CLINICAL STUDY PROTOCOL
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NCT04228302

A SINGLE-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 1A SINGLE ASCENDING DOSE STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SEQUENTIAL DOSE REGIMENS OF ORAL EC5026 IN HEALTHY MALE AND FEMALE SUBJECTS

PROTOCOL NO. EC5026-1-01

Sponsor:	EicOsis Human Health, Inc. 140 B Street Suite 5, Number 346 Davis, CA 95616
Sponsor Contact:	[redacted]
Medical Monitors:	[redacted]
Version of Protocol:	2.0
Date of Protocol:	15 October 2019

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Single-Center, Double-Blind, Placebo-Controlled, Phase 1a Single Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Sequential Dose Regimens of Oral EC5026 in Healthy Male and Female Subjects

PROTOCOL NUMBER: EC5026-1-01

[redacted]

10/17/2019
Date

[redacted]

10/17/19
Date

[redacted]

10/17/2019
Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Single-Center, Double-Blind, Placebo-Controlled, Phase 1a Single Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Sequential Dose Regimens of Oral EC5026 in Healthy Male and Female Subjects" in accordance with the guidelines and all applicable government regulations, including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

[redacted]

22 OCT 2019
Date

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1. INTRODUCTION

1.1 BACKGROUND

Many of the current pharmaceutical therapies for pain have limited efficacy and/or dose-limiting side effects. This is particularly true for chronic pain conditions where the need for alternative therapeutics has become more urgent with an aging population. In addition, an increased understanding of the significant risks associated with high-dose and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 selective inhibitors (COXIBs) limits the utility of these most commonly prescribed therapies. Opioids are often prescribed for chronic pain when other treatments fail to provide sufficient relief; however, the risks of addiction and death resulting from overuse of opioids are also well known. Given the paucity of current therapeutic options, there is a significant need to develop new effective and safe drugs to provide pain relief and thereby also reduce the prescribing of opioids to chronic pain sufferers.

EicOsis Human Health, Inc. (EicOsis) is developing EC5026 (BPN-19186) as an oral analgesic with a new mechanism of action targeting the soluble epoxide hydrolase (sEH) enzyme that is downstream in the cytochrome P450 (CYP) pathway of the arachidonic acid (AA) cascade. This approach is based on the recognition that the epoxy-fatty acids (EpFAs) formed from AA via the CYP pathway, known as epoxyeicosatrienoic acids (EETs), are potent, naturally occurring analgesics. Epoxyeicosatrienoic acids are chemically stable and produced at high local concentrations in areas of tissue damage and inflammation but are rapidly metabolized by the sEH enzyme into inactive or pro-inflammatory compounds. Therefore, effective inhibition of sEH activity prolongs the ability of EETs to exert their analgesic activity which has been demonstrated in preclinical models.

Moreover, this rapid metabolism of EpFAs in general, and EETs in particular, is a problem because these natural analgesic mediators are degraded to polar and rapidly excreted diols from AA epoxides (dihydroxyeicosatetraenoic acids) that are inactive or even pro-inflammatory in some cases, suggesting an additional benefit of inhibiting sEH activity.

EC5026 is a potent and selective sEH inhibitor with greater than 60,000-fold selectivity against related enzymes. It has a predicted efficacious dose in humans of 5 mg. The therapeutic index ranges from 37 to 374 times the efficacious dose based on both pharmacokinetic (PK) and efficacy studies of neuropathic pain in rodents and good laboratory practice (GLP) safety studies in rodents and dogs. EC5026 is not an NSAID, COXIB, or an opioid. Targeting the sEH has shown no addiction potential in a conditioned

place preference assay. In addition, EC5026 does not show gastrointestinal erosion or cardiovascular side effects associated with NSAIDs and COXIBs.

Further information on the study drug can be found in the latest version of the investigator's brochure.

1.2 RATIONALE FOR STUDY

This is a first-in-human study with EC5026 and is designed to provide initial safety, tolerability, and PK data regarding EC5026 for future clinical studies. Analysis of urine and plasma concentrations of EC5026 will characterize the single-dose PK of EC5026 and help to refine the dosing strategy for subsequent multiple-dose studies.

1.3 RATIONALE FOR DOSE SELECTION

Based on the no-observed-adverse-effect level (NOAEL) of 5 mg/kg/day in rats, the most sensitive species (28-day rat GLP safety study M386-18) and a ≥10-fold safety factor of the maximum recommended starting dose, the initial oral clinical dose has been selected to be 0.5 mg.

The following formula was used to predict the human equivalent dose (HED) using animal dose and animal weight as described in the US Food and Drug Administration (FDA) Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (DHHS 2005):

$$\text{HED} = \text{animal dose (mg/kg)} \times \left[\frac{\text{animal weight (kg)}}{\text{human weight (kg)}}\right]^{0.33}$$

After each cohort completes dosing, safety data will be reviewed, and the next highest dose will be administered sequentially.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are as follows:

- To investigate the safety and tolerability of escalating dose regimens of EC5026 administered once orally in healthy male and female subjects

- To investigate the PK of escalating dose regimens of EC5026 administered once orally in healthy male and female subjects.

2.2 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are as follows:

- To investigate the response of various biomarkers to a single dose of EC5026 administered to healthy male and female subjects
- To investigate putative metabolites of EC5026 following single oral administration of EC5026 in healthy male and female subjects.

All exploratory studies will be conducted independently by EicOsis, LLC, and reported separately from the EC5026-1-01 clinical study report (CSR).

3. STUDY DESIGN

This is a Phase 1a, first-in-human, randomized, single-center, double-blind, placebo-controlled, single ascending dose (SAD) study to investigate the safety, tolerability, and PK of EC5026 in healthy male and female subjects. This study will have up to 5 cohorts with a total of up to 40 subjects (8 subjects per cohort). An optional sixth cohort (maximum 48 subjects) will be considered after completion of 5 dose cohorts. The starting dose of EC5026 will be 0.5 mg and the planned doses for subsequent cohorts are 2, 8, 16, and 32 mg. An optional 6th dose cohort (48 mg) may be added upon approval of the sponsor (EicOsis), the funding agency (NINDS), the CRO (PPD) and the safety review committee (SRC). If approved, this will increase the total to up to 48 subjects.

The study will consist of a screening period (Days –28 to –2), Check-in (Day –1), study drug administration (Day 1), treatment period (Days 1 to 7), clinic visit (Day 7), and a follow-up/end-of-study (EOS) visit (Day 14).

In each cohort, 6 subjects will be randomly assigned to receive EC5026 and 2 subjects will receive placebo. Subjects will be stratified to include an approximately equal number of male and female subjects within each dose cohort. Separate groups of healthy male and female subjects will be used for each dose cohort. The doses will be escalated in a stepwise fashion following acceptable safety and tolerability of the preceding dose(s).

A blinded sentinel group of 2 subjects (1 active and 1 placebo) will be dosed at least 2 days before the remaining 6 subjects (5 active and 1 placebo) will receive blinded doses of active study drug or placebo. If either of the sentinel subjects experiences a serious adverse event (SAE) or an adverse event (AE) that fulfills the stopping rule criteria (Section 9.2.1.1), the dosing will be stopped for all subjects in the study pending a safety review; the remaining subjects will not initiate dosing until the safety incident is resolved.

The planned dose levels are provided in Table 3-1.

Table 3-1 Planned Dosing Levels

	Dose	Number of Subjects Receiving Study Drug	Number of Subjects Receiving Placebo
Cohort			
1A (Sentinel Group)	0.5 mg	1	1
1B	0.5 mg	5	1
2A (Sentinel Group)	2 mg	1	1
2B	2 mg	5	1
3A (Sentinel Group)	8 mg	1	1
3B	8 mg	5	1
4A (Sentinel Group)	16 mg	1	1
4B	16 mg	5	1
5A (Sentinel Group)	32 mg	1	1
5B	32 mg	5	1
6A (Sentinel Group)†	48 mg	1	1
6B†	48 mg	5	1

†Optional 6th dose cohort

Safety and PK data through Day 7, after completion of each cohort, will be reviewed by the safety review committee (SRC) in a blinded fashion before escalating to the next dose cohort. In each period, subjects will fast overnight (nothing to eat or drink, except water) for at least 10 hours before study drug administration. Subjects will remain fasted for 4 hours after dosing with study drug.

Safety, PK, and biomarker endpoints will be evaluated in the study.

Subjects will be confined to the clinical unit from Day –1 until discharge on Day 5. A clinic visit will occur on Day 7, and a follow-up visit (EOS visit) will occur on Day 14. The duration of the study, including a 28-day screening period, is approximately 43 days.

3.1 SCHEDULE OF EVENTS

Procedure[a] / Phase / Day	Screening −28 to −2	Check-in −1	Treatment Period 1	2	3	4	5	7	FU/EOS/ET 14 (±2)
Admission to clinic		X							
Randomization			X						
Discharge from clinic							X		
Outpatient visit[b]								X	X
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical and medication history	X	X							
Physical examination[c]	X	X	X	X	X	X	X	X	X
Height, weight, and BMI[d]	X	X	X						
Vital sign measurements[e]	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X	X	X	X	X	X	X	X
ECG telemetry[f]		X	X	X	X	X			
Clinical laboratory testing[g]	X	X	X	X	X	X	X	X	X
Viral serology[h]	X								
Urine drug and alcohol screen[i]	X	X							
Serum pregnancy test[j]	X	X							X
Serum FSH[k]	X								
EC5026 administration[l]			X						
PK blood sample collection[m]			X	X	X	X	X	X	X
Blood samples for external biomarker assessments[n]			X	X	X	X	X	X	X
Urine volume, electrolytes[o]		X	X	X	X	X			
Urine samples for EC5026[p]			X	X					
Fasting period[q]		X	X						
Non-fasting period[r]				X	X	X	X	X	
AEs[s]		X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; FU, follow-up; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula.

Notes:

(a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

(b) Follow-up/EOS visit will occur on Day 14 (± 2 days) or 2 days after ET.

(c) A full physical examination will be performed at Screening, Check-in (Day –1), and on Days 1, 2, 3, 4, 5, 7, and 14 (or ET). A full physical examination will include skin, head, ears, eyes, nose, throat, neck, thyroid, respiratory, neurological, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities.

(d) Height and weight will be measured, and BMI calculated at Screening only. Only weight will be measured on Days –1 and 1.

(e) Vital signs will be measured at Screening, on Day –1, and on Day 1 within 45 minutes prior to study drug dosing (predose) and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours following study drug dosing after the subject has been in the seated position for at least 5 minutes. On other days, evaluations will be performed in the morning. Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature.

(f) Twelve-lead ECGs will be performed at Screening, on Day –1, and on Day 1 within 45 minutes prior to study drug dosing (predose) and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours following study drug dosing after the subject has been in the supine position for at least 5 minutes. On other days, evaluations will be performed in the morning. A single repeat measurement is permitted at Screening for eligibility determination. Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and QTcF. Assessments should include comments on whether the tracings are normal or abnormal; rhythm (if abnormal, specify the abnormality); presence of arrhythmia or conduction defects; morphology; any evidence of myocardial infarction; or ST-segment, T-Wave, and U-Wave abnormalities.

(g) Clinical laboratory testing will occur at Screening, on Day –1, and on Days 1, 2, 3, 4, 5, 7, and 14 (or ET). A complete list of assessments is provided in Section 6.3.2. Blood and urine samples will be collected under fasted conditions and prepared per the clinic's standard procedures.

(h) Viral serology testing (Screening only) will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus types 1 and 2 antibodies.

(i) Urine drug and alcohol screen will occur at Screening and on Day –1 per the clinic's standard procedures.

(j) A serum pregnancy test will be performed at Screening, on Day –1, and Day 14 (or ET) in premenopausal women of childbearing potential or women who are surgically sterile.

(k) A serum FSH test will be performed at Screening to confirm postmenopausal status in older women.

(l) The time of study drug dosing will be called "0" hour in each period and is denoted with grey shading. Study drug will be administered with 240 mL of room temperature water. Subjects will maintain an upright (ie, seated or standing) position for at least 4 hours after dosing.

(m) Blood samples for PK analysis of EC5026 in plasma will be collected prior to study drug dosing and at 1.25, 2.25, 4.25, 6.25, 8.25, 12.25, 24, 36, 48, 72, 84, 96, and 108 hours after study drug dosing and after vital signs have been recorded. Additional blood samples will be obtained on the mornings of Days 7 and 14 (or ET). Postdose PK blood samples should be collected within ±5 minutes of the scheduled collection time for the first 8.25 hours, then within ±15 minutes of the scheduled collection time up to 24 hours, and within ±30 minutes of the scheduled collection time up to clinic discharge on Day 5. Pharmacokinetic samples may be collected at any time during the day on Days 7 and 14. The actual time of blood sampling will be recorded in the source documents and electronic case report form.

(n) Blood samples (0.1 mL frozen plasma from each PK sample) for external exploratory biomarker assessments will be collected, stored, and shipped in bulk to the sponsor for poststudy biomarker measurements.

(o) Total voided urine will be combined and collected over the following intervals: –16 to –8, –8 to 0, 0 to 8, 8 to 16, 16 to 24, 24 to 32, 32 to 40, 40 to 48, 48 to 56, 56 to 64, and 64 to 72 hours. Urinalysis on pooled samples includes sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate.

(p) Urine samples for PK analysis of EC5026 will be collected before study drug administration (predose) and collected and pooled over the following intervals: 0 to 8, 8 to 16, 16 to 24, 24 to 32, 32 to 40, and 40 to 48 hours after study drug administration. Additional aliquots from each period will be collected for exploratory urinary metabolite profiling; samples will be collected, stored, and shipped in bulk to the sponsor for poststudy evaluation.

(q) During fasting periods, subjects should have nothing to eat or drink, except water, from 10 hours prior to EC5026 dosing until 4 hours after dosing. Water is permitted as desired except for the period 1 hour before and 1 hour after administration of study drug (other than as permitted for study drug dosing).

(r) During nonfasting periods, subjects should receive standardized meals per the clinic's standard procedures that are scheduled at approximately the same time each day.

(s) Adverse events will be assessed from the time of EC5026 dosing until Day 14 (or ET) and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

4. STUDY POPULATION

Approximately 40 healthy male and female subjects (or approximately 48 subjects with optional 6th cohort) will be enrolled at a single center in the United States to achieve up to 8 evaluable subjects per cohort.

4.1 INCLUSION CRITERIA

Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is male or female 18 to 65 years of age, inclusive.
2. The subject is able and willing to provide written informed consent to participate in the study.
3. The subject is considered by the investigator to be in good general health as determined by prestudy medical history, physical examination findings, clinical laboratory test results, and 12-lead electrocardiogram (ECG) results.
4. The subject is willing and able to remain in confinement at the study unit from Day –1 to Day 5 and return to the unit at Days 7 and 14 for additional blood tests and safety evaluations.
5. The subject has a body mass index of 19.0 to 32.0 kg/m^2, inclusive, at Screening.
6. The subject has normal blood pressure (systolic blood pressure 90 to 140 mm Hg, diastolic blood pressure 50 to 90 mm Hg), and heart rate (resting heart rate 45 to 90 beats per minute) without medication.
7. The subject has a clinical chemistry profile including electrolytes, alkaline phosphatase (ALP), lactate dehydrogenase, creatine phosphokinase (CPK), creatinine, and urea within the normal range without medication at Screening.
8. The subject has urinalysis results including urinary creatinine within the normal range.
9. The subject is a nonsmoker or is willing to abstain from smoking starting 2 weeks prior to randomization and for the duration of the study.
10. The subject is able to read, understand, and follow the study instructions.

11. Male subjects and their female partners must agree to use double-barrier contraception during the study and for 2 months after receiving the last dose of study drug or provide proof of postmenopausal state (minimum 1 year) or surgical sterility.

12. Male subjects must not donate sperm during the study and for 12 months after receiving the last dose of study drug.

13. Female subjects must be nonpregnant, nonlactating, and either postmenopausal for at least 1 year, or surgically sterile for at least 3 months, or agrees to use double-barrier contraception from 28 days prior to randomization and/or their last confirmed menstrual period prior to study randomization (whichever is longer) until 2 months after discharge from the clinic. Double-barrier contraception may include, but is not limited to, nonhormonal intrauterine device with spermicide, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide; having a male sexual partner who agrees to use a male condom with spermicide; or having a sterile sexual partner. Female subjects will refrain from using hormonal contraceptives for at least 28 days prior to study entry until the EOS visit (Day 14). All female subjects of childbearing potential must have a negative pregnancy test result at Screening and baseline (Day –1).

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has any abnormalities in any of the following: liver function tests, CPK, or urinalysis results. Liver function tests, CPK, or urinalysis tests may be repeated at the discretion of the investigator, if necessary, to confirm any abnormalities.

2. The subject has used any nonstudy medication(s), including low-dose aspirin for cardiovascular prophylaxis, within 1 week before administration of study drug.

3. The subject has used chemotherapy agents or has a history of cancer, other than nonmetastatic skin cancer that has been completely excised, within 5 years prior to screening.

4. The subject has a history of bacterial, fungal, or viral infection requiring treatment with antibiotics, antifungal agents, or antivirals within 1 month prior to randomization.

5. The subject has a presence or history of peripheral edema within the past 5 years.

6. The subject has a history of congestive heart failure.

7. The subject has used drugs which are CYP inducers or inhibitors within 30 days of randomization (eg, cimetidine, paroxetine, fluoxetine, haloperidol, ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin; see Appendix 5: cytochrome p450 inducers or inhibitors).

8. The subject has used any dietary aids, supplements, or foods that are known to modulate drug metabolizing enzymes (eg, St. John's wort, grapefruit juice) within 14 days of administration of study drug.

9. The subject has difficulty in swallowing oral medications.

10. The subject has a history of seizure disorder.

11. The subject has serious psychosocial comorbidities as determined by the principal investigator.

12. The subject has cognitive or psychiatric disorders, or any other condition that could interfere with compliance with study procedures and/or confinement in a study unit for 5.5 days.

13. The subject has a history of drug or alcohol abuse within 1 year prior to Screening.

14. The subject has used any other investigational drug within 1 month or 5 half-lives, whichever is longer, prior to randomization.

15. The subject has used prescription drugs within 1 month or 5 half-lives, whichever is longer, prior to randomization.

16. The subject has used over-the-counter medication excluding routine vitamins, but including mega-dose vitamin therapy, within 1 week prior to randomization.

17. The subject has donated and/or received any blood or blood products (more than 450 mL) within 3 months prior to randomization.

18. The subject has a presence or history of active gastrointestinal, renal, hepatic, or coagulant disorder within 1 month prior to randomization.

19. The subject has a presence or history of esophageal or gastroduodenal ulceration within 1 month prior to randomization.

20. The subject has a family history of significant cardiac disease (ie, sudden death in first-degree relative; myocardial infarction prior to 50 years old).

4.3 WITHDRAWAL CRITERIA

General criteria for subject withdrawal and the handling of withdrawals can be found in Appendix 2.

4.4 SUBJECT REPLACEMENT

Any subject who is withdrawn or discontinued from the study after receiving study drug will not be replaced. Subjects who withdraw consent before dosing may be replaced. Subjects enrolled but not dosed may be included in subsequent cohorts.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

All subjects will receive the study treatments as described in Section 3 and according to the schedule of events (SOE; Section 3.1). Additional instructions for dosing, fasting periods, and nonfasting periods can be found in the SOE.

5.1.1 Dose Escalation

The sponsor will form an SRC for a blinded review of safety data for each subject and the entire cohort and will make a recommendation on whether to proceed to the next dose level. Study assessments (eg, AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG, ECG telemetry, and physical examination results) will be used to evaluate safety and tolerability of a given dose level. The SRC will be composed of the following individuals: EicOsis medical monitor, the clinical research unit's principal investigator, the independent (PPD) medical monitor, and a pharmacokineticist. All 4 individuals will be voting members of the SRC. A recommendation to stop dosing will be binding. The plasma concentration-time data and PK parameters for all subjects will be reviewed by the SRC.

As the study involves a blinded sentinel dosing design, the SRC will be responsible for approving the respective dose level for a cohort after a blinded review of safety data through at least 2 days after dosing of the first 2 sentinel subjects. The SRC will review physical examination results, vital sign measurements, and clinical laboratory test results before approving dosing the rest of the cohort. If either of the sentinel subjects experiences an SAE

or an AE that fulfills the stopping rule criteria (Section 9.2.1.1), the dosing will be stopped pending a potential unblinded safety review and the remaining subjects will not initiate dosing until the safety incident is resolved.

The overall safety findings and blinded PK exposures for a cohort will dictate whether to escalate to the next cohort. Escalation to the next higher dose level will proceed after blinded data obtained through Day 7 have been evaluated and approval to proceed is granted. The SRC may require smaller dose increments or a discontinuation of the study if there are safety signals that exceed established parameters based on vital signs, behavioral health, clinical laboratory parameters, or other parameters that are established in the charter of the SRC.

Based on the review of safety and PK data, EicOsis and the investigator may choose to repeat a dose level, administer a dose less than the previous dose, or escalate to a dose lower than the next planned dose. Before implementing any change, the institutional review board (IRB) will be notified and provided with the rationale.

5.1.2 Dose-Limiting Toxicities

A dose-limiting toxicity (DLT) is defined as a treatment-emergent AE (TEAE) of moderate or higher severity (Section 9.3.4) or a SAE (Section 9.3.1) experienced by a subject, who after unblinded safety review, is confirmed to have received EC5026 and the event is considered related to EC5026 (Section 9.3.5).

5.1.3 Dose Escalation Stopping Criteria

Dose escalation will be suspended pending additional review if any of the following occur:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with EC5026.
- Any SAE related to study drug in a dose cohort (hence a DLT).
- Data from the previous dose cohort indicating safety concerns for the next cohort to be dosed at a higher level, such as unanticipated responses (eg, clinically significant changes in clinical laboratory data, 12-lead ECGs, ECG telemetry, vital signs, or physical examinations).
- One or more subjects in a dose cohort experience AEs of severe intensity (Grade 3 or higher) attributable to study participation.

- Two or more subjects have >3 × upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 × ULN for bilirubin or ALP.
- One or more subjects have >3 × ULN of ALT or AST and >2 × ULN for bilirubin.
- One or more subjects have >5 × ULN for ALT or AST, or >3 × ULN for bilirubin.
- One or more subjects achieve PK stopping rules for C_{max} and/or AUC_{0-48} detailed in Section 7.5.

Dose escalation may also be suspended if, in the opinion of the investigator or sponsor, any other significant safety or tolerability issues are identified in the comprehensive review of available data that warrant further evaluation before additional subjects are dosed. This may include emerging preclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns even if the event(s) per se does not meet the protocol-specified definition of a DLT.

5.2 INVESTIGATIONAL PRODUCTS

The study drug that will be used is provided in Table 5-1.

Table 5-1 Investigational Product Formulation and Administration

Investigational Product[a] Dosage	Supplied Formulation Administration
0.5 mg EC5026	1 × 0.5 mg capsule
2 mg EC5026	4 × 0.5 mg capsule
8 mg EC5026	1 × 8 mg capsule
16 mg EC5026	2 × 8 mg capsule
32 mg EC5026	1 × 32 mg capsule
48 mg EC5026†	(1 × 32 mg capsule) + (2 × 8 mg capsule)

[a] Investigational product will be compounded at the clinical pharmacy.
†Optional 6th dose cohort

The EC5026 drug product for use in initial clinical studies is an extemporaneously compounded immediate-release capsule intended for oral administration. EC5026 capsules (0.5, 8, or 32 mg strength) will be prepared by filling a solution, heated at 70°C, consisting of 0.5, 8, or 32 mg EC5026 drug substance dissolved in 80% polyethylene glycol (PEG) 400/20% PEG 3350 (w/w) into size 0, white, opaque, hard-gelatin capsules. Placebo capsules

for EC5026 will be prepared similarly, without the active drug substance. Active and placebo capsules will be hand filled by volume with heated solution and allowed to cool prior to capping at the clinical site pharmacy in accordance with pharmacy compounding procedures.

Further information on the study drug can be found in the latest version of the investigator's brochure.

5.2.1 Study Drug Preparation and Storage

Albany Molecular Research, Inc. will provide the investigator and clinical unit with adequate quantities of EC5026 and matching placebo. Detailed instructions for the preparation of study treatments will be provided in a separate pharmacy manual.

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

PPD will generate the randomization schedule. After all entry criteria have been satisfied before dosing on Day 1, eligible subjects within each cohort will be randomly assigned at a ratio of 1:1 of Active:Placebo for 2 sentinel subjects, and 5:1 of Active:Placebo for the remaining 6 subjects. Each cohort will be independently randomly assigned by a qualified person who is not directly involved in study conduct, data management, or data analysis.

5.4 BLINDING

5.4.1 Blinding Procedures

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by using active and placebo dosage forms of similar appearance. Access to the randomization code will be strictly controlled according to the standard operating procedures of PPD.

5.4.2 Breaking the Blind

A subject or subjects may be unblinded in the event of a DLT, SAE, or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will be terminated. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the independent medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF) as outlined in Section 9.4.2.3.

- Details of additional standard study procedures can be found in Appendix 2.
- The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

The following PK parameters for EC5026 will be calculated as endpoints using standard noncompartmental methods: AUC_{0-t}, AUC_{0-inf}, AUC_{0-48}, C_{max}, T_{max}, K_{el}, $t_{1/2}$, CL/F, and V_z/F. The following urine PK parameters for EC5026 will be calculated as endpoints using standard noncompartmental methods: CL_R, Ae, $Ae_{(t1-t2)}$, and Fe%.

- The timing and frequency of PK sample collection is listed in the SOE (Section 3.1).

- Definitions of the PK parameters can be found in the list of abbreviations, Appendix 1.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical unit separately.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay for EC5026 in human plasma and urine. Assay details, results, and validation will be provided in a separate bioanalytical report.

6.2 PHARMACODYNAMIC ASSESSMENTS AND ENDPOINTS

Exploratory biomarker assessments will be determined by EicOsis and reported separately from the CSR. The timing and frequency of exploratory biomarker sample collection is listed in the SOE (Section 3.1).

6.2.1 Pharmacodynamic Sample Collection

Details for the collection, processing, storage, and shipping of pharmacodynamic (PD) samples will be provided to the clinical unit separately.

6.2.2 Pharmacodynamic Sample Analysis

Analysis of exploratory biomarkers will be provided in a separate protocol.

6.3 SAFETY ASSESSMENTS AND ENDPOINTS

The timing and frequency of all safety assessments is listed in the SOE (Section 3.1).

Safety and tolerability endpoints will include monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, ECG telemetry, physical examination findings, and TEAEs compared with EC5026 blood levels.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and that may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance

will be documented and an AE reported on the AE page of the subject's electronic case report form (eCRF). The investigator will monitor the subject until the result has reached the reference range or the result at Screening, or until the investigator determines that follow-up is no longer medically necessary.

6.3.1 Adverse Events

Definitions and procedures for reporting of AEs can be found in Appendix 3. For this study, the following contact information is to be used for SAE reporting:

PPD Medical Monitor: [redacted]

EicOsis Medical Monitor: [redacted]

6.3.2 Clinical Laboratory Assessments

The following clinical laboratory assessments will be performed:

Hematology	Complete blood count including red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count, differential white blood cell count, and platelet count
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio
Serum Chemistry	Albumin, ALP, ALT, AST, bicarbonate, total bilirubin, blood urea nitrogen, calcium, chloride, total cholesterol, creatinine, gamma-glutamyltransferase, glucose, lactate dehydrogenase, phosphorus, potassium, total protein, sodium, magnesium, total protein, CPK, and uric acid
Urinalysis	Protein, glucose, blood, microalbumin, and microscopy under reflex
Serology	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (Screening only)

Other analyses	All subjects: Urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opioids [including heroin, codeine, and oxycodone]) and alcohol screen Female subjects: Serum follicle-stimulating hormone test for postmenopausal females and serum pregnancy test for premenopausal females

- The clinical laboratory that performs the tests will provide the reference ranges for all clinical laboratory parameters.

- Clinical laboratory tests may be repeated at the discretion of the investigator, if necessary, for assessment of inclusion and exclusion criteria or evaluation of clinical laboratory abnormalities.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

The nominal sample size for this study (N = 40 or N=48 with inclusion of the optional 6th cohort) is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient to evaluate the objectives of the study.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The safety population will include all subjects who receive a single dose of study drug.

- The PK population will include subjects who receive a single dose of EC5026 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Subjects who experience vomiting within 2 times the median T_{max} after study drug dosing will be excluded from the PK analysis.

- The PD population will include subjects who receive a single dose of EC5026 and have a postdose PD measurement.

7.3 STATISTICAL ANALYSES

Details of all statistical analyses will be described in a separate statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis

population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

Baseline demographic and background variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Pharmacokinetic Analyses

Plasma and urine concentration data will be listed and summarized by time point for each dose level using descriptive statistics (number of subjects, mean, SD, coefficient of variation [CV], median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentrations versus scheduled time profiles will be presented graphically by dose.

The PK parameters of EC5026 will be analyzed based on the actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina). Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}48}$, and C_{max}.

Dose proportionality will be tested using the power regression model for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}48}$, and C_{max}, defined as:

$$\ln[\text{PK parameter}] = \beta_0 + \beta_1 \ln[\text{dose}]$$

where the PK parameter is an AUC or C_{max}. The null hypothesis being tested is that the AUC and C_{max} values are dose proportional, or slope (β_1) = 1.

7.3.2 Pharmacodynamic Analyses

Exploratory PD assays may include biomarker assessments and plasma epoxide:diol ratios to evaluate potential target engagement of EC5026 versus the sEH enzyme. Exploratory PD assays will be reported separately.

7.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing.

7.4 HANDLING OF MISSING DATA

Concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study. A blinded safety data review will be performed for each cohort before dose escalation is allowed (Section 5.1.1). An interim safety analysis will be performed on a blinded basis within 1 week following the end of each

dosing sequence (ie, within 5 business days or 7 calendar days after each SAD sequence is administered). Placebo data will be pooled from all completed cohorts to create the placebo control for each successive interim dose comparison. Any SAE and a higher-than-placebo incidence of nonserious AEs will be evaluated on an ad hoc basis and presented to the sponsor for consideration before subjects will be enrolled in the next dose cohort.

The plasma concentration-time data and PK parameters for all subjects will be reviewed by the SRC. Pharmacokinetic stopping rules will be implemented based on the mean NOAEL of male and female animals from the most sensitive preclinical species considered for this study (28-day rat GLP safety study M386-18). Dose escalation will be stopped, and data will be reviewed by the SRC, if EC5026 C_{max} is equal to 920 ng/mL and/or if AUC_{0-48} is equal to 8400 ng•h/mL in any single subject within each cohort.

8. REFERENCE LIST

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (US). Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005 [cited 30 July 2019] [30 screens]. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007 [cited 30 July 2019] [10 screens]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical.

9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
AA	arachidonic acid
Ae	amount of drug excreted unchanged in the urine
$Ae_{(t1-t2)}$	amount of drug excreted within the time interval t1 to t2
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-48}	area under the plasma concentration versus time curve from time 0 to 48 hours post dose
AUC_{0-inf}	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
BLQ	below the limit of quantification
CFR	Code of Federal Regulations
CL/F	apparent total body clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
COX	cyclooxygenase
COXIB	cyclooxygenase-2 inhibitor
CPK	creatine phosphokinase
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EETs	epoxyeicosatrienoic acids
EicOsis	EicOsis Human Health, Inc.
EOS	end of study
EpFAs	epoxy fatty acids
FDA	Food and Drug Administration
Fe%	fraction of eliminated dose (expressed as percent)
GLP	good laboratory practice
HED	human equivalent dose
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board

Abbreviation	Term
K_{el}	terminal elimination rate constant
NINDS	National Institute of Neurological Diseases and Stroke
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PEG	polyethylene glycol
PK	pharmacokinetic(s)
SAE	serious adverse event
sEH	soluble epoxide hydrolase
SOE	schedule of events
SRC	safety review committee
$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution based on the terminal elimination rate constant

9.2 APPENDIX 2: STANDARD PROCEDURES

9.2.1 Removal of Subjects From Therapy or Assessment

9.2.1.1 General Criteria for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject meets any of the following criteria:

1. Is noncompliant with the protocol
2. Experiences an SAE or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study
3. Has laboratory safety assessments that reveal clinically significant hematologic or biochemical changes from baseline values
4. Develops symptoms or conditions that are listed in the exclusion criteria during the course of the study
5. Requires a medication prohibited by the protocol
6. Requests early discontinuation for any reason.

Within each dose cohort, if 1 or more subjects experience AEs of severe intensity (Grade 3 or higher) or 1 or more subjects experience an SAE, the cohort and the study will be temporarily stopped. In particular, if 1 or more subjects have gastrointestinal bleeding or worsening of renal function (mild to moderate renal impairment), this will result in the cohort and the study being temporarily stopped.

The complete AE and vital sign experience of these subjects will be reviewed along with the relevant safety experience of other subjects. After a full review and safety determination, the SRC will determine if additional exposure of volunteer subjects is warranted.

The investigator can also withdraw a subject upon the request of the sponsor, or if the sponsor terminates the study. If withdrawal is considered because of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an

AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

9.2.1.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, any subject who prematurely withdraws from the study will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in a reasonable attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

9.2.2 Prior and Concomitant Medications and Therapies

Restrictions for prior and concomitant medications and therapies are provided in Sections 4.1 and 4.2. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

9.2.2.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the ICF will be recorded in the subject's eCRF.

9.2.2.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

9.2.3 Treatment Compliance

All doses of study drug will be administered in the clinical unit under direct observation of clinic personnel and will be recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

9.3 APPENDIX 3: ADVERSE EVENT DEFINITIONS AND REPORTING

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

9.3.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as

anticipated from the pharmacologic properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

9.3.2 Eliciting and Documenting Adverse Events

During the treatment period of the study, participants will be asked about AEs. All AEs that occur during the course of the study must be collected, documented, and reported to the principal investigator. The occurrence of AEs will be assessed at baseline and daily while in the clinical research unit and at each follow-up clinic visit.

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used

any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

9.3.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (version 14.0 or higher) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or which meets SAE criteria (Section 9.3.1) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator and the independent medical monitor will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

Contact information to be used for SAE reporting can be found in Section 6.3.

9.3.4 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities. The severity of all AEs will be graded by the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a severity rating is **NOT** appropriately defined in the FDA Guidance Document (DHHS 2007), severity will be rated according to the following definitions: The investigator will assess the intensity of each AE/SAE based on his/her clinical judgment. The intensity of each event should be assigned to one of the following categories:

- Mild (Grade 1): An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate (Grade 2): An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe (Grade 3): An event that prevents normal everyday activities. Subject may experience intolerable discomfort or pain.
- Potentially life threatening (Grade 4): An event that results in an emergency room visit or hospitalization.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

9.3.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacologic properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with re-challenge, if applicable).

9.3.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

9.4 APPENDIX 4: STUDY GOVERNANCE

9.4.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonization (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the CSR.

9.4.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.4.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.4.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that is to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.4.2.3 Subject Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study.

Before recruitment and randomization, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

9.4.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

9.4.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the disease under study.

9.4.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval;
- An original investigator-signed investigator agreement page of the protocol;
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current;
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study;
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians;

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

9.4.2.7 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.4.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.4.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.4.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.4.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.4.2.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

9.4.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.4.3 Study Management

9.4.3.1 Monitoring

9.4.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.4.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.4.3.2 Management of Protocol Amendments and Deviations

9.4.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects are enrolled into an amended protocol.

9.4.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.4.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last subject completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the CSR.

9.4.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that CSRs are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that CSR in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the CSR, the investigator(s) will be provided with the final approved CSR, as appropriate.

9.5 APPENDIX 5: CYTOCHROME P450 INDUCERS OR INHIBITORS

A link to the Drug Interactions Flockhart Table™ is provided as follows:
https://drug-interactions.medicine.iu.edu/main-table.aspx