A PHASE 1, OPEN-LABEL, SINGLE-DOSE, NON-RANDOMIZED STUDY TO EVALUATE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BETRIXABAN IN PEDIATRIC PATIENTS

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Statistical Analysis Plan

SAP Version:	Draft v 1.0
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Sponsor:	Portola Pharmaceuticals, Inc. 270 East Grand Avenue, Suite 22 South San Francisco, CA 94080, USA
Study Title:	A Phase 1, Open-Label, Single-Dose, Non-Randomized Study to Evaluate Pharmacokinetics, Pharmacodynamics, and Safety of Betrixaban in Pediatric Patients
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Author(S):	PPD PPD Portola Pharmaceuticals, Inc.

APPROVAL SHEET

Product: Betrixaban

Protocol Number: 16-021

Version: Version 0.1

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The undersigned have reviewed this statistical analysis plan and find it to be consistent with the protocol as it applies to their respective areas.

Approver	Signature	Date
PPD Portola Pharmaceuticals, Inc.		
PPD PPD PPD Portola Pharmaceuticals, Inc.	PPD	6/2/2020
PPD PPD Portola Pharmaceuticals, Inc.		

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event
CI	Confidence Interval
CP	Completers Population
CT	Computed Tomography
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ETP	Endogenous Thrombin Potential
FFP	Fresh Frozen Plasma
FX	Factor X
FXa	Factor Xa
HCP	Host Cell Protein
ITT	Intent-to-Treat
kg	Kilogram
MAR	Missing at Random
MI	Multiple Imputation
mL	Milliliter
MRI	Magnetic Resonance Imaging
ng	Nanogram
PCC	Prothrombin Complex Concentrate
PP	Per Protocol
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
TE	Thrombotic Event
TEAE	Treatment-Emergent Adverse Event

1.0 INTRODUCTION

This document details the statistical analyses that will be performed to evaluate the pharmacokinetics and safety of betrixaban in pediatric patients enrolled in Study 16-021. Documents related to this analysis plan are:

- Betrixaban Study Protocol, titled "A Phase 1, Open-Label, Single-Dose, Non-Randomized Study to Evaluate Pharmacokinetics, Pharmacodynamics, and Safety of Betrixaban in Pediatric Patients"

Betrixaban, an oral direct FXa inhibitor, is approved in the United States for the indication of:

- prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

The present study, Study 16-021, was performed to evaluate the pharmacokinetics, pharmacodynamics, and safety of betrixaban in pediatric patients.

Study 16-021 was originally designed to have 2 parts, however, Portola has elected not to continue to the development of betrixaban, thus only part 1 of this study was performed.

2.0 STUDY OBJECTIVES

In pediatric patients at risk for VTE, the objectives of this study are as follows:

2.1. Primary Objective

- To determine the pharmacokinetic (PK) parameters of betrixaban in the pediatric patients in the following age categories: 12 to < 18 years of age, and 2 to < 12 years of age.

2.2. Secondary Objective

- To assess the pharmacodynamic (PD) activity of betrixaban in pediatric patients in the following categories: 12 to < 18 years of age, and 2 to < 12 years of age.

Note: this was originally a secondary objective, but was de-prioritized and the PD activity was not measured.

2.3. Safety Objectives

The following safety objective will be evaluated:

- To assess the safety of betrixaban in the pediatric patients in the following categories: 12 to < 18 years of age, and 2 to < 12 years of age.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design Summary

This is a multiple-center, open-label, study of the PK, PD, and safety of a single dose of betrixaban at up to 80 mg in pediatric patients who meet study entry criteria. To adequately assess PD, any last dose of anticoagulant must not have been taken within one week prior to receiving betrixaban in this study.

Following a 30-day screening period, eligible patients who have provided Assent and whose parent or legal guardian has signed an Informed Consent will receive a single, oral dose of betrixaban at 40 mg or 80 mg. The screening visit may be an outpatient visit. Patients will enter (or if hospitalized, remain in) the hospital, clinical research unit, or Phase 1 unit on Day -1, the day before dosing with betrixaban is anticipated, and remain domiciled through 24 hours after betrixaban is administered. They may undergo the remainder of procedures as outpatients, including a Day 7 follow-up safety phone call.

Part 1 (the initial opening of the study) will be conducted in 21 adolescent patients (12 to < 18 years of age) who are assessed to be at risk for VTE but do not require immediate anticoagulation and whose coagulation parameters are normal. Each patient will receive a single, oral, hard gelatin capsule of betrixaban. The dose administered initially to adolescent patients will be 40 mg. After review of the safety data from patients who received 40 mg, additional adolescent patients may be dosed with 80 mg. There will be 2 cohorts of patients in Part 1 of the study. The cohorts are defined as follows:

- Cohort 1 will enroll 3 patients (at least one of each sex), each of whom will receive a single, oral dose of betrixaban at 40 mg in the fed state, and have 10 PK blood sampling time points.

- Cohort 2 will enroll 18 patients (6 patients in each of 3 PK sampling sequences), each of whom will receive a single, oral dose of betrixaban at 80 mg in the fed state, and undergo 5 PK sampling time points.

After dosing, patients will undergo serial blood sampling for PK-PD evaluations (the Schedule of Assessments detailing all procedures is provided in Table 5). The PK and PD data from Part 1 will be used for dose determination for the next youngest age group using POP PK and PBPK modeling and simulation. The primary PK parameters to be determined are $AUC_{(0\text{-last})}$ and C_{max}. Other PK parameters to be determined are Total AUC ($AUC_{(0\text{-}\infty)}$), $t_{½}$, T_{max}, CL/F, and V_d/F. These will be estimated using POP PK methodology for age groups except the initial group of patients for which rich PK sampling is done.

Following analysis of Part 1 data and an amendment to the protocol, a Part 2 of the study was originally planned to commence. However, since Portola decided not to continue to develop the betrixaban program, Part 2 of this study will no longer be performed.

For both of the cohorts in Part 1, safety assessments (evaluation of AEs, concomitant medications, routine chemistries [hematology, coagulation, serum chemistries]) will occur at protocol-specified time points.

The schema of the original study design is depicted in Figure 1. Note that Part 2 will not be performed.

Figure 1: Schema of Study 16-021

Study Part	Part 1	Part 1	Part 2 - TBD Amendment
Cohort No.	Cohort 1	Cohort 2	Cohort 3
Age	12 to < 18 years	12 to < 18 years	2 to < 12 years
Dose	40 mg	80 mg	TBD
n =	3 patients (one of each gender)	18 patients (at least two of each gender)	12 patients (at least two of each gender)
PK Sampling	Rich - 10 time points	Sparse - 5 time points	Sparse – TBD time points
PK Time Points	Pre-dose, 0.5, 1, 2, 3, 4, 6, 12, 24, 120 hours	Sequence A: pre-dose, 1, 3, 12, 120 hours Sequence B: pre-dose, 0.5, 2, 4, 24 hours Sequence C: pre-dose, 2, 3, 12, 24 hours	Sequence D: TBD Sequence E: TBD

A detailed Schedule of Activities can be found in Protocol, Appendix A.

3.2. Number of Patients

A total of 33 patients are planned: 21 in Part 1 (age 12 years to < 18 years), and 12 in Part 2.

4.0 EFFICACY AND SAFETY VARIABLES

4.1. Pharmacokinetic Parameters

Plasma levels will be assessed at baseline, during the first 24 hours, and 120 hours post dosing and will be used to estimate betrixaban population PK parameters shown below for each age and dose group based on average profiles or individual profiles if available:

Primary PK Parameters:

- Area under the concentration-time curve to the last measurable concentration above the quantitation limit ($AUC_{(0\text{-last})}$)
- Maximum observed plasma concentration (C_{max})

Other PK Parameters:

- Total area under the plasma concentration–time curve from 0 to infinity ($AUC_{(0\text{-}\infty)}$), if calculable
- Terminal plasma half-life ($t_{½}$) if calculable
- Time of maximum observed plasma concentration (T_{max}) per age group or patient, as data allows
- Clearance (CL/F) and volume of distribution (V_d/F) per age group

4.2. Pharmacodynamic & Safety Parameters

- In the original design, PD endpoints, including anti-fXa activity, and the inhibition of thrombin generation during the first 24 hours post dosing were to be measured. However, this was not done and therefore there are no PD endpoints.
- Safety endpoint is the clinical assessment of AEs and other safety measurements (vital signs, ECGs, laboratory tests, etc.).

5.0 DATA QUALITY

Study data are to be reported on a validated, Part 11 compliant EDC program provided by the Sponsor or Designee. One electronic case report book will be completed for each patient. Paper-based source documents will contain adequate information to allow for verification of subject identity throughout the study.

The Sponsor/designee will train study data management staff on procedures for electronic data reporting into the Web-based system, if not previously trained in the same system. Additionally, staff will be trained by Sponsor/designee on guidelines for maintenance of electronic ID codes and passwords. Access to the system will be protected by login identification and password. Data entry as well as all data modification will be documented by the system and available in audit trails. De-identified study data resides on a server at Portola Pharmaceutical or designee.

After the data are entered and submitted into the system, automated data queries may be raised. In addition, post data entry, the site coordinator, Principal Investigator, Medical Monitor, Portola data management, or the Study Statisticians may generate additional queries. It will be the responsibility of the person(s) designated for data reporting to respond to all queries. An audit trail will be available for any amended data entry including the date, time and person performing the data change.

Upon conclusion of the study, after eCRFs are marked as complete, and edit checks are resolved, the Principal Investigator will sign the case books and the Sponsor/designee data manager will lock the database. Database lock must be approved by PTLA Data Management, Clinical Project Manager, Medical Monitor, and study Statistician. The final data set will be transferred to SAS and/or R for analysis. At the end of the study, the Principal Investigator will receive from the Sponsor/or designee an electronical copy of the database containing `de-identified data entered into the Web-based system for archiving purposes.

Study records, including Study Subject’s signed informed consent, and other study-related documents pertaining to the conduct of the study will be kept in a secure area, based on local regulatory requirements. Subject information will remain confidential. However, consent forms and other records that identify subjects may be inspected by the sponsor or its authorized designees and regulatory agencies including but not limited to, the Department of Health and Human Services (DHHS), the United States Food and Drug Administration (FDA), other foreign regulatory bodies and the Institutional Review Board/Ethics Committee for this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications; however, subject identity will not be disclosed in such publications.

6.0 STATISTICAL METHODS

6.1. General Considerations

After final database lock, all analyses will be performed according to this Statistical Analysis Plan (SAP).

All parameters will be summarized descriptively. No hypothesis tests will be performed. For continuous variables, number of observations, mean, median, standard deviation, and minimum and maximum values, and 95% CI will be presented. For categorical variables, counts, percentages, and 95% CI will be tabulated for each category.

It is anticipated that statistical summaries will be performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics and for statistical methodology not available in SAS.

6.2. Analysis Population

The analysis population will consist of all enrolled patients who received the study treatment.

6.3. Study Patients

6.3.1. Patient Demographics

Summary statistics of the patient demographics including age, sex, race, ethnicity and baseline characteristics will be presented by cohort. Additionally, a listing table will be provided.

6.3.2. Patient Disposition

An accounting of study patient disposition, including total number of patients enrolled, early study drug discontinuations, early withdrawal from study, and summary of reasons for study drug discontinuation and study withdrawal, will be presented by cohort. Also, a listing with the reasons for early study drug discontinuations and study withdrawals will be provided.

6.4. Concomitant Therapy

Concomitant medications will be coded using the WHO Drug Dictionary. Prior medications that are ongoing at the time of study enrollment will also be recorded. A listing table of all concomitant medications will be provided.

6.5. Pharmacokinetic Analysis of Betrixaban

6.5.1. Primary PK Parameters

The primary PK Parameters are as follows and will be presented per age group by dose, and for individuals, where possible:

- Area under the concentration-time curve to the last measurable concentration above the quantitation limit ($AUC_{(0\text{-last})}$)
- Maximum observed plasma concentration (C_{max})

Summary statistics and listing tables of C_{max} and AUC will be provided for each age and dose cohort. The subjects who only had 5 time points each will have PK parameters calculated as an average, as it would not be appropriate to assume Cmax or calculate AUC based on the limited time points.

6.5.2. Other PK Parameters

The other PK Parameters are as follows and will be presented per age group by dose, and for individuals, where possible:

- Total area under the plasma concentration–time curve from 0 to infinity ($AUC_{(0\text{-}\infty)}$), if calculable
- Terminal plasma half-life ($t_{½}$) if calculable
- Time of maximum observed plasma concentration (T_{max}) per age group or patient, as data allows
- Clearance (CL/F) and volume of distribution (V_d/F) per age group

Since Portola is no longer developing the Betrixaban program, no analyses will be performed for the other PK parameters.

6.6. Pharmacodynamic Analysis

6.6.1. Anti-fXa Activity

Anti-fXa activity during the first 24 hours post-dosing was not collected, and therefore will not be analyzed.

6.6.2. Thrombin Generation

Thrombin generation measurements were not collected, and therefore will not be analyzed.

6.7. Safety Analysis

Safety will be assessed by examination of AEs, ECG, laboratory parameters, and vital signs.

6.7.1. Adverse Events

All AE analyses will be summarized by cohort.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events are defined as events that first occurred or

worsened after baseline following study treatment administration. In the analysis of Treatment-Emergent AEs (TEAEs), all events recorded as occurring before study treatment administration will be considered baseline conditions.

All TEAEs will be summarized by system organ class and preferred term.

The number of events, the number of patients, and the percentage of patients who experienced at least one TEAE will be presented.

TEAEs that lead to early withdrawals; and serious TEAEs will be summarized in the same manner.

Additionally, a listing table of all TEAEs will be provided.

6.8. ECG Parameters

A listing table will be provided for the ECG results.

6.9. Laboratory Parameters

A listing table, shift tables and number and percent of patients with values outside the normal range for the following labs will be provided by cohort:

- Hemoglobin
- Hematocrit
- Creatinine Clearance
- aPTT
- PT
- INR

6.10. Vital Signs

A listing table will be provided for the vital signs.

6.11. Changes in the Conduct of the Study or Planned Analyses

The original study design included two parts: Part 1 and Part 2. Only Part 1 was conducted. The study was discontinued early because Portola decided not to continue developing the drug.

The original design called for measuring anti-fXa levels and thrombin generation in Part 1, however, this was not done.