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

Unique Protocol ID:	16-021
NCT Number:	NCT03346083
EudraCT Number:	2018-002562-40
Date of Protocol:	26 November 2018

BETRIXABAN (PRT054021)

PROTOCOL NUMBER 16-021

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

DRUG NAME:	Betrixaban IND #072679
PROTOCOL NUMBER:	16-021
PHASE:	1
TRIAL SPONSOR:	Portola Pharmaceuticals, Inc. 270 East Grand Avenue South San Francisco, CA 94080
MEDICAL MONITOR:	PPD PPD Portola Pharmaceuticals, Inc. Phone: PPD Fax: PPD Email: PPD
PROTOCOL DATE:	**Amendment 2.1: 26 November 2018** Amendment 2: 6 April 2018 Amendment 1: 12 July 2017 Original: 11 November 2016

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for betrixaban. I have read Protocol Number 16-021 entitled "*A PHASE 1, OPEN-LABEL, SINGLE-DOSE, NON-RANDOMIZED STUDY TO EVALUATE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BETRIXABAN IN PEDIATRIC PATIENTS"* and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree to comply with the ICH Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Operations Manager	PPD PPD	Portola Pharmaceuticals, Inc. 270 East Grand Avenue South San Francisco, CA 94080 PPD
Responsible Physician	PPD PPD	Same
Drug Safety Contact	PPD PPD	Same
SAE Reporting	C3i Solutions	PPD

SUMMARY OF KEY CHANGES

Protocol Version	Key Changes
11 Nov 2016	Original Protocol
12 July 2017	Amendment 1 1. Modified Inclusion Criterion #2 to clarify patient population. Enrollment limited to pediatric patients requiring anticoagulant therapy. 2. Revised Exclusion Criterion #6 to more conservative criteria. Patients with liver disease associated with transaminase levels of ≥ 2.5 x ULN or bilirubin ≥ 1.5 x ULN at baseline will be excluded from the trial. 3. Redundantly emphasized protocol requirement for a subsequent protocol amendment and ethics approval prior to the commencement of Part 2 (ages 2–12 years) and again prior to the commencement of Part 3 (ages 28 days to 2 years) to specify age appropriate blood sampling volumes and time points following review of data from the previous age cohorts. It is intended that a reduction of blood sampling time points and therefore volumes will be possible during the study of progressively younger age groups by selecting the most informative time points based on data review. 4. Provided additional guidance to minimize pain and discomfort to pediatric subjects during blood sampling. Sampling may occur via IV catheter or butterfly needle followed by saline flush. For patients with pre-existing Central Venous catheter or Access Devices (CVAD) (i.e., central line, central venous line, or central venous access catheter) sampling may occur via these access points. 5. Updated the status of betrixaban as an FDA approved drug as of June 2017. 6. Added text to Section 11 with respect to obligations and requirements for data reporting and case report forms, deviations from the protocol, drug accountability, and disclosure of data. 7. Made additional clarifications, deletions, and administrative additions/corrections to improve clarity and consistency.
6 April 2018	Amendment 2 1. Modified Inclusion Criterion #2 to exclude patients requiring immediate anticoagulation therapy. 2. Reduced size of Cohort 1 (40 mg) from 12 patients to 3 patients. Cohort 1 will serve as the single cohort containing 10 PK time points per patient. This rich sampling schedule will serve as the basis for bridging to pediatric PK from adult PK. To minimize the number patients subjected to a rich sampling schedule, Cohort 2 (80 mg) will employ a sparse sampling schedule consisting of 5 PK time points per patient that will be combined to compile a complete average plasma concentration time course. The overall reduction of sampling time points is intended to minimize pain and discomfort to pediatric subjects. Part 1 of the study will now consist of: • Cohort 1: Single dose, 40 mg, fed (n=3), rich PK sampling • Cohort 2: Single dose, 80 mg, fed (n=18), sparse PK sampling Following review of safety data from Cohort 1 (40 mg), the Sponsor may authorize continued enrollment into Cohort 2 (80 mg). 3. Reduced the number of PK sampling from 10 to 5 blood sampling time points to minimize pain and discomfort to pediatric subjects. Subjects in Cohort 2 will be assigned one of three blood sampling sequences. In aggregate, sequences will cover the majority of PK sampling time points. PK sampling sequences are described as: • Sequence A: predose, 1, 3, 12, and 120 hours post-dose • Sequence B: predose, 0.5, 2, 4, and 24 hours post-dose • Sequence C: predose, 2, 3, 12, and 24 hours post-dose

	4. Deleted fasting cohorts (previously Cohorts 2, 5, and 7; n=18) as the implementation of and compliance to 10 consecutive fasting hours is not feasible in these pediatric age groups. Remaining cohorts will be renumbered. 5. Removed the study of the youngest age group (28 days to 2 years old) from this protocol, which was previously referred to as Part 3 of the study. 6. Reduced overall study size from 60 subjects to be studied in 7 cohorts to 33 subjects to be studied in 3 cohorts, The age group to be studied include 12 to < 18 years old and 2 to < 12 years old. Part 1 of the study will now consist of children 12 to < 18 years old: • Cohort 1: Single dose, 40 mg, fed (n=3), rich PK sampling • Cohort 2: Single dose, 80 mg, fed (n=18), sparse PK sampling Part 2 of the study will now consist of children 2 to < 12 years old: • Cohort 3: Single dose TBD, fed (n=12), sparse PK sampling TBD Part 2 of the study will not proceed until data from Part 1 have been analyzed and dose and PK sampling details are described in an amendment to the protocol. 7. Modified PK study objectives to be consistent with analyses possible with limited time points being taken per subject. Individual subject data will be pooled and aggregated using POP PK modeling approach for PK parameters estimation. 8. Clarified that pre-dose local lab samples may be taken up to 3 days prior to Day -1 to verify continued eligibility and safety prior to dosing. Guidance previously documented in the Schedule of Assessments has been incorporated in the body of the protocol. 9. Clarified Exclusion Criterion #2 with respect to assessment of active bleeding such that results from Screening and Day -1 urinalysis and fecal occult blood tests will be included in this assessment. Confirmation of negative occult blood stool sample must occur at least once prior to dosing. 10. Modified Exclusion Criterion #6 with respect to the definition of pediatric hypertension to allow for regional and ethnic standards to prevail as determined by the Investigator. Removed United States-specific blood pressure tables as reference in Appendix A. 11. Modified Exclusion Criterion #12 from QTcF to QTc to allow for QT interval correction based on other correction formulas. 12. Modified Exclusion Criterion #13 to exclude planned or anticipated need for antiplatelet use (including aspirin) on day of dosing through the 24hr sampling time point. 13. Added Exclusion Criterion for positive Drugs of Abuse result. Drugs of Abuse test will be limited to adolescent subjects enrolled in Part 1 of the study defined as age 12 to < 18 years old. Drugs of Abuse tests are not required for subjects younger than 12 years old. Positive Drugs of Abuse results will exclude participation in the trial with the exception of medications prescribed by a physician during the current hospital stay. 14. Removed requirement for virology blood tests 15. Updated Schedule of Assessments and associated footnotes. 16. Additional edits and clarifications, deletions, and administrative corrections were made throughout to the document and Appendices to improve clarity and consistency.
26 November 2018	Amendment 2.1 1. Modified Inclusion Criterion #2.b to point out specific diseases and medical conditions that may qualify. 2. Modified Inclusion Criterion #7 to clarify Informed Consent Form signatory requirements.

SYNOPSIS

Name of Sponsor/Company:
Portola Pharmaceuticals, Inc.

Name of Investigational Product:
Betrixaban capsules 40 mg or 80 mg

Name of Active Ingredient: Betrixaban

Title of Study:

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

Study Center(s): Multiple study centers in the United States, EU, Russia, and Ukraine

Principal Investigator: TBD

Investigators: TBD

Studied period (years):	**Phase of development:** 1
Estimated date first patient enrolled: September 2017 Estimated date last patient completed: April 2022	

Objectives:

Primary: 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.

Secondary:

- 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.
- 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.

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 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 ($AUC_{(0\text{-}\infty)}$)
- 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

Additional Endpoints (Pharmacodynamic and Safety):

- PD endpoints include anti-FXa activity and the inhibition of thrombin generation during the first 24 hours post dosing, evaluated by the percent change in thrombin level from baseline, or the values measured may be used.
- Safety endpoint is the clinical assessment of AEs and other safety measurements (vital signs, ECGs, laboratory tests, etc.).

Methodology: Multiple-center, open label study of the PK, PD, and safety of a single dose of betrixaban at up to 80 mg in 33 pediatric patients who meet study entry criteria.

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. Each patient will receive a single, oral, hard gelatin capsule of betrixaban. The dose administered initially to adolescent patients will be 40 mg, followed by dosing with 80 mg. The cohorts in Part 1 are defined as follows:

- Cohort 1 will enroll 3 patients (at least one of each gender), each of whom will receive a single, oral dose of betrixaban at 40 mg in the fed state, and undergo 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 PK and PD data from Part 1 will be used for dose determination for the next youngest age group using population 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. All parameters will be determined per age group in a population PK type analysis except for those patients who have rich PK samples available for analysis.

Following analysis of Part 1 data and an amendment to the protocol, Part 2 of the study will commence and enroll 12 patients 2 to < 12 years of age. Each patient will receive an open-label, single oral dose of betrixaban; these patients must be able to take either the hard gelatin capsule or an oral, liquid formulation (once it has been developed). Similar to Cohort 2, Cohort 3 will employ separate PK sampling sequences (TBD) based on data from Part 1 and described in an amendment to the protocol. Analysis will be done using POP PK methodology. The cohort is defined as follows:

- Cohort 3 will enroll 12 patients (6 patients in each of 2 PK sampling sequences), each of whom will receive a single, oral dose of betrixaban in a fed state at a dose and route to be determined, based on the analysis of Part 1 data.

After dosing, patients will undergo serial blood sampling for PK/PD evaluations.

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

Number of patients (planned):
33 total: 21 in Part 1, 12 in Part 2

Diagnosis and main criteria for inclusion:

Pediatric patients who are assessed to be at risk for VTE. To be eligible for enrollment in the study, a patient must meet all of the inclusion and none of the exclusion criteria listed below. All inclusion criteria must be satisfied within 30 days of enrollment.

Inclusion Criteria

1. Pediatric patients in the following age categories: 12 to < 18 years of age and 2 to < 12 years of age. **Part 1 of the study will enroll only adolescent patients 12 to < 18 years of age.**
2. Patient is a pediatric subject who is assessed to be at risk for VTE but does not require immediate anticoagulant therapy, for example:
   a. Has previous thrombosis and completed a course of anti-coagulant therapy, and is considered to have a risk for recurrence of VTE, or
   b. Has any stable disease with a risk for arterial or venous thromboembolism e.g. inflammatory or autoimmune disease, estrogen use within past 2 months, obesity, congenital heart disease, oncologic diagnosis, hip or knee reconstruction, family history of thromboembolism, immobility, trauma, surgery or lower extremity bone fracture, or
   c. Has any functional CVAD (Central Venous Access Device) in the upper or lower venous system.
3. Patient must be able to have regular intake of a small amount of food (e.g., ≥ 100 mL) and eat before taking study medication, when instructed.
4. Patient has normalized coagulation parameters (INR or PTT, as appropriate) within 7 days of study drug administration.
5. Patient is sexually abstinent or, if not sexually abstinent, agrees to use an approved method of contraception (if applicable).
6. Patient has adequate venous access to allow for blood sampling.
7. Patient has provided Assent and the Informed Consent Form has been signed by the responsible parent(s) or guardian(s) in accordance with applicable local laws and regulations.

Exclusion Criteria

Patients who meet *any one* of the following exclusion criteria will be excluded from the study:

1. Patient received any dose of anticoagulant therapy within 7 days of Day 1.
2. Patient has active bleeding or has a comorbid disorder that places the patient at high risk for bleeding, including a positive fecal occult blood test or hematuria within 30 days prior to Day -1.
3. Patient has a comorbid disorder that places the patient at risk of death within 90 days of enrollment.
4. Patient has abnormal coagulation tests at baseline (within 3 days of Day -1).
5. Patient has had recent or planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study.
6. Patient has hepatic disease associated with one or more of the following:
   - Transaminase levels ≥ 2.5 × Upper Limit of Normal (ULN) or bilirubin ≥ 1.5 × ULN at baseline.
   - Coagulopathy leading to a clinically relevant bleeding risk, or hepatic transaminase level of > 2 × ULN or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total.
   - Platelet count < 75 × 10^9/L or hemoglobin < 10.0 mg/dL.
   - Hypertension.
7. Patient has known congenital or acquired bleeding diathesis.
8. Patient requires concomitant therapy with a strong P-gp inhibitor.
9. Patient has previous history of any non-traumatic bleeding event that was life threatening or required

medical attention.

10. Patient had been administered thrombolytic therapy, or had undergone thrombectomy, or insertion of a caval filter to treat prior VTE.
11. Patient has known inherited or acquired bleeding diathesis or coagulopathy.
12. Patient has abnormal QTc interval on baseline ECG.
13. Patient will/has receive(d) a dose of any antiplatelet medication (including aspirin) within 14 days before study drug dosing. Planned or anticipated use of antiplatelet medication (including aspirin) in the first 24 hours following dosing shall exclude the patient.
14. Patient has malabsorption disorders (e.g., cystic fibrosis or short bowel syndrome).
15. Patient has an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min.
16. Patient is unable or reluctant to cooperate with the study procedures.
17. Patient has hypersensitivity to other Factor Xa inhibitors, or the components of the dosage form.
18. Patient has participated in a study with an investigational drug or medical device within 30 days prior to administration of betrixaban.
19. Patient is female and of childbearing potential and is either pregnant or breastfeeding a child.
20. Patient is sexually active and is not using medically accepted contraceptive method (if applicable).
21. Patient has positive Drugs of Abuse urine test at Screening (Part 1 subjects only) at Screening excluding medications prescribed by a physician during the current hospital stay.

Investigational product, dosage and mode of administration:
Betrixaban as either 40 mg or 80 mg hard gelatin capsules, or an oral pediatric formulation to facilitate dosing determined by weight.

Duration of treatment:
Single dose

Reference therapy, dosage and mode of administration:
None

Criteria for Evaluation:

Pharmacokinetics: Blood samples for PK analysis will be collected using 3.2% Na Citrate as the anticoagulant. Blood samples for PK assessments will be collected 30 minutes prior to the dose administration, and at 0.5, 1, 2, 3, 4, 6, 12, 24, and 120 hours post dose. The plasma portion of the blood samples will be assayed for determining the PK parameters of betrixaban for all patients in the rich PK sampling group. A subset of the samples (except the 6 hour time point) will be collected for patients assigned to each sequence in the POP PK groups. The following PK parameters will be calculated by age group using POP PK methodology, except for patients with rich PK sampling:

- Terminal plasma half-life ($t_{½}$), determined by linear regression of the log concentration on the terminal portion of the plasma concentration–time curve. This will be calculated if appropriate data is available. Half-life is calculated as:
  - ln(2)/(-ß), where ß is the slope of the terminal portion of the log concentration–time curve.
- Time to maximum observed plasma concentration (T_{max}).
- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration–time curve from 0 to last available measurable concentration ($AUC_{(0\text{-}last)}$) computed using the linear trapezoidal rule.
- Clearance (CL/F), calculated by dividing the administered dose by the $AUC_{(0\text{-}\infty)}$.
- Volume of Distribution (Vd/F), calculated by dividing the dose administered by the plasma concentration at the first time point measured.
- Total area under the plasma concentration–time curve from time 0 to infinity (total AUC), computed as:
  - Total AUC ($AUC_{(0\text{-}\infty)}$) = $AUC_{(0\text{–}last)}$ + CP_{last} /(-ß) where $AUC_{(0\text{–}last)}$ is the area under the curve from time 0 to the time point of the last measurable concentration above the quantitation limit; CP_{last} is the last

measurable concentration above the quantitation limit; and ß as defined as above.

Pharmacodynamic Assessment:

The following PD assessment will be determined at a sub-set of timepoints collected for PK analysis. Data may be normalized to pre-dose samples and expressed as % of pre-treatment or the values measured may be used.

- Anti-FXa activity
- TF-initiated thrombin generation assay in platelet poor plasma.

Safety:

Safety and tolerability will be determined by change from baseline in symptoms, signs, and laboratory tests, by elicitation of treatment emergent AE (TEAEs), and by concomitant medication usage. All AE events will be followed until resolution and appropriately reported on the AE Case Report Form. Laboratory abnormalities will be reported as AEs if deemed to be clinically significant per the Principal Investigator.

Statistical Methods:

Primary PK parameters, $AUC_{(0\text{-last})}$, and C_{max} will be determined for each patient using plasma level of betrixaban assessed at baseline, during the first 24 hours, and 120 hours post dosing. Other PK parameters, Total AUC ($AUC_{(0\text{-}\infty)}$) $t_{1/2}$, T_{max}, CL, and V_d/F will also be determined, data permitting. Descriptive statistics such as geometric mean and 90% CI for PK parameters will be summarized by gender for each age group.

The PD endpoint, the inhibition of thrombin generation during the first 24 hours post dosing, will be evaluated by the percent change in thrombin level from baseline. Correlation analysis will be performed for the thrombin change and the betrixaban level during the first 24 hours. The maximum change (the nadir of thrombin level) from baseline will be derived for each patient and summarized by gender for each age group.

Safety and tolerability will be evaluated by clinical assessment of AEs and other safety measurements (vital signs, EKGs, laboratory tests, etc.). Treatment-emergent AE will be coded by the updated version of MedDRA and summarized as event rate by SOC and Preferred terms. Change in vital signs, laboratory tests, and EKG parameters from baseline to each post-dosing assessment will be derived for each patient. Appropriate summary statistics will be provided for each age group.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AF	Atrial Fibrillation
AUC	Area Under the plasma concentration versus time Curve
$AUC_{(0\text{-last})}$	Area Under the plasma concentration versus time Curve over the dosing interval at steady state, from time of drug administration, zero, to the last concentration above the lower limit of quantitation
$AUC_{(0\text{-}\infty)}$	Area Under the plasma concentration versus time Curve extrapolated to infinity
CL/F	Clearance
C_{max}	Highest concentration of study drug within a dosing interval
CRF	Case Report Form
CVAD	Central Venous catheter or Access Devices
EDTA	Ethylenediaminetetraacetic Acid
CVC	Central Venous Catheter
F	Oral bioavailability (fraction of the total dose reaching the systemic circulation)
FDA	United States Food and Drug Administration
FXa	Factor Xa
GCP	Good Clinical Practice
hr	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IR	Immediate Release
IRB	Institutional Review Board
IV	Intravenous
L	Liter
LMWH	Low Molecular Weight Heparin
min	Minute
mL	Milliliter
msec	Millisecond

Abbreviation or Specialist Term	Explanation
PBPK	Physiological-Based Pharmacokinetic
PD	Pharmacodynamic
PK	Pharmacokinetic
POP PK	Population Pharmacokinetic
QTc	Corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-life associated with the terminal elimination
TEAE	Treatment Emergent Adverse Event
TGI	Thrombin Generation Inhibition
T_{max}	Observed sample time of highest concentration within a dosing interval
UH	Unfractionated Heparin
USP	United States Pharmacopeia
V_d/F	Volume of distribution
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

1.0 INTRODUCTION

Betrixaban is an oral anticoagulant that is a potent and specific inhibitor of human Factor Xa (FXa), an important validated target in the blood coagulation pathway. It binds to the active site of FXa to prevent thrombosis. As the maleate salt, betrixaban has a Molecular Weight (MW) of 567.98 and is available for oral administration as an Immediate Release (IR) capsule. It is rapidly absorbed with mean peak concentrations occurring 3 to 4 hours after oral administration. Oral bioavailability of an 80 mg dose is approximately 34%, and protein binding is approximately 60%. The drug exhibits nonlinear kinetics within the expected therapeutic dosing range with greater than proportional increases in plasma concentrations occurring with increased dose; maximum plasma concentration (C_{max}) and Area Under the Curve (AUC) at steady-state increased approximately 3-fold when the dose was doubled from 40 mg to 80 mg. Excretion is mostly unchanged through the bile with renal clearance approximately 17% of the absorbed dose. When administered after a high-fat, high-calorie breakfast, C_{max} and AUC were reduced by approximately 50% as compared to the fasting state.

Betrixaban is only weakly metabolized by major cytochrome P450 enzymes. It is a substrate for efflux proteins including permeability glycoprotein (P-glycoprotein or P-gp). When co-administered with the potent P-gp inhibitor ketoconazole, betrixaban concentrations were increased more than approximately 2-fold. Based on Population Pharmacokinetic (POP PK) analysis from the Phase 2 EXPLORE Xa study (Connolly et al., 2013) [1], a similar effect was observed when betrixaban was given concomitantly with amiodarone, another strong P-gp inhibitor. A drug interaction study with the P-gp substrate, digoxin, showed no significant interaction, and one with the strong inhibitor verapamil suggests that co-administration in fasted state increases both C_{max} and exposure to betrixaban.

To date, of 4,969 subjects including patient volunteers and healthy volunteer subjects were exposed to at least one dose of betrixaban in Phase 1 to 3 studies: 3,716 in APEX, 741 in Phase 2 studies in indications other than the target indication, and 512 in Phase 1 studies. Twenty Phase 1 studies were conducted in 551 healthy subjects, of these patients, 512 received betrixaban. Three Phase 2 studies have also been conducted, one in patients after joint replacement surgery and two in patients with chronic Atrial Fibrillation (AF). Several Phase 1 studies assessed the Pharmacokinetics (PK) and/or Pharmacodynamics (PD) of betrixaban in healthy men and women across a range of ages and weights. These studies demonstrated well-behaved and predictable PK and the expected PD effects of a reversible FXa inhibitor, as well as good tolerability. In particular, a dose-dependent decrease in thrombin generation could be demonstrated. Included in these studies were special population studies, formulation studies, drug-drug interaction studies, and a thorough QT cardiac safety study.

The three Phase 2 studies included one trial of 215 patients trial (Study 05-003; EXPERT [Turpie et al., 2009]) [2] for the prevention of Venous Thromboembolism (VTE) after Total Knee Replacement (TKR), one trial in 508 patients (Study 08-015; EXPLORE Xa [Connolly et al., 2013]) [1] for the prevention of stroke in AF, and one dose-exposure ranging trial in 189 patients with AF (Study PN006, on file at Portola Pharmaceuticals, Inc.). These studies, while underpowered to establish either safety or efficacy, showed betrixaban has similar effects to the active comparators (Low Molecular Weight Heparin [LMWH] for the orthopedic study, warfarin for the studies of patients with AF). These results supported moving forward into a Phase 3 program that resulted in the submission of a New Drug Application (NDA) in 2016. Betrixaban was approved in the United States by the FDA in June 2017 for the prophylaxis of 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.

In Phase 1 studies enrolling healthy patients, single doses between 5 and 550 mg were well tolerated, as were 10-day regimens of 40, 80, and 120 mg every 12 hours. In the EXPERT study (Turpie et al., 2009) [2], betrixaban doses of 15 and 40 mg twice daily (BID) showed activity in the prevention of VTE after TKR when compared to historical control and a small concurrent enoxaparin control group. Major and minor bleeding rates were low and comparable between the betrixaban and enoxaparin treated groups. The results of the EXPERT study indicate that prophylaxis with betrixaban appeared comparable to optimal use of enoxaparin. Results of the EXPLORE Xa study (Connolly et al., 2013) [1] demonstrate that once-daily doses of 40, 60, and 80 mg for stroke prevention in patients with non-valvular AF were well tolerated, with all doses of betrixaban having a favorable bleeding profile compared to warfarin. Very low rates of stroke in all treatment groups that were observed in this study suggests active anticoagulant effect.

One Phase 3 study with betrixaban has been completed, Study 11-019, entitled "*A multicenter, randomized, active–controlled efficacy and safety study comparing extended duration betrixaban with standard of care enoxaparin for the prevention of venous thromboembolism in acute medically ill patients*" (the APEX study). In this study, patients who were immobilized due to an acute medical illness (acute heart failure, acute infection, acute respiratory failure, acute stroke, or acute rheumatic disorder) and with risk factors for VTE were randomized 1:1 to either extended prophylaxis (35–42 days with betrixaban) or to 10 ± 4 days of enoxaparin, the standard of care in this indication (Cohen et al., 2016) [3]. The primary endpoint was the occurrence of any of the following events through Visit 3:

- Asymptomatic proximal Deep Vein/Venous Thrombosis (DVT) as detected by ultrasound.
- Symptomatic DVT (proximal or distal), non-fatal Pulmonary Embolism (PE), or VTE-related death on or before the day of Visit 3 or Day 42, whichever was earlier.

In this study, the primary endpoint was analyzed in three successively larger cohorts of patients:

- Cohort 1: Those whose D-dimer on admission was ≥ 2× the Upper Limit of Normal (ULN).
- Cohort 2: Those who met this D-dimer criteria and/or were ≥ the age of 75.
- Cohort 3: All patients enrolled in the study who received at least one dose of the study drug and who had had assessment of any one of the components of the primary efficacy outcome endpoint (primary efficacy outcome population, PEOP).

Table 3 displays the results for these cohorts.

Table 3: APEX Primary Efficacy Results in Cohort 1, Cohort 2 and Overall Patient Population (PEOP)

Cohort	Enoxaparin	Betrixaban	RRR (95% CI)	p-Value
1	8.5% (166/1,956)	6.9% (132/1,914)	19.4% (-0.4-35.3)	0.054
2	7.1% (204/2,893)	5.6% (160/2,842)	20.0% (2.3, 34.5)	0.029
PEOP	7.0% (223/3,174)	5.3% (165/3,112)	24.0% (7.7, 37.5)	0.006

CI = Confidence interval; RRR = Relative risk reduction

Note: APEX = Portola Pharmaceuticals, Inc. Protocol No. 11-019 "*Multicenter, Randomized, Active–Controlled Efficacy and Safety Study Comparing Extended Duration Betrixaban with Standard of Care Enoxaparin for the Prevention of Venous Thromboembolism in Acute Medically Ill Patients*." Patients who were immobilized due to acute heart failure, acute infection, acute respiratory failure, acute stroke, or acute rheumatic disorder were randomized 1:1 to either extended prophylaxis (35–42 days) or to 10 ± 4 days of enoxaparin, the standard of care in this indication.

The relative risk reduction in all 3 cohorts was achieved without a clinically important increase in bleeding risk. The incidence of major bleeding was almost identical between the treatment groups. There was an increase in clinically relevant non-major bleeding among patients receiving betrixaban as compared to enoxaparin, but the point estimate of the incidence of intracranial bleeding was lower among betrixaban-treated patients. Table 4 displays the bleeding results by treatment group.

Table 4: The APEX Study – Bleeding Events, Safety Population

Endpoint	Enoxaparin	Betrixaban	p-Value
Major Bleeding	0.57% (21/3716)	0.67% (25/3716)	0.55
Major and or Clinically Relevant Non-major Bleeding	1.59% (59/3716)	3.12% (116/3716)	< 0.001
Intracranial Hemorrhage	0.19% (7/3716)	0.05% (2/3716)	0.18

Note: APEX = Portola Pharmaceuticals, Inc. Protocol No. 11-019 *"Multicenter, Randomized, Active–Controlled Efficacy and Safety Study Comparing Extended Duration Betrixaban with Standard of Care Enoxaparin for the Prevention of Venous Thromboembolism in Acute Medically Ill Patients."* Patients who were immobilized due to acute heart failure, acute infection, acute respiratory failure, acute stroke, or acute rheumatic disorder were randomized 1:1 to either extended prophylaxis (35 to 42 days) or to 10 ± 4 days of enoxaparin, the standard of care in this indication.

The results of the APEX study indicated the effectiveness and safety of betrixaban as an anticoagulant in a population of immobilized adults with acute medical illness and risk factors for VTE. In addition, the results of the Phase 1 and 2 studies demonstrated an appropriate safety profile for betrixaban. Betrixaban has been administered to almost 5,000 adult patients and the primary Adverse Effect (AE) noted has been a modest increase in bleeding events, as is expected with any anticoagulant therapy. No specific off-target toxicities noted at the therapeutic dose of betrixaban have been identified. A separate thorough QTc study in adults (Study 07-013) demonstrated that 140 mg betrixaban had no effect on the QTc interval as measured by time-matched mean change in QTc.

Therapeutic anticoagulation in children, however, has not been well studied, and currently, no products are approved for anticoagulant therapy in children. Major reasons are that VTE events are uncommon in pediatric patients compared with adults and that conducting rigorous clinical investigations, particularly randomized, controlled studies is difficult.

Anticoagulants are employed when children develop VTE or are believed to be at high risk of VTE. Current medical practice employs LMWH or Unfractionated Heparin (UH), or Vitamin K antagonists (VKAs) as appropriate prophylaxis for VTE in pediatric patients. These agents are effective but there are limitations in LMWH and UH must be administered subcutaneously or Intravenously (IV). The VKAs are administered orally but require frequent monitoring by blood tests and are difficult to maintain within the therapeutic range due to variations in diet and inter-individual metabolism.

Prophylaxis of VTE with anticoagulants in hospitalized pediatric patients is not standard practice. Rather, the decision to use prophylaxis is considered on an individual basis and is more likely to be implemented in certain clinical situations (prolonged intensive care unit or hospital stay with central venous line placement, requirement for total parenteral nutrition, those admitted

with severe respiratory, oncologic, or infectious diseases). There are rare pediatric patients who have experienced VTE due to acquired, congenital, or idiopathic reasons who do receive chronic secondary prophylaxis for VTE; however, such patients receive high-intensity anticoagulation, for which betrixaban will not be recommended. Practice-based guidelines for diagnosis, prophylaxis, and treatment of pediatric VTE have not been extensively evaluated in randomized clinical trials. Guidelines based on the best available information have been published by the British Committee for Standards in Haematology (Chalmers et al., 2011) [4] and the American College of Chest Physicians (Monagle et al., 2012) [5]. In Europe, the approach to nonclinical and clinical investigation in pediatric patients was discussed at the Pediatric Anticoagulation Therapy Expert Meeting of the EMA in London, UK on 06 November 2012. In addition, based on an extensive literature search, The Netherlands developed a country-wide guideline that determines whether pediatric patients are placed on prophylaxis for VTE when hospitalized (http://richtlijnendatabase.nl/module/preventie_trombose_neonaten_kinderen_tot_18.html) [6].

Prophylaxis of VTE in children has been an area of discussion in the professional literature for some time. Noting the lower risk of VTE and a lower rate of bleeding complications with anticoagulant therapy, authors have urged individual assessment of risk. However, one randomized clinical trial of the LMWH reviparin has been performed in hospitalized children with an indwelling central venous catheter (CVC; the most common predisposing factor to VTE in pediatric patients). This study, however, was terminated early due to poor enrollment; also, the trial had a higher incidence of VTE in the reviparin-treated group (Massicotte et al, 2003 – the PROTEKT trial) [7]. For lack of an evidence-based indication, primary pharmacologic routine prophylaxis is therefore currently not recommended for hospitalized pediatric patients solely on the basis of an indwelling CVC (Monagle et al., 2012) [5]. Nonetheless, persistent observations of VTE in hospitalized adolescent patients have led to the development of several risk prediction scores based on observational studies that include multiple clinical factors (Raffini et al., 2011; Hanson et al., 2012; Jackson et al., 2008; Sharathkumar et al, 2012) [8-11]. An algorithm to determine eligibility of pediatric patients has recently been published by the University of Cincinnati (Meier et al., 2015) [12]. Prolonged immobilization (> 72 hours) was found to be the most significant risk factor for VTE in hospitalized adolescents.

Given the unmet medical need for anticoagulant therapy in hospitalized adolescents, the current study (Protocol 16-021) represents an initial step to extend the clinical development of betrixaban into the pediatric population by evaluating the safety, PK, and PD of a single, oral dose of betrixaban.

The dose level to be tested was based on the profile of betrixaban derived from the Phase 3 APEX trial in acute medically ill adults. In this study, two doses were tested. The standard dose was 80 mg, but a 40 mg dosage strength was used in order to dose adjust for patients in whom increased exposure was expected, i.e., those on strong P-gp inhibitors or with severe renal deficiency (CrCl < 30 mL/min). The POP PK analysis found that dose adjustment for patients

with severe renal deficiency was not needed and that dose adjustment should be limited to patients only on certain strong P-gp inhibitors when betrixaban was administered in the fed state, as was done in APEX. There is no evidence from any of the nonclinical or clinical PK studies conducted to date that suggests the mechanisms of Absorption, Distribution, Metabolism, and Excretion (ADME) of betrixaban will be different in the adolescent population. Therefore, POP PK simulations were used to predict the likely exposure response of a single 40 mg dose for the adolescent pediatric subset. Typical weights for adolescents (male and female) were obtained from the National Health and Nutrition Examination Survey (NHANES; USA). Males ranged from 40.7 to 67.3 kg and females from 41.8 to 56.2 kg. The range of body weight simulated overlaps with that of the patient population used in the adult POP PK models. The preliminary modeling studies suggested that for at least larger adolescents, the 80 mg dose would result in similar exposures to those observed in adults and that the relative exposure of a 40 mg dose in adolescent males is predicted to be approximately 60 to 88% of that of the male adult exposure receiving the 80 mg dose. Exposure in adolescent females is predicted to be 60 to 74% of that in adult females.

Portola Pharmaceuticals, Inc. plans to investigate betrixaban in a step-wise manner in pediatric subjects. The PK and PD parameters will be evaluated in the first study, starting with adolescents (12 to < 18 years of age) who can take a hard gelatin capsule and then proceeding to include progressively younger age groups (2 to < 12), as an oral pediatric formulation becomes available. For each age group, the PK and safety data will be analyzed and used to predict the weight-based dose to be used in the next younger age group in future studies. The doses predicted from Study 16-021 may then be used in the subsequent clinical efficacy and safety studies in pediatric patients.

Under Protocol 16-021, pediatric patients who meet study entry criteria will receive an open-label, single dose of orally administered betrixaban. The following age categories will be tested: 12 to < 18 years, and 2 to < 12 years. Part 1 will enroll 21 adolescents 12 to < 18 years of age, grouped in to 2 cohorts; each cohort will be dosed sequentially. The first cohort (3 patients) will receive betrixaban at 40 mg in the fed state, and have rich PK sampling consisting of 10 sampling time points. The second cohort (18 patients) will receive betrixaban at 80 mg in the fed state, and undergo one of three sequences of sparse PK sampling consisting of 5 sampling time points per sequence. Based on the results obtained in Part 1, the protocol will be amended and Part 2 will enroll 12 patients 2 to < 12 years of age who will receive a single oral dose of betrixaban based on weight as predicted by the results of the PK modeling and safety in the adolescents. An oral pediatric formulation is being developed in parallel with Part 1 of this study so that weight-based dosing of smaller pediatric patients will be possible. Part 2 PK sampling sequences will be determined following analysis of Part 1 data.

Data collected from this initial PK study in adolescents will be used to confirm both the POP PK and PBPK models, the appropriateness of weight-based dosing in adolescents, and recommend the weight-based dosing levels in children 2 to < 12 years of ageand adolescents who are below the weight range for the dose of the capsule determined to be appropriate for adolescents based on the PK study.

This trial will be conducted subject to the permission of a local Ethical Review Board, according to the Declaration of Helsinki, according to Good Clinical Practice and local regulatory requirements, and in compliance with this protocol.

2.0 OBJECTIVES

2.1. Primary Objective

The primary objective is to determine the PK parameters of betrixaban in pediatric patients in the following age categories: 12 to < 18 years of age, and 2 to < 12 years of age.

2.2. Secondary Objectives

The secondary objectives are as follows:

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

2.3. Pharmacokinetic Parameters

The plasma levels will be assessed at baseline, during the first 24 hours, and 120 hours post dosing and will be used to determine the PK parameters shown below for each patient.

2.3.1. Primary Pharmacokinetic Parameters

The primary PK parameters to be determined are as follows:

- Area under the concentration-time curve to the last measurable concentration above the quantitation limit ($AUC_{(0\text{-}last)}$) per age group except for individuals with rich PK sampling
- Maximum observed plasma concentration (C_{max})

2.3.2. Other Pharmacokinetic Parameters

Other PK parameters to be determined are as follows:

- Terminal plasma half-life ($t_{½}$), data permitting
- Time to maximum observed plasma concentration (T_{max}) per age group
- Clearance (CL/F) and volume of distribution (V_d/F) for each age group

2.4. Additional Endpoints

- The PD endpoints include anti-FXa activity and the inhibition of thrombin generation during the first 24 hours post dosing, evaluated by the percent change in thrombin level from baseline.
- The safety endpoint is the clinical assessment of AEs and other safety measurements (vital signs, electrocardiograms [ECGs], laboratory tests, etc.)

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design

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 an up to 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 gender), 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, Part 2 of the study will commence and enroll 12 patients 2 to < 12 years of age. Each patient will receive an open-label, single oral dose of betrixaban; these patients must be able to take either the hard gelatin capsule or an oral, liquid formulation (once it has been developed and described in a future amendment to this protocol). Similar to Cohort 2, subjects will be assigned one of two PK sampling sequences based on data from Part 1. The cohort in Part 2 is defined as follows:

- Cohort 3 will enroll 12 patients (6 patients in each of 2 PK sampling sequences), each of whom will receive a single, oral dose of betrixaban in a fed state at a dose and route to be determined, based on the analysis of Part 1 data.

After dosing, patients will undergo serial blood sampling for PK-PD evaluations.

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

The schema of the study is depicted in Figure 1. The Schedule of Assessments for the study is provided in Table 5.

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

TBD = To be determined and later specified in a subsequent amendment to this protocol

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. Part 2 of the study will only commence upon written approval of an amendment to this protocol by applicable regulatory bodies (i.e., IEC/IRB, MOH, and CA, as appropriate).

3.3. Treatment Assignment

Each patient will receive an open-label, single oral dose of betrixaban as specified in Section 3.1. The first 3 patients in the study will be assigned to Cohort 1 in the study. Subsequently, Sponsor/study management will centrally maintain and provide Sequence assignments.

3.4. Enrollment

A patient is considered to be enrolled in the study at the time the patient's parent or guardian signs the Informed Consent Form. Subjects will be replaced if they do not receive study medication.

3.5. Dose Adjustment Criteria

Not applicable.

3.6. Duration of Study

The duration of the study for each individual patient may be up to approximately 37 days (screening period of up to 30 days, Day -1, followed by administration of a single dose of betrixaban on Day 1, followed by blood sampling on Days 1, 2, and 6, and a safety follow-up phone call on Day 7).

The study is expected to enroll over approximately 50 months.

3.7. Data Safety Monitoring Board

There is no Data Safety Monitoring Board (DSMB) for this single-dose PK study.

3.8. Criteria for Study Termination

3.8.1. Halting or Termination of Enrollment

In the event of a Serious and Unexpected Adverse Reaction (SUSAR) or an episode of major bleeding, patient enrollment will be halted until a full accounting of the event and determination of its relationship to betrixaban has been completed by the Sponsor.

Major bleeding is defined as follows:

- Fatal or a life-threatening bleeding.
- Clinically overt bleeding resulting in a rapid decrease in hemoglobin level of more than 2 g/dL in 24 hours.
- Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system.
- Bleeding that requires a transfusion of a blood product and which is not directly attributable to the patient's underlying medical condition.
- Bleeding that requires surgical intervention in an operating suite.

If a patient is noted to develop a new QTc interval longer than 450 msec, or if change from baseline QTc interval of > 10 msec is observed in any patient, enrollment will be halted.

3.8.2. Sponsor Termination of the Study

The Sponsor may terminate the study at any time, for any reason. Typical reasons for termination of a study include, but are not limited to, the following:

- Unacceptable rate of enrollment.
- Unacceptable difficulty encountered with administration of study medication (e.g., patient cannot swallow or vomits medicine).
- Unacceptable incidence of AEs, including SUSARs or prolonged QTc interval, as noted in Section 3.8.1.
- Unacceptable incidence of noncompliance (e.g., notable percentages of patients refuse to allow blood sampling or provide urine samples).

3.8.3. Individual Patient Withdrawal

Criteria for withdrawal of individual patients as well as reporting procedures for AEs associated with halting or termination of enrollment are provided in Section 9.2.

The Schedule of Assessments for Study 16-021 is provided in Table 5.

Table 5: Schedule of Assessments: Study 16-021 (2 Pages)

	Screening	Day -1 [a]	Pre-Dose	Post Dose 0.5 to 24 Hours (Day 1 - Day 2)								Post Dose 120 Hours	Day 7 Follow-up Phone Call
Procedure/Assessment	(≤ 30 days prior to dosing)	(Day -4 to Day -1)	(Day 1)									(Day 6)	
Time:	**NA**	**NA**	**0.0 hr**	**0.5 hr**	**1.0 hr**	**2.0 hr**	**3.0 hr**	**4.0 hr**	**6.0 hr**	**12 hr**	**24 hr**	**120 hr**	
Window:	**NA**	**NA**	**NA**	**5 min**	**± 5 min**	**± 5 min**	**± 10 min**	**± 10 min**	**± 10 min**	**± 20 min**	**± 30 min**	**± 120 min**	
Study Day:	**-30 > -1**	**-4 > -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**6**	**7**
General													
IC/Assent	X												
Eligibility	X	X	X										
Medical History	X	X											
Full PE [b] / Limited PE [c]	X [b]	X [c]									X [c]	X [c]	
Height (cm)	X												
Weight (kg)	X	X									X	X	
Vital Signs / Temp	X	X	X	X	X	X	X	X	X	X	X	X	
Safety													
AE's (continuous)	X	X	X	[----------X----------]									X
Con Meds (continuous)	X	X	X	[----------X----------]									X
12-lead ECG	X						X				X		
Local Safety Labs (Hem., Coag., Chem.)	X	X									X	X	
Urinalysis (to include blood in urine)	X	X									X	X	
Serum pregnancy (for females of childbearing potential)	X	X											
Stool for occult blood	[---X---]		[---X, if/when sample available---]										
Urine drug screen (age 12 to <18 only)	X	X											
Fluid restriction			at least 1 hr pre-dose	at least 1 hr post-dose									
Food restriction				at least 2 hrs post-dose									

	Screening	Day -1 [a]	Pre-Dose	Post Dose 0.5 to 24 Hours (Day 1 - Day 2)								Post Dose 120 Hours	Day 7 Follow-up Phone Call
Procedure/Assessment	(≤ 30 days prior to dosing)	(Day -4 to Day -1)	(Day 1)									(Day 6)	
Time:	**NA**	**NA**	**0.0 hr**	**0.5 hr**	**1.0 hr**	**2.0 hr**	**3.0 hr**	**4.0 hr**	**6.0 hr**	**12 hr**	**24 hr**	**120 hr**	
Window:	**NA**	**NA**	**NA**	**5 min**	**± 5 min**	**± 5 min**	**± 10 min**	**± 10 min**	**± 10 min**	**± 20 min**	**± 30 min**	**± 120 min**	
Study Day:	**-30 > -1**	**-4 > -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**6**	**7**
Cohort 1 - Rich Sampling													
Dosing under fed conditions			**X**										
PK Sampling - BTX			X	X	X	X	X	X	X	X	X	X	
PD sampling - anti-fXa; TGI			X			X	X				X	X	
Cohort 2 - Sequence A Sampling													
Dosing under fed conditions			**X**										
PK Sampling - BTX			X		X		X			X		X	
PD sampling - anti-fXa; TGI			X		X		X			X		X	
Cohort 2 - Sequence B Sampling													
Dosing under fed conditions			**X**										
PK Sampling - BTX			X	X		X		X			X		
PD sampling - anti-fXa; TGI			X	X		X		X			X		
Cohort 3 - Sequence C Sampling													
Dosing under fed conditions			**X**										
PK Sampling - BTX			X			X	X			X	X		
PD sampling - anti-fXa; TGI			X			X	X			X	X		

[a] Unless performed ≤ 3 days prior to Day -1, i.e., on Days -4, -3, -2, and -1.

[b] Complete PE as described in Section 9.1.2.1.

[c] Brief PE as described in Section 9.1.2.2.

4.0 SELECTION AND WITHDRAWAL OF PATIENTS

To be eligible for enrollment in the study, a patient must meet *all* of the inclusion and *none* of the exclusion criteria as shown below. All entry criteria must be satisfied within 30 days of enrollment.

4.1. Inclusion Criteria

1. Pediatric patients in the following age categories: 12 to < 18 years of age, and 2 to < 12 years of age. **Part 1 of the study will enroll only adolescent patients 12 to < 18 years of age.**
2. Patient is a pediatric subject who is assessed to be at risk for VTE but does not require immediate anticoagulant therapy, for example:
   a. Has previous thrombosis and completed a course of anticoagulant therapy, and is considered to have a risk for recurrence of VTE; or
   b. Has any stable disease with a risk for arterial or venous thromboembolism e.g. inflammatory or autoimmune disease, estrogen use within past 2 months, obesity, congenital heart disease, oncologic diagnosis, hip or knee reconstruction, family history of thromboembolism, immobility, trauma, surgery or lower extremity bone fracture, or
   c. Has any functional Central Venous Access Device (CVAD) in the upper or lower venous system.
3. Patient must be able to have regular intake of a small amount of food (e.g., ≥ 100 mL) and eat before taking study medication, when instructed.
4. Patient has normalized coagulation parameters (INR or PTT, as appropriate) within 7 days of study drug administration.
5. Patient is sexually abstinent or, if not sexually abstinent, agrees to use an approved method of contraception (if applicable).
6. Patient has adequate venous access to allow for blood sampling.
7. Patient has provided Assent and the Informed Consent Form has been signed by the responsible parent(s) or guardian(s) in accordance with applicable local laws and regulations.

4.2. Exclusion Criteria

Patients who meet *any one* of the following exclusion criteria will be excluded from the study:

1. Patient received any dose of anti-coagulant therapy within 7 days of Day 1.
2. Patient has active bleeding or has a comorbid disorder that places the patient at high risk for bleeding, including a positive fecal occult blood test or hematuria within 30 days prior to Day -1.

3. Patient has a comorbid disorder that places the patient at risk of death within 90 days of enrollment.
4. Patient has abnormal coagulation tests at baseline (within 3 days of Day -1).
5. Patient has had recent or planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study.
6. Patient has hepatic disease associated with one or more of the following:
   - Transaminase levels ≥ 2.5 × ULN or bilirubin ≥ 1.5 × ULN at baseline.
   - Coagulopathy leading to a clinically relevant bleeding risk, or hepatic transaminase level of > 2 × ULN or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total.
   - Platelet count < 75 × 109/L or hemoglobin < 10.0 mg/dL.
   - Hypertension.
7. Patient has known congenital or acquired bleeding diathesis.
8. Patient requires concomitant therapy with a strong P-gp inhibitor.
9. Patient has previous history of any non-traumatic bleeding event that was life threatening or required medical attention.
10. Patient had been administered thrombolytic therapy, or had undergone thrombectomy, or insertion of a caval filter to treat prior VTE.
11. Patient has known inherited or acquired bleeding diathesis or coagulopathy.
12. Patient has abnormal QTc interval on baseline ECG.
13. Patient will/has receive(d) a dose of any antiplatelet medication (including aspirin) within 14 days before study drug dosing. Planned or anticipated use of antiplatelet medication (including aspirin) in the first 24 hours following dosing shall exclude the patient.
14. Patient has malabsorption disorders (e.g., cystic fibrosis or short bowel syndrome).
15. Patient has an estimated Glomerular Filtration Rate (eGFR) < 30 mL/min.
16. Patient is unable or reluctant to cooperate with the study procedures.
17. Patient has hypersensitivity to other Factor Xa inhibitors, or the components of the dosage form.
18. Patient has participated in a study with an investigational drug or medical device within 30 days prior to administration of betrixaban.
19. Patient is female and of childbearing potential and is either pregnant or breastfeeding a child.

20. Patient is sexually active and is not using medically accepted contraceptive method (if applicable).
21. Patient has positive drugs of abuse urine test (age 12 to <18 years only) at Screening excluding medications prescribed by a physician during the current hospital stay.

4.3. Patient Withdrawal Criteria

Only one dose of study medication will be administered. Therefore, it is hoped that after patients take that dose, they will comply readily with the follow-up procedures (e.g., blood draws, urine sampling) specified for this Phase 1 study.

A patient who refuses to continue with study procedures is considered a "non-adherer." A patient who withdraws consent for any further contact with the study personnel is considered a "true withdrawer."

A patient can be withdrawn from the study for any of the following reasons:

- In the opinion of the Investigator, the patient cannot safely perform the procedures required by the protocol (e.g., provide blood or urine samples).
- The patient has an AE that is unacceptable to the patient or Investigator.
- The patient needs a concomitant medication that makes the patient ineligible for further participation in the study.
- The Investigator or Portola Pharmaceuticals, Inc. Medical Monitor decides it is in the patient's best interest not to continue in the study.
- The patient refuses to or cannot comply with study procedures, e.g., refuses study medication, blood sampling, or urine sampling ("non-adherer").
- The patient withdraws consent for any further contact with study personnel ("true withdrawer").

NOTE: Patients are free to withdraw from the study at any time for any reason. Reasons for all withdrawals will be recorded. If a patient discontinues the study due to an AE, that AE must be evaluated to determine whether it should be classified as a Serious AE (SAE). Any SAE that causes a patient to terminate the study must be reported by telephone to the Portola Pharmaceuticals, Inc. Medical Monitor immediately by the Investigator. The SAE form must be filed within 24 hours of awareness of the event. If feasible, all procedures described under the Study Termination Visit (Section 7.5) will be performed.

5.0 TREATMENT OF PATIENTS

5.1. Description of Study Drug

In Part 1, the investigational product, betrixaban capsules, is a hard gelatin capsule. A description of the study drug used in Part 1 is shown in . See Section 6.0 for details of packaging, labelling, administration, accountability, handling, and disposal.

Description of study drug for Part 2 of the study will be provided in an amendment to the protocol.

Table 6: Description of Study Drug in Part 1

Name	Betrixaban capsules at 40 mg or 80 mg in pediatric patients 12 to < 18 years of age
Dose	Single oral dose 40 mg or 80 mg
Formulation	30% (as free base) betrixaban maleate 64.75% (w/w) dextrose monohydrate 1.25% (w/w) magnesium stearate 4% (w/w) croscarmellose sodium
Physical Description	Size 2 gelatin capsule shell, or Size 4 gelatin capsule shell

5.2. Concomitant Medications

5.2.1. Prohibited Medications

Ensure that the therapeutic course of anticoagulant has been fully discontinued and that the appropriate coagulation parameters (i.e., INR or PTT) have been confirmed as normal before the patient receives treatment with betrixaban.

The following medications are prohibited:

- Strong P-glycoprotein inhibitor
- Anti-platelets (including anti-inflammatory medications that exert anti-platelet effects)

5.2.2. Permitted Medications

The following medication is permitted:

- Acetaminophen for treatment of pain, if necessary

5.3. Treatment Compliance

Compliance will be assured by having the patient take the single dose of betrixaban while domiciled and under the supervision of study staff.

5.4. Randomization and Blinding

Not applicable. This is an open-label study.

6.0 STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

A description of the study drug, betrixaban capsules, is provided in Table 6.

6.2. Study Drug Packaging and Labeling

For Part 1 of the study (conducted in adolescents 12 to < 18 years of age), packaging consists of HDPE bottles with white polypropylene child-resistant caps with induction seal liners, in packaging supplied by Portola Pharmaceuticals, Inc. A liquid or other formulation of betrixaban is expected to be developed and described in a future amendment to this protocol.

6.3. Study Drug Storage

Containers of capsules should be stored under Controlled Room Temperature conditions, defined as 20 to 25°C (68–77°F) in packaging supplied by Portola Pharmaceuticals, Inc.

6.4. Study Drug Preparation

Special preparation is not required. Sufficient quantities of capsules will be provided for clinical study conduct and sample retention.

6.5. Administration of Study Drug

In Part 1 of the study, the single betrixaban capsule will be taken with 240 mL of water under the supervision of study staff. Fed patients will have a light meal or snack prior to taking betrixaban. Patients will not be fed for at least 2 hours following administration of betrixaban. Patients will not have water (fluids) for 1 hour following dosing. Water volumes for Part 2 will be specified in future amendments to the protocol.

6.6. Study Drug Accountability, Handling, and Disposal

The investigator must maintain accurate records of the amounts and dates study drugs were received from Portola Pharmaceuticals, Inc. and dispensed to the patients. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used and unused supplies must be returned promptly to Portola Pharmaceuticals, Inc. or destroyed at the site in accordance with approved written site procedures. The investigator will maintain a record of the amount and dates when unused supplies were returned to Portola Pharmaceuticals, Inc. All records will be retained as noted in Section 14.0.

7.0 STUDY CONDUCT

All procedures occurring during Part 1 of the study (administration of betrixaban in adolescents 12 to < 18 years of age) are detailed in Table 5, the Schedule of Assessments for Protocol 16-021. The patient will be domiciled in the hospital, clinical study site, or Phase 1 unit for Day 1 assessments, dosing, and through 24 hours post dose (i.e., start of Day 2). The 120-hour visit (i.e., Days 6) may be an outpatient visit. Part 1 of the study will enroll 21 adolescents 12 to < 18 years of age.

In Part 1 of the study, a total of approximately 53 to 63 mL of blood (depending on Cohort) will be drawn from each patient over a period of approximately 5 weeks. Approximately 2 mL will be drawn for each PK sample, 4.5 mL for each PD sample, and approximately 5 mL for hematology, chemistry, and coagulation samples, per local institution requirements.

This protocol will be amended prior to the commencement of Part 2 to specify age appropriate blood sampling volumes and time points.

To minimize pain and discomfort to pediatric patients during the blood sampling time points, sampling may occur via IV catheter or butterfly needle followed by saline flush. For patients with pre-existing central venous catheter or CVAD (i.e., central line, central venous line, or central venous access catheter) sampling may occur via these access points.

7.1. Screening Visit

The screening visit will take place within 30 days prior to the first dosing day. The following procedures will be completed for patients in all age categories (12 to <18 years of age, and 2 to < 12 years of age):

- Obtain Informed Consent from parent or legal guardian and Assent from patient.
- Review eligibility (i.e., review Inclusion and Exclusion criteria, Sections 4.1 and 4.2).
- Obtain medical history, including concomitant medication use (past 30 days), and demographics (Section 9.1.1).
- Conduct complete Physical Examination (PE), including vital signs and body temperature (degrees Celsius [°C]), and weight (Sections 9.1.2, 9.1.3, and 9.1.4).
- Measure height in centimeters (Section 9.1.4).
- Draw blood for hematology, coagulation assessments (Section 9.1.6.1), and blood chemistry analysis (Section 9.1.6.2).
- Draw blood for serum pregnancy test (females of childbearing potential only; Section 9.1.6.6).
- Collect urine for urinalysis, include testing for blood in urine (Section 9.1.6.3).

- Collect urine sample for drug abuse screen – adolescents age 12 years to <18 years. (Section 9.1.6.5).
- Collect stool samples (if available) for occult blood testing (Section 9.1.6.4).
- Conduct 12-lead ECG (Section 9.1.5).

7.2. Day -1 (the day before anticipated dosing)

The patient may check into the hospital, clinic study site, or Phase 1 unit the day before dosing with betrixaban is anticipated. The following procedures will be completed/repeated (unless performed ≤ 3 days prior to Day -1 visit, for example Days -4, -3, and -2):

- Review eligibility criteria (Sections 4.1 and 4.2).
- Review medical history and update, if appropriate (Section 9.1.1).
- Obtain cohort assignment from Sponsor.
- Conduct limited PE (Section 9.1.2), including vital signs and body temperature (degrees Celsius [°C]), and weight (Sections 9.1.2, 9.1.3, and 9.1.4).
- Draw blood for hematology and coagulation assessments (Section 9.1.6.1), and blood chemistry analysis (Section 9.1.6.2).
- Draw blood for serum pregnancy test (females of childbearing potential only; Section 9.1.6.6).
- Collect urine for urinalysis, include testing for blood in urine (Section 9.1.6.3).
- Collect urine sample for drug abuse screen (Section 9.1.6.5).
- Verify negative result for fecal occult blood testing during Screening period (≤ 30 days prior to dosing). (Section 9.1.6.4).
- Record AEs since screening visit.
- Record concomitant medications since the screening visit.

7.3. Day 1 (Dosing with Betrixaban)

7.3.1. Pre-Dose Assessments and Dosing

7.3.1.1. Prior to Dosing

- Review eligibility criteria (Sections 4.1 and 4.2).
- Review medical history and update, if appropriate (Section 9.1.1).
- Review pre-dose laboratory results to confirm continued eligibility.
- Draw blood for betrixaban plasma PK analysis (Section 8.1).
- Draw blood for PD assessments, i.e., TGI and anti-fXa levels (Section 8.2).
- Obtain vital signs (sitting) and body temperature (°C) ≤ 30 minutes prior to dosing (Section 9.1.2).

- Ensure that patient does not have fluids 1 hour prior to dosing.
- Collect stool samples (if available) for occult blood testing (Section 9.1.6.4).
- Record AEs.
- Record concomitant medications.

7.3.1.2. Dosing (0.0 Hours, Day 1)

- Administer 1 betrixaban capsule with 240 mL of water (in adolescents 12 to < 18 years of age).
  - Patients will have a low-fat breakfast or snack prior to dosing (e.g., apple sauce, biscuit, fruit, crackers, or commercial nutritional supplement.).
- Ensure that patient does not have fluids 1 hour after dosing.
- Ensure that patient waits 2 hours after dosing before ingesting food; there are no post dose restrictions regarding food intake. The 2 hour PK sample will be taken before ingesting food.

7.3.2. Post Dose Procedures, Day 1

7.3.2.1. Between 0.5 Hour and 24.0 Hour Post Dose

- Collect stool samples (if available) for occult blood testing (Section 9.1.6.4).

7.3.2.2. 0.5 Hour Post Dose (Day 1)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.2).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Record AEs.
- Record concomitant medications.

7.3.2.3. 1.0 Hour Post Dose (Day 1)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Provide patient with fluids.
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Record AEs.
- Record concomitant medications.

7.3.2.4. 2.0 Hours Post Dose (Day 1)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Meal allowable after blood sampling. There are no post dose restrictions regarding food intake after this timepoint.
- Record AEs.
- Record concomitant medications.

7.3.2.5. 3.0 Hours Post Dose (Day 1)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.6.1).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Perform 12-lead ECG (Section 9.1.5)
- Record AEs.
- Record concomitant medications.

7.3.2.6. 4.0 Hours Post Dose (Day 1)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.6.1).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Record AEs.
- Record concomitant medications.

7.3.2.7. 6.0 Hours Post Dose

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Record AEs.
- Record concomitant medications.

7.3.2.8. 12.0 Hours Post Dose

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.

- Record AEs.
- Record concomitant medications.

7.4. Day 2: 24 Hours Post Dose

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Conduct limited PE, (Section 9.1.2); including weight.
- Draw blood for hematology, coagulation assessments (Section 9.1.6.1), and blood chemistry analysis (Section 9.1.6.2).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Collect urine for urinalysis, include testing for blood in urine (Section 9.1.6.3).
- Record AEs.
- Record concomitant medications.
- Perform 12-lead ECG (Section 9.1.5).

7.5. Day 6: 120 Hours Post Dose (Study Termination Visit)

- Obtain vital signs (sitting) and body temperature (°C) (Section 9.1.3).
- Conduct brief PE (Section 9.1.2); including weight.
- Draw blood for hematology, coagulation assessments (Section 9.1.6.1), and blood chemistry analysis (Section 9.1.6.2).
- Confirm PK-PD sampling requirement (Section 8.1, Section 8.2) based on subject-specific Cohort and Sequence Assignments. Refer to Table 5, Schedule of Assessments.
- Collect urine for urinalysis, include testing for blood in urine (Section 9.1.6.3).
- Record AEs.
- Record concomitant medications.
- Collect stool samples (if available) for occult blood testing (Section 9.1.6.4).

7.6. Day 7: Safety Follow-up Contact

One safety follow-up phone call/contact to the patient (if appropriate), parent, or legal guardian will occur on Day 7; the following procedure will be performed:

- Record AEs.
- Record concomitant medications.

8.0 PHARMACOLOGICAL ASSESSMENTS

8.1. Pharmacokinetic Assessments

The plasma portion of the blood samples will be assayed for determining the PK parameters of betrixaban. The following PK parameters will be calculated for each age groups using POP PK methodology as long as sufficient data is available:

- Terminal plasma half-life ($t_{½}$), determined by linear regression of the log concentration on the terminal portion of the plasma concentration–time curve. Half-life is calculated as ln(2)/(-β), where β is the slope of the terminal portion of the log concentration–time curve.
- Time to maximum observed plasma concentration (T_{max}).
- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration–time curve from 0 to last available measurable concentration ($AUC_{(0\text{-}last)}$) computed using the linear trapezoidal rule.
- Clearance (CL/F), calculated by dividing the administered dose by the $AUC_{(0\text{-}\infty)}$.
- Volume of Distribution (V_d/F), calculated by dividing the dose administered by the plasma concentration at the first time point measured.
- Total area under the plasma concentration–time curve from time 0 to infinity (total AUC), computed as:
    - Total AUC ($AUC_{(0\text{-}\infty)}$) = $AUC_{(0\text{–}last)}$ + Cp_{last} /(-β) where $AUC_{(0\text{–}last)}$ is the area under the curve from time 0 to the time point of the last measurable concentration above the quantitation limit; Cp_{last} is the last measurable concentration above the quantitation limit; and β as defined above.

8.1.1. Blood Sample Collection

Blood samples for PK analysis will be collected using 3.2% Na Citrate as the anticoagulant. Blood samples for PK assessments will be collected 30 minutes prior to the dose administration, and at 0.5, 1, 2, 3, 4, 6, 12, 24, and 120 hours post dose with the 6 hour time point only being collected in the patients with rich PK sampling. Blood samples for patients in the POP PK analysis groups will be taken at time points based on the sequences to which each patient is assigned.

8.1.2. Urine Sample Collection

Urine samples will not be collected for centralized testing.

8.2. Pharmacodynamic Assessments

The following PD assessment will be determined with the blood samples collected. Data may be normalized to pre-dose samples and expressed as % of pre-treatment or the values measured may be used.

9.0 ASSESSMENT OF SAFETY

9.1. Safety Parameters

Safety and tolerability will be determined by change from baseline in symptoms, signs, and laboratory tests, by elicitation of AEs (Section 9.2) and by concomitant medication usage (Section 5.2). All events will be followed until resolution and appropriately reported on the AE Case Report Form. Laboratory abnormalities should be reported as AEs if clinically significant per the Principal Investigator (Section 9.2.5.3).

9.1.1. Demographic/Medical History

A medical history, including demographics (i.e., age, race, sex) and concomitant medication usage will be obtained at the screening visit.

9.1.2. Physical Examination

9.1.2.1. Complete Physical Examination

A complete physical examination (PE) will be conducted at the screening visit and Day -1; this consists of measurements/examination of the following:

- Weight
- Height
- Eyes
- Ears, Nose, Mouth, Throat
- Neck
- Respiratory
- Cardiovascular
- Chest (Breasts)
- Gastrointestinal (Abdomen)
- Genitourinary (to be performed at the discretion of the Principal Investigator to follow-up on any relevant medical history e.g., menstrual bleeding)
- Lymphatic
- Musculoskeletal
- Skin
- Neurologic

9.1.2.2. Brief Physical Examination

A brief PE will be conducted 24 hours post dose (i.e., on Day 2) and 120 hours post dose (i.e., on Day 6). The brief physical examination will consist of measurements/examination of the following:

- Weight
- Eyes
- Ears, Nose, Mouth, Throat
- Neck
- Respiratory
- Cardiovascular

9.1.3. Vital Signs and Body Temperature

Vital signs (heart rate, blood pressure, respiratory rate) will be measured pre-dose (≤ 30 minutes before dosing) and at the time points specified in the Table 5, *Schedule of Assessments*, after the patient has been in the sitting position for at least 5 minutes. Body temperature will be measured in degrees Celsius (°C).

9.1.4. Weight and Height

Weight will measured at the screening visit, Day -1, 24 hours post dose (i.e., on Day 2) and 120 hours post dose (i.e., on Day 6, at the study termination visit) and will be recorded in kilograms.

Height will be measured at the screening visit only and will be recorded in centimeters. (See Table 5, *Schedule of Assessments*.)

9.1.5. Electrocardiogram

Each patient will undergo a standard 12-lead ECG at baseline at the screening visit, 3.0 hours post dose, and 24 hours post dose. The ECG will be obtained after the patient is in the supine position for at least 5 minutes (optimally 10 minutes).

9.1.6. Routine Clinical Laboratory Assessments

In Part 1 of the study, a total of approximately 53 to 63 mL of blood (depending on Cohort) will be drawn from each patient over a period of approximately 5 weeks. Approximately 2 mL will be drawn for each PK sample, 4.5 mL for each PD sample, and approximately 5 mL for hematology, coagulation, and chemistry samples, per local institution requirements. Urinalysis will also be performed.

To minimize pain and discomfort to pediatric subjects during the blood sampling time points, sampling may occur via IV catheter or butterfly needle followed by saline flush. For patients with pre-existing central venous catheter or CVAD (i.e., central line, central venous line, or central venous access catheter) sampling may occur via these access points.

This protocol will be amended prior to the commencement of Part 2, and again prior to the commencement of Part 3 to specify age appropriate blood sampling volumes and time points. Part 2 and Part 3 of the study will only commence upon written approval of an amendment to this protocol by applicable regulatory bodies (i.e., IEC/IRB, MOH, and CA, as appropriate).

9.1.6.1. Hematology

Hematology assessments comprise a Complete Blood Count (CBC) and coagulation panel, as specified below:

- **CBC:** Absolute Neutrophil Count (ANC), basophils, differential, eosinophils, Hematocrit (HCT), Hemoglobin (Hgb), lymphocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), monocytes, neutrophils, platelet count, Red Blood Cell (RBC) count, Red cell Distribution Width (RDW), reticulocyte, and White Blood Cell (WBC) count relative and absolute.
- **Coagulation Panel:** Activated Partial Thromboplastin Time (aPTT), Pro-Thrombin and International Normalized Ratio (PT/INR).

9.1.6.2. Blood Chemistry

Blood chemistry analyses comprise a complete blood chemistry analysis and, if applicable, analysis of Gamma-Glutamyl Transpeptidase (GGT), as specified below:

- **Complete Blood Chemistry Analysis:** Alanine transaminase, albumin, Alkaline Phosphatase (ALK/ALP/ALKP), Aspartate Aminotransferase (AST), bilirubin (total), Blood Urea Nitrogen (BUN), calcium (Ca), chloride (Cl), creatinine, glucose, Lactate Dehydrogenase (LDH), potassium (K), SGOT (AST), SGPT (ALT), sodium (Na), uric acid, GGT.

9.1.6.3. Urinalysis

Obtain urine samples at protocol-specified time points (Table 5, *Schedule of Assessments*) for a complete urinalysis and microscopic urinalysis, if applicable.

- **Complete Urinalysis:** Bilirubin, blood, color, glucose, ketone/acetone, leukocytes, nitrite, pH, protein, specific gravity, turbidity (clarity), urobilinogen.
- **Microscopic Urinalysis** will be performed only if there is more than a trace amount of blood detected.

9.1.6.4. Stool Sample for Occult Blood

At the screening visit, stool samples will be collected for analysis, if feasible. During the domicile portion of the study, stool samples (if feasible) will be tested once daily (if feasible).

9.1.6.5. Urine Drug Screen

At the screening visit and/or within 3 days prior to Day -1, urine samples will be collected to detect drugs of abuse in adolescents (age 12 to < 18 years). These drugs include, but are not limited to, the following: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and urine ethanol. Positive results will exclude the subject from participation with the exception of medications prescribed by the physician during the current hospital stay.

9.1.6.6. Serum Pregnancy Screen

At the screening and within 3 days prior to Day -1 visit, blood samples will be collected and a serum pregnancy test performed for females of childbearing potential only. Positive pregnancy test results will exclude the subject from participation.

9.1.6.7. Low Fat Breakfast or Snack

The single dose of betrixaban will be administered orally with 240 mL water following a low-fat breakfast or snack (e.g., apple sauce, biscuit, fruit, crackers, or commercial nutritional supplement).

- Patient will not have fluids 1 hour prior to dosing.
- Patient will have breakfast or snack.
- Patient will have 240 mL water with dose.
- Patient will not have fluids 1 hour after dosing.
- Patient will wait 2 hours after dosing before ingesting food; there are no post dose restrictions regarding food intake.

For patients enrolled in Part 2 (age 2 to < 12 years old) water intake volumes may differ and will be specified in an amendment to the protocol.

9.2. Adverse and Serious Adverse Events

9.2.1. Definition of Adverse Events

9.2.1.1. Adverse Event

An AE is any undesirable event or any untoward medical occurrence that occurs to a participant during the course of a study, or the protocol-defined time after study termination, whether or not that event is considered study drug-related. A Treatment-Emergent AE (TEAE) is one that occurs following the receipt of any amount of study drug.

Examples of AEs include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the patient's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder]).
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug.
- Apparently unrelated illnesses.
- Injuries or accidents.
- Extensions or exacerbations of symptomatology, patient-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.
- Abnormal laboratory findings considered by the Investigator to be clinically significant, and that represent a worsening from baseline (see also Section 9.2.5.3). An abnormal laboratory value should be recorded as an AE if it:
    - Is associated with clinical signs or symptoms,
    - Requires an intervention,
    - Results in a serious adverse event (including the "medically important" criteria), or
    - Results in study termination or interruption/discontinuation of study treatment.

When recording an AE resulting from a laboratory abnormality, the resulting medical condition, if known, rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

When a unifying diagnosis has been made that accounts for several possible signs and/or symptoms, the unifying diagnosis should be selected as the AE term. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as "upper respiratory syndrome" if this diagnosis has been made, rather than reporting the individual symptoms as separate events.

9.2.1.1.1. Serious Adverse Event

A SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that meets any of the following criteria:

- Results in death

- Is immediately life-threatening
  Life-threatening means that, in the opinion of the Investigator or Study Sponsor, the patient was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
  Hospital admissions and/or surgical operations scheduled to occur during the study period, but planned before the signing of the ICF, are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability or incapacity.
  Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
  An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 in-patient hospitalization, or the development of drug dependency or drug abuse.

9.2.1.1.2. Other Adverse Event (OAE)

Not applicable.

9.2.2. Assessing Severity (Intensity) of Adverse Events, Including Serious Adverse Events

Severity (intensity) of each AE will be assessed according to the scale in Table 7:

Table 7: Assessing the Severity (Intensity) of Adverse Events

Classification	Description
Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort sufficient to cause interference with normal activities
Severe	Incapacitating, with inability to perform normal activities

A distinction should be made between the terms "serious" and "severe" since a SAE is not synonymous with an AE assessed as "severe." The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as an SAE, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours' duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted serious criteria (such as requiring hospitalization). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2.3. Assessing Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Unlikely Related, Possibly Related, or Probably Related). Using the guidelines in Table 8 the Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

The categories described in Table 8 should be used to assess the causality (i.e., relationship) of AEs to study drug.

Table 8: Assessment of Causality of Adverse Events

Classification	Description
Probable	The AE • Follows a reasonable temporal sequence from the time of study drug administration; and/or • Follows a known response pattern to the study drug; and • Was unlikely to have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.
Possible	The AE • Follows a reasonable temporal sequence from the time of study drug administration; and/or • Follows a known response pattern to the study drug; • But could have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.
Unlikely	The AE • Does not follow a reasonable temporal sequence from the time of study drug administration; and/or • Does not follow a known response pattern to the study drug; and • Was most likely produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.
Unrelated	This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention, or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

9.2.4. Recording and Reporting Pregnancy and Outcomes of Pregnancy

Any pregnancy that occurs from the time of enrollment to the last day of follow-up must be recorded on the appropriate page of the eCRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of any pregnancy (e.g., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are classified as SAEs. Spontaneous miscarriages are also SAEs. Elective abortions without complications are not AEs.

9.2.5. Recording and Reporting Adverse Events, Including Serious Adverse Events, and Abnormal Laboratory Values

9.2.5.1. General Principles

Any AE reported spontaneously by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Please see Section 9.2.5.3 for procedures for recording abnormal laboratory values.

The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study. All AEs must be reported on the appropriate page of the eCRF and entered in the clinical database.

9.2.5.2. Reporting Policies for Serious Adverse Events

If an AE is determined to be serious in nature (i.e., is classified as an SAE), it must be reported on the SAE page of the CRF and reported to the safety team within 24 hours of the investigator becoming aware of the event.

Submit all SAE reports to the Sponsor:

Portola Pharmacovigilance

PPD

Contact the Portola Pharmaceuticals, Inc. Medical Monitor for any inclusion/exclusion or study-related questions.

Record all SAEs (related and unrelated) from the signing of the ICF through the last day of follow-up. Any SAE discovered by the Investigator at any time after the study should be reported to the Sponsor Pharmacovigilance contact details above on an SAE form within 1 business day of awareness. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and submit all SAE reports to Portola Pharmaceuticals, Inc. at the contact information specified above.

Submit additional follow-up information, if required or available, to Portola Pharmaceuticals, Inc. within 1 business day of receipt on a follow-up SAE form and placed with the original SAE information. Record the information on the appropriate section of the CRF and/or study file.

Portola Pharmaceuticals, Inc. is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports, also known as SUSARs) that occur at any site during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

9.2.5.3. Reporting Abnormal Laboratory Tests as Adverse Events

The Investigator will monitor laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed up on at the discretion of the Investigator. Abnormal laboratory tests may, in the opinion of the Investigator or the Sponsor, be considered clinically significant and, thus, must be reported as an AE. In such cases, abnormal laboratory test findings must be reported on the AE CRF.

10.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

10.1. Study Design and Objectives

The primary objective of this open-label, multicenter trial in pediatric patients is designed to determine the PK parameters of betrixaban in the pediatric population in several defined age groups: 12 to < 18 years of age and 2 to < 12 years of age. The secondary objectives are to assess the PD activity and safety of betrixaban in the pediatric age categories specified above. The design of the study is summarized in Section 3.1.

10.2. Randomization

No randomization will be needed. In this open-label study, each patient will receive one dose of betrixaban, as defined for each age group.

10.3. General Considerations

No formal hypothesis testing will be performed.

It is anticipated that all statistical analyses will be performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics and for statistical methodology not provided by this software package.

A Statistical Analysis Plan (SAP) will be created for this study with complete details and definitions of all planned analyses. The SAP will be finalized prior to database lock.

10.4. Determination of Sample Size

Sample size for each age group is determined by the variance for $AUC_{(0\text{-last})}$ and C_{max} observed from the adult PK studies of betrixaban. The between-subject variability seen in $AUC_{(0\text{-last})}$ as measured by percent coefficient of variation was around 45%. A minimum of 12 subjects are required to target a 90% confidence interval within 60% and 140% of the geometric mean estimates of the $AUC_{(0\text{-last})}$ with at least 80% power.

10.5. Analysis Populations

The evaluable PK population will include all individual patients who receive study drug and have sufficient blood samples through Day 1 to compute either C_{max} or total AUC assessments. For the POP PK analysis all samples from all patients will be included in the POP PK analysis.

The Safety population will include all patients who receive any amount of study drug.

10.6. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients, the safety population, and the PK population. Data will be summarized using descriptive statistics such as frequencies, means, medians, standard deviations, minimums, and maximums. No formal statistical comparisons are planned.

PK Parameters Determination

The plasma level of betrixaban assessed at baseline, during the first 24 hours, and 120 hours post dosing will be used to determine the following PK parameters for each age group using POP PK methodology or for individual patients with rich PK sampling:

10.6.1. Primary PK Parameters

- $AUC_{(0\text{-last})}$
- C_{max}

10.6.2. Other PK Parameters

- $t_{1/2}$
- T_{max}
- CL/F and V_d/F

Summary statistics for the PK parameters will be tabulated by gender for each age group.

10.7. PD Endpoints and Analyses

The inhibition of thrombin generation during the first 24 hours post dosing will be evaluated by the percent change in thrombin level from baseline. Correlation analysis will be performed for the thrombin level or thrombin change versus betrixaban level over time. The maximum change (the nadir of thrombin level) from baseline will be derived for each patient and summarized by gender for each age group.

10.7.1. Missing Data

If a patient has insufficient data to compute a given PK parameter, it will be considered as missing data. Replacement patients may be enrolled to have adequate evaluable patients for the primary PK parameters determination.

10.8. Safety

Safety and tolerability will be evaluated by clinical assessment of AEs and other safety measurements (vital signs, EKGs, laboratory tests, etc.). Treatment-emergent AE will be coded by the updated version of MedDRA and summarized as event rate by SOC and Preferred terms. Change in vital signs, laboratory tests, and EKG parameters from baseline to each post-dosing assessment will be derived for each patient. Appropriate summary statistics will be provided for each age group.

11.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

The investigator will allow representatives of Portola Pharmaceuticals, Inc. to periodically audit, at mutually convenient times before, during and after the study has been completed, all CRFs and relevant portions of office, clinical and laboratory records for each patient. The monitoring visits provide Portola Pharmaceuticals, Inc. with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable regulations and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

Before an investigational site can enter a patient into the study, a representative of Portola Pharmaceuticals, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Portola Pharmaceuticals, Inc. or its representatives. This will be documented in a Clinical Study Agreement between Portola Pharmaceuticals, Inc. and the investigator.

During the study, a monitor from Portola Pharmaceuticals, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously reported.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been reported and those SAEs that met criteria for reporting have been forwarded to the Institutional Review Board (IRB).

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.2. Audits and Inspections

Authorized representatives of Portola Pharmaceuticals, Inc., a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Portola Pharmaceuticals, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Portola Pharmaceuticals, Inc. immediately if contacted by a regulatory agency about an inspection.

11.3. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11.4. Data Reporting and Case Report Forms

Data for each subject will be entered into the CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject's clinical status.

The Investigator or designated representative should complete the CRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 Code of Federal Regulations (CFR) Part 11-compliant system.

11.5. Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the subject from immediate hazard, and then notify the Portola Pharmaceuticals, Inc.'s Medical Monitor and the IRB or IEC promptly regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the source documents. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by Portola Pharmaceuticals, Inc. and the IRB or IEC—before the changes or deviations are implemented. Portola Pharmaceuticals, Inc. will not assume any responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol.

11.6. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates study drugs were received from Portola Pharmaceuticals, Inc. and dispensed to the subjects, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site, in accordance with approved written procedures, or returned to Portola Pharmaceuticals, Inc. after written authorization is obtained from Portola Pharmaceuticals, Inc. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola Pharmaceuticals, Inc. All records will be retained as noted in Section 14.2 *Retention of Records*.

11.7. Disclosure of Data

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the US FDA and the study sponsor, Portola Pharmaceuticals, Inc., and its agents will need to review subject medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the subject's identity will remain confidential.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Portola Pharmaceuticals, Inc. may conduct a quality assurance audit. Please see Section 11.2 for more details regarding the audit process.

13.0 ETHICS

13.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Portola Pharmaceuticals, Inc. before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Portola Pharmaceuticals, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

13.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements, and Portola Pharmaceuticals, Inc.'s policy on Bioethics.

13.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient has provided assent and the responsible parent or guardian is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. The responsible parent or guardian must also be notified that they are free to discontinue from the study at any time. The responsible parent or guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The responsible parent or guardian's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the responsible parent or guardian.

14.0 DATA HANDLING AND RECORD KEEPING

14.1. Inspection of Records

Portola Pharmaceuticals, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

14.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Portola Pharmaceuticals, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15.0 REFERENCES

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16.0 APPENDICES