16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan for Interventional Studies (Protocol DLZ-201) Version 1.0 dated 24-May-2019

Note to File - Update of final tables dated 14-July-2020

Note to File - Minor edits of SAP v1.0 dated 24-May-2019

Statistical Analysis Plan for Interventional Studies

Sponsor Name: Catalyst Biosciences, Inc.

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

Protocol Version and Date: v 2.0, Amendment 1 (17-Oct-2018)

Syneos Health Project Code: 1011852

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Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**
v1.0	24-May-2019	Anja Schulze	Initial Release Version

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Events of Special Interest
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Lower limit of quantification
BMI	Body Mass index
CAD	Coronary artery disease
CBC	Complete blood count
CD4	Cluster of differentiation 4
CI	Confidence Interval
CL	Clearance
Cmin	Concentration at the end of the dosing interval
Cr	Creatinine
CV	Coefficient of Variation
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EOS	End of study
eCRF	electronic Case Report Form
F1+2	Prothrombin fragment 1+2
FIX	Factor IX

Abbreviation	Description
GGT	Gamma-glutamyl transpeptidase
GM	Geometric Mean
GCV	Geometric Coefficient of Variation
GS	Gilbert's syndrome
ICF	Informed consent form
ICH	International Conference on Harmonization
IMT	Immunomodulatory therapy
IQR	Interquartile range
IV	Intravenous
LCM	Least Square Means
LLN	Lower limit of normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure

Abbreviation	Description
t1/2	Half-life
TAT	Thrombin-antithrombin complexes
TBIL	Total bilirubin level
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
Tmax	Time that studied drug is present at the maximum concentration
ULN	Upper limit of normal
VTE	Venous thromboembolic event
Vz	Volume of distribution at steady state
WHO	World Health Organization

2. Purpose

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

2.1. Responsibilities

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

2.2. Timings of Analyses

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

3. Study Objectives

3.1. Primary Objective

The primary objective is:

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

3.2. Secondary Objectives

The secondary objectives are:

- To determine the PK of a 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 a SC regimen of CB2679d.

3.3. Brief Description

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 subject enrollment until completion of last subject last visit. The study will enroll and dose SC a total of 6 adult male subjects with severe congenital hemophilia B. Participants will be given a SC prophylaxis CB2679d regimen 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 intravenous (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 informed consent form (ICF) at the Screening Visit, prior to any study procedures. Eligibility to participate in the study will be determined by inclusion and exclusion criteria from medical history, hemophilia history, laboratory investigations, and electrocardiogram (ECG). The screening period duration may be up to 4 weeks.

At enrollment, subjects will receive training on diary entry of self-administered study drug administration, injection site assessment, bleeding episodes and treatment, and evaluation and entry of adverse events (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, 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). Prothrombin time and activated partial thromboplastin time (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 central laboratory, 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.

3.4. Subject Selection

3.4.1. 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.

3.4.2. Exclusion Criteria

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

1. Subjects 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 (eg, known history of coronary artery disease (CAD), ischemic stroke), 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 asparatate aminotransferase (AST) levels ≥5 × 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 ≤ lower limit of normal (LLN)
    - Serum creatinine (Cr) level >1.25 × ULN

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

12. Factor IX gene mutation 128G>A.

3.5. Determination of Sample Size

Six (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.

3.6. Treatment Assignment and Blinding

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

3.7. Administration of Study Drug

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

3.8. Study Procedures and Flowchart

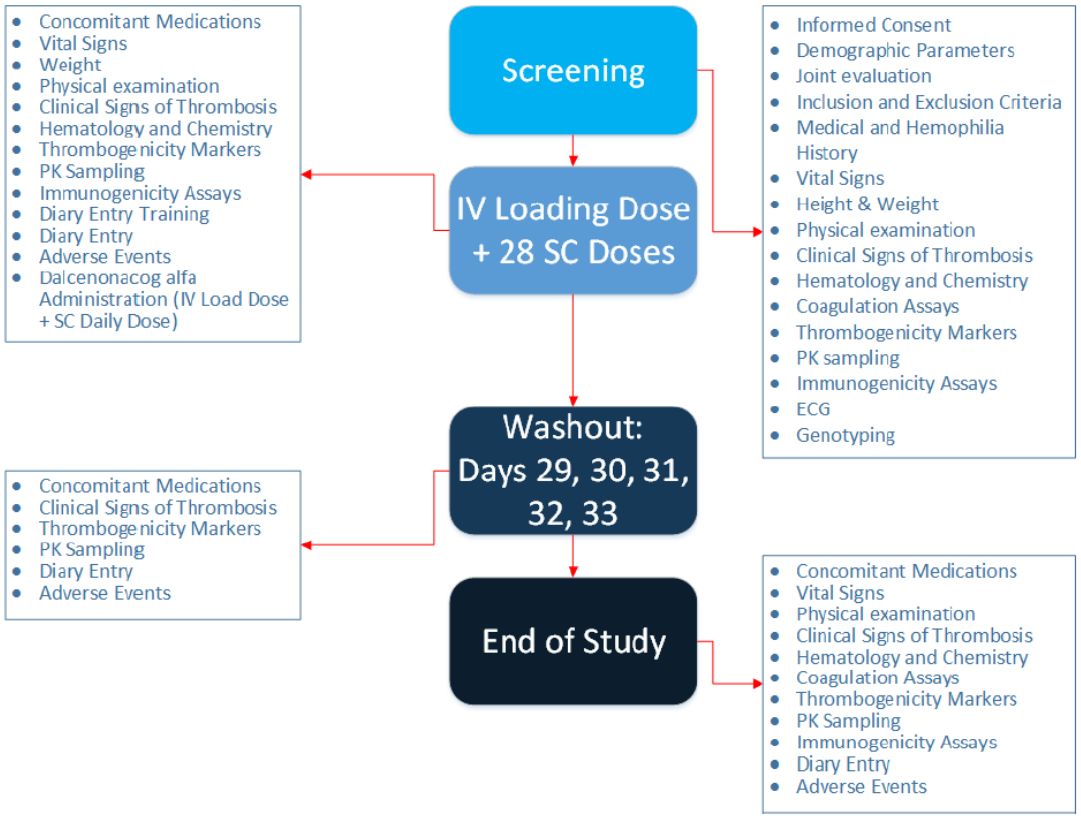

Figure 1: Schematic of study design

Statistical Analysis Plan for Interventional Studies
Sponsor: Catalyst Biosciences, Inc.; Protocol No.: DLZ-201

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	←----------											→
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 – complete blood count (CBC) and platelet count. Chemistry - Sodium, potassium, chloride, bicarbonate, hepatic enzymes (ALT, AST, Gamma-glutamyl transpeptidase (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 – Prothrombin time 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.

Table 1: Schedule of Activities

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary endpoint is:

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

4.2. Secondary Efficacy Endpoints

The secondary endpoints will include:

- Change in FIX activity levels and fibrinogen from pre-dose.
- Occurrence of clinically significant levels of thrombogenicity markers resulting from SC administration of CB2679d
- Occurrence of a confirmed antibody response to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX®.

4.3. Pharmacokinetic Endpoints

The PK endpoints of SC regimen will include standard PK parameters as described in Section 9.

4.4. Pharmacodynamic Endpoints

The PD endpoints of SC regimen will include the results of specific coagulation assays and thrombogenicity biomarkers as described in Section 10.

4.5. Safety Endpoints

The following safety assessments will be documented:

- Occurrence of Adverse Events (AE).
- Occurrence of antibody formation resulting in a endogeneous decreased level of FIX
- Occurrence of a clinical thrombotic event not attributable to another cause

5. Analysis Populations

5.1. Screened Population

The Screened Population will include all subjects screened. Unless specified otherwise, this population will be used for subject listings and for summaries of subject disposition.

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

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.

5.2. Safety Population

The Safety Population will include all subjects who were administered at least one dose of study medication. Subjects will be analyzed according to treatment received. The Safety Population will be used for all analyses of efficacy in respect to PK and PD and safety endpoints and for the presentation of subjects in subject listings.

5.3. Pharmacokinetic (PK) Population

The PK population is defined as any subject who was administered at least one week of daily SC dosing and had FIX activity values at four or more time points. The PK data will be listed for this population and used in all PK analyses. The PK data for subjects with protocol deviations affecting the results may be excluded from summaries and analyses. Any protocol deviations pertaining to the validity of PK analyses (and thus inclusion in the PK population) will be determined before the database lock based on a review of all protocol deviations.

5.4. Pharmacodynamic (PD) Population

PD population is defined as any subject who was administered at least one week of daily SC dosing and who had at least one non-missing PD parameter. The PD data will be listed for this population and used in all PD analyses. The PD data for subjects with protocol deviations affecting the results may be excluded from summaries and analyses. This will be determined before the database lock based on review of all protocol deviations.

5.5. Protocol Deviations

All protocol deviations will be documented in the electronic Case Report Form (eCRF). Protocol deviations will be analyzed in frequency tables and will be listed with information describing each deviation in detail. All protocol deviations will be discussed in detail prior to database lock. Protocol deviations which will results in an exclusion of the subject from an analysis population will be tablulated.

6. General Aspects for Statistical Analysis

6.1. General Methods

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), 95% confidence interval (if applicable), median, interquartile range (IQR) (defined as difference of 75% and 25% quartiles) minimum (Min), and maximum (Max).

Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.

All relevant subject data will be included in listings..

6.2. Key Definitions

6.2.1. Baseline and Change from Baseline

Baseline is defined as the last assessment (pre-dose) before the first administration of study drug.

Change from baseline = (post-baseline value – baseline value).

Maximum absolute change from baseline will be calculated as the maximum of the absoulute changes from baseline over all visits during treatment period.

6.3. Missing Data

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

6.4. Visit Windows

All data will be organized and analyzed according to the scheduled visits outlined in the protocol. However, if the scheduled visit is not available in the dataset, unscheduled visit will be mapped to a scheduled visit for analysis using the date and/or time of collection/assessment to mapped to the intended visit using the visit window specified below.

If more than one record occurs within the same visit window where only one assessment is expected, then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Visit in Protocol	Time point	Time Window	Visit Window
Day 1	Pre IV dose	no limitation	no window as only one day
	Post IV dose, pre SC Dose	35 +/- 5 minutes post IV dose, - 5 minutes pre SC dose	no window as only one day
Day 2 – Day 3	Pre SC dose	- 5 minutes pre SC Dose	no window as only one day

Day 4 – Day 28	Pre SC dose	- 5 minutes pre SC Dose	+/- 1 days

6.5. Pooling of Centers

Not applicable to this study.

6.6. Subgroups

Not applicable to this study.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

Subject disposition will be summarized overall and presented for the number and percentage of subjects for the following:

- Screened subjects (only number of subjects will be presented)
- Subjects did not complete the screening period or enter the treatment period (Screen Failure) and the reason for not completing screening
- Safety Population
- PK Population
- PD Population
- Subjects who completed the treatment
- Subjects who discontinued the treatment and the reason for discontinuation
- Subjects who completed the study
- Subjects who discontinued the study and the reason for discontinuation

7.2. Demographic and Other Baseline Characteristics

Descriptive statistics will be presented for demographic and baseline characteristics using the Safety Population. Demographic and baseline characteristics, including age, sex, race, ethnicity, baseline ECG (PR interval, QRS interval, QTcF interval and Overall interpretation) and baseline vital signs (i.e., blood pressure (BP), heart rate (HR), respiration rate (RR), body temperature (in C), weight, height and Body Mass Index (BMI)), will be summarized overall and listed.

The below conversion will be used:

Body temperature (in C) = (body temperature in (F) – 32) * 5/9

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

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

7.3. Medical History

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

subjects with history in each SOC and each PT for the Safety Population. Medical history of each subject will be listed as well.

7.4. Hemophilia History

Hemophilia history will be listed and summarized overall based on the Safety Population for the categories below:

- Number and percentage of severe congenital hemophilia.
- Age at diagnosis.
- Number, percentage and the 95% CI for proportion calculated by using the Wilson Score method (Wallis 2013) for each type of of clinical setting of hemophilia diagnosis (prenatal, at birth, and unanticipated/unexpected bleeding).
- FIX level (Lowest Reported FIX level).
- Number and percentage of history of orthopedic procedure, and type of orthopedic procedure (joint aspiration, synovectomy, fusion, joint replacements, other).

The FIX genotype test results as part of the hemophilia history will be listed only.

7.5. Hemophilia Bleed History

Hemophilia bleed history will be summarized descriptively in the past 6 months for the Safety Population.

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

Hemophilia bleed history will be listed.

7.6. Medication

7.6.1. Prior and Concomitant Medication

Medications started and stopped prior to the first administration of study drug will be classified as prior medication. Ongoing Medication started before the date of the first administration of study drug will be classified as concomitant medication (Ongoing). Medication started on or after the date of the first administration of study drug will be classified as concomitant medication (newly started).

The number and percentage of subjects using each prior and concomitant medication (ongoing and newly started) will be summarized overall according to the World Health Organization (WHO) Drug Month B3 Sep 2017 for the Safety Population. Anatomical Therapeutic Chemical (ATC) level 3 and PT will be used.

Subjects with multiple uses of a prior and concomitant medication will be counted only once for a given PT in a given ATC level 3 term and only once within a given ATC level 3 term.

In addition, prior and concomitant medication (ongoing and newly started) will be listed.

7.6.2. Prior and Concomitant Hemophilia Specific Medication

As described for prior and concomitant medication, the number and percentage of subjects using prior and concomitant hemophilia specific medication (ongoing and newly started) will be summarized for Safety Population by ATC level 3 and PT.

The invidivual dose, number of doses, and total daily dose by PT will be summarized for Safety Population, as well.

In addition, prior and concomitant hemophilia (ongoing and newly started) specific medication will be listed.

8. Efficacy

8.1. Primary Efficacy Endpoint and Analysis

The primary endpoint is the number and percentage of subjects who achieve a steady-state FIX activity level above 12% with daily dosing.

On Day 1, FIX activity level will be assessed at pre-IV dose and repeated 35 (+/- 5) minutes later prior to the SC dose. Subsequent FIX activity assessment will be performed pre-dose on days 2, 3, 7, 14, 21 and 28, and during washout period on days 29, 30, 31, 32, and 33.

Number and percentage of subjects and list of the subjects with a FIX activity level >12% will be summarized during treatment period for the PK and the Safety Population.

8.2. Secondary Efficacy Endpoints and Analyses

8.2.1. Change in FIX activity levels from pre-dose

Actual and change from baseline (including maximum absolute change from baseline) values for FIX activity level will be summarized by time point for the PK and the Safety Population. Different PK parameters will be summarized as well as described in Section 9.

8.2.2. Occurrence of clinically significant levels of thrombogenicity markers resulting from SC administration of CB2679d

The following thrombogenicity markers during the treatment period will be assessed for the PD and the Safety Population:

- Fibrinogen,
- D-dimer,
- F1+2,
- TAT

Detailed PD analysis is described in Section 10.

8.3. Additional Analyses

In addition to the primary endpoint analysis, the number and percentage of subjects with a FIX activity level >30% and >50% will be summarized during treatment period for the PK and the safety population.

9. Analysis of Pharmacokinetics

PK analysis will be performed by Catalyst Biosciences, Inc. using compartmental and non-compartmental analysis in Demitasse 2000 (M.Lee, UCLA). The PK Tables, Listings, and Figures (TLFs) will be produced using SAS statistical package version 9.4 or higher. PK analysis will be performed for the PK and the Safety Population.

9.1. PK Sampling Schedule

PK sampling schedule will be specific to each dose administration. The PK data will be measured as FIX activity levels.

During treatment period: On Day 1, PK assessments will be done at pre-IV dose and repeated 35 (± 5) minutes later prior to the SC dose. Subsequent PK assessments will be performed pre-dose on days 2, 3, 7, 14, 21 and 28.

Washout Period: PK 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.

9.2. Plasma PK Endpoints

Various pharmacokinetic parameters will be calculated as listed below, including:

- clearance (CL) (from Day 28 and subsequent samples during washout)
- volume of distribution at steady state (Vz) (from Day 28 and subsequent samples during washout),
- Highest recorded clotting activity level after nadir value from the IV infusion
- and terminal (beta phase) half-life t1/2, will be calculated from Day 28 and subsequent samples during washout

A semiparametric model described by Lee et al. (Lee et al, 1990) will be used to calculate the terminal t1/2. This analysis will be performed using the program Demitasse 2000 (Lee et al, 1997). Other parameters will be calculated using a standard non-compartmental approach.

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data

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

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

- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- Post-dose BLQ values after the first quantifiable time point will be treated as zero.
- If the actual time of sampling is missing, the planned time may be used.

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

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

No further imputation will be applied to any missing values.

9.3.2. Listing and Presentation of Individual PK Data

Individual PK FIX activity levels and actual sampling time of PK blood sample collection will be listed for each subject for treatment period and washout period and will include the deviation in time from the scheduled time, if applicable. Subjects with protocol deviation affecting PK may be flagged and excluded from PK Population.

Individual subject intense PK parameters will be listed for the Safety population. Unreliable PK parameters will be listed but flagged and excluded from summary by PK Specialist.

The following figures will be produced:

- Individual intense PK concentration-time provided for FIX activity levels with all subjects in the same figure on linear scales.

9.3.3. Summary of PK Concentrations and Parameter in Plasma

The PK concentration for FIX activity level will be summarized overall and will be based on actual dose administration.

PK parameters and activity level will be summarized by time point using the following descriptive statistics:

Variable	**Summarized with:**
PK FIX activity level at each nominal time point	n Number and %BLQ mean +/- SD Coefficient of variance (CV) [%] median ± IQR Min - Max
CL, Vz	n mean +/- SD CV [%] median ± IQR Min – Max GM (GCV)
Washout period t1/2	n mean +/- SD CV [%] median ± IQR Min - Max

Note: GM = geometric mean, GCV = geometric CV [%]

CV [%] = SD/mean in %

IQR = 3rd Quartile – 1st Quartile

%BLQ = total number of subjects who have BLQ values / total number of subjects at each time point in %

Mean concentrations, SD, and CV will not be presented if 70% or more of the actual values at any time point are BLQ or missing.

9.4. PK Parameters Derivation: Attainment of Steady State for FIX Activity

Attainment of steady state will be estimated using aggregate assessment of trough concentration if sufficient data will be available.

To assess whether steady state was achieved for FIX activity after daily dosing of CB2679d, aggregate assessment of trough concentration will be used to evaluate attainment of steady state (Maganti et al 2008). The approach is based on the comparison of log-transformed normalized trough concentration values for each dose to the mean of the results for all the following doses.

This analysis will be done using repeated measures analysis only if the data are sufficient to support; i.e., analysis will be carried out only on subjects who have at least 3 valid FIX activity level results out of 6 pre-dose samples). Alternatively, analysis of variance (ANOVA) comparison will be carried out on log-transformed Cmin (concentration at the end of the dosing interval = FIX activity level pre-dosing) pre-dose on days 2, 3, 7, 14, 21 and 28. The following SAS code may be used to conduct the analysis:

PROC MIXED;

CLASS <time> <subject>;

MODEL log_base_e_ <FIX actual level> = <time> /DDFM = KR;

LSMEANS <time>;

RUN;

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

Contrasts will be tested between a time point and the pooled mean over all remaining time points. For example, the following contrasts will be tested as example:

- Day 3 vs Days 7, 14, 21, and 28
- Day 7 vs Days 14, 21, and 28
- Etc.

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

10. Analysis of Pharmacodynamics

PD analysis will be performed using SAS statistical package version 9.4 or higher. PD analysis will be performed for PD and Safety Population.

10.1. PD Sampling schedule

PD analysis includes following PD parameters

Coagulation assays:

Prothrombin Time

aPTT

Thrombogenicity markers

Fibrinogen

D-dimer

F1+2

TAT

Sample for coagulation assays are collected at Screening and at end of study (EOS). Thrombogenicity markers are assessed pre-dose on days 2, 3, 7, 14, 21 and 28.

10.2. PD Biomarkers Analysis

Actual and change from baseline (including maximum absolute change from baseline) for all PD parameters (e.g., Prothrombin Time, aPTT, Fibrinogen, D-dimer, F1+2, and TAT) will be summarized by time point. Coagulation assays and thrombogenicity markers will be tabulated separately.

10.3. Presentation of PD Data

Actual measurements for each parameter will be listed by subject and time point. The actual assessment time or sampling of PD parameters will be listed for each subject and will include the deviation only if the sample was taken after the dose instead of pre-dose, if applicable.

Subjects with protocol deviation affecting PD may be flagged and excluded from PD Population.

Individual PD data-time profiles of thrombogenicity markers for actual measurement and change from baseline results will be presented with all subjects in the same figure on linear scales.

Mean +/- SD PD data-time profiles of thrombogenicity markers for actual measurements and change from baseline results will be presented in the same figure.

11. Safety

The population used for safety analyses will be the Safety Population. No inferential statistics will be performed; only summary statistics will be provided. Missing safety data will not be imputed. Safety will be assessed on the basis of AE, hematology and chemistry, ECG, physical examinations, vital signs, occurrence of a confirmed antibody response to CB2679d, occurrence of thrombotic events, and whether it is inhibitory and cross-reactive to BeneFIX and difficulites due to hemophilia after last dose of study drug.

11.1. Extent of Exposure

Exposure to study drug (in days) will be calculated:

Exposure overall = number of days where study drug was administered.

Exposure will be summarized and listed. Details on study drug administration and drug accountability will be listed as well.

11.2. Treatment Compliance

Study drug compliance (%) is calculated as ratio of the number of days study drug reported as administered and the number of days of administration expected. [in days]. Compliance will be summarized and listed.

11.3. Adverse Events

Adverse events will be coded using MedDRA Version 20.1 to classify events under primary SOC and PT. A treatment emergent adverse event (TEAE) is defined as an AE that either begins after the first dose of study drug in this study or worsens after the first dose of study drug in this study but not later than the date of last dose + 30 days. AEs with a missing start date and a stop date on or after the first dose of study medication, or AEs with both a missing start and stope date are also defined as TEAE.

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

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (in the following order: severe, moderate and mild). Missing severity will be considered as not recorded.
- Incidence of TEAE by relationship to study drug (related, not related). Missing relationship will be considered as related.
- Incidence of serious TEAEs
- Incidence of serious TEAEs by relationship to study drug
- Incidence of TEAEs leading to study drug discontinuation
- Incidence of Injection Site Reactions
- Incidence of Adverse Events of Special Interest (AESI)

Definition of AESI is documented in Section 8.4.7 of the Protocol.

All AEs will be listed.

11.4. Laboratory Evaluations

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

Laboratory data will be summarized by the type of laboratory test. Data will be flagged according to the reference limits (high or low) if applicable.

Descriptive statistics will be calculated for each numeric laboratory test parameter by visit for actual values and change from baseline (including maximum absolute change from baseline). For chemistry and hematology lab tests, shift tables showing baseline and post-baseline visit will be performed for the categories low, normal, and high. Additionally, the shift from the study baseline to the final value will be provided.

All laboratory will be listed by subject and time of measurements.

11.5. Vital Signs

Descriptive summaries of actual values and changes from study baseline will be calculated for vital signs by visit, which includes BP, HR, RR, body temperature (in C), weight and BMI. In addition, change from baseline (including maximum absolute change from baseline) will be summarized.

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

11.6. 12-Lead Electrocardiogram

ECG parameters at Screening will be summarized (see section 7.1) and listed.

11.7. Physical Examination

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

11.8. Occurrence of a confirmed antibody response to CB2679d and whether it is inhibitory and cross-reactive to BeneFIX.

Antibody response and neutralizing antibodies will be measured. The schedule of assessments of immunogenicity will be defined as follows: Screening, pre-dose on Day 7, Day 14, Day 21, Day 28, and EOS.

Following endpoints will be analyzed: occurrence of antibody response to CB2679d, BeneFIX and neutralizing activity to CB2679d and BeneFIX for the Safety Population.

The sampling for immunogenicity results will be listed combining all time points and confirmation assay in binary form (Positive/Negative) with the value of titer for positive immune response.

The immunogenicity results will be summarized by frequency of anti-drug antibody (ADA) positive subjects at each time point for the Safety Population.

11.9. Occurrence of clinical thrombotic event not attributable to another cause

The following categories will be summarized for the Safety Population:

- Number and percentage of subjects with thrombotic events (1 or more events).
- Number and percentages of subjects with 1 thrombotic event.
- Number and percentage of subjects with 2 thrombotic events.

- Number and percentage of subjects with 3 thrombotic events.

The data will be listed.

11.10. Bleeding Episode

The duration of bleeding episode in days is defined as end date minus start date + 1. It will be summarized for Safety Population. The diary entry of any bleeding episodes will be listed.

Individual figures to show the bleeding duration will be presented pre and post treatment.

11.11. Injection Site Reaction – Diary Data

Subjects' recorded site injection reactions in their daily diaries will be listed only.

11.12. Follow-up difficulties – Diary Data

Difficulties due to hemophilia after last dose of study drug will be listed.

12. Interim Analyses

No interim analysis is conducted during the study.

13. Changes from Analysis Planned in Protocol

According to the protocol, “Occurrence of antibody formation resulting in a endogeneous decreased level of FIX” and “Occurrence of a clinical thrombotic event not attributable to another cause” are listed below efficacy assessment. For the statistical analysis they will be considered as safety endpoints.

The definition of the PK and PD populations in Sections 5.3 and 5.4 used for the efficacy endpoint analysis is different from the population description in the protocol.

There have been some changes in the PK section of this SAP as compared to what is presented in the protocol. The protocol requires derivation of area under the curve, concentration maximum, time that studied drug is present at the maximum concentration (Tmax) and T_{max} for the FIX activity levels which is not possible due to limited sampling and nature of the study. Instead, highest recorded activity level after nadir value from the IV infusion will be reported. Furthermore, CL and Vd will only be possible to derive for Day 28 and subsequent samples during the washout period. The detail of these changes is described into Section 9.2 of this SAP.

14. Reference List

Sean Wallis. Binomial Confidence Intervals and Contingency Tests:Mathematical Fundamentals and the Evaluation of Alternative Methods, Journal of Quantitative Linguistics. 2013; 20:3, 178-208.

Lee ML, Poon Wai-Yin, Kingdon HS. A two-phase linear regression model for biologic half-life data. Journal of Laboratory and Clinical Medicine. 1990;115(6):745-748.

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

Maganti L, Panebianco DL, Maes AL. Evaluation of Methods for Estimating Time to Steady State with Examples from Phase 1 Studies. The AAPS Journal. 2008; 10(1):141-147

Kenward, MG and Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics, 1997, 53(3), 983–997.

15. Programming Considerations

15.1. General Considerations

All TLFs, and statistical analyses will be generated using SAS® for Windows, Release 9.4 or later version (SAS® Institute Inc., Cary, NC, USA) on a SAS server. Additional software may be employed for graphing or other analysis.

Changes to the software version (eg upgrades), or use of additional software consistent with the SAP will not be considered a violation of the SAP.

15.2. Table, Listing, and Figure Format

15.2.1. General

All TLFs will be produced in accordance with Syneos Health QC Processes (see Section 17).

- Individual SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered in rtf format
- Numbering of TLFs will follow International Conference on Harmonisation (ICH) E3 guidance
- Combined documents (including all outputs as pdf) will be delivered, too

Format of all unique TLFs (header, titles, footnotes, and data display) are defined in separated documents.

- All TLFs will be produced in landscape American letter format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch blank margin on all 4 sides.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text style, such as bolding, italics, borders, shading, and superscripted and subscripted test, will not be used in the TLFs, unless otherwise specified.
- Only standard keyboard characters will be used in the TLFs. Special characters will not be used.
- Mixed case will be used for all titles, footnotes, column headers, and programmers –supplied formats, as appropriate.

15.2.2. Headers and footers

All output should have the following header at the top left of each page:

```
Catalyst Biosciences, Inc. Protocol DLZ-201 (Syneos Health study number 1010852)
Dry/Draft/Final Run
```

All output should have Page n of N at the top right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

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

15.2.3. Display Titles

Each TLFs should be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.x and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are

identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

```
Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety Population)
```

15.2.4. Column Headers

Column headings are displayed immediately below the solid line described above in initial upper-case characters

In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment column.

For numeric variables, include “unit” in column or row heading when appropriate.

Analysis set sizes will be presented in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

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

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

15.2.5.2. *Table Conventions*

Units will be included where available

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

Severity Rating	N
severe	0
moderate	8
mild	3

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

If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean(SD)	XX.X (xx.xx)
95% CI	XX.X - XX.X
Median +/- IQR	xx.xx +/- xx.xx
Min - Max	xx.x - xx.x

Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Display values that round down to 0.0 to 0.0. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC level 3 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated are reported as "-".

For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote and programming note if the subject is included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

15.2.5.3. *Listing Conventions*

Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.

Missing data are represented on subject listings as either a blank space (" "), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

Units will be included where available

15.2.5.4. *Figure Conventions*

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

15.2.6. Footnotes

A solid line spanning the margins will separate the body of the data display from the footnotes.

All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

Subject specific footnotes are avoided, where possible.

Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page will be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source

```
Cross References: Listing 16.2.x.y
Program: txxxxabc.sas Table Generation: ddMMMyyyy hh:mm
```

16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in “SAS® Programming and Validation Plan”.

Syneos Health Standard Operating Procedures (SOPs) as well as the Quality Control process are defined in this document.

17. Index of Tables

The shells of the tables are provided in a separate document called “Mock Tables”. Potential changes to the table numbering or content would not be considered a deviation.

Header	Table Number	Name (Analysis Population)
14.		Tables, Figures, and Graphs Referred to but not Included in the Text
14.1		Demographic Data Summary Tables
14.1.1		Subject Disposition
	14.1.1.1	Subject Disposition (Screened Population)
14.1.2		Protocol Deviations
	14.1.2.1	All Reported Protocol Deviations (Safety Population)
	14.1.2.2	Major Protocol Deviations (Safety Population)
	14.1.2.3	Reasons for Exclusion from Analysis Populations (Safety Population)
14.1.3		Demographic and Baseline Characteristics
	14.1.3.1	Demographic and Baseline Characteristics (Safety Population)
	14.1.3.2	Medical History (Safety Population)
	14.1.3.3	Hemophilia History (Safety Population)
	14.1.3.4	Hemophilia Bleed History (Safety Population)
14.1.4		Medications
	14.1.4.1	Prior Medications (Safety Population)
	14.1.4.2	Concomitant Medications (Ongoing) (Safety Population)
	14.1.4.3	Concomitant Medications (Newly Started) (Safety Population)
	14.1.4.4	Prior Hemophilia Specific Medications (Safety Population)
	14.1.4.5	Concomitant Hemophilia Specific Medications (Ongoing) (Safety Population)
	14.1.4.6	Concomitant Hemophilia Specific Medications (Newly Started) (Safety Population)
	14.1.4.7	Prior Hemophilia Specific Medications: Summary of Total Daily Dose (Safety Population)
	14.1.4.8	Concomitant Hemophilia Specific Medications (Ongoing): Summary of Total Daily Dose (Safety Population)
	14.1.4.9	Concomitant Hemophilia Specific Medications (Newly Started): Summary of Total Daily Dose (Safety Population)
14.1.5		Treatment Exposure and Compliance
	14.1.5.1	Drug Exposure and Compliance (Safety Population)
14.2		Efficacy Data Summary Tables
14.2.1		Primary Efficacy Parameter
	14.2.1.1	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 12% (PK Population)
	14.2.1.2	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 12% (Safety Population)
14.2.2		Secondary Efficacy Parameters

Header	Table Number	Name (Analysis Population)
14.2.2.1		Secondary Efficacy: FIX Activity Level
	14.2.2.1.1	FIX Activity Level: Summary of Actual and Change from Baseline (PK Population)
	14.2.2.1.2	FIX Activity Level: Summary of Actual and Change from Baseline (Safety Population)
14.2.2.2		Secondary Efficacy: PK Parameter
	14.2.2.2.1	Summary of PK Parameters (PK Population)
14.2.2.3		Secondary Efficacy: PD Parameter
	14.2.2.3.1	PD parameters: Coagulation assays: Summary of Actual and Change from Baseline (PD Population)
	14.2.2.3.2	PD parameters: Thrombogenicity markers: Summary of Actual and Change from Baseline (PD Population)
	14.2.2.3.3	PD parameters: Coagulation assays: Summary of Actual and Change from Baseline (Safety Population)
	14.2.2.3.4	PD parameters: Thrombogenicity markers: Summary of Actual and Change from Baseline (Safety Population)
14.2.2.4		Additional Analyses
	14.2.2.4.1	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 30% (PK Population)
	14.2.2.4.2	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 50% (PK Population)
	14.2.2.4.3	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 30% (Safety Population)
	14.2.2.4.4	FIX Activity Level: Summary of Subjects who Achieve a FIX Activity Level > 50% (Safety Population)
14.2.3		Analysis: Attainment of Steady State
	14.2.3.1	Analysis of Attainment of Steady State for CB2679d by Repeated Measures ANOVA (PK Population)
	14.2.3.2	Analysis of Attainment of Steady State for CB2679d by Repeated Measures ANOVA (Safety Population)
14.3		Safety Data Summary Tables
14.3.1		Adverse Events
	14.3.1.1	Treatment Emergent Adverse Events (TEAE) - Overall Summary (Safety Population)
	14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
	14.3.1.3	Treatment Emergent Adverse Events by Relationship to Study Drug by System Organ Class and Preferred Term (Safety Population)
	14.3.1.4	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Population)
	14.3.1.5	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

Header	Table Number	Name (Analysis Population)
	14.3.1.6	Treatment Emergent Serious Adverse Events by Relationship to Study Drug by System Organ Class and Preferred Term (Safety Population)
	14.3.1.7	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Population)
	14.3.1.8	Adverse Events of Special Interest by System Organ Class and Preferred Term (Safety Population)
14.3.2		Listings of Deaths, Other Serious and Significant Adverse Events
14.3.4		Laboratory Evaluation and Vital Signs
14.3.4.1		Clinical Laboratory Data
14.3.4.1.1		Hematology Data
	14.3.4.1.1.1	Clinical Laboratory Tests: Hematology - Summary of Actual and Change from Baseline (Safety Population)
	14.3.4.1.1.2	Clinical Laboratory Tests: Hematology - Shift from Baseline in Laboratory Value (Safety Population)
14.3.4.1.2		Chemistry Data
	14.3.4.1.2.1	Clinical Laboratory Tests: Chemistry - Summary of Actual and Change from Baseline (Safety Population)
	14.3.4.1.2.2	Clinical Laboratory Tests: Chemistry - Shift from Baseline in Laboratory Value (Safety Population)
14.3.4.2		Vital Signs
	14.3.4.2.1	Vital Signs – Summary of Actual Value and Change from Baseline (Safety Population)
14.3.4.3		Immunogenicity
	14.3.4.3.1	Summary of Confirmed Antibodies Response to CB2679d (Safety Population)
14.3.4.4		Clinical Thrombotic Events
	14.3.4.4.1	Summary of Occurrence of Clinical Thrombotic Events (Safety Population)
14.3.4.5		Hemophilia Bleeding Episodes
	14.3.4.5.1	Hemophilia Bleeding Episodes – Summary of Duration of Bleeding Episodes (Safety Population)

18. Index of Figures

The shells of the figures are provided in a separate document called “Mock Figures”. Potential changes to the figure numbering or content would not be considered a deviation.

Header	Figure Number	Name (Analysis Population)
14.2.2.1		Secondary Efficacy: FIX Activity Level
	14.2.2.1.3	Individual Profiles of FIX Activity Levels - Linear Scale (PK Population)
14.2.2.3		Secondary Efficacy: PD Parameter
	14.2.2.3.3	Individual PD Profiles - Linear Scale (PD Population)
	14.2.2.3.4	Mean (SD) PD Profiles (PD Population)
14.3.4.5		Hemophilia Bleeding Episodes
	14.3.4.5.2	Pre- and Post-Treatment Bleeding Intervals (Safety Population)

19. Index of Listings

The shells of the listings are provided in a separate document called “Mock Listings”. Potential changes to the listing numbering or content would not be considered a deviation.

Header	Listing Number	Name (Analysis Population)
16.2		Subject Data Listings
16.2.1		Discontinued Subjects
	16.2.1.1	Subject Disposition (Screened Population)
	16.2.1.2	Study Visit (Screened Population)
16.2.2		Protocol Deviations
	16.2.2.1	Protocol Deviations (Safety Population)
16.2.3		Subjects Excluded from the Efficacy Analysis
	16.2.3.1	Screen Failures (Screened Population)
	16.2.3.2	Inclusion and Exclusion Criteria (Screened Population)
	16.2.3.3	Subject Exclusions from Analysis Populations (Screened Population)
16.2.4		Demographic Data
	16.2.4.1	Demographics and Baseline Characteristics (Safety Population)
	16.2.4.2.1	Medical History (Safety Population)
	16.2.4.2.2	Hemophilia History (Safety Population)
	16.2.4.2.3	Hemophilia Bleed History (Safety Population)
	16.2.4.2.4	FIX Genotyping Test Results (Safety Population)
	16.2.4.3.1	Prior Medications (Safety Population)
	16.2.4.3.2	Concomitant Medications (Ongoing) (Safety Population)
	16.2.4.3.3	Concomitant Medications (Newly Started) (Safety Population)
	16.2.4.3.4	Prior Hemophilia Specific Medications (Safety Population)
	16.2.4.3.5	Concomitant Hemophilia Specific Medications (Ongoing) (Safety Population)
	16.2.4.3.6	Concomitant Hemophilia Specific Medications (Newly Started) (Safety Population)
16.2.5		Study Drug Exposure
	16.2.5.1	Study Drug Administration – Diary Data (Safety Population)
	16.2.5.2	Study Drug Accountability (Safety Population)
	16.2.5.3	Study Drug Exposure and Compliance (Safety Population)
	16.2.5.4	Study Drug Administration (Safety Population)
16.2.6		Individual Efficacy Response Data
	16.2.6.1	Listing of PK Sampling and FIX Activity Level (Safety Population)
	16.2.6.2	Listing of PK Parameters (Safety Population)
	16.2.6.3	Listing of Sampling for Coagulation and Thrombogenicity PD Assessments and Results (Safety Population)
16.2.7		Adverse Events Listings
	16.2.7.1	Adverse Events (Safety Population)
	16.2.7.2	Study Drug Information for Serious Adverse Events (Safety Population)
	16.2.7.3	Serious Adverse Events (Safety Population)

Header	Listing Number	Name (Analysis Population)
	16.2.7.4	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Safety Population)
	16.2.7.5	Deaths (Safety Population)
16.2.8		Listing of individual laboratory measurements, vital signs and Diary Entry by subject
	16.2.8.1	Clinical Laboratory Results – Hematology (Safety Population)
	16.2.8.2	Clinical Laboratory Results – Chemistry (Safety Population)
	16.2.8.3	Vital Signs (Safety Population)
	16.2.8.4	12-Lead Electrocardiogram at Screening (Safety Population)
	16.2.8.5	Physical Examination (Safety Population)
	16.2.8.6	Listing of Immunogenicity Sampling and Results (Safety Population)
	16.2.8.7	Occurrence of Clinical Thrombotic Event (Safety Population)
	16.2.8.8	Bleeding Episode Diary Data (Safety Population)
	16.2.8.9	Diary Entry of Injection Site Assessment (Safety Population)
	16.2.8.10	Difficulties due to Hemophilia after Last Dose of Study Drug (Safety Population)

Syneos Health	**Note to File**

Project /Protocol No.	Catalyst Biosciences, DLZ-201
Date:	14-July-2020
CC:	TMF
RE:	Update of final tables 14.2.1.1 and 14.2.1.2, and ad hoc request of 14.2.2.1.1.ah and 14.2.2.1.2.ah

Catalyst Biosciences reviewed the first draft of Clinical Study Report (CSR), which was provided to Catalyst on 22-Jun-2020. Catalyst requested updates to the CSR table 11-1 (source table 14.2.1.1) and additional analysis in CSR table 11-2 (source table 14.2.2.1.1) for a more concise interpretation of the results.

CSR table 11-1 (table 14.2.1.1) is presenting the frequency of subjects who achieved FIX Level > 12% between Day 7 and Day 28. As the study drug absorption from the subcutaneous injection site could take up to 24 hours, Catalyst requested to add Day 29 of the Follow-up period (24 hours post the last dose at Day 28) to this summary table. This affects both tables 14.2.1.1 (PK population) and 14.2.1.2 (Safety Population).

CSR table 11-2 (table 14.2.2.1.1) is the summary of actual and change from baseline of the FIX activity level. As indicated in the Statistical Analysis Plan (v1.0, dated 24-May-2019), baseline is defined as the last assessment before the first administration of study drug. For subject 7100110, high values of 56.5 and 38.9 IU/dl (retest) were reported at Day 1 IV Pre-Dose, compared to <1.2 IU/dl at Screening. According to the subject diary, the first SQ dose had been taken prior to the first IV dose at 20-Jan-2020 at 09:30 (Listing 16.2.5.4), and thus prior to the results reported in the external laboratory dataset at Day 1, IV Pre-Dose (at 20-Jan-2020 at 12:15, Listing 16.2.6.1). Therefore, two ad-hoc tables (14.2.2.1.1.ah and 14.2.2.1.2.ah) will be provided, with baseline defined as the lowest activity result before first administration of study drug. The additional tables will have the suffix ".ah" indicating the ad hoc analysis.

The mocks of the updated tables and ad hoc tables are presented in the appendix of this file note.

The ad hoc request for the additional derivation of baseline will be done with an additional Analysis Dataset, to ensure the already final outputs are not affected by this ad hoc request. This new Analysis Dataset will be a repeat of the "Pharmacokinetic Analysis Dataset" and called "Ad Hoc Pharmacokinetic Analysis Dataset" (ADPCAH). The only difference between both Analysis Datasets will the derivation of the baseline flag. This ad hoc Analysis Dataset will be added to the define.xml and the Analysis Reviewer's Guide.

Note to File, 14-July-2020
Sponsor: Catalyst Biosciences; Protocol No.: DLZ-201

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Anja Schulze, Sr Biostatistician	Anja Schulze *Electronically signed by: Anja Schulze Reason: I am the author Date: Jul 15, 2020 07:59 GMT+2*	Jul 15, 2020
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Sumita Majumdar, Sr Project Manager	Sumita Majumdar *Electronically signed by: Sumita Majumdar Reason: I am the approver Date: Jul 15, 2020 08:47 GMT+1*	Jul 15, 2020
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Catalyst Biosciences, Inc. Approval:		
Frank Del Greco, Vice President, Clin Ops		14 Jul 2020
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Appendix:

Table 14.2.1.1
FIX Activity Level: Summary of Subjects who Achieve a FIX Level > 12%
(PK Population)

Visit Subject ID*	Statistics	Overall (N = xx)
Day 7	n (%)	xx (xx.x)
xx	value	xx.x %
yy	value	xx.x %
zz	value	xx.x %
Day 14	n (%)	xx (xx.x)
xx	value	xx.x %
yy	value	xx.x %
zz	value	xx.x %
Day 21	n (%)	xx (xx.x)
xx	value	xx.x %
yy	value	xx.x %
zz	value	xx.x %
Day 28	n (%)	xx (xx.x)
xx	value	xx.x %
yy	value	xx.x %
zz	value	xx.x %
Day 29	n (%)	xx (xx.x)
xx	value	xx.x %
yy	value	xx.x %
zz	value	xx.x %

Note: *Subject ID who achieve a FIX Level of > 12%
Percentages are calculated based on the number of subjects in the PK population.
In case of retest, the average of the different test results were considered for the summary analyses.
Patient 7100109 received a higher IV dose than allowed per protocol (150 IU/kg) at Day 1. The IV dose would be eliminated within 6 days and therefore did not affect any later results.

Cross References: Listing 16.2.x.y
Program: txxxxabc.sas Table Generation: ddmonyyyy hh:mm

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If PK population is different to Safety population then repeat Table 14.2.1.1 for

Table 14.2.1.2
FIX Activity Level: Summary of Subjects who Achieve a FIX Level > 12 %
(Safety Population)

Adapt footnote accordingly.

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Table 14.2.2.1.1.ah
FIX Activity Level - Summary of Actual and Change from Baseline
(PK Population)

Visit	Statistics	Actual Value (%)	Change from Baseline (%)
Screening	n	xx	
	Number and %BLQ	xx (xx.x)	
	Mean (SD)	xx.xx (xx.xxx)	
	CV (%)	xx.x	
	Median (IQR)	xx.xx (xx.xx)	
	Min, Max	xx.x, xx.x	
Day 1, IV Pre-dose	n	xx	
	Number and %BLQ	xx (xx.x)	
	Mean (SD)	xx.xx (xx.xxx)	
	CV (%)	xx.x	
	Median (IQR)	xx.xx (xx.xx)	
	Min, Max	xx.x, xx.x	
Day 1, SQ Dose	n	xx	xx
	Number and %BLQ	xx (xx.x)	
	Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
	CV (%)	xx.x	xx.x
	Median (IQR)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Min, Max	xx.x, xx.x	xx.x, xx.x
Day x etc.			
EOS	n	xx	xx
	Number and %BLQ	xx (xx.x)	
	Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
	CV (%)	xx.x	xx.x
	Median (IQR)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Min, Max	xx.x, xx.x	xx.x, xx.x
Maximum change from baseline during dosing	n		xx
	Number and %BLQ		xx (xx.x)
	Mean (SD)		xx.xx (xx.xxx)
	CV (%)		xx.x
	Median (IQR)		xx.xx (xx.xx)
	Min, Max		xx.x, xx.x

Note: Baseline is defined as the lowest assessment before the first administration of study drug. Maximum change from baseline is calculated as the maximum of the changes from baseline over all visits during treatment period. FIX activity level BLQ were set to zero.
In case of retest, the average of the different test results were considered for the summary analyses.
Patient 7100109 received a higher IV dose than allowed per protocol (150 IU/kg) at Day 1. The IV dose would be eliminated within 6 days and therefore did not affect any later results. Values at Day 1, SQ Dose, Day 2, and Day 3 were excluded from this analysis.
Cross References: Listing 16.2.x.y
Program: txxxxabc.sas Table Generation: ddmonyyyy hh:mm

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If PK population is different to Safety population then repeat Table 14.2.2.1.1.ah for

Table 14.2.2.1.2.ah
FIX Activity Level - Summary of Actual and Change from Baseline
(Safety Population)

Use as footnote:

Note: Baseline is defined as the lowest assessment before the first administration of study drug. Maximum change from baseline is calculated as the maximum of the changes from baseline over all visits during treatment period. FIX activity level BLQ were set to zero.
In case of retest, the average of the different test results were considered for the summary analyses.
Patient 7100109 received a higher IV dose than allowed per protocol (150 IU/kg) at Day 1. The IV dose would be eliminated within 6 days and therefore did not affect any later results.
Cross References: Listing 16.2.x.y
Program: txxxxabc.sas Table Generation: ddmonyyyy hh:mm

Syneos Health	**Note to File**

Project /Protocol No.	Catalyst Biosciences, DLZ-201
Date:	24-July-2020
CC:	TMF
RE:	Minor edits of SAP v1.0 dated 24-May-2019

The following edits were made to the SAP v.1.0 dated 24-May-2019 before database lock. As those edits were only minor, no updated version of the SAP werde needed.

Section	Revised from	Revised to
6.2.1 Baseline and Change from Baseline	Maximum ~~absolute~~ change from baseline will be calculated as the maximum of the ~~absolute~~ changes from baseline over all visits during treatment period.	Maximum change from baseline will be calculated as the maximum of the changes from baseline over all visits during treatment period.
8.2.1 Change in FIX levels from pre-dose	Actual and change from baseline (including maximum ~~absolute~~ change from baseline) values for FIX activity level will be summarized by time point for the PK and the Safety Population. Different PK parameters will be summarized as well as described in Section ***Error! Reference source not found.***.	Actual and change from baseline (including maximum change from baseline) values for FIX activity level will be summarized by time point for the PK and the Safety Population. Different PK parameters will be summarized as well as described in Section ***Error! Reference source not found.***.
9.3.2 Listing and Presentation of Individual PK Data	The following figures will be produced: ~~Individual intense~~ PK concentration-~~time~~ provided for FIX activity levels ~~with all subjects in the same figure on linear scales.~~	The following figure will be produced: **Box plots of** PK concentration provided for FIX activity levels by visits.
9.3.3 Summary of PK Concentrations and Parameter in Plasma		Added: **Geometric CV = sqrt (exp ((log (geometric SD)) ^2) – 1) * 100%**
9.4 PK Parameters Derivation: Attainment of Steady State for FIX Activity		Added: **REPEATED <time> /type = un SUBJECT = <subject>**
10.2 PD Biomarkers Analysis	Actual and change from baseline (including maximum ~~absolute~~ change from baseline) for all PD parameters (e.g., Prothrombin Time, aPTT, Fibrinogen, D-dimer, F1+2, and TAT) will be summarized by time point. Coagulation assays and thrombogenicity markers will be tabulated separately.	Actual and change from baseline (including maximum change from baseline) for all PD parameters (e.g., Prothrombin Time, aPTT, Fibrinogen, D-dimer, F1+2, and TAT) will be summarized by time point. Coagulation assays and thrombogenicity markers will be tabulated separately. Added: **In case that thrombogenicity markers are below limit of quantification, then all analysis are done with the imputed midpoint of the potential values**

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Section	Revised from	Revised to
		for this observation. For coagulation assays, the limit of quantification is used for the analysis.
10.3 Presentation of PD Data	Removed: ~~Individual PD data-time profiles of thrombogenicity markers for actual measurement and change from baseline results will be presented with all subjects in the same figure on linear scales.~~ ~~Mean +/- SD PD data-time profiles of~~ thrombogenicity markers for actual measurements ~~and change from baseline results~~ will be presented ~~in the same figure.~~	**Box plots of** thrombogenicity markers for actual measurements will be presented **by visit.**
11.4 Laboratory Evaluations	Descriptive statistics will be calculated for each numeric laboratory test parameter by visit for actual values and change from baseline (including maximum ~~absolute~~ change from baseline).	Descriptive statistics will be calculated for each numeric laboratory test parameter by visit for actual values and change from baseline (including maximum change from baseline).
11.5 Vital Signs	Descriptive summaries of actual values and changes from study baseline will be calculated for vital signs by visit, which includes BP, HR, RR, body temperature (in C), weight and BMI. In addition, change from baseline (including maximum ~~absolute~~ change from baseline) will be summarized.	Descriptive summaries of actual values and changes from study baseline will be calculated for vital signs by visit, which includes BP, HR, RR, body temperature (in C), weight and BMI. In addition, change from baseline (including maximum change from baseline) will be summarized.
title of output 14.3.1.6	Treatment Emergent Serious Adverse Events by Relationship to Study Drug by System Organ Class and Preferred Term (Safety Population)	Treatment Emergent Serious Adverse Events by **Highest** Relationship to Study Drug by System Organ Class and Preferred Term (Safety Population)
Title of output 14.2.2.1.3	~~Individual Profiles of~~ FIX Activity Levels ~~- Linear Scale~~ (PK Population)	**Box Plots** of FIX Activity Levels (PK Population)
Title of output 14.2.2.3.3	Removed: ~~Individual PD Profiles - Linear Scale (PD Population)~~	
Title of output 14.2.2.3.3	~~Mean (SD) PD Profiles of~~ Thrombogenicity Markers (PD Population)	**Box Plots** of Thrombogenicity Markers (PD Population)
Title of output 16.2.4.2.3	Hemophilia Bleed History (Safety Population)	Hemophilia Bleed History **in the last 6 Months** (Safety Population)

Bolded=added/revised; Strikethrough=removed.

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Catalyst Biosciences, Inc. Approval:		
Frank Del Greco, Vice President, Clin Ops		24 Jul 2020
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