN FIGURE 3. CB2679D PHASE 1/2 STUDY: COHORT 5 & 6 FIX ACTIVITY RESULTS
4.1 Overall Design	Updated	Each subject will participate for approximately 6-weeks of SQ CB2679d drug administrations: **Part 1; Weeks 1 and 2:** Each participant will receive an IV loading dose of 70 IU/kg followed 35 ± 5 minutes later by a SQ dose of 140 IU/kg. **Daily** SQ doses of 140 IU/kg will be administered until Day 14 (14 total SQ doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 30 minutes later prior to the SQ dose. Subsequent PK, PD and safety assessments will be performed 7 hours post-SQ dose on Day 1, Day 2 at hour 24 post-SQ dose and pre-dose on days 5, 8, 11 and 14. With:

		Treatment: Day 1 to Day 28: Each participant will receive an IV loading dose of 50 IU/kg followed 35 ± 5 minutes later by a SC dose of 100 IU/kg. **Daily** SC doses of 100 IU/kg will be administered until Day 28 (28 total SC doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 35 (± 5) minutes later prior to the SC dose. Subsequent PK, PD and safety assessments will be performed pre-dose on days 2, 3, 7, 14, 21 and 28.
4.1 Overall Design	Deletions	*Every Second Day SQ study drug administration* Part 2; Week 3: The subject will receive a SQ dose every second day of 280 IU/kg, starting on Day 15 until Day 21 (total of 4 SQ doses). On Day 15 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD and safety assessments will be performed on Day 16 at hour 24 and pre-dose on days 17, 19 and 21. *Every Third Day SQ study drug administration* Part 3; Weeks 4 and 5: The subject will receive a SQ dose every third day of 420 IU/kg, starting on Day 23 until Day 32 (total of 4 SQ doses). On days 23 and 32 only, PK, PD, and safety assessments will be done at pre-dose and repeated at hour 7. Subsequent PK, PD, and safety assessments will be performed at Day 24 at hour 24 and pre-dose on days 26, and 29.
4.1 Overall Design: Washout Period	Updated	**Days 33, 34, 35, 37, and 38** With: **Days 29, 30, 31, 32, and 33**
4.1 Overall Design: Measurements	Added	Genotype testing will be performed at screening.
4.1 Overall Design: Measurements	Updated	***Immunogenicity assays:*** **Specimens for immunogenicity testing (antibody to CB2679d, wild-type FIX cross reactivity, and**

		neutralizing activity) will be drawn at screening, pre-dose on days 1, 8, 15, 23, 32 and end of study. With: ***Immunogenicity assays:*** **Specimens for immunogenicity testing (antibody to CB2679d, BeneFIX®, and neutralizing activity) will be drawn at screening, pre-dose on days 7, 14, 21, 28 and end of study.**
4.6 End of Study Definition	Updated	**The duration of treatment for each subject is approximately 6 weeks.** With: **The duration of treatment for each subject is approximately 4 weeks (28 days).**
5.2 Exclusion Criteria	Added	12. FIX mutation 128G>A.
6.1.2 Dosing and Administration	Updated	**CB2679d loading dose of 70 IU/kg IV, followed 30 minutes later with a 140 IU/kg, SQ administration daily x 14 (total 1 IV dose and 14 SQ doses); then a 280 IU/kg, SQ administration every second day, starting on Day 15 until Day 21 (total 4 SQ doses); then a 420 IU/kg SQ every third day, starting on Day 23 until Day 32 (total of 4 SQ doses).** With: **CB2679d loading dose of 50 IU/kg IV, followed 35 ± 5 minutes later with a 100 IU/kg, with SC administration daily until Day 28 (total 1 IV dose and 28 SC doses).**
6.4 Study Intervention Compliance	Updated	**Reasonable efforts should be made to ensure that study drug administration is administered according to the schedule. However, if an unavoidable disruption of the administration occurs, and a dose is not administered on the assigned day then the subject should take the dose as soon as possible. In the event that the**

		subject remembers more than 2 days late, then the subject must contact the research site for instructions on how to proceed. With: **Reasonable efforts should be made to ensure that study drug administration is administered daily according to the schedule. However, if an unavoidable disruption of the administration occurs, and a dose is not administered on the assigned day then the subject should take the dose as soon as possible. In the event that the subject does not take study drug for more than 2 days, then the subject must contact the research site for instructions on how to proceed prior to administering a dose.**
7.1 Participant Discontinuation/Withdrawal from Study	Updated	**Replacement of a subject occurs for the following reason:** • **If a subject does not complete at least 2 doses of every third day SQ dosing as defined in the protocol, another subject may be enrolled.** With: **Replacement of a subject occurs for the following reason:** • **If a subject does not complete 21 days of daily SC dosing, as defined in the protocol, another subject may be enrolled.**
8.1.1 Study Procedures: Screening	Additions	**PK: FIX activity** **FIX genotype test**
8.1.2 Study Procedures: Screening	Updated	**Part 1; Weeks 1 and 2 (Duration 7 days)** With: **Treatment (Duration 28 days)**
8.1.2.1 Study Procedures: Day 1 Pre-dose evaluations	Updated	**Study Subject training on drug administration and injection site assessment**

		With: **Study Subject training on diary entry, drug administration, adverse events and injection site assessment**
8.1.2.1 Study Procedures: Day 1 Pre-dose evaluations	Deletion	**Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment**
8.1.2.1 Administration	Update	CB2679d administration (Every day from Day 1 to Day 14) • Subjects will receive a loading **IV dose of 70 IU/kg**, followed 35 ± 5 minutes later with a **140 IU/kg SQ dose** of CB2679d • Subjects will then administer a **140 IU/kg daily SQ dose** of CB2679d • SQ CB2679d should be self-administered by subjects at approximately the same time every day. With: CB2679d administration (Daily from Day 1 to Day 28) • Subjects will receive a loading **IV dose of 50 IU/kg**, followed 35 ± 5 minutes later with a **100 IU/kg SC dose** of CB2679d • Subjects will then administer a **100 IU/kg daily SC dose** of CB2679d from Day 2 until Day 28 • Daily SC dosing of CB2679d should be self-administered by subjects at approximately the same time every day.
8.1.2.4 Day 2 and 3 Pre-SC dose	Addition	**Hematology and chemistry – platelet count only (see Footnote 4 and 5 in Section 1.3, SOA)**

8.1.2.4 Day 2 and 3 Pre-SC dose evaluations	Updated	Day 1 Post-SQ dose (Hour 7) and Day 2 Post-SQ dose (Hour 24) evaluations Blood will be collected at hour 7 post-dose on Day 1 and hour 24 post-dose on Day 2 for the following evaluations: • Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT • PK: CB2679d activity Other evaluations will include: • Concomitant medications • Vital sign • Physical examination • Clinical signs of thrombosis (see **Appendix A**) • Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment • Adverse events (from Hr 6 to 24 hours) **With:** Day 2 and 3 Pre-SC dose evaluations Blood will be collected pre-dose on Day 2 for the following evaluations: • Hematology and chemistry – platelet count only (see Footnote 4 and 5 in **Section 1.3, SOA**): Day 2 ONLY • Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT • PK: FIX activity Other evaluations will include: • Concomitant medications

		• Vital sign • Physical examination • Clinical signs of thrombosis (see **Appendix A**) • Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment • Adverse events
8.1.2.5 Day 7, 14, 21 and 28 Pre-dose evaluations	Updated	**8.1.2.5 Day 5, 8, 11 and 14 Pre-dose evaluations** With: **8.1.2.5 Day 7, 14, 21, and 28 Pre-dose evaluations**
8 Study Assessments	Deletion of Selections	**8.1.3 Part 2, Week 3 (Duration: 7 days)** **8.1.3.1 CB2679d administration (Day 15, Day 17, Day 19, and Day 21)** **8.1.3.2 Day 15 Pre-dose evaluations** **8.1.3.3 Day 15 Post-dose (Hour 7), Day 16 Post-dose (Hour 24), Day 17 and Day 19 Pre-dose evaluations** **8.1.3.4 Day 21 Pre-dose evaluations** **8.1.4 Part 3, Weeks 4 and 5 (Duration: 14 days)** **8.1.4.1 CB2679d administration (Day 23, Day 26, Day 29, and Day 32)** **8.1.4.2 Day 23 and Day 32 Pre-dose evaluations** **8.1.4.3 Day 23 Post-dose evaluations (Hour 7)** **8.1.4.4 Day 24 Post-dose (Hour 24) and Day 26 and Day 29 Pre-dose evaluations**

		8.1.4.5 Day 32 Post-dose evaluations (Hour 7)
8.1.5 Washout period evaluations	Updated	**8.1.5.1 Washout period evaluations (Days 33, 34, 35, 37, and 38)** With: **8.1.3.1 Washout period evaluations (Days 29, 30, 31, 32, and 33)**
8.2.1 Efficacy Assessments	Updated	**All ongoing conditions and relevant medical and hemophilia history (including all major hospitalizations and surgeries), as well as the subject's current medical status will be recorded at the screening visit.** With: **All ongoing conditions and relevant medical and hemophilia history (including all major hospitalizations and surgeries), as well as the subject's current medical status and genotype will be recorded at the screening visit.**
8.2.4 Hematology	Added	Genotype test will be performed at screening.
9.1 Study Hypothesis	Updated	**The dose required to achieve steady-state levels >12%, >30% and >50% will be reported for daily, every second day and every third day dosing, including 95% confidence intervals.** With: **The dose required to achieve steady-state levels >12% will be reported for daily dosing, including 95% confidence intervals.**
9.1 Study Hypothesis	Updated	**Primary Endpoint** The primary endpoint will include: • Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing. With:

		Primary Endpoint The primary endpoint will include: Number of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.
9.1 Study Hypothesis	Deletion	Feasibility of using an adjusted-dose SQ prophylaxis treatment regimen clinically.
9.2 Sample Size Determination	Updated	**5 subjects are sufficient to provide guidance on range of dose required to achieve steady-state activity 12%, >30% or >50% and starting SQ dose for subsequent studies.** With: **6 subjects are sufficient to provide guidance on range of dose required to achieve steady-state activity >12% and starting SC dose for subsequent studies.**
9.3 Populations for Analyses	Updated	**Efficacy/PD population**: any patient who receives at least one week of dosing and PK specimens obtained **With:** **Efficacy/PD population**: any patient who receives at least one week of daily SC dosing and PK specimens obtained.
9.4.2 Analysis of Primary Efficacy Endpoint(s)	Updated	**Number of subjects who achieve a steady-state FIX activity level above 12%, 30% and 50% with daily, every second day or every third day dosing.** With: **Number of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.**
10.2 Protocol Amendment History	Updated	**2.0, Amendment 1, 17 October 2018**
Appendix B: Detailed Study Schema	Updated	**Updated Schema according to changes**

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

ABBREVIATIONS

%	Percent
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATIII	Anti-thrombin III
AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the curve from time 0 to the last measurable concentration
$AUC_{0\text{-}t}$	Area under the curve-time curve
CAD	Coronary artery disease
CB2679d	Recombinant Factor IX variant
CBC	Complete blood count
CD4	Cluster of differentiation 4
CFR	Code of Federal Regulations
C_{max}	Concentration maximum
CMO	Chief Medical Officer
Cr	Creatinine
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
F1+2	Prothrombin fragment 1+2
FDA	Food and Drug Administration
FVIII	Factor VIII

FVIIIa	Factor VIII activated
FIX	Factor IX
FIXa	Factor IX activated
FX	Factor X
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GS	Gilbert's syndrome
Hr	Hour
HTC	Hemophilia Treatment Centre
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMT	Immunomodulatory therapy
IND	Investigational New Drug Application
IP	Investigational product
IRB	Institutional Review Board
IU	International unit
IV	Intravenous
Kg	Kilogram
L	Liter
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
Min	Minute
NCT	National Clinical Trial
OTC	Over-the-counter
PD	Pharmacodynamics
pdFIX	Plasma-derived factor IX

PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QoL	Quality of life
r	Recombinant
rFIX	Recombinant factor IX
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
$T_{1/2}$	Half-life
TAT	Thrombin-antithrombin complexes
TBIL	Total bilirubin level
TE	Thromboembolic event
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time that studied drug is present at the maximum concentration in serum
µmol	Micromole
ULN	Upper limit of normal
US	United States
VTE	Venous thromboembolic event
WFH	World Federation of Hemophilia

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TABLE OF CONTENTS

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title of Study: Phase 2b study to evaluate the pharmacokinetics, pharmacodynamics, efficacy and safety of a subcutaneous prophylaxis treatment regimen of CB2679d in adult subjects with hemophilia B

Primary Objective: To evaluate the dose required to achieve a steady-state of >12% factor IX (FIX) levels.

Secondary Objectives:

- To determine the pharmacokinetics (PK) of a subcutaneous (SC) regimen of CB2679d.
- To determine the pharmacodynamics (PD) of a SC regimen of CB2679d.
- To evaluate the levels of thrombogenicity markers of a SC regimen of CB2679d.
- To evaluate for evidence of the development of antibodies to CB2679d and to determine if these are neutralizing antibodies.
- To monitor and evaluate safety parameters of SC regimens of CB2679d.

Study Population: Six male subjects, aged 18 or older, with confirmed diagnosis of severe congenital hemophilia B (<2% FIX level).

Phase of Development: Phase 2b

Description of Sites: Single center study.

Study Duration: Approximately 6 months.

Participant Duration: The duration of treatment for each subject is approximately 4 weeks (28 days).

Screening: Up to 4 weeks.

Study Drug Administration: SC prophylaxis treatment regimens over a 4-week period with the goal to achieve steady-state levels above 12% FIX activity when dosed daily.

Note: Where interruptions to study drug dosing days occur, study duration may be extended to incorporate full dosing schedule.

Follow-up: 30 days (± 2 days) after last dose for PK/PD/safety follow-up.

Study Methodology

This single-center, open-label Phase 2b study will evaluate the PK, PD, efficacy and safety parameters of SC prophylaxis treatment regimens with CB2679d in adult subjects with hemophilia B. The study will enroll and dose subcutaneously, a total of 6 adult male subjects with severe congenital hemophilia B.

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

At enrollment, subjects will be provided with a diary in which they will be instructed to record any adverse events (AEs) and concomitant medication.

After the initial intravenous (IV) dose of CB2679d, and with subsequent SC doses, the following will be monitored daily: injection site reaction, any AEs the subject may experience, and any bleeding episodes (location, inciting event if not spontaneous, and treatment administered).

IV/SC Study Drug Administration and Assessments:

Initial IV Load Dose Followed by Daily SC Study Drug Administration

Treatment: Day 1 to Day 28: The subject will receive an IV loading dose of 50 IU/kg followed 35 ± 5 minutes later by a SC dose of 100 IU/kg. Daily SC doses of 100 IU/kg will be administered until Day 28 (28 total SC doses). On Day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 35 (± 5) minutes later prior to the SC dose. Subsequent PK, PD and safety assessments will be performed pre-dose on days 2, 3, 7, 14, 21 and 28.

Washout Period

PK, PD, and safety assessments will be done on Days 29, 30, 31, 32 and 33. Daily FIX activity levels will be measured, unless FIX activity level is known to be < 5%, as measured by local laboratory.

An End of Study visit will occur 30 days (± 2 days) after the last dose of study drug.

Treatment of a bleeding episode: Subjects will self-administer their currently prescribed FIX replacement product for treatment of any spontaneous or traumatic bleed that occurs while on study drug. If treatment for a breakthrough spontaneous bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event; treatment dose administered; and arrange for an urgent follow-up visit to the study site for additional evaluation and laboratory testing, if needed.

Dose interruption: SC study drug injections will be interrupted if any of the following occurs: a thrombotic event; clinical evidence of inhibitor formation; or laboratory results suggesting a high titer antibody may be developing; trough activity levels >80%, where subsequent dosing will be determined in consultation with the sponsor.

Surgery: If there is an urgent need for a surgical procedure or an event requiring extended (>48 hours) hospitalization, a FIX activity level will be urgently obtained and measured prior to the event, and the PI will confer with the Sponsor Medical representative regarding the need for any additional treatment and whether study drug requires interruption.

***Measurements*:**

PK, PD, and safety assessments: FIX activity levels, as well as fibrinogen, D-dimer, prothrombin fragment 1+2 (F1+2), and thrombin-antithrombin complexes (TAT). PT and aPTT will be measured at screening and end of study visit only. Genotype testing will be performed at screening.

Immunogenicity assays: Specimens for immunogenicity testing (antibody to CB2679d, BeneFIX®, and neutralizing activity) will be drawn at screening, on days 7, 14, 21, 28 and end of study.

If the FIX activity level decreases unexpectedly by more than 25%, ie, IU/dL, as measured by the central or local lab, if applicable, FIX activity levels will be drawn for analysis within 24 hours and immediately sent to the central laboratory. Specimens for fibrinogen, D-dimer, F1+2, and TAT and immunogenicity testing will also be drawn.

Number of planned subjects: 6

Trial population:

***Inclusion criteria*:**

1. Confirmed diagnosis of severe (<2%) congenital hemophilia B.
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. (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.

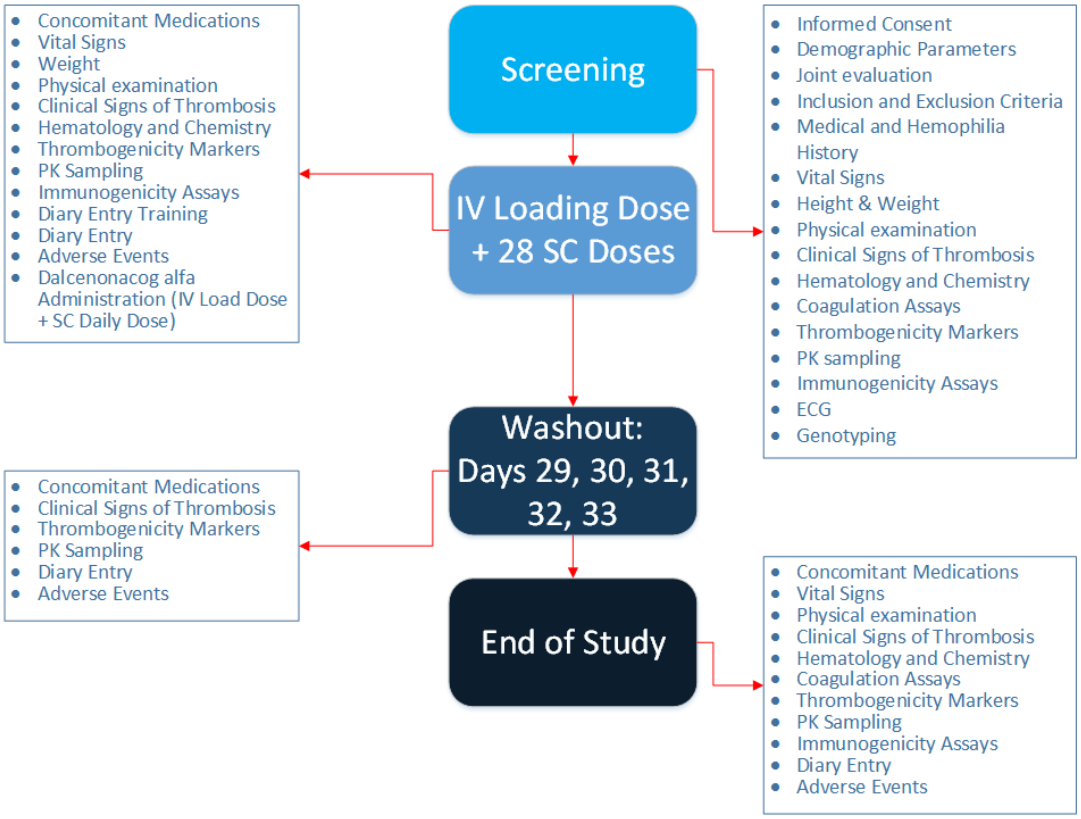
***Exclusion criteria*:**

1. Patients with a history or a family history of FIX inhibitors.
2. Positive antibody to FIX detected by central laboratory at screening.
3. Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 3-half-lives, whichever is longer, or absence of clinical effect.
4. History of clinically relevant coagulation disorders other than congenital hemophilia B including Factor V Leiden or other identified activated Protein C resistance.
5. Platelet count <100,000 based on screening laboratory assessments.
6. 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.
7. Known or suspected allergy to trial product or related products.
8. Known absolute cluster of differentiation 4 (CD4) count <200 cells/µL.
9. Receiving immunomodulatory therapy (IMT).
10. Compromised hepatic or renal function:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥5 times the upper limit of normal (ULN)
    - Total bilirubin level (TBIL) ≥2 mg/dL (>35 µmol /L) unless there is a known history of Gilbert's syndrome (GS)
    - Serum albumin ≤ the lower limit of normal (LLN)
    - Serum creatinine (Cr) level >1.25 x 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.

12. Factor IX gene mutation 128G>A.
Investigational product, dose, and mode of administration: ***Investigational Product:*** Recombinant FIX variant; CB2679d ***Dosage and mode of administration:*** IV loading dose of 50 IU/kg, followed 35 ± 5 minutes later with 100 IU/kg SC administration, then daily SC administration until Day 28 (28 total SC doses).
Reference therapy: None
Concomitant Medications: In the event of spontaneous or traumatic bleeding, treatment for a bleeding episode will be permitted using the subject's current treatment regimen.
Efficacy and Safety Evaluations
Primary endpoints: • Number of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.
Secondary endpoints: • Safety assessments: Occurrence of antibody formation resulting in a decreased endogenous level of FIX; occurrence of a clinical thrombotic event not attributable to another cause. • Occurrence of a conformed antibody response with high titer to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX®. • Change in FIX activity levels, and from pre-dose. • Clinically significant levels of thrombogenicity markers resulting from SC administration of CB2679d.
Statistics **Primary Analysis Plan:** Appropriate descriptive statistics of all measured parameters will be reported, including 95% confidence intervals. The dose required to achieve steady-state levels >12% will be reported for daily dosing, including 95% confidence intervals.
Rationale for Number of Subjects: 6 subjects will provide guidance on dose required to achieve steady-state activity >12% and starting SC dose for subsequent studies.
Name of sponsor: Catalyst Biosciences

1.2 SCHEMA

FIGURE 1. SCHEMATIC OF STUDY DESIGN



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1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Period	Screening	Treatment Period								Wash-out[8]	Unscheduled Visit	End of Study[9]
Study Day	Day -28 to -1	Day 1, IV Pre-dose (-5 min)	Day 1, SC dose, 35 (±5) min Post IV	Day 2	Day 3	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21 (± 1 day)	Day 28 (± 1 day)	Days 29, 30, 31, 32, 33		
Informed Consent	X											
Demographic Parameters	X											
Inclusion and Exclusion Criteria	X											
Medical and Hemophilia History[2]	X										X	
Vital Signs	X	X	X	X	X	X	X	X	X		X	X
Height (screening only) & Weight	X	X									X	X
Physical Examination[2]	X	X	X	X	X	X	X	X	X		X	X
Clinical Signs of Thrombosis[3]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and Chemistry[4]	X	X		X		X	X	X	X		X	X
Coagulation Assays[5]	X											X
Thrombogenicity Markers[5]	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Sampling[5]	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Assays[5]	X					X	X	X	X		X	X
Genotyping	X											
ECG	X											
Diary entry training[6]		X										
Diary entry of any bleeding episodes, AEs, injection site reactions[6]				←----------								
Adverse Events	X		←----------									
Concomitant Medications	X		←----------									
CB2679d[7] Administration[8]			X		←----------							

1. As per Standard of Care at hemophilia treatment center.
2. Complete evaluation at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit. Joint evaluation will be performed at Screening.
3. **Clinical Signs of Thrombosis** per protocol
4. Local Laboratory: **Hematology** - CBC and platelet count. **Chemistry** - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, GGT), bilirubin, albumin, creatinine. For Days 2, 3, 7, 14, 21, and 28, blood will be collected at Pre-dose (- 5 minutes).
5. Central Laboratory: **Coagulation assays** – PT and aPTT. **Thrombogenicity markers** – Fibrinogen, D-dimer, F1+2, and TAT. **Pharmacokinetics** – FIX activity. **Immunogenicity assays** – to CB2679d and BeneFIX®. For Days 2, 3, 7, 14, 21, and 28, blood will be collected at Pre-dose (- 5 minutes).
6. Diary entry training and entry consists of investigational drug administration, injection site assessment, adverse events, any bleeding episodes & treatment.
7. IV load dose (50 IU/kg) followed by SC dose (100 IU/kg) 30 minutes (+ 30 mins) after. **Daily SC** (100 IU/kg) dosing until Day 28 (28 total SC doses).
8. Daily FIX activity levels needed unless FIX activity level known to be < 5%, as per local lab.
9. End of Study Visit will occur 30 ± 2 days after the last dose.

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2. INTRODUCTION

2.1 STUDY RATIONALE

The rapid clearance of FIX necessitates frequent intravenous (IV) administrations to achieve effective prophylaxis for patients with hemophilia B. Subcutaneous (SC) administration, a preferred administration route, has historically been limited by low bioavailability and potency. CB2679d, formerly known as ISU304, was developed using a rational design approach to be the next-generation SC coagulation prophylactic FIX therapy.

2.2 BACKGROUND

Hemophilia B, or sometimes referred to as Christmas disease, is a hereditary X chromosomal-linked recessive bleeding disorder caused by Factor IX (FIX) deficiency.[1] Hemophilia B, especially in severe phenotypes, is characterized by frequent and spontaneous bleeding[1,2] into joints, muscles and body cavities, and can lead to arthropathy with progressive cartilage damage, chronic pain, disability, diminished quality of life (QoL) and ultimately joint destruction.[1] Disease classification of mild (factor activity >5 % and <40%), moderate (1 to 5%) or severe phenotype (<1%) is based on residual plasma FIX levels.[3,4] The number of patients with mild, moderate and severe phenotypes of hemophilia B is not well established, however community studies have estimated that 60–70% of patients with hemophilia B have a moderate or severe form.[5-7] Historically, treatment for hemophilia B has been on demand, that is, clotting FIX replacement therapy administered when a hemorrhage occurs or before a surgical procedure.[8] Currently, the standard of care treatment for hemophilia B is FIX replacement therapy administered prophylactically, at regular intervals to maintain FIX levels greater than 1%, to prevent the onset of bleeding episodes.[8-11] Routine prophylaxis therapy has been demonstrated to substantially reduce the frequency of bleeding episodes[11-13], prevent joint diseases[11,14] and even reduce the risk of death. [15,15] Treatment with FIX products, initially purified from plasma-derived factor IX product (pdFIX) and subsequently as recombinant human FIX (rFIX), require 2 or 3 IV infusions per week to achieve effective bleeding prevention due mostly to the half-life ($t_{1/2}$)[17-20], rFIX has a $t_{1/2}$ of approximately 18 hours.[21] High frequency of infusions can be a major barrier to adhering to the prescribed prophylactic regimen, especially in pediatric patients; in those with poor venous access[22-24]; and in those concerned about the associated complications of infection and thrombosis.[25-27] A FIX product with a longer $t_{1/2}$ to prolong the protective hemostatic effect, would potentially enable fewer injections, thereby reducing the need for repeated venous access. This could potentially improve the

acceptance of prophylactic regimens by patients with hemophilia. SC administration is the preferred route of administration for convenience and less pain but has been limited historically by low bioavailability and potency of the marketed FIX products.[28]

2.2.1 Rationale for Prophylaxis with SC Administration of FIX

There is currently no cure for hemophilia.[29] The prevention of bleeding episodes in hemophilia patients requires life-long prophylaxis.[29,30] Due to the short $t_{1/2}$ of rFIX, prophylaxis and treatment for bleeding episodes requires frequent IV dosing (2-3 IV infusions per week).[17-21] IV dosing often requires a medical professional or family member to perform the venipuncture, making home prophylaxis cumbersome, particularly for pediatric patients.[30,31] Other challenges include patient adherence, and reliable IV access.[32,33] 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.[32]

SC administration presents a major advantage over IV administration because it enables at-home injection, improves quality of life, and reduces health care costs.[33] While home IV administration has been essential to the provision of comprehensive hemophilia care, it nonetheless remains a significant barrier.[32] 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.[33]

CB2679d, a novel rFIX variant, is being developed by Catalyst Biosciences (the Sponsor) to address the unmet need for medical management of hemophilia B patients. CB2679d was developed using a rational design approach with three-point mutations in two loops within the FIX protein: (1) arginine-318 is transformed into tyrosine (Arg318Tyr) located in 'loop-150'(also known as the autolysis loop), can stabilize the activation structure of activated FIX (FIXa), as well as directly interact with factor X (FX), a substrate of FIX and anti-thrombin III (ATIII), a key inhibitor; (2) arginine-338 is transformed into glutamic acid (Arg338Glu); and (3) threonine-343 is transformed into arginine (Thr343Arg), both located in 'loop-170', can significantly enhance affinity to the cofactor VIII and stabilize FIXa. These mutations in the molecular structure enable CB2679d to increase catalytic activity (CB2679d has demonstrated 3 times the catalytic efficiency to factor X [substrate]); increase affinity for activated factor VIII (FVIIIa) (CB2679d has a 10 times higher affinity to cofactor FVIIIa) and improve resistance to inhibition by ATIII (CB2679d has 15 times the resistivity to inhibitor ATIII compared to wild-type FIX), with a resultant 20-fold enhanced potency in vitro (clotting activity) and in vivo (tail clip model) and 8-fold increased duration of aPTT activity in vivo compared

with recombinant wild-type FIX dosed at the same mass.[34-35] The SC half-life in mini-pig studies was found to be 33 hours and the bioavailability was 20-42%.[36]

These qualities are expected to prolong the interval between doses, improve convenience of treatment, and facilitate use of the product for bleeding prophylaxis.

2.2.2 Experience with CB2679d in the Clinic

To date, the safety, PK, and PD of CB2679d, is being evaluated in an open-label IV to SC cross-over clinical study (NCT03186677), which will recruit 12 adult subjects with hemophilia B (all male).[37,38] The trial design is provided below. IV PK (antigen and activity) was sampled at pre-dose, 0, 0.25, 0.5, 1, 3, 6, 9, 24, 48 and 72 hours. SC PK was sampled at pre-dose, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours. Cohort 5 has PK sampled before each injection, 6 hours after first and 6th injection and 24 hours after 6th daily injection. Hematology, chemistry and coagulation was measured at Seoul Clinical Laboratories (Yongin-si, South Korea). FIX antigen and FIX activity, anti-drug antibody to BeneFIX® and CB2679d and neutralizing antibody were measured at Haematologic Technologies Inc (Essex Junction, VT). A safety follow-up was done 2 weeks after last visit. FIX antigen was measured using VisuLize™ Factor IX Antigen KitAG (Affinity Biologicals, Inc, Ancaster, ON, Canada) and FIX activity was measured using a one-stage clotting assay using ACL TOP 700 and Instrumentation Laboratories (Bedford, MA) reagents. The calculation of area under the curve (AUC) was based on the trapezoidal rule. To calculate the additional AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}inf}$), the log-linear regression line for the last three-time points was fit and extrapolated to the x-intercept. The calculation of $t_{1/2}$ was based on the use of Demitasse 2000 (version 1.1.3, M. Lee, 2000) which uses an iterative piecewise fitting algorithm based on a robust (M-regression) log-linear model. All activity data were adjusted for baseline before analysis, assuming exponential falloff after IV administration and a $t_{1/2}$ of 20 hours. Bioavailability was calculated from the AUC-time curve ($AUC_{0\text{-}t}$) for the IV and SC data using FIX activity data.

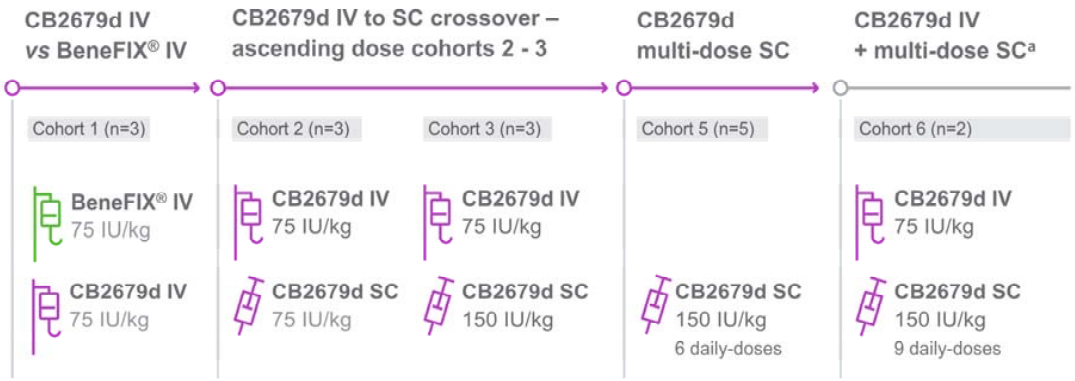
Subject safety was reviewed by an external Data Safety Monitoring Board and also an internal Data Monitoring Committee.

Interim results showed PK and activity of CB2679d as 22-fold greater potency over BeneFIX® and longer mean residence time. Single-dose bioavailability was 18.2-23.6%, SC beta $t_{1/2}$ was 66-103 hours and time that CB2679d is present at the maximum concentration in serum (T_{max}) was 6-24 hours. One subject reported transient fever and a mild SC injection site reaction. Cohort 4 was omitted as sufficient data had been gained from single dosing SC in Cohorts 2 and 3. The SC dose in Cohort 5 was reduced from 300 IU/kg to 150 IU/kg daily. PK and activity

levels after 6 daily doses in 5 subjects reached a median of 15.7% [interquartile range 14.9% to 16.6%] Four of 5 subjects had levels above 12%. Half-life was 63.2 hours [interquartile range 60.2 to 64.0 hours]. The interim study results support the aim of achieving normal or high mild hemophilia FIX levels in individuals with hemophilia B with repeated SC dosing. Mild pain, erythema and redness was reported at the injection site in initial injections and not a later injection. One subject reported these adverse events to be moderate for the first 2 injections and mild thereafter. An IV loading dose has been added to cohort 6 in this study to see if it eliminates injection site adverse events as they are believed to be due to low FIX levels because of washout of prior treatment (**Figure 2**).

The nadir activity after IV plus SC dosing was 20% in both subjects in cohort 6 and thereafter levels increased to >30%. It is clear that the IV loading dose increased the bioavailability of SC CB2679d by increasing the saturation of the extravascular compartment and resulted in greater activity levels than simple addition of SC to IV activity. Neutralizing antibodies developed in both subjects (transiently in one subject). A root cause analysis determined that the most likely cause was a 3-month gap between dosing in cohort 5 and cohort 6 in these 2 participants (**Figure 3**).

FIGURE 2. CB2679D PHASE 1/2 OPEN LABEL STUDY DESIGN



IV, intravenous; SC, subcutaneous.
[a]First SC dose 30 minutes post-IV.

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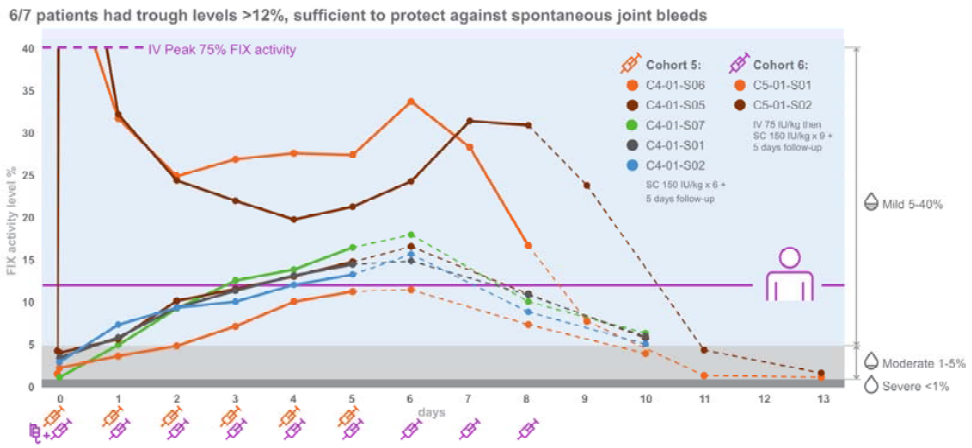
FIGURE 3. CB2679D PHASE 1/2 STUDY: COHORT 5 & 6 FIX ACTIVITY RESULTS



FIX, factor IX; IV, intravenous; SC, subcutaneous.

3. OBJECTIVES

3.1 PRIMARY

The primary objective is:

- To evaluate the dose required to achieve steady-state FIX levels >12% of a SC prophylaxis treatment regimen of CB2679d, in adult subjects with hemophilia B.

3.2 SECONDARY

The secondary objectives are:

- To determine the PK of a SC regimen of CB2679d.
- To determine the PD of a SC regimen of CB2679d.
- To evaluate the levels of thrombogenicity markers of a SC regimen of CB2679d.
- To evaluate for evidence of the development of antibodies to CB2679d and to determine if these are neutralizing antibodies.
- To monitor and evaluate safety parameters of a SC regimen of CB2679d.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, open-label Phase 2b study designed to evaluate the PK, PD, efficacy and safety of SC prophylaxis treatment regimens with CB2679d in adult subjects with hemophilia B. It is an open-label study, so subjects and members of the clinical study team will not be blinded to treatment. It is estimated that it will take approximately 6 months from when the study opens enrollment until completion of last patient last visit. The study will enroll a total of 6 adult male subjects with severe congenital hemophilia B. Participants will be given SC prophylaxis CB2679d regimens over a 4-week period, with the goal to achieve steady-state levels above 12% FIX activity when dosed daily.

Each subject will participate for approximately 4-weeks (28 days) of SC CB2679d drug administrations:

Treatment: Day 1 to Day 28: Each participant will receive an IV loading dose of 50 IU/kg followed 35 ± 5 minutes later by a SC dose of 100 IU/kg. **Daily** SC doses of 100 IU/kg will be administered until Day 28 (28 total SC doses). On day 1, PK, PD, and safety assessments will be done at pre-IV dose and repeated 35 (± 5) minutes later prior to the SC dose. Subsequent PK, PD and safety assessments will be performed pre-dose on days 2, 3, 7, 14, 21 and 28.

Washout Period

PK, PD, and safety assessments will be done on Days 29, 30, 31, 32 and 33. Daily FIX activity levels will be measured, unless FIX activity level is known to be < 5% as measured by local laboratory.

An End of Study visit will occur 30 days (± 2 days) after the last dose of study drug.

Subjects will sign an ICF at the Screening Visit, prior to any study procedures. Eligibility to participate in the study will be determined by inclusion and exclusion criteria from medical history, hemophilia history, laboratory investigations and ECG. The screening period duration may be up to 4 weeks.

At enrollment, subjects will receive training and diary entry of self-administered investigational drug administration & injection site assessment, bleeding episodes & treatment, evaluation & entry of AEs.

Treatment of a spontaneous or traumatic bleeding episode: Subjects will use their current prescribed treatment regimen for any spontaneous or traumatic bleed that occurs while on study drug. If treatment for a spontaneous or traumatic bleeding episode is needed, then subjects will contact the clinical

investigative team immediately to report the event, treatment dose administered, and determine follow-up plans for that event including whether to arrange for a blood specimen to be drawn (if feasible) before further administration of either study drug or the current prescribed treatment regimen used. Decision whether to continue daily study drug administration will also be determined by the clinical study team after discussion with the Sponsor.

Dose interruption: SC study drug injections will be interrupted if any of the following occurs: a thrombotic event; clinical evidence of inhibitor formation; or laboratory results suggesting a high titer antibody may be developing; trough activity levels >80% where subsequent dosing will be determined in consultation with the sponsor.

Surgery: If there is an urgent need for a surgical procedure or an event requiring extended (>48 hours) hospitalization, a FIX activity level will be urgently obtained and measured prior to the event, and the PI will confer with the Sponsor Medical representative regarding the need for any additional treatment and whether study drug requires interruption.

Measurements:

PK, PD, and safety assessments: FIX activity levels, as well as fibrinogen, D-dimer, F1+2, and TAT. PT and aPTT will be measured at screening and end of study visit only. Genotype testing will be performed at screening.

Immunogenicity assays: Specimens for immunogenicity testing (antibody to CB2679d, BeneFIX®, and neutralizing activity) will be drawn at screening, pre-dose on days 7, 14, 21, 28 and end of study.

If the FIX activity level decreases unexpectedly by more than 25%, ie, IU/dL, as measured by the central or local lab, FIX activity levels will be drawn for analysis within 24 hours and immediately sent to the central laboratory. Specimens for fibrinogen, D-dimer, F1+2, and TAT and immunogenicity testing will also be drawn.

4.2 END OF STUDY DEFINITION

The duration of treatment for each subject is approximately 4 weeks (28 days).

Up to 4 weeks for screening period; SC prophylaxis treatment regimens over a 4-week period with the goal to achieve steady-state levels above 12% FIX activity when dosed daily.

Where interruptions to study drug dosing days occur, study duration may be extended to incorporate full dosing schedule.

The end of study visit will be 30 days ± 2 days after the last dose of study drug treatment.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Confirmed diagnosis of severe (<2%) congenital hemophilia B.
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. (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. Patients with a history or a family history of FIX inhibitors.
2. Positive antibody to FIX detected by central laboratory at screening.
3. Previous participation in and subsequent treatment in a clinical trial within the previous 30 days or 3-half-lives, whichever is longer, or absence of clinical effect.
4. History of clinically relevant coagulation disorders other than congenital hemophilia B including Factor V Leiden or other identified activated Protein C resistance.
5. Platelet count <100,000 based on screening laboratory assessments.
6. 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.
7. Known or suspected allergy to trial product or related products.
8. Known absolute CD4 count <200 cells/µL.
9. Receiving IMT.
10. Compromised hepatic or renal function:
    - ALT and AST levels ≥5 x ULN
    - TBIL ≥2 mg/dL (>35 µmol /L) unless there is a known history of GS
    - Serum albumin ≤ LLN
    - Cr level >1.25 x 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.
12. Factor IX gene mutation 128G>A.

5.3 LIFESTYLE CONSIDERATIONS

There are no specific lifestyle considerations.

5.4 SCREEN FAILURES

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

6. STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 Study Intervention Description

Description and Composition of the Drug Product

Recombinant Factor IX variant; CB2679d, formerly known as ISU304, will be provided as a powder for injection, at a 2.0 mg/vial dosage strength. The drug product is supplied in a 5-mL vial that is sealed with a 20mm lyophile stopper and 20mm aluminum over-seal. CB2679d is supplied in vials which contain excipients (stabilizer, buffer, etc.) and packaged in a lyophilized form. Before lyophilization, each vial contains 1.42 mg/mL of CB2679d drug substance is filled with 1.4 mL of formulation buffer. The lyophilized drug product will be reconstituted for SC injection.

6.1.2 Dosing and Administration

This is an open-label study. Each subject will receive the study drug:

CB2679d loading dose of 50 IU/kg IV, followed 35 ± 5 minutes later with a 100 IU/kg, with SC administration daily until Day 28 (total 1 IV dose and 28 SC doses).

6.1.2.1 Guidelines for Treatment Interruption

CB2679d SC study injections will be interrupted, as needed, when:

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

CB2679d SC study injections may be interrupted, as needed, when:

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

Subjects will use their current treatment regimen for any spontaneous or traumatic bleed that occurs while on study. A spontaneous bleeding episode is defined as one that is precipitated by normal activities of daily living (ADL). If treatment for a spontaneous or traumatic bleeding episode is needed, then subjects will contact the clinical investigative team immediately to report the event; treatment dose administered; and determine follow-up plans for that event, including to arrange for a blood specimen to be drawn (if feasible). This information will also be recorded in the subjects' diary.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and Accountability

Upon receipt of the CB2679d shipment, the pharmacist, or a designee, will conduct an inventory and return an acknowledgement that all IP was received refrigerated and undamaged, thereby maintaining the Good Manufacturing Practice (GMP) status of the product during shipment.

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

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of the 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 IPs 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.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of 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 (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the 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. Site staff will instruct subjects on the storage requirements for take home medications including how to report temperature excursions.

6.2.3 Preparation

CB2679d will be provided as a powder for injection, at a 2.0 mg/vial dosage strength, and is supplied in a 5-mL vial. The lyophilized drug product will be reconstituted with 1.4 mL sterile water for SC injection.

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

At the study site, the CB2679d SC dose will be prepared and administered by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

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

6.4 STUDY INTERVENTION COMPLIANCE

Reasonable efforts should be made to ensure that study drug administration is administered daily according to the schedule. However, if an unavoidable disruption of the administration occurs, and a dose is not administered on the assigned day then the subject should take the dose as soon as possible. In the event that the subject does not take study drug for more than 2 days, then the subject must contact the research site for instructions on how to proceed prior to administering a dose.

6.5 CONCOMITANT THERAPY

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

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

There are no concomitant medication restrictions.

If an individual has previously been enrolled on a clinical trial evaluating a treatment (as specified in exclusion criteria #3) in clinical investigation he will be permitted to enroll onto this study, provided it is greater than 30 days since exposure to that study drug, or 3-half-lives, whichever is longer, or absence of clinical effect.

The following medications will be permitted during the study:

- In the event of spontaneous or traumatic bleeding, treatment for a spontaneous or traumatic bleeding episode will be permitted using the subject's current prescribed treatment regimen which could be BeneFIX® or Rixubis®.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

The reason for participant discontinuation or withdrawal from the study and the date will be recorded on the eCRF.

Replacement of a subject occurs for the following reason:

- If a subject does not complete 21 days of daily SC dosing, as defined in the protocol, another subject may be enrolled.

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

7.2 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 will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

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

8. STUDY ASSESSMENTAND PROCEDURES

8.1 STUDY PROCEDURES

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

8.1.1 Screening

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

- Informed consent
- Demographic parameters
- Joint evaluation (as per SOC at hemophilia treatment center)
- Inclusion and Exclusion Criteria review
- Medical and hemophilia history
- Concomitant medications
- Vital signs
- Height (screening only) and weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry: (see Footnote 4 in **Section 1.3**, **Schedule of Activities**)
- Coagulation assays: PT and aPTT (both at screening and end of study visit only)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity
- Immunogenicity assays: antibody to CB2679d and BeneFIX®
- ECG
- FIX genotype test
- Adverse events

8.1.2 Treatment (Duration 28 days)

Please refer to **Section 1.3**, **Schedule of Activities (SOA)** for the sequence of events.

8.1.2.1 Day 1 Pre-dose evaluations

- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 in **Section 1.3**, **SOA**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity
- Study Subject training on diary entry, drug administration, adverse event reporting and injection site assessment
- Adverse events

8.1.2.2 CB2679d administration (Daily from Day 1 to Day 28)

- Subjects will receive a loading **IV dose of 50 IU/kg**, followed 35 ± 5 minutes later with a **100 IU/kg SC dose** of CB2679d
- Subjects will then administer a **100 IU/kg daily SC dose** of CB2679d from Day 2 until Day 28
- Daily SC dosing of CB2679d should be self-administered by subjects at approximately the same time every day.

8.1.2.3 Day 1 at SC dose administration (35 minutes post-IV dose)

Blood will be collected at 35-minutes post-IV dose for the following evaluations:

- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity

Other evaluations will include:

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.2.4 Day 2 and 3 Pre-SC dose evaluations

Blood will be collected pre-dose (- 5 minutes), as close to the timing of the prior SC injection, on Day 2 and Day 3 for the following evaluations:

- Hematology and chemistry – platelet count only (see Footnote 4 and 5 in **Section 1.3, SOA**): Day 2 ONLY
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity

Other evaluations will include:

- Concomitant medications
- Vital sign
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.2.5 Day 7, 14, 21 and 28 Pre-dose evaluations

Blood will be collected at pre-dose (-5 minutes) for the following evaluations:

- Hematology and chemistry (see Footnote 4 in **Section 1.3, SOA**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity
- Immunogenicity assays to CB2679d and BeneFIX®

Other evaluations will include:

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3 Washout Period, Unscheduled Visits and End of Study evaluations

Please refer to **Section 1.3, Schedule of Activities (SOA)** for the sequence of events that should occur during the washout period and end of study process.

8.1.3.1 Washout period evaluations (Day 29, 30, 31, 32, and 33)

- Concomitant medications
- Clinical signs of thrombosis (see **Appendix A**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity
    - Daily FIX activity levels will be measured, unless FIX activity level is known to be < 5% as measured by local laboratory
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3.2 Unscheduled visit evaluations

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

- Medical and Hemophilia History
- Concomitant medications
- Vital signs
- Weight
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 in **Section 1.3**, **SOA**)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT
- PK: FIX activity
- Immunogenicity assays to CB2679d and BeneFIX®
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.1.3.3 End of Study visit evaluations (30 days after last dose)

The following procedures will be performed:

- Concomitant medications
- Vital signs
- Physical examination
- Clinical signs of thrombosis (see **Appendix A**)
- Hematology and chemistry (see Footnote 4 in **Section 1.3**, **SOA**)
- Coagulation assays: PT and aPTT (both at screening and end of study visit only)
- Thrombogenicity markers: Fibrinogen, D-dimer, F1+2, and TAT

- PK: FIX activity
- Immunogenicity assays to CB2679d and BeneFIX®
- Review of diary entry of investigational drug administration, injection site assessment, adverse events, bleeding episodes & treatment
- Adverse events

8.2 STUDY ASSESSMENTS

8.2.1 Efficacy Assessments

Subjects will be asked to record daily SC injections, any injection site reactions, any AEs experienced, and all spontaneous or traumatic bleeding episodes and concomitant medications administered into the Diary, including (but not limited to) the following:

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

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

Investigators will document:

- Subject demographics (sex, age, race and ethnicity) will be recorded at the screening visit.
- All ongoing conditions and relevant medical and hemophilia history (including all major hospitalizations and surgeries), as well as the subject's current medical status and genotype will be recorded at the screening visit.
- Diagnosis of severe congenital hemophilia B will be documented including the frequency of spontaneous or traumatic bleeding episodes in the past 6 months and in the past 50 days.

- Notation will be made regarding history of orthopedic procedures including joint aspiration, synovectomy, fusion, or joint replacements or other complications of hemophilia including pseudotumors.
- Concomitant medication use including treatment used for control of spontaneous or traumatic bleeding events (infusion therapies, anti-fibrinolytic agents, local agents) and for management of pain and other complications related to hemophilia.
- Vital signs, height, weight, general physical examination will be performed at screening.

8.2.2 Physical Examination

A full physical assessment of the major body systems will be recorded at Screening followed by interim targeted evaluation, per Investigator's discretion, as indicated on presentation of subject at study visit.

8.2.3 Vital signs

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

8.2.4 Hematology

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

8.2.5 Chemistry

Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST and GGT), TBIL, albumin, and creatinine (Cr) will be measured using standard laboratory testing methods at a local laboratory.

8.2.6 Coagulation assays

PT and aPTT (at screening and end of study ONLY) will be performed at a central laboratory.

8.2.7 Thrombogenicity markers

Fibrinogen, D-dimer, F1+2, and TAT. These evaluations will be performed at a central laboratory.

8.2.8 Immunogenicity Assays

Antibody response and neutralizing antibodies to Dalcinonacog alfa and BeneFIX®. These evaluations will be performed and tested at a central laboratory.

8.2.9 Pharmacokinetic Sampling

Evaluations related to PK and PD will include:

- FIX activity levels over time post-dose and calculation of standard PK parameters. Study evaluations will be performed at a central laboratory. However, FIX activity levels may be performed at a local laboratory for safety and during the wash-out period.

8.2.10 Clinical signs of thrombosis (**Appendix A**)

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

8.2.11 Concomitant medications

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

8.2.12 ECG

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

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

8.3 SAFETY AND OTHER ASSESSMENTS

Evaluations related to safety will include:

8.3.1 AEs and SAEs

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

8.3.2 Injection site reactions

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

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 Definition of Adverse Events (AE)

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

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

8.4.2 Definition of Serious Adverse Events (SAE)

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

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

All AEs will be assessed by the study clinician using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 where applicable.[39]

For those AEs that are not included under the CTCAE v5.0, the following guidelines will be used to describe severity.

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

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

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

8.4.3.2 Relationship to Study Drug

All AEs must have their relationship to study drug assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded

using the categories below. In a clinical trial, the study product must always be suspect.

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

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

8.4.3.3 Action Taken

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

Permanently discontinued: Study drug was discontinued and not restarted

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

8.4.3.4 Expectedness

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

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

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

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

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

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

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

Subject Withdrawal from the Study Due to an Adverse Event:

Every reasonable effort should be made to maintain subject compliance and participation in the study. All enrolled subjects who received the study drug must be followed through the Follow-Up visit, regardless of the reason for withdrawal. If a subject who has a clinically significant laboratory abnormality or AE withdraws from the study, every effort must be made to follow these events until satisfactory resolution.

8.4.5 Adverse Event Reporting

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

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

Resolved: The subject recovered from the AE.

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

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

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

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

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

All bleeds should be entered into the diary including spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery (see **Section 4.1**). Only bleeds (spontaneous bleeds, traumatic bleeds or bleeds related to procedure/surgery) that are considered serious as per definition (see **Section 8.4.6**) should be reported as *an* SAE in the CRF. Non-serious bleeds *are not considered adverse events for the purpose of this protocol and* should not be reported as adverse event in the eCRF.

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

Thrombotic events (see Appendix A)

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

Development of Drug Antibodies and Inhibitors

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

Skin injection site may become reddened or painful.

Risks associated with blood collection:

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

8.4.6 Serious Adverse Event Reporting

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

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

Resolved:	The subject recovered from the AE.
Ongoing:	At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death. No AE stop date should be recorded with an AE that is ongoing.
Chronic/Stable:	At the time of the last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated.
Death:	The AE directly caused death.
Unknown:	There is an inability to access the subject or the subject's records to determine the outcome (ie, subject withdraws consent or is lost to follow-up).

Definitions:

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

Life threatening AE: Any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (*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 pre-planned hospitalizations for pre-existing conditions that did not worsen during the study.

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

8.4.7 Adverse Events of Special Interest (AESIs)

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

1. Thromboembolic events (TEs) based on information associated with other drugs for treatment of hemophilia. TEs include myocardial infarction (MI); venous thrombosis, and pulmonary embolism (PE); and stroke. See **Appendix A** for signs and symptoms listed for the subjects and the study team personnel as those requiring urgent reporting and attention.
2. Immune response resulting in antibody formation and potentially an inhibitory antibody response. This will also be monitored for throughout the study.

8.4.8 Reporting of Pregnancy

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

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

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

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

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

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

9. STATISTICAL CONSIDERATIONS

9.1 STUDY HYPOTHESIS

The study hypothesis is that a daily SC dose of CB2679d results in levels sufficient to provide protection from spontaneous bleeding.

Primary Analysis Plan:

Appropriate descriptive statistics of all measured parameters will be reported, including 95% confidence intervals.

The dose required to achieve steady-state levels >12% will be reported for daily dosing, including 95% confidence intervals.

Primary Endpoint

The primary endpoint will include:

- Number of subjects who achieve a steady-state FIX activity level above 12%, with daily dosing.

Secondary Endpoints

The secondary endpoints will include:

- Safety assessments: Occurrence of antibody formation resulting in a decreased endogenous level of FIX; occurrence of a clinical thrombotic event not attributable to another cause.
- Occurrence of a conformed antibody response with high titer to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX®.
- Change in FIX activity levels.
- Occurrence of clinically significant levels of thrombogenicity markers resulting from SC administration of CB2679d.

9.2 SAMPLE SIZE DETERMINATION

6 subjects are sufficient to provide guidance on range of dose required to achieve steady-state activity >12% and starting SC dose for subsequent studies. As this study is not inferential, no formal sample size calculation is required.

9.3 POPULATIONS FOR ANALYSES

Safety population: any patient who receives at least one dose.

Efficacy/PD population: any patient who receives at least one week of daily SC dosing and PK specimens obtained.

If a subject does not complete the study as defined in the protocol another subject will need to be enrolled in replacement.

9.4 STATISTICAL ANALYSIS

9.4.1 General Approach

Various pharmacokinetic parameters will be calculated, including area under the time curve (o-t and 0-infinity), clearance, volume of distribution at steady-state, T_{max} and C_{max}, and terminal (beta phase) $t_{1/2}$, will be calculated. A semi-parametric model described by Lee et al[40] will be used to calculate the terminal $t_{1/2}$. Other parameters will be calculated using a standard noncompartmental approach. Descriptive statistics will be reported for each parameter and will include mean ± standard deviation and median ± interquartile range.

The evaluation of the primary endpoint is descriptive, but 95% confidence intervals will be calculated as appropriate.

There will be a formal Statistical Analysis Plan (SAP) completed prior to database lock.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The analysis of the primary endpoint will include:

- Number of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.

9.4.3 Analysis of the Secondary Endpoint(s)

Study drug exposure and compliance will be provided.

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 FIX.
- Change in coagulation parameters (fibrinogen, and FIX activity levels) from pre-dose.
- Occurrence of an antibody response to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX®.
- Clinically significant levels of thrombogenicity markers resulting from SC administration of CB2679d

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

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

9.4.4 Safety Analysis

Adverse Events

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

Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown for. Incidence rates will also be displayed based on severity and relationship to study drug. AEs with a relationship of "possibly" or "probably" related will be considered by the Sponsor as "related" to the study drug. Events assessed as "unrelated", "unlikely" related, or where the

relationship was not reported will be considered by the Sponsor as "not related" to the study drug. The incidence of SAEs will be provided. All incidence rates will be categorized and displayed by system organ class and preferred term.

Vital Signs

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

9.4.5 Baseline Descriptive Statistics

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

9.4.6 Planned Interim Analyses

Not applicable to this study.

9.4.7 Sub-Group Analyses

Not applicable to this study.

9.4.8 Tabulation of Individual Participant Data

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

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

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

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

10.1.2 Institutional Review Board/Independent Ethics Committee

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

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

- All SAEs (including deaths) regardless of cause and whether anticipated or unanticipated (reported immediately)
- Significant findings that become known in the course of the study that might affect the willingness of subjects to continue to participate

- Protocol, or consent amendments prior to the implementation of the change
- Study progress reports at least once a year, if applicable
- Notification of study completion or termination.

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

10.1.3 Study Discontinuation and Closure

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

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

10.1.4 Confidentiality and Privacy

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

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

10.1.5 Future Use of Stored Specimens and Data

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

10.1.6 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 ICH GCP, and with applicable regulatory requirement(s).

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

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

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

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

10.1.7 Quality Assurance (QA) and Quality Control (QC)

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

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

Diary data will be entered into the eCRF.

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

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

10.1.8 Data Handling and Record Keeping

10.1.8.1 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.

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

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

10.1.8.2 Study Records Retention

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

10.1.9 Protocol Amendments

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

10.1.10 Publication and Data Sharing Policy

The final clinical study report is also intended to form the basis for a manuscript intended for publication in a peer-reviewed scientific journal. The authorship, timetable and any arrangements for review by the participating investigators will be coordinated by Catalyst Biosciences. No partial subset of data from

individual investigational sites can be presented or published until after the primary manuscript for the entire study has been accepted for publication in a peer reviewed scientific journal.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	23 March 2018		
2.0, Amendment 1	17 October 2018	Removed Part 2 and 3	

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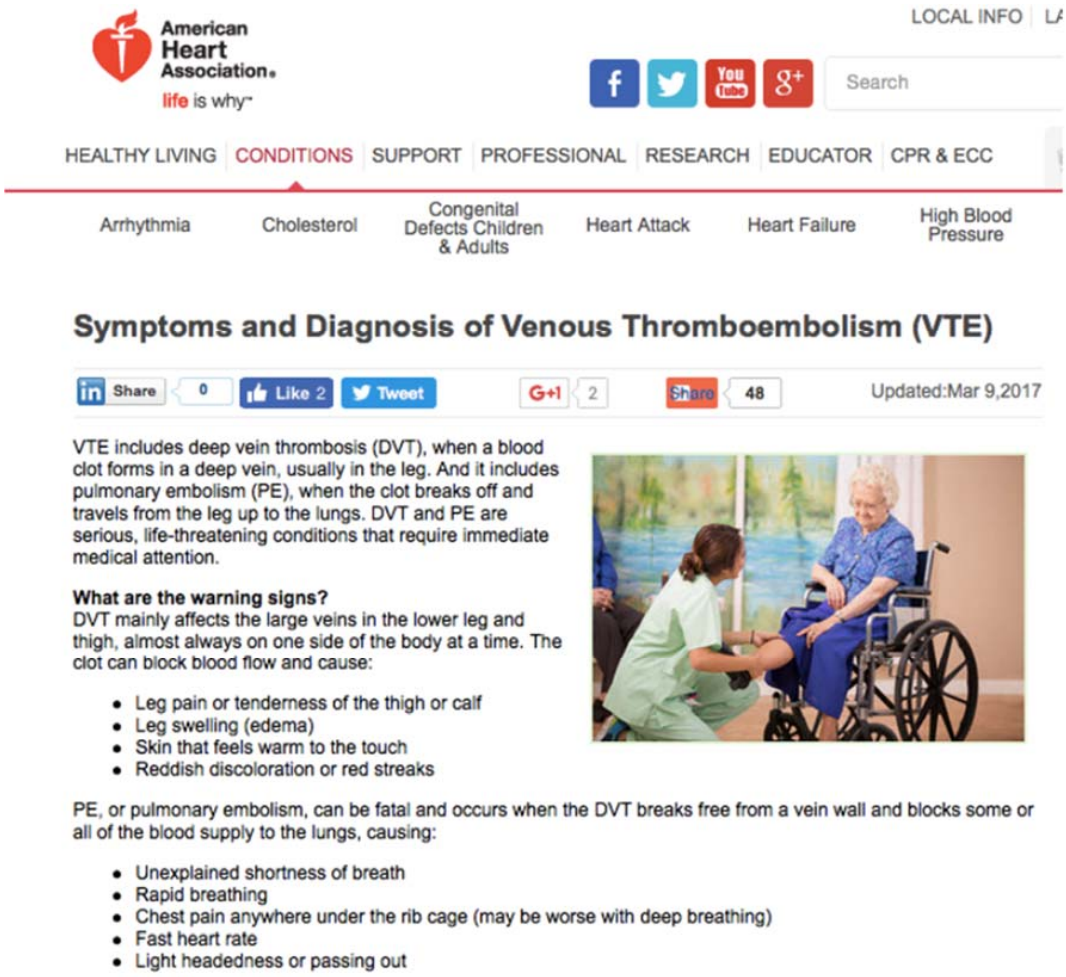
APPENDICES

APPENDIX A – CLINICAL SIGNS OF THROMBOSIS



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Symptoms and Diagnosis of Venous Thromboembolism (VTE)

Share 0 | Like 2 | Tweet | G+1 2 | Share 48 | Updated:Mar 9,2017

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

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

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

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

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

http://www.heart.org/HEARTORG/Conditions/VascularHealth/VenousThromboembolism/Symptoms-and-Diagnosis-of-Venous-Thromboembolism-VTE_UCM_479057_Article.jsp#

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http://www.heart.org/HEARTORG/Conditions/HeartAttack/WarningSignsofaHeartAttack/Warning-Signs-of-a-Heart-Attack_UCM_002039_Article.jsp#.WkkEAWeYpfw

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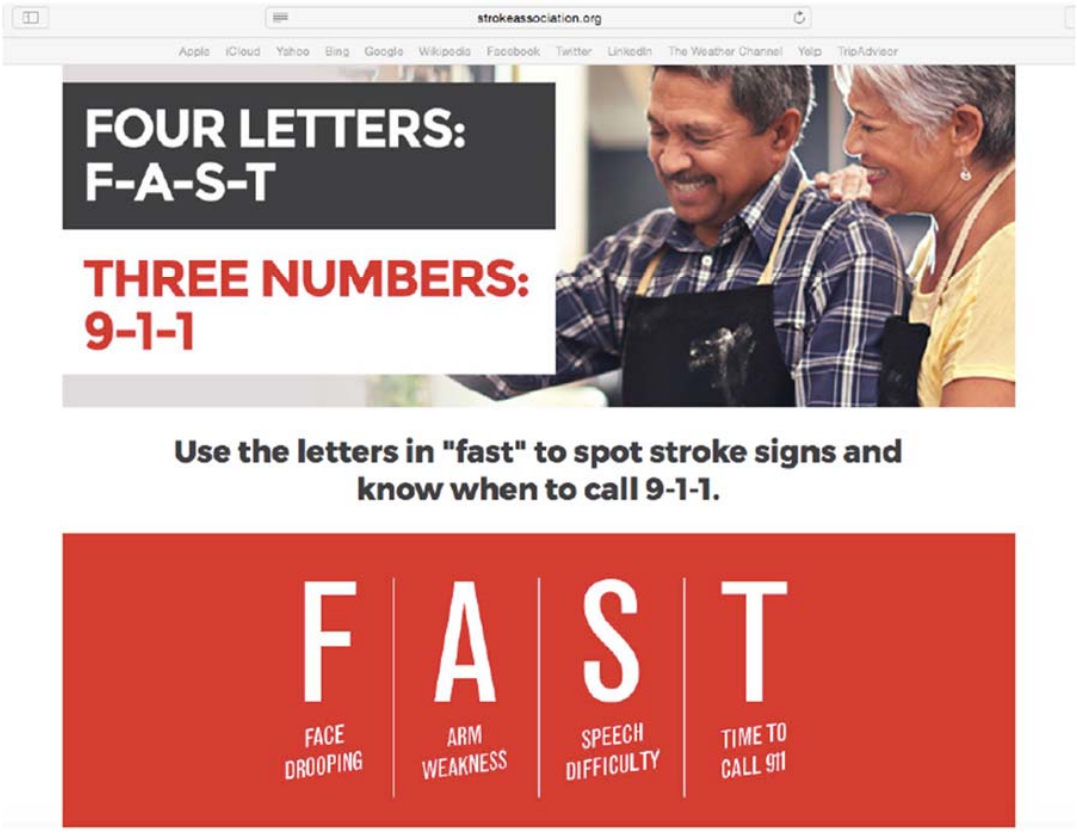

http://www.strokeassociation.org/STROKEORG/WarningSigns/Stroke-Warning-Signs-and-Symptoms_UCM_308528_SubHomePage.jsp

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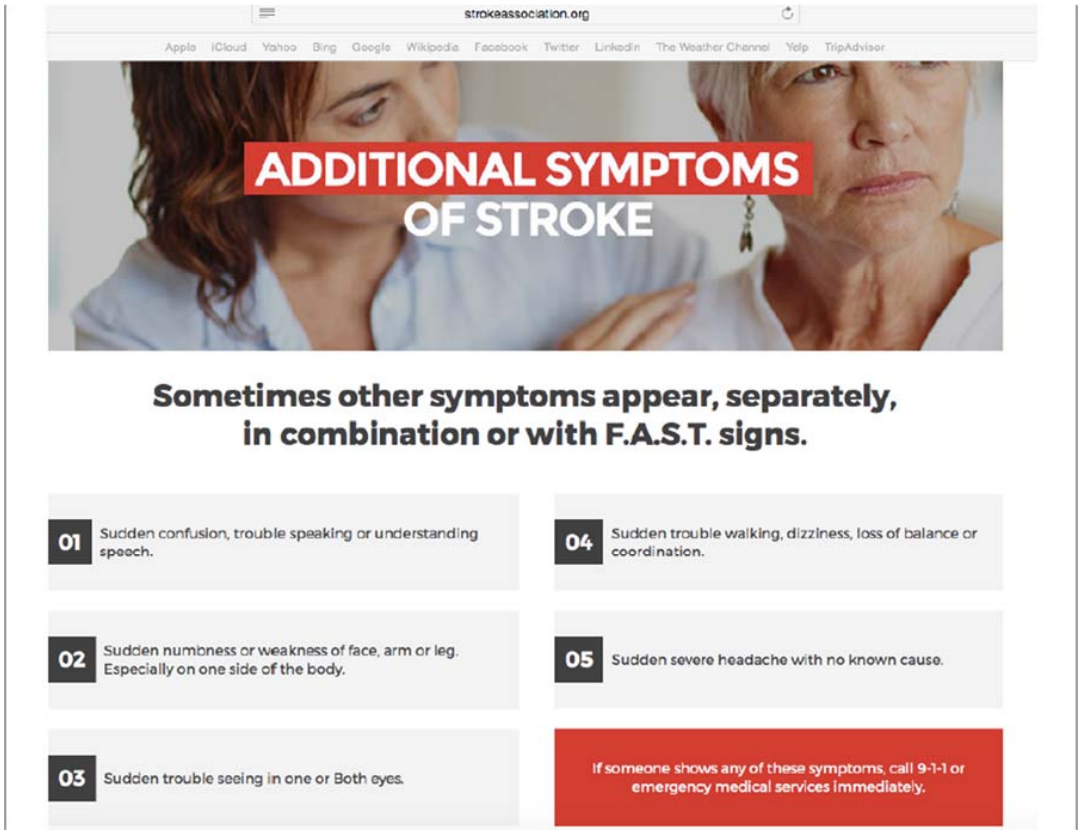

Symptoms and Signs of Venous Thromboembolism – Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):

Leg pain or tenderness of the thigh or calf

Leg swelling (edema)

Skin that feels warm to the touch

Reddish discoloration or red streaks

Unexplained shortness of breath

Rapid breathing

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

Fast heart rate

Light headedness or passing out

Common Heart Attack Warning Signs

Pain or discomfort in the chest

Lightheadedness, nausea, or vomiting

Jaw, neck, or back pain

Discomfort or pain in arm or shoulder

Shortness of breath

Stroke Signs

Face Drooping

Arm Weakness

Speech Difficulty

Sudden confusion, trouble speaking or understanding speech

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

Sudden trouble seeing in one or both eyes.

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

Sudden severe headache with no known cause.

Signs and Symptoms of Thrombosis

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

Table. Clinical Spectrum of VTE

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

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

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

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

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APPENDIX B – DETAILED STUDY SCHEMA

SCREENING	
Up to 4 weeks prior	Screening

- Obtain informed consent
- Review demographic parameters
- Conduct a joint evaluation as per the SOC at hemophilia treatment center
- Screen potential subjects by inclusion and exclusion criteria
- Obtain medical and hemophilia history, document
- Check vital signs, height and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, immunogenicity assays, genotyping and ECG

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Treatment – 28 days	
Day 1 Pre-IV Dose – 5 min	**Day 1**
• Evaluate concomitant medications, check vital signs, and weight • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling • Conduct study subject diary training	
Day 1 IV Dose Followed by SC Dose; Day 2 to Day 28 SC Dose	**Day 1**
• Day 1: Administer single IV 70 IU/kg loading dose of Dalcenonacog alfa • Day 1: 30 minutes later administer SC 140 IU/kg dose of Dalcenonacog alfa • Day 2 to 28: Administer SC 140 IU/kg dose of Dalcenonacog alfa	
Post-Dose SC Dose – (30 min and Hr 7)	**Day 1**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs • Conduct platelet count only on Day 1, Hour 7	
24 Hours Post-SC Dose	**Day 2**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for thrombogenicity markers, PK sampling • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs	
Pre-SC Dose	**Days 7, 14, 21, 28**
• Evaluate concomitant medications and check vital signs • Conduct physical examination, check for clinical signs of thrombosis • Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling, immunogenicity assays • Diary entry of bleeding episodes, AEs, injection site assessment • Check for AEs	

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Washout Period - Days 29, 30, 31, 32, 33

- Evaluate concomitant medications, check for clinical signs of thrombosis
- Conduct testing for thrombogenicity markers, PK sampling
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs

Unscheduled

- Review medical and hemophilia history, document
- Evaluate concomitant medications, check vital signs, and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, thrombogenicity markers, PK sampling, immunogenicity assays
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs

End of study

- Evaluate concomitant medications and check vital signs and weight
- Conduct physical examination, check for clinical signs of thrombosis
- Conduct testing for hematology and chemistry, coagulation assay, thrombogenicity markers, PK sampling, immunogenicity assays
- Diary entry of bleeding episodes, AEs, injection site assessment, check for AEs