

**CLINICAL STUDY PROTOCOL**

A Phase 1A Single Ascending Dose and Multiple Ascending Dose  
Double-Blind, Placebo-Controlled, Randomized Trial of Oral Inhalation  
PK10571 in Healthy Adult Subjects  
Protocol Number: 4004002

VERSION 5.3

DATE: 31 Jul 2018

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Protocol 4004002 V.5.3 Final

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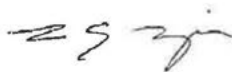
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Double-Blind, Placebo-Controlled, Randomized Trial of Oral Inhalation  
PK10571 in Healthy Adult Subjects

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## 1 INTRODUCTION

Unless noted otherwise, the information provided in [Section 1](#) was excerpted from the Investigational Brochure for PK10571.<sup>1</sup>

### 1.1 Background

Gossamer Bio, Inc. plans to develop PK10571 for the treatment of pulmonary arterial hypertension (PAH), an orphan disease associated with high morbidity and mortality. Despite recent advances in vasodilator therapy for PAH, more effective treatments are needed.

PK10571 has not been previously studied in humans.

#### 1.1.1 Pharmacology

PK10571 is a potent and selective tyrosine kinase inhibitor which has shown efficacy in animal models of PAH.

The following studies of PK10571 have been performed:

- In vitro kinase assays
- In-cell Westerns to measure inhibition of platelet-derived growth factor BB (PDGFBB) stimulated AKT (also known as protein kinase B) phosphorylation
- Enzyme-linked immunosorbent assays (ELISA) to estimate IC<sub>50</sub> for inhibition of phosphorylation of PDGF receptors in human lung fibroblasts
- Endothelial cell permeability assays
- Human ether-à-go-go-related gene (hERG) channel activity assay
- Metabolism study in human hepatocytes
- Biliary excretion study
- Metabolism in lung microsomes
- Preclinical efficacy study in the rat monocrotaline plus pneumonectomy model
- Preclinical efficacy study in the rat Sugén 5416 (SU5416) hypoxia model
- Platelet aggregation studies

PK10571 is well absorbed from the lung [REDACTED] in both rats and dogs and accumulation did not appear to be an issue in either species.

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

## 1.2 Dose Selection Rationale

The first in human exposure of PK10571 will be a single dose ranging study followed by multiple dose (7 day) administration in healthy volunteers. The results from the preclinical program were used to select the starting dose for this phase IA clinical trial.

The starting dose is based on the Food and Drug Administration (FDA) Guidance for Industry “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers” dated July 2005.

[REDACTED]

[REDACTED]

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[REDACTED]

[illegible]

\_\_\_\_\_

[REDACTED]

[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

(b) (7)(C), (b) (7)(D)

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[REDACTED]

[REDACTED] Escalation will be carried out with careful clinical monitoring and in accordance with dose escalation and halting rules described in the protocol. It should be noted that if a higher maximum dose of [REDACTED] is warranted in the clinical trial, the nonclinical data would also support this dose with an animal:human dose multiple of 15.

### 1.3 Study Rationale

Because PAH represents a serious orphan medical condition with a critical need for better therapies, Gossamer Bio, Inc. plans to work closely with the Food and Drug Administration (FDA) in order to ensure an efficient development program.

Gossamer Bio, Inc. will evaluate PK10571 in an initial Phase 1A single-dose/multiple-dose study in normal, healthy volunteers. [REDACTED]

Part A of the phase 1A study is a single ascending dose (SAD) double-blind, placebo-controlled randomized trial of inhaled dry powder PK10571 in healthy human volunteers for determination of safety. Part A will consist of at least 4 cohorts and up to 5 cohorts. Within each cohort, subjects will be randomly assigned to receive either active drug or placebo. The initial dose will be determined based on the results of animal toxicology studies.

After completion and review of the SAD trial (Part A), the multiple ascending dose (MAD) clinical trial (Part B) will be performed. The MAD clinical trial is a double-blind, placebo-controlled randomized repeat dose trial of inhaled dry powder PK10571 in healthy human volunteers. There will be up to 3 dose cohorts, and within each cohort subjects will be randomly assigned to receive either active drug or placebo. Study subjects will be administered active drug or placebo once daily for 7 days.

[REDACTED]

## 2 OBJECTIVES

The objectives of this study are:

- To determine the safety and tolerability of single ascending inhalation doses of PK10571 formulated as a dry powder with excipient L-leucine in healthy adult subjects (Part A)
- To determine the safety and tolerability of multiple ascending inhalation doses of PK10571 formulated as a dry powder with excipient L-leucine in healthy adult subjects (Part B)
- To evaluate the bioavailability of PK10571 following single- and multiple-dose regimens
- [REDACTED]

## 3 STUDY DESIGN SUMMARY

This is a first-in-human, single-center, randomized, double-blind, placebo-controlled, two-part study in healthy adult males and females of non-childbearing potential. Because the safety profile of PK10571 in humans is unknown and this is the first clinical study to assess PK10571 in humans, a single-ascending dose escalation design will be used in Part A of the study. Part B will be a multiple-ascending dose escalation design, to be run only after review of safety and pharmacokinetic data from Part A.

In the single ascending dose study (Part A) at least 4 dose levels of PK10571 will be tested: [REDACTED]

[REDACTED] An optional fifth dose level of up to [REDACTED] may be added, based on safety and pharmacokinetic data from the first 4 cohorts. Subjects will be randomized into one dose cohort and receive either PK10571 or placebo. Within each cohort, 6 subjects will receive active drug and 2 subjects will receive placebo.

In the multiple ascending dose study (Part B), up to three dose levels of PK10571 will be tested. The daily dose will be administered daily for 7 days with close clinical monitoring. The dose for the first cohort of Part B will be determined by review of the safety and pharmacokinetic data from Part A by the Safety Review Committee. The dose interval for the first cohort of Part B (i.e., once daily, twice daily, or up to three times daily) will be determined by review of the safety and pharmacokinetic data from Part A by the Safety Review committee. Subsequent doses and dosing intervals will be determined by review of the safety and pharmacokinetic data from the prior cohort.

For both Part A and Part B, for each cohort, randomization will occur in 2 blocks as follows: In the first block, 2 subjects (sentinel subjects) will be randomized 1:1 to receive PK10571 or placebo; in the second block, 6 subjects will be randomized 5 PK10571: 1 placebo. If PK10571 is well-tolerated in the sentinel subjects, the remainder of the cohort ( $n = 6$ ) will be randomized. There will be a minimum of 48 hours between dosing of the 2 sentinel subjects and the remainder of the cohort.

The safety, tolerability, and pharmacokinetics of PK10571 will be evaluated in each sequential cohort prior to each dose cohort escalation, assessing the totality of all the safety data prior to initiating the next cohort.

Gender distribution will be based on sequential screening of volunteers who meet entry criteria, with a minimum of 4 females per cohort, in order to ensure 2 females per active dose group. Subjects will be assigned numbers in an ascending order, based on successful completion of the screening process. Each subject will participate in only one cohort.

Subjects who withdraw from the study may be replaced at the discretion of the Principal Investigator and Sponsor. Replacement subjects will be given a new randomization number in the 9000 series and assigned to the same treatment as the subject they replace.

Safety assessments will include adverse events; vital signs; oxygen saturation; physical examination; 12-lead electrocardiogram (ECG); clinical laboratory examinations; and pulmonary function tests (spirometry).

Blood and urine will be collected for pharmacokinetic analysis.

Blood will be collected for buffy coat analysis.

### **3.1 Part A**

Part A of the study is a single ascending dose study design. Up to 5 dose levels will be studied. Subjects will receive either PK10571 or placebo. Part A will enroll up to 40 subjects; 8 subjects per cohort. The data from each cohort will be analyzed before deciding whether to proceed with the next cohort.

Each cohort will include a sentinel group of 2 subjects (1 active and 1 placebo) who will be dosed at least 48 hours before the remaining subjects (5 active and 1 placebo). Dosing of the remaining subjects will occur following a safety evaluation of the sentinel group.

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Subjects will receive one of the treatments listed in Table 1. Within each cohort, subjects will be assigned to either active treatment or placebo in randomized fashion.

**Table 2 Part A: Planned Doses for Cohorts 1, 2, and 3**

Cohort	Test Formulation Dose	Placebo
1 - starting dose	PK10571 [REDACTED] (n= 6)*	Placebo (n=2)
2 - second dose	PK10571 [REDACTED] (n=6)*	Placebo (n=2)
3 - third dose	PK10571 [REDACTED] (n=6)*	Placebo (n=2)
4 – fourth dose	PK10571 up to [REDACTED] (n=6)¶	Placebo (n=2)
5 – fifth dose	PK10571 up to [REDACTED] (n=6)ρ	Placebo (n=2)
FPD = fine particle dose; n = number of subjects * Capsules with a nominal fill weight of [REDACTED] will be administered sequentially to achieve the target FPD for Doses 1-3. ¶ Capsules with a nominal fill weight of [REDACTED] will be administered to achieve the dose for cohort 4 (nominal 18 mg FPD (5 capsules) ρ The capsule fill weight, FPD, and number of capsules to be administered will be determined to achieve the target dose for cohort 5, if the Safety Review Committee decides to proceed with this dose.		

Each dose will be administered using an oral inhalation device following a 10-hour overnight fast. After dosing, no food will be allowed until 4 hours postdose. Meals will be standard and scheduled at approximately the same times relative to dose for each cohort.

No water may be consumed for 1 hour prior through 1 hour after dose, except for 60 mL of room temperature water which will be given to subjects to rinse their mouths after dosing. Subjects will swish the 60 mL of water in their mouths then spit it out.

Blood samples for pharmacokinetic evaluation will be obtained prior to dose administration and following dose administration at selected times through 48 hours postdose. A total of 14 pharmacokinetic blood samples will be collected from each subject. Plasma pharmacokinetic samples will be analyzed for PK10571 using a validated analytical method. Appropriate pharmacokinetic parameters will be calculated for each formulation using non-compartmental methods.

Subjects will be housed at the clinical research site for observation for 3 days and then followed up by phone daily for the next 7 days. Subjects will return to the clinical research site for a safety evaluation on Day 11.

### 3.2 Part B

Part B is a multiple ascending dose study design. Subjects will receive either PK10571 or placebo. Approximately 24 subjects will be enrolled in Part B. Subjects will be enrolled in 3 cohorts of 8 subjects each.

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The initial dose for Part B will be determined after review of the safety and pharmacokinetic data from Part A by the Safety Review Committee.

Data from the lower dose cohort will be analyzed before deciding whether to proceed with the higher dose cohort. Alternatively, a lower dose may be administered, depending upon review of previous cohort's safety and pharmacokinetic data.

Subjects will receive one of the treatments listed in [Table 3](#). The assigned treatment will be given either as a single daily dose (QD), or divided into two daily doses (BID), or divided into three daily doses (TID; each dose to be separated by 6 hours on a given day).

Subjects will be assigned to either active treatment or placebo in randomized fashion.

**Table 3 Part B: Planned Doses for Cohorts 1–3**

Cohort	Test Formulation (n = 6)	Placebo (n = 2)
1	PK10571 initial dose	Placebo
2	PK10571 mid dose*	Placebo
3	PK10571 high dose*	Placebo

n = number of subjects

Note: The dosing regimen will be either once daily (QD), twice daily (BID), or three times daily (TID) for 7 consecutive days. For TID dosing, each daily administration will be separated by 6 hours.

\* Alternately, Cohort 2 or 3 will receive a lower dose, depending upon safety and pharmacokinetic data from Cohort 1 or 2, respectively.

Each dose will be administered using an oral inhalation device. Meals will be the same and scheduled at approximately the same times relative to dose for each cohort, if possible. Refer to [Section 5.5.1](#) for details regarding timing of meals for each proposed dosing regimen (QD, BID, and TID).

No water may be consumed for 1 hour prior through 1 hour after each dose, except for 60 mL of room temperature water which will be given to subjects to rinse their mouths after dosing. Subjects will swish the 60 mL of water in their mouths then spit it out.

Blood samples for pharmacokinetic evaluation will be obtained before the first dose of the day on Day 1 and Day 7 and at selected times through 36 hours after the first dose on Day 1, before the first dose on Days 3-6, through 36 hours after the first dose on Day 7, and on Day 9, Day 10, Day 14, and Day 35.

For QD dosing, a total of 34 pharmacokinetic blood samples will be collected from each subject in Part B.

For BID dosing, a total of 30 pharmacokinetic blood samples will be collected from each subject in Part B.

For TID dosing, a total of 30 pharmacokinetic blood samples will be collected from each subject in Part B. Plasma pharmacokinetic samples will be analyzed for PK10571 using a validated analytical method. Appropriate pharmacokinetic parameters will be calculated for each formulation using non-compartmental methods.

Subjects will be housed at the clinical research site for observation until Day 9 (48 hours after the last dose) and return to the clinical research site for safety evaluation and pharmacokinetic blood collection on Days 10, 14, and 35.

### 3.3 Safety Review Team

A Safety Review Committee consisting of the Principal Investigator or designee (e.g., a medically qualified sub-investigator) and Sponsor representatives with appropriate expertise will meet and review, at minimum, the 24-hour safety data for the sentinel group of each cohort in Part A prior to dosing the remainder of the cohort.

The Safety Review Committee will review the safety and pharmacokinetic data from each cohort in Part A. Dose escalation to the next level will occur only after review of the 24-hour pharmacokinetic data, and safety data up to and including Day 11 from the preceding cohort(s). The factors to be used in determining the next incremental dose are described in [Section 3.4](#). There will be at least 2 weeks between dosing of each cohort.

The Safety Review Committee will review the safety and pharmacokinetic data of Part A before starting Part B. The pharmacokinetic data from the first 24 hours of Part B, Cohort 1 up to and including Day 7, and the safety data up to and including Day 14 will be reviewed prior to dosing of Part B, Cohort 2.

All available safety data will be assessed prior to each dose escalation, including but not limited to the following:

- All adverse events (AEs)
- Safety laboratory tests (i.e., hematology, chemistry and urinalysis)
- Coagulation tests
- Vital signs
- Physical examinations
- ECGs (12-lead)
- Pulmonary function tests (spirometry)

If the initial dose administered to Cohort 1 is not tolerated, a lower dose cohort may be allowed.

In subsequent cohorts, the dose may be decreased from the planned dose depending on results of safety and pharmacokinetic data.

### 3.4 Dose Escalation

Dose escalation will proceed after the review of all available safety data from subjects in the preceding cohort(s) is completed, the assessment has determined that the prior dose(s) is/are safe, and escalation to the next dose level is recommended.

The following factors will be considered for determining the next incremental dose:

1. Observation of clinical adverse effects based on symptoms and signs;
2. Observed abnormalities in clinical chemistries, complete blood count (CBC), liver function tests, or coagulation tests;
3. Pharmacokinetic parameters: maximum concentration ( $C_{max}$ ) and area under the plasma versus concentration curve (AUC).
4. For Part A, if no adverse effects are observed at the starting dose [REDACTED], the next dose will be [REDACTED] the third dose will be [REDACTED] (2 times the second dose), the fourth dose will be up to [REDACTED] (up to two times the third dose), and the fifth dose will be up to [REDACTED] (one and a half times the fourth dose).
5. For Part B, if no adverse effects are observed at the starting dose regimen (whether QD, BID, or TID), then the next dose will be a mid-dose to be determined by the Safety Review Committee, and if no adverse effects are seen at the mid-dose, then the next dose will be higher dose to be determined by the Safety Review Committee. In the event of adverse effects at a given dose the Safety Review Committee may recommend a decrease in dose for the next dosing cohort.

### 3.5 Stopping Rules for Dose Escalation

The following will result in a decision not to continue dose escalation if judged by the Safety Review Committee to be related to study drug:

1. Onset of respiratory symptoms postdose suspected to be related to study medication including but not limited to bronchospasm (wheezing), stridor, clinically significant moderate dyspnea, oxygen desaturation with dyspnea, evidence of significant airflow obstruction on spirometry in at least 2 subjects.
2. Three-fold increase in aspartate transaminase (AST) or alanine transaminase (ALT) above the upper limit of normal in at least 2 subjects;
3. Two-fold increase in creatinine in at least 2 subjects;
4. Gastrointestinal (GI) bleed in at least 1 subject;

5. New onset atrial fibrillation in at least 1 subject in which case the Safety Review Committee will determine if dose escalation can be undertaken with additional monitoring (such as telemetry)
6. Clinically significant decrease in hemoglobin in at least 2 subjects;
7. Platelet count drop to less than 60,000 in at least 2 subjects;
8. Fifty percent drop in total white blood cell (WBC) count in at least 2 subjects; or
9. Two-fold increase in International Normalized Ratio (INR) in at least 2 subjects.

### **3.6 Stopping Rules for Study Discontinuation**

The study will be discontinued if a serious adverse event (SAE) occurs that is deemed directly related to study drug by the Safety Review Committee. In the event of an SAE the safety committee will meet to determine if a stopping rule for study termination has been met and if so will stop the study before any other subjects are dosed.

Serious adverse events include: death, respiratory distress requiring hospitalization (acute respiratory distress syndrome [ARDS], pulmonary edema, pulmonary embolus, hemoptysis), GI bleed requiring blood transfusion, intracranial hemorrhage or stroke, renal failure requiring dialysis, MI, heart failure, ventricular tachycardia (torsades), heart block requiring temporary or permanent pacemaker, anaphylaxis, exfoliative dermatitis.

## **4 SUBJECT SELECTION**

### **4.1 Inclusion Criteria**

All volunteers must satisfy the following criteria to be considered for study participation.

1. Male or female.
  - a) Female subjects must not be of childbearing potential. Women are not considered of childbearing potential if one of the following is reported and documented on the medical history:
    - Postmenopausal with spontaneous amenorrhea for at least 1 year, or spontaneous amenorrhea for less than 1 year with serum follicle-stimulating hormone (FSH) levels >40mIU/ml; or
    - Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to Screening.
  - b) Male subjects must have a history of vasectomy greater than 6 months, or use a double-barrier local contraception (i.e., spermicidal gel plus condom) when

engaging in sexual activity with women of childbearing potential while on study medication and for 28 days after the last dose of study medication.

2. Subject must be between 18 and 55 years of age (inclusive).
3. Subject's body mass index (BMI) must be between 18 and 32 kg/m<sup>2</sup> (inclusive), and subject must weigh a minimum of 50 kg (110 lbs).
4. Subject must voluntarily consent to participate in this study and provide their written informed consent prior to start of any study-specific procedures.
5. Subject is willing and able to remain in the study unit for the entire duration of the confinement period (or periods) and return for outpatient visits.
6. Subject must be a non-smoker.
7. Subject must demonstrate ability to use a dry powder inhaler effectively.

#### **4.2 Exclusion Criteria**

Subjects will be excluded for any of the following.

1. Hospitalization within the 6 months prior to the first dose of study treatment.
2. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, GI, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
3. History or presence of active lung disease (i.e., asthma, chronic obstructive pulmonary disease [COPD], pulmonary fibrosis, hemoptysis, bronchiectasis) or prior intubation.
4. Currently uses an inhaler.
5. History or presence of heart disease (i.e., prior myocardial infarction [MI], coronary artery disease, heart failure, hypertension, pulmonary hypertension, valve disease, atrial fibrillation, other arrhythmia, or prolonged QT syndrome).
6. History or presence of cancer (with the exception of basal cell skin cancer that has been effectively treated).
7. History of diabetes mellitus.
8. History of thyroid disease other than hypothyroidism control with levothyroxine and documented normal thyroid-stimulating hormone (TSH).
9. History of tuberculosis, Lyme disease, or other chronic or opportunistic infection.

10. History of positive purified protein derivative (PPD) skin test, or positive PPD test at screening.
11. Has a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) at screening or has been previously treated for hepatitis B, hepatitis C, or HIV infection.
12. History of smoking within the past 15 years.
13. Is a female with a positive pregnancy test result, or who has the ability to become pregnant, or who is lactating.
14. Has forced expiratory volume in 1 second (FEV1) less than 80% predicted, forced vital capacity (FVC) <80% predicted, or resting oxygen saturation less than 97% on room air at screening or baseline.
15. Upper respiratory infection within the 3 months prior to the first dose of medication.
16. History of major bleeding or major surgical procedure of any type within 6 months prior to the first dose of medication.
17. History of minor bleeding disorders such as epistaxis, rectal bleeding (spots of blood on toilet paper), and gingival bleeding within 3 months before the study treatment.
18. History of bleeding disorder or coagulopathy.
19. Females with history of dysfunctional uterine bleeding, including history of menorrhagia or metrorrhagia, unless subject has had a hysterectomy.
20. History of GI bleed.
21. Has used any over-the-counter (OTC) medication, nutritional or dietary supplements, herbal preparations, or vitamins within 7 days prior to the first dose of medication.
22. Has used any antiplatelet agents such as acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel (or similar agent) or anti-coagulants within 7 days prior to the first dose of medication.
23. Has used any prescription medication, except female hormonal replacement therapy, within 14 days prior to the first dose of study medication.
24. Has been treated with any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study

medication and that in the Investigator's judgment may impact subject safety or the validity of the study results.

25. History of peripheral vascular disease.
26. History of autoimmune or collagen vascular disease.
27. History of sleep apnea.
28. History of clinically significant allergy to medications.
29. History of anaphylaxis.
30. History of liver disease
31. History of alcohol or drug abuse.
32. Prolonged QTc on 12-lead ECG (i.e., QTc corrected using Fridericia's formula [QTcF] >450 msec), PR >210 msec, or QRS >110 msec at screening.
33. Evidence of prior MI on ECG; presence of atrial fibrillation on ECG; presence of pre-excitation, 2nd or 3rd degree heart block, or abnormal waveform morphology that would preclude accurate measurement of the QT interval duration or other clinically significant abnormalities.
34. Chest x-ray reveals presence of infiltrate or other abnormality (mass, granuloma, fibrosis, pulmonary thickening, pleural effusion, pulmonary edema, wide mediastinum, cardiomegaly, or clinically significant increased interstitial markings).
35. History of neurologic disorder (i.e., multiple sclerosis, amyotrophic lateral sclerosis [ALS], cerebrovascular accident [CVA], transient ischemic attack [TIA])
36. History of deep vein thrombosis or pulmonary embolus.
37. History of clotting disorder.
38. History of mental illness requiring drug treatment or hospitalization.
39. History of renal failure or proteinuria (defined as 2+ proteinuria:  $\geq 100$  mg/dL on isolated urinalysis).
40. Test results greater than the upper limit of normal (ULN) for AST, ALT, or total bilirubin
41. Test results greater than the upper limit of normal on the following coagulation tests: INR, prothrombin time (PT), or partial thromboplastin time (PTT).
42. Total cholesterol >250 mg/dL or triglycerides >300 mg/dL at screening (based on fasting lipid profile).

43. Estimated creatinine clearance less than 60 mL/min at the screening visit using the Modification of Diet in Renal Disease (MDRD) equation.
44. Hemoglobin at screening of <11.5 g/dl (if female subject) or <12.5 g/dl (if male subject).
45. Has a clinically significant abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at screening. Note: Subjects with abnormal laboratory results not specifically excluded by this protocol may be enrolled if the Investigator deems the out-of-range values as not clinically significant.
46. History of treatment with a kinase inhibitor.
47. Has been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
48. Has donated blood or plasma within 30 days prior to the first dose of study medication.
49. Has participated in another clinical trial (randomized subjects only) within 30 days prior to the first dose of study medication.
50. Has a positive urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates) or cotinine.
51. Vital signs (measured sitting after 3 minutes rest) at screening that are not within the following ranges (inclusive): heart rate: 40–100 beats per minute [bpm]; systolic blood pressure (BP): 90–145 mmHg; diastolic BP: 50–95 mmHg. Out-of-range vital signs may be repeated once. Blood pressure will be measured in both arms at screening, with a 3-minute rest between each measurement. Predose vital signs will be assessed by the Principal Investigator or designee (e.g., a medically qualified sub-investigator) prior to study drug administration. The Principal Investigator or designee will verify the eligibility of each subject with out-of-range vital signs and document approval prior to dosing.
52. Significant difference (i.e., greater than 15 mmHg) between the systolic blood pressure in each arm at screening.
53. History of lactose intolerance.

#### **4.3 Restrictions**

1. Subject must not take any OTC medication, nutritional or dietary supplements, herbal preparations, or vitamins within 7 days prior to the first dose of study medication until the end of study visit without evaluation and approval by the Investigator.

2. Has used any antiplatelet agents such as ASA, NSAIDs, or anti-coagulants within 7 days prior to the first dose of medication until the end-of-study visit without evaluation and approval by the Investigator.
3. Subject must not take any prescription medication, with the exception of female hormone replacement therapy, from 14 days prior to the first dose of study medication until the end-of-study visit without evaluation and approval by the Investigator.
4. Subject must not consume beverages and foods containing alcohol, grapefruit, or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end-of-study visit. Subjects will be instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the Investigator based on the potential for interaction with the study drug.
5. Subject must not donate blood or plasma from 30 days prior to the first dose of study medication until the end-of-study visit. It is recommended that blood/plasma donations not be made for at least 30 days after the end-of-study visit.
6. Subjects must not use tobacco or any products that contain tobacco or nicotine at any time during the study until after the end-of-study study visit.
7. Subject must not engage in strenuous exercise from 48 hours prior to the first dose of study medication until after the end-of-study visit.
8. Male subjects must refrain from sperm donations while on study drug, for the entire duration of the study, and for 30 days after the last dose of study drug.

#### 4.4 Screening

The informed consent document will be discussed with each potential participant, and each individual will sign an informed consent document for the study prior to any study-specific procedures being performed. Each potential study participant will have the following assessments by the Investigator or designee within 28 days prior to study start:

- Medical and medication history
- Demographic data, including: sex, age, race, ethnicity, body weight (kg), height (cm), BMI ( $\text{kg}/\text{m}^2$ ), and smoking habits
- Physical examination
- Vital signs measurements: blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry

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- ECG performed after subject has been in supine position for a minimum of 5 minutes
- Clinical laboratory tests: hematology, serum chemistry, and urinalysis
- Serology testing: hepatitis B, hepatitis C, and HIV
- Fasting glucose
- Fasting lipid profile
- Coagulation tests (PT, INR, and PTT)
- Urine drug, alcohol, and cotinine screen tests.
- Serum pregnancy tests (all female subjects)
- FSH tests (female subjects claiming post-menopausal status for less than 1 year)
- Pulmonary function tests: spirometry, including FVC and FEV1
- Chest X-ray (posteroanterior [PA] and lateral)
- PPD test (will be evaluated 48 to 72 hours post placement)

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs will be enrolled in the study.

A positive test result for pregnancy, HIV, hepatitis B, hepatitis C, or urine drug/cotinine screen will end the screening process.

#### 4.5 Laboratory Tests

A Clinical Laboratory Improvement Amendments (CLIA) certified laboratory will perform the following clinical laboratory tests for this study. Tests will be performed at the times noted in the Events Schedule ([Section 12](#)).

*Hematology:* The following will be evaluated: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count (RBC), and platelet count.

*Serum Chemistry:* The following will be evaluated: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), chloride (Cl<sup>-</sup>), lactate dehydrogenase (LDH), calcium (Ca), uric acid, total cholesterol, triglycerides, globulin, and fasting glucose.

*Thyroid-stimulating hormone (TSH):* The following will be evaluated: TSH at the times indicated.

*Lipid profile:* The following will be evaluated: fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides

*Serology:* Blood will be tested for hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV).

*Coagulation:* The following will be evaluated: INR, PT, and PTT.

*Platelet aggregation:* The following will be evaluated: collagen-induced platelet aggregation

*Urinalysis:* The following will be evaluated by an automated or manual urine “dipstick” method: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed.

*Urine Drug, Cotinine, and Alcohol Screens:* Urine samples will be tested for drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates), alcohol, and cotinine.

*Pregnancy Test (Female Subjects Only):* Serum pregnancy test will be performed on all female subjects at screening. A urine pregnancy test will be performed on all female subjects at check-in.

*Follicle-Stimulating Hormone:* Female subjects claiming post-menopausal status for less than 2 years must have FSH test results equal to or greater than 40.0 mIU/mL at screening.

## **5 STUDY PROCEDURES**

### **5.1 Subject Assignment**

Up to 40 subjects will be dosed in Part A of this study.

Up to 24 subjects will be dosed in Part B of this study.

The sample size is not based on statistical considerations. The number of subjects planned for enrollment is considered sufficient to achieve the study objectives.

The maximum duration of the study from screening to study exit for each subject will be approximately 39 days for subjects enrolled in Part A and 63 days for subjects enrolled in Part B.

Each subject will receive an assigned treatment based on the randomization schedule prepared by the clinical site. In order to achieve gender distribution with a minimum of

4 females per cohort, and 2 females per active dose group, subjects will be randomized in blocks of 4 by gender.

Subjects who successfully qualified for the study but did not dose (for example, backup subjects) may be enrolled in a subsequent cohort if they continue to meet all of the inclusion requirements and none of the exclusion requirements in the timeframe specified.

## **5.2 Blinding**

The study will be conducted under double-blind conditions at the Clinical Site. An unblinded pharmacist will be required at the Clinical Site to comply with the study's randomization and blinding requirements. At the Clinical Site, prior to study initiation, the Principal Investigator will be responsible for designating a qualified pharmacist to serve as the unblinded pharmacist in the study. At his/her discretion, the Principal Investigator may also designate a back-up unblinded pharmacist.

Throughout the study, the unblinded pharmacist will be responsible for all drug accountability issues, including preparing, labeling, and dispensing study drug according to the randomization code provided, yet remain independent of all subject assessments.

The unblinded pharmacist will be trained on the requirements of the study and the contents of the Pharmacy Manual. Specific topics covered in the training will include the randomization procedure, drug dispensing procedures, and drug accountability guidelines.

Randomization codes will be provided to the unblinded pharmacist. Confirmation of receipt of the randomization code will be required by the Sponsor. The unblinded pharmacist will be responsible for maintaining the blind, consistent with protocol design, throughout the study. All documentation is to be filed in the Pharmacy Manual. Access to this manual by study personnel will be restricted to the unblinded pharmacist and back-up pharmacist (if applicable).

The subjects, Principal Investigator, and all other clinical personnel involved with subject assessments will remain blinded to the actual treatment assignments of the subjects (active drug or placebo). The Principal Investigator will be ultimately responsible for ensuring that the integrity of the blind is maintained throughout the study and will be required to notify the Sponsor in the event of any breaking of the blind for any reason.

### **5.2.1 Staff**

All observers who evaluate any reported adverse event, laboratory abnormalities, ECGs, and changes in the ECGs will be blinded as to whether the subject is being dosed with active drug or placebo.

The bioanalytical laboratory and pharmacokineticist will be unblinded to allow for interim analysis between cohorts.

#### 5.2.2 Subjects

All subjects will be blinded as to treatment with active drug or placebo. In order to maintain the blind of the study, on the designated dosing days, all subjects will be administered an oral inhalation dose of a study medication.

#### 5.2.3 Unblinding Procedures

The treatment assignment should be unblinded to the Principal Investigator or clinical staff prior to completion of the study only in the case of an emergency, when knowledge of the study drug assignment is absolutely necessary for the clinical management or welfare of the subject. Breaking of the blind under any other circumstances will be considered a protocol violation.

The Investigator is strongly encouraged to contact the Sponsor before unblinding the study drug assignment prior to the scheduled assessment of tolerance and safety data. If the blind is broken for any reason, the Investigator must notify the Sponsor within one business day, and an SAE form must be completed, if appropriate. In addition, the Investigator will record the date and reason for revealing the blinded study drug assignment for that subject in the source documents and appropriate CRF page(s).

### 5.3 Check-In Procedures

Subjects will be admitted to the research facility on the day prior to study drug administration. The following procedures will be completed following admission to the unit:

- All subjects will be asked to affirm that the exclusion criteria and restrictions have not been violated since the screening.
- Review concomitant medications
- Assess for adverse events
- Collect blood for serum chemistry, hematology (complete blood count), and coagulation testing
- Collect urine for urinalysis
- Collect urine for drug, alcohol, and cotinine testing
- Spirometry
- Collect urine for pregnancy testing (female subjects only)

If at any time the drug, cotinine, alcohol, or pregnancy test is positive, the subject will be discontinued from study participation.

All subjects will be trained in the use of the dry powder inhaler. Instructions for training subjects will be provided in the Pharmacy Manual.

## **5.4 Confinement**

All subjects will check-in at an appropriate time the day before dosing to allow time for predose procedures, training in the use of the dry powder inhaler, and to fast overnight for at least 10 hours.

*Part A:* Subjects will remain in the research center for observation until Day 3 and will be followed up by phone daily for the next 7 days (Days 4-10). Subjects will return to the clinical research site for a safety evaluation on study Day 11.

*Part B:* Subjects will be released from the research center on Day 9 and return for outpatient visits on study Days 10, 14, and 35.

## **5.5 Fasting/Meals/Beverages**

### **5.5.1 Fasting/Meals**

#### **Part A (SAD)**

Optional meals may be provided the day of check-in. All subjects will then be required to fast for at least 10 hours prior to dosing. The subjects will fast for 4 hours thereafter. Standard meals will be provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter. Meal/snack menus will be the same for all SAD cohorts.

#### **Part B (MAD)**

Optional meals may be provided the day of check-in. All subjects will then be required to fast for at least 10 hours prior to dosing.

For QD dosing, each dose will be administered following a 10-hour overnight fast. After dosing on Day 1 and Day 7, no food will be allowed until 4 hours postdose. On other dosing days (Days 2–6), subjects will have nothing to eat for at least 1 hour postdose.

For BID dosing, the first dose of the day will be administered in the morning following a 10-hour overnight fast. After the morning dose on Day 1 and Day 7, no food will be allowed until 4 hours postdose. On other dosing days (Days 2–6), no food will be allowed for at least 1 hour after the morning dose. Subjects will have nothing to eat for at least 2 hours before the second dose of each day and for at least 1 hour after the second dose.

For TID dosing, the first dose of the day will be administered in the morning following a 10-hour overnight fast. On Day 1 and Day 7, no food will be allowed until 4 hours after the first dose of the day. On other dosing days (Days 2–6), no food will be allowed for at least 1 hour after the first dose of the day. Subjects will fast for at least 1.5 hours before the second and third doses of each day.

Meal/snack menus will be the same for all MAD cohorts.

#### 5.5.2 Beverages

Water will be allowed ad lib up to 1 hour prior to study treatment administration. Each subject will be given 60 mL of water with which to rinse their mouths after dosing. Subjects will swish the water in their mouths and then spit it out.

After 1 hour postdose, subjects will be encouraged to drink water ad lib.

### 5.6 Drug Administration

Worldwide Clinical Trials pharmacy staff will package and dispense the study treatment. Prior to dosing, subjects will receive training in use of the oral inhalation device as indicated in the Events Schedules ([Section 12](#)) or as needed if additional training is determined.

Details for dose preparation, device training, and dose administration will be provided in a separate pharmacy manual.

Each subject will receive an oral inhalation dose of the assigned treatment (active drug or placebo). All doses of investigational product will be administered under the supervision of clinical study personnel.

For QD dosing, the subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to adverse events (AEs), for the first 4 hours after dosing.

For BID and TID dosing, the subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after the first morning dose on Day 1 and Day 7. For other doses, subjects will remain seated for at least 1 hour after dosing. During the times when subjects are to remain seated, they will not be allowed to lie down, except as directed by clinical staff secondary to adverse events (AEs).

### 5.7 Blood Sampling, Processing and Shipment

Pharmacokinetic blood samples will be collected as detailed in [Appendix I](#), Pharmacokinetic Sample Collection, Processing, and Shipment Instructions.

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**Part A**

A total of 84 mL (14 x 6 mL samples) will be collected from each subject in Part A for pharmacokinetic analysis.

In addition, approximately 114 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 198 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.

Blood samples collected up to and including 24 hours postdose within  $\pm 2$  minutes of scheduled time will not be considered deviations. Blood samples collected after 24 hours through 48 hours within  $\pm 5$  minutes of scheduled time will not be considered deviations. Blood samples collected after 48 hours postdose within  $\pm 10$  minutes of scheduled time will not be considered deviations.

**Table 4 Total Amount of Blood to be Collected for Testing in Part A**

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	25	25
Clinical labs during study (check-in, 24 and 48 hours postdose)	3	15	45
Clinical labs at end-of-study	1	15	15
Platelet aggregation	2	6.5	13
Buffy coat samples	2	8	16
Pharmacokinetic analysis	14	6	84
Total			198

**Part B**

*Note: The information in this section applies to QD dosing only. The blood sample volumes for BID and TID dosing are provided in [Appendix 4](#) and [5](#), respectively.*

A total of 204 mL (34 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.

In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 377.5 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.

Blood samples collected up to and including 24 hours postdose within  $\pm 2$  minutes of scheduled time will not be considered deviations. Blood samples collected after

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24 hours through 48 hours after the last dose within  $\pm 5$  minutes of scheduled time will not be considered deviations, with the following exception: when blood collection is scheduled for the same time as dose administration (at times other than the first dose administration) samples collected within -5 minutes of scheduled time will not be considered deviations. Blood samples collected after 48 hours postdose after the last dose within  $\pm 10$  minutes of scheduled time will not be considered deviations.

**Table 5 Total Amount of Blood to be Collected for Testing in Part B**

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	25	25
Clinical labs during study (check-in, Days 2, 4, 7, 9, and 14)	6	15	90
Clinical labs end-of-study	1	15	15
Platelet aggregation	3	6.5	19.5
Buffy coat samples	3	8	24
Pharmacokinetic analysis	34	6	204
Total			377.5

### 5.8 Urine Sampling, Processing and Shipment

Pharmacokinetic urine samples will be collected as detailed in [Appendix II](#), Urine Sample Collection, Processing, and Shipment Instructions.

Urine will be collected predose (spot collection) and for 24 hours postdose for the determination of drug levels.

### 5.9 End-of-Study/Early Termination Procedures

End-of-study procedures will be performed on Day 11 of Part A and on Day 35 of Part B.

The following procedures and assessments will be performed:

- Concomitant medications review
- Vital signs measurements (blood pressure, pulse rate, respiration rate, pulse oximetry, and temperature).
- Physical examination
- ECG

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- Chest X-ray (PA and lateral) (required for Part A; at the Investigator's discretion for Part B)
- Spirometry
- Clinical laboratory tests
- Coagulation tests
- Urinalysis
- Pregnancy testing (female subjects)
- Adverse event assessment

When possible, end-of-study procedures will be performed in the event of a subject's early termination from the study.

## **5.10 Safety Monitoring and Procedures**

### **5.10.1 Vital Signs**

A full set of vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at screening, at 0 hour (predose), and at the end-of-the study visit (Day 11 of Part A and Day 35 of Part B).

In Part A, blood pressure, pulse rate, and pulse oximetry will be measured at the following times:

- 10 minutes and 1, 2, 4, 8, 12, 16, 24, and 48 hours postdose

*Note: The information in this section for Part B applies to QD dosing only. The timing of vital sign measurements for BID and TID dosing are provided in [Appendix 4](#) and [5](#), respectively.*

In Part B, blood pressure, pulse rate, and pulse oximetry will be measured at the following times:

- 10 minutes and 1, 2, 4, 8, 12, 16, and 24 hours after Dose 1
- 1, 2, and 4 hours after Doses 2-6
- 10 minutes and 1, 2, 4, 8, 12, 16, 24 hours after Dose 7
- Day 9 (prior to discharge)
- Day 10
- Day 14

At the screening visit, each subject will have blood pressure measured in both arms. If there is no significant difference (i.e., greater than 15 mmHg) between the systolic

blood pressure in each arm at screening, then at other times the subject may have blood pressure measured in the dominant arm. Should one set of blood pressure measurements be out of range, the blood pressure reading will be repeated in the same arm.

For purposes of qualifying any given subject for study participation, out-of-range vital signs may be repeated once.

Additional vital signs measurements may be performed as deemed medically necessary by research personnel. All vital signs measurements will be taken after the subject has completed a minimum 3-minute sit.

#### 5.10.2 Pulmonary Function Tests (Spirometry)

Part A: Pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be performed at screening, check-in, at 1, 8, and 24 hours after dose administration, and at the end of the study (Day 11).

Part B: In the case of QD dosing, pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be performed at screening, check-in, at 1, 4, 8, and 23 hours after administration of the first and last morning doses (Day 1 and Day 7), 1 hour after dosing on Day 4, on Day 14, and at the end of the study (Day 35).

In the case of BID dosing, pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be performed at screening, check-in, at 1, 4, 8, and 23 hours after administration of the first morning dose on Day 1 and Day 7, at least 1 hour after the first dose on Day 4, on Day 14, and at the end of the study (Day 35).

In the case of TID dosing, pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be performed at screening, check-in, and at 1 hour after the first morning dose on Day 1, Day 4, and Day 7, at least 1 hour before second dose on Day 1 and Day 7, 23 hours after the first morning dose on Day 1 and Day 7, on Day 14 and at the end of the study (Day 35).

Repeat spirometry will be allowed at the Investigator's discretion.

#### 5.10.3 Physical Examination

Part A: Physical examinations will be conducted for all subjects at screening, predose, daily while confined in the clinical research unit, and at the end of the study (Day 11).

Part B: Physical examinations will be conducted for all subjects at screening, predose on Day 1, on Days 2, 4, 7, 9, 14, and at the end of the study (Day 35).

Assessments will include: physical exam for general appearance; head, ears, eyes, nose and throat; thyroid; lymph nodes; back and neck; heart; chest; lungs; abdomen; skin; and extremities, musculoskeletal and neurological.

#### 5.10.4 Electrocardiograms

All subjects will have ECGs performed at screening. All ECGs will be performed after subject has been in supine position for at least 5 minutes.

In Part A ECGs will be performed at the following times: predose, 10 minutes postdose, 2, 4, 8, and 24 hours postdose, and at the end of the study.

In Part B, ECGs will be performed at the following times (relative to the first dose): predose, 10 minutes postdose, 2, 4, 8, and 24 hours postdose, Day 9 (prior to check-out), Day 14, and at the end of the study.

#### 5.10.5 Chest X-Ray

All subjects will undergo chest X-rays (PA and lateral) at screening and on Day 11 of Part A and Day 9 of Part B. Additionally, subjects in Part B may undergo chest X-rays on Day 35 if clinically indicated, as determined by the Investigator.

#### 5.10.6 PPD Test

*PPD*: A PPD skin test will be performed at screening to assess for exposure to tuberculosis. The test site will be evaluated 48 to 72 hours after placement.

#### 5.10.7 Other

Subjects will be closely monitored during the confinement period in the research facility. Subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Should the need to move about occur during the first 4 hours after dose administration (or after the first dose in Part B), subjects may be escorted to such procedures or activities by research personnel as deemed medically necessary.

Following dose administration, each subject will be queried periodically about changes in their health. Responses will be transcribed in each subject's source documentation.

Subjects will be instructed to inform the study physician and/or research personnel of any AEs that occur at any time during the study.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

Medical emergency personnel trained in advanced cardiac life support will be on site to monitor subjects during the confinement period in the research center. Emergency medical equipment including but not limited to intubation equipment, pulse oximetry, crash cart, and defibrillator shall be maintained on site to administer appropriate medical care should it be required. A physician will remain on site for a minimum of 4 hours after dose administration and will be available immediately by cell phone or pager thereafter.

## **6 ADVERSE EVENTS**

Subjects will be monitored for any AEs from the beginning of confinement until the end-of-study visit. The Investigator or a medically qualified designee will review each event. The Investigator or a Sub-Investigator will assess its relationship to the study drug. Each sign or symptom will be graded for severity, and the date and time of onset, cessation and resolution will be recorded. Treatment of any adverse reactions will be evaluated and managed by a physician, either at the study site or at a nearby hospital emergency room, as appropriate. All non-serious AEs will be reported on a regular basis or as specified by the Sponsor.

### **6.1 Definitions**

#### **6.1.1 Adverse Event**

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without judgment to causality. An AE can arise from any use of the drug (eg, use in combinations with another drug) and from any route of administration, formulation, or dose, including an overdose.

#### **6.1.2 Serious Adverse Event/Serious Suspected Adverse Reaction**

A serious AE (SAE) or serious suspected adverse reaction, in the view of either the investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### **6.1.3 Life-Threatening Adverse Event/Life-Threatening Suspected Adverse Reaction**

A life-threatening AE/life-threatening suspected adverse reaction, in the view of either the Investigator or Sponsor, places the patient or subject at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death.

#### 6.1.4 Unexpected Adverse Event/Unexpected Suspected Adverse Reaction

An unexpected AE/unexpected suspected adverse reaction is an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

### 6.2 Serious Adverse Event Reporting

The Investigator or designee will notify the appropriate sponsor contact immediately after the SAE detection, observation, or report of occurrence (regardless of the relationship to test article). The sponsor contact information for SAE reporting is provided below:

Lawrence S. Zisman, MD  
CEO  
Gossamer Bio, Inc.  
3013 Science Park Rd. Ste. 200  
San Diego CA 92121  
Phone: 518.472.0952  
24-hour contact number: 518.573.8315  
Email: lzisman@gossamerbio.com

These SAE reports must contain the following information:

- A. Study name/number (for EU also the Eudract number)
- B. Study drug
- C. Investigator details (name, phone, fax, e-mail)
- D. Subject number
- E. Subject initials
- F. Subject demographics
- G. Clinical event
  - 1) Description
  - 2) Date of onset
  - 3) Treatment (drug, dose, dosage form)
  - 4) AE relationship to study drug
  - 5) Action taken regarding study drug in direct relationship to the AE
- H. If the AE was fatal or life-threatening
- I. Cause of death (whether or not the death was related to study drug)
- J. Autopsy findings (if available)

Any new SAE that occurs within one month after the study period and is considered to be possibly related to the Investigational Medicinal Product (IMP) should be recorded and reported immediately to the Sponsor.

The person responsible for the study shall take care that the study has been carried out in accordance with pharmacovigilance local regulations.

All serious event reporting will adhere to 21 CFR 312.32 for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (IRB) will be notified of the alert reports per FDA regulations.

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the case report form (CRF).

The Sponsor will be responsible for reporting and processing any SAEs to the FDA or other applicable regulatory agency.

### **6.3 Relationship to Study Treatment**

The relationship between the AE and the investigational product will be determined by the Principal Investigator or Sub-Investigator on the basis of his/her clinical judgment and the following definitions:

#### **Related:**

The AE follows a reasonable temporal sequence from the study product administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

The AE follows a reasonable temporal sequence from the study product administration, and represents a known reaction to the drug under study or other drugs in its class, or is predicted by the known pharmacological properties of the drug.

The AE resolves with discontinuation of the investigational product and/or recurs with rechallenge, if applicable.

#### **Possibly Related:**

An AE may be considered possibly related if or when (at least two of the following):

- It follows a reasonable temporal sequence from administration of the study product;
- It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known pattern of response to the study product.

**Not Related:**

The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

**6.4 Pregnancies**

Any pregnancy will be considered a protocol violation. Pregnancies will not be documented or reported as AEs unless directed to do so by the Sponsor. However, if at any time the pregnancy falls under the scope and definition of an SAE, it will then be reported as such.

**7 GENERAL CONSIDERATIONS**

**7.1 Basic Principles**

This research will be carried out in accordance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6), and applicable regulatory requirements(s) including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).

**7.2 Institutional Review Board**

This protocol will be reviewed by an appropriate IRB and study enrollment will not commence until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the U.S. Code of Federal Regulations (21 CFR Part 56).

**7.3 Informed Consent**

Written informed consent will be obtained from each subject prior to performing any baseline study-specific evaluations. The informed consent document is prepared by the Investigator or designee, subject to review and approval by the Sponsor, and forwarded to a qualified IRB for final review and approval. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent. Only the most recently IRB-approved Informed Consent Document must be used to consent prospective study subjects. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/site.

**7.4 Indications for Subject Withdrawal**

Subjects will be free to withdraw at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

The final report will include reasons for withdrawals. In the event of an early termination, subjects will undergo the procedures described in [Section 5.9](#).

#### **7.5 Termination of the Study**

The Principal Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

#### **7.6 Documentation**

All documents pertaining to the study, including a copy of the approved protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act (HIPAA) documents, completed CRFs (where applicable), drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study (not merely the Investigator's portion of the study, if it involved more than one investigator) is completed, terminated, or discontinued, and the FDA is notified.

Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors, and auditors, the FDA, other government offices, and the IRB.

#### **7.7 Trial Monitoring**

Sponsor personnel (or designees) will be responsible for monitoring the study to ensure compliance with the protocol and Good Clinical Practice (GCP). Compliance may be verified by one or more of the following methods: on-site visits, frequent communication with the Investigator, and/or review of CRFs and source documents. The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities and the IRB.

#### **7.8 Reimbursement, Indemnity, and Insurance**

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

## 8 PHARMACOKINETIC ANALYSIS

### 8.1 Analytical Methodology

Plasma and urine samples will be analyzed for PK10571 using validated assays. The samples from all evaluable subjects who complete their study period will be analyzed.

### 8.2 Pharmacokinetic Analysis

Pharmacokinetic parameters for PK10571 will be calculated using non-compartmental analysis. The following pharmacokinetic parameters will be determined:

The maximum plasma concentration ( $C_{\max}$ ) and time to  $C_{\max}$  ( $T_{\max}$ ) will be taken directly from the data. The elimination rate constant,  $\lambda_z$ , will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve; the range of data to be used will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Elimination half-life ( $T_{1/2}$ ) will be calculated according to the following equation:

$$T_{1/2} = 0.693 / \lambda_z$$

Area under the curve to the final sample with a concentration greater than the limit of quantitation (LOQ), ( $AUC_{\text{last}}$ ), will be calculated using the log trapezoidal method and extrapolated to infinity using:

$$AUC_{\text{inf}} = AUC_{\text{last}} + C_{\text{last}} / \lambda_z$$

where  $C_{\text{last}}$  is the final concentration  $\geq$  LOQ.

All evaluable subjects will be included in the pharmacokinetic analysis.

Pharmacokinetic calculations will be performed using appropriate software, e.g. Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> (Version 6.3 or higher, Pharsight Corporation) and/or SAS<sup>®</sup> (Version 9.3 or higher, SAS Institute Inc.).

### 8.3 Statistical Analysis

Comparison of the log-transformed pharmacokinetic parameters  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\text{inf}}$  for PK10571 across treatments will be performed using an ANOVA model and the two one-sided t-tests procedure. The ANOVA model will include factors for subject, treatment, and cohort. The ratios of the geometric means and 90% confidence intervals will be reported. Statistical analyses will be performed using appropriate software, e.g. Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> (Version 6.3 or higher, Pharsight Corporation) and/or SAS<sup>®</sup> (Version 9.4 or higher, SAS Institute Inc.). Additional details regarding statistical analysis will be provided separately in the statistical analysis plan (SAP).

## **9 FACILITIES**

### **CLINICAL TRIAL SITE**

Worldwide Clinical Trials Early Phase Services, LLC  
2455 N.E. Loop 410, Suite 150  
San Antonio, Texas 78217  
Telephone: 210.635.1500  
Fax: 210.635.1646

### **CLINICAL LABORATORY**

Worldwide Clinical Trials Early Phase Services, LLC  
2455 N.E. Loop 410, Suite 150  
San Antonio, Texas 78217  
Telephone: 210.635.1500  
Fax: 210.635.1646

### **ANALYTICAL LABORATORY**

Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc.  
8609 Cross Park Drive  
Austin, Texas 78754  
Telephone: 512.834.7766

### **DATA MANAGEMENT**

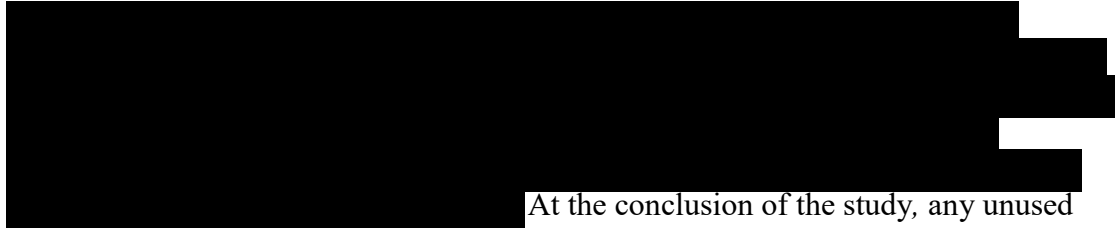
Worldwide Clinical Trials, Ltd  
1st Floor, Waterfront House  
Beeston Business Park  
Beeston, Nottingham  
NG9 1LA, UK  
Telephone: +44(0)115.956.7711  
Fax: +44(0)115.922.0960

## **10 DRUG SUPPLIES**

Gossamer Bio, Inc. will supply sufficient quantities of the study drug formulation, capsules, closures, desiccants, and monodose inhalers to allow completion of this study. Study drug formulations of PK10571 for oral inhalation and placebo for oral inhalation will be shipped to Worldwide Clinical Trials Early Phase Services, LLC pursuant to site standard operating procedures (SOPs). Upon receipt of the study drug products, the supplies will be inventoried and stored in the appropriately designated environmentally controlled and secure, limited access area. The lot numbers of the PK10571 or placebo powder along with the retest dates will be recorded and copies of the Certificate of

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Analysis (where available) will be maintained on file. Records will be maintained of the receipt and dispensation of the drugs supplied.



At the conclusion of the study, any unused study drug will be returned to Gossamer Bio, Inc. or destroyed by the site pursuant to written authorization by the sponsor and applicable federal and state regulations.

## **11 ADMINISTRATIVE ISSUES**

The Investigator is referred to the Investigator Brochure, information provided during the study initiation visit, information provided by the study monitor, and ICH Guidelines for Good Clinical Practice for information regarding the study drug, details, or general considerations to be followed during the course of this study.

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## 12 EVENTS SCHEDULES

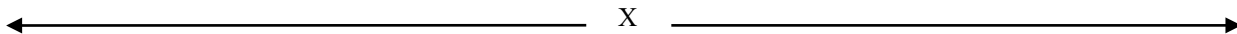
**Table 6 Part A Events Schedule**

Part A	Day -28 to Day -1	Day -1	Day 1													Day 2	Day 3	Days 4-10	Day 11/ End- of- Study
Procedure	Screening	Check- in	Pre- dose	0 hr	Serial time- points	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hrs	48 hrs		
Informed consent	X																		
Demographics and smoking history	X																		
Medical and medication histories	X																		
Concomitant medication review	X	X																X	X
Vital signs and pulse oximetry <sup>a</sup>	X			X		X		X	X	X	X		X	X		X	X		X
Physical examination <sup>b</sup>	X		X													X	X		X
12-lead ECG <sup>c</sup>	X		X				X		X	X	X					X			X
Chest X-ray	X																		X
Pulmonary function tests <sup>d</sup>	X	X						X			X					X			X
TSH, HIV, hepatitis B and C, PPD <sup>e</sup>	X																		
Fasting lipid panel	X																		X
Serum chemistry	X	X														X	X		X

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Part A	Day -28 to Day -1	Day -1	Day 1													Day 2	Day 3	Days 4-10	Day 11/ End- of- Study
Procedure	Screening	Check- in	Pre- dose	0 hr	Serial time- points	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hrs	48 hrs		
Hematology	X	X														X	X		X
Coagulation (PT, PTT, INR)	X	X				X										X	X		X
Platelet aggregation <sup>f</sup>			X			X													
Blood collection for buffy coat analysis <sup>f</sup>			X			X													
FSH (postmenopausal female subjects)	X																		
Pregnancy (female subjects only)	X	X																	X
Urinalysis	X	X														X			X
Urine drug/alcohol/cotinine screens	X	X																	
Meals		X								X		X				X	X		
Dose inhalation training		X	X																
Dose administration				X															
Blood collection for PK analysis <sup>g</sup>			X		X											X	X		
Urine collection for PK analysis <sup>h</sup>			X		X											X			
Confinement <sup>i</sup>		X	X	X						X	X	X	X	X	X	X	X		
Phone calls <sup>j</sup>																		X	

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Part A	Day -28 to Day -1	Day -1	Day 1													Day 2	Day 3	Days 4-10	Day 11/ End-of-Study
Procedure	Screening	Check-in	Pre-dose	0 hr	Serial time-points	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hrs	48 hrs		
Outpatient visits <sup>k</sup>	X																		X
Adverse event assessment <sup>l</sup>																			

BUN = blood urea nitrogen; CR = creatinine; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PPD = positive purified protein derivative skin test; PT = prothrombin time; PTT = partial thromboplastin time; T<sub>max</sub> = time of maximum concentration; TSH = thyroid stimulating hormone

- A full set of vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at screening, at 0 hour (predose), and at the end-of-the study visit (Day 11). Blood pressure, pulse rate, and pulse oximetry will be measured at 10 minutes postdose and at the following hours postdose: 1, 2, 4, 8, 12, 16, 24, and 48. At the screening visit, each subject will have blood pressure measured in both arms. If there is no significant difference (i.e., greater than 15 mmHg) between the systolic blood pressure in each arm at screening, then at other times the subject may have blood pressure measured in one arm.
- Physical examinations will be conducted for all subjects at screening, predose, daily while confined in the clinical research unit, and at the end-of-study visit on Day 11.
- All subjects will have ECGs at screening, predose, 20 minutes postdose, 2, 4, 8, and 24 hours postdose, and at the end-of-study visit on Day 11. All ECGs will be performed after subject has been in supine position for at least 5 minutes.
- Pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) to be performed using spirometry. Repeat spirometry will be allowed at the Investigator's discretion.
- PPD test to be read 48-72 hours after placement.

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- f) To be performed 10 minutes after dosing of Cohort 1; for subsequent cohorts, to be performed at  $T_{\max}$ , based on analysis from previous cohort(s).
- g) Blood samples for pharmacokinetic analysis will be collected at 0 hour (predose), and then at 3, 10, 20, 30, 40 minutes, and 1, 2, 4, 8, 12, 24, 36, and 48 hours after the start of study treatment administration. Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.
- h) Urine samples for pharmacokinetic analysis will be collected predose (spot collection) and for the first 24 hours after dosing.
- i) Subjects will remain in the research center for observation for 3 days after dosing (Days 1-3).
- j) Subjects will be followed up by phone daily on Days 4-10.
- k) Subjects will return to the clinical research site for a safety evaluation on Day 11.
- l) Subjects will be monitored for adverse events from the beginning of confinement until the end-of-study visit.

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**Table 7 Part B Events Schedule (Once Daily [QD] Dosing)**

Part B	Study Day(s)																						
	-28 to -1	-1		1												2		3 to 6	7	8	9	10	14
Procedure	Screening	Check-in	Pre-dose	0 hr	3/5 min	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hr	36 hr						
Informed consent	X																						
Demographics and smoking history	X																						
Medical and medication histories	X																						
Concomitant medication review	X																				X	X	X
Vital signs and pulse oximetry <sup>a</sup>	X		X		X			X	X	X	X		X	X		X		X	X	X	X	X	X
Physical examination <sup>b</sup>	X		X													X		X <sup>b</sup>	X		X		X
12-lead ECG <sup>c</sup>	X		X				X		X	X						X				X			X
Chest X-ray	X																				X		X <sub>o</sub>
Pulmonary function tests <sup>d</sup>	X	X						X		X	X					X			X <sub>e</sub>	X <sub>e</sub>			X
PPD <sup>f</sup>	X																						
TSH	X																						X
HIV, hepatitis B and C	X																						

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Part B	Study Day(s)																							
	-28 to -1	-1		1												2		3 to 6	7	8	9	10	14	35
Procedure	Screening	Check-in	Pre-dose	0 hr	3/5 min	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hr	36 hr							
Fasting lipid panel	X																				X			
Serum chemistry <sup>g</sup>	X	X														X		X	X		X		X	X
Hematology <sup>g</sup>	X	X														X		X	X		X		X	X
Urinalysis <sup>g</sup>	X	X														X		X	X		X		X	X
Coagulation (PT, PTT, INR) <sup>g</sup>	X	X														X		X	X		X		X	X
Platelet aggregation <sup>h</sup>			X			X													X					
Buffy coat <sup>i</sup>			X			X													X					
FSH (postmenopausal female subjects)	X																							
Pregnancy (females subjects only)	X	X																					X	X
Urine drug/alcohol/cotinine screens	X	X																						
Meals		X								X		X				X		X	X	X				
Dose inhalation training		X	X													X								
Dose administration				X												X		X	X					

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Part B	Study Day(s)																								
	-28 to -1	-1		1												2		3 to 6	7	8	9	10	14	35	
Procedure	Screening	Check-in	Pre-dose	0 hr	3/5 min	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	24 hr	36 hr								
Blood collection for PK analysis <sup>j</sup>			X		X											X	X	X	X	X	X	X	X	X	X
Urine collection for PK analysis <sup>k</sup>			X		X																				
Confinement <sup>l</sup>		X				X											X	X	X	X	X				
Outpatient visits <sup>m</sup>	X																				X	X	X		
Adverse event assessment <sup>n</sup>			<div>←————— X —————→</div>																						

BUN = blood urea nitrogen; CR = creatinine; ECG = electrocardiogram; FSH = follicle-stimulating hormone; hr = hours; HIV = human immunodeficiency virus; INR = international normalized ratio; min = minutes; PK = pharmacokinetic; PPD = positive purified protein derivative skin test; PT = prothrombin time; PTT = partial thromboplastin time; T<sub>max</sub> = time of maximum concentration; TSH = thyroid stimulating hormone

- A full set of vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at screening, at 0 hour (predose), and at the end-of-the study visit on Day 35. Blood pressure, pulse rate, and pulse oximetry will be measured 10 minutes after the first dose and at the following hours after the first dose: 1, 4, 8, 12, 16, 24, then daily on Days 3-9 (48, 72, 96, 120, 144, 168, 192, and 216 hours postdose) and at the outpatient visits on Day 10 and 14. At the screening visit, each subject will have blood pressure measured in both arms. If there is no significant difference (i.e., greater than 15 mmHg) between the systolic blood pressure in each arm at screening, then at other times the subject may have blood pressure measured in one arm.
- Physical examinations will be conducted for all subjects at screening, predose on Day 1, and on Days 2, 4, 7, 9, 14, and 35.

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- c) All subjects will have ECGs performed at screening and at the following times (relative to the first dose): predose, 20 minutes postdose, 2, 4, 8, and 24 hours postdose, Day 9 (prior to check-out), Day 14, and at the end of the study.
- d) Pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) to be performed using spirometry. Repeat spirometry will be allowed at the Investigator's discretion.
- e) To be performed at 1, 8, and 24 hours post Day 7 dose.
- f) PPD test to be read 48-72 hours after placement.
- g) Safety labs (chemistry, hematology, coagulation, and urinalysis) will be collected at the following time points: screening, check-in, Day 2, Day 4, Day 7, Day 9, Day 14, and Day 35 (end of study)
- h) To be performed on Day 1 predose and 10 minutes postdose (or  $T_{max}$ , based on analysis from previous cohort) and on Day 7 at 10 minutes postdose (or  $T_{max}$ , based on analysis from previous cohort).
- i) To be performed predose on Day 1 and 5 minutes postdose (or  $T_{max}$ , based on analysis from previous cohort) on Day 1 and Day 7.
- j) Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on Day 8, Day 9, Day 10, Day 14, and Day 35 (total of 34 samples). For multi-dose administrations, the 3-minute blood collection will be performed after dosing procedures are complete. Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.
- k) Urine samples for pharmacokinetic analysis will be collected predose (spot collection) and for the first 24 hours after dosing.
- l) Subjects will remain in the research center for observation until 48 hours after the last dose (Day 9).
- m) Subjects will return to the clinical research site for a safety evaluation and PK blood draws on Days 10, 14, and 35.
- n) Subjects will be monitored for adverse events from the beginning of confinement until the end-of-study visit.
- o) Subjects may undergo a chest x-ray on Day 35 if clinically indicated as determined by the investigator.

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## 13 REFERENCES

1. [Investigational Brochure PK10571, A PDGF Receptor Kinase Inhibitor Formulated for Inhalation as a Dry Powder to Treat Pulmonary Arterial Hypertension, Date: 28 May 2017](#)
2. “Guidance For Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations” U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003.

**APPENDIX 1 PHARMACOKINETIC BLOOD SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS****A. Collection and Processing**

A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the investigator site file.

<b>Processing Instructions</b>	
<b>1</b>	Blood samples will be collected into 6 mL Vacutainer tube(s) containing K <sub>2</sub> -EDTA. The time and date of collection for each sample will be recorded. Samples will be placed on ice after collection and remain on ice throughout processing.
<b>2A</b>	<b>PART A:</b> Samples will be collected at 0 hour (predose) and then at 3, 10, 20, 30, 40 minutes, and 1, 2, 4, 8, 12, 24, 36, and 48 hours after study treatment administration.  (Note: The predose sample will be collected within 150 minutes of dose administration. Predose blood samples obtained from backup subjects who are randomized into the study may exceed the predose collection window.)
<b>2B</b>	<b>PART B:</b> If QD dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on Day 8, Day 9, Day 10, Day 14, and Day 35 (total 34 samples).  If BID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, and on Day 8, Day 9, Day 10, Day 14, and Day 35 (total of 30 samples).  If TID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. An additional sample will be obtained on Day 2 (12 hours after the 3 <sup>rd</sup> dose on Day 1). Blood samples will also be collected before the first dose on Days 2-6, and on Day 8 (6 hours and 12 hours after the 3 <sup>rd</sup> dose on Day 7), Day 9, Day 10, Day 14, and Day 35 (total of 30 samples). For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.

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3	The predose sample on Day 1 will be collected within 150 minutes of dose administration. Predose blood samples obtained from backup subjects who are randomized into the study may exceed the predose collection window.
4	Blood samples will be centrifuged at approximately 3000 rpm for 10 minutes at 4 degrees Centigrade.
5	The resulting plasma samples will be harvested and transferred in approximately equal aliquots into two appropriately labeled polypropylene screw-cap tubes.
6	Samples will be placed in an upright position in a freezer at approximately -20 degrees Centigrade within 60 minutes of collection.
6	Samples will remain frozen until assayed.

Part A Sample Collection Summary					
Number of Subjects	Number of time points per period	Number of Periods	Sample type	Tube type	Number of tubes per sample
Up to 40	14	1	Collection	6 mL K <sub>2</sub> EDTA Vacutainer	1
			Aliquot	3 mL Polypropylene screw Cap	2

Part B Sample Collection Summary					
Number of Subjects	Number of time points per period	Number of Periods	Sample type	Tube type	Number of tubes per sample
Up to 24	34 (if QD) 30 (if BID) 30 (if TID)	1	Collection	6 mL K <sub>2</sub> EDTA Vacutainer	1
			Aliquot	3 mL Polypropylene screw Cap	2

#### B. Labeling of aliquot tubes

1. Labels will contain at least the following information:
  - a. Sponsor study number
  - b. Subject identification

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- c. Study Part; sampling time
- d. Aliquot number (1 or 2)

**C. Shipment**

1. The samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. The second set of samples will be shipped after the bioanalytical laboratory confirms receipt of the first set of samples.
2. Samples will be packaged into separate bags and sorted by subject.
3. Prior to shipment, the samples will be appropriately packed in a cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours.
4. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. Expected samples that are not present will be identified.
5. All frozen pharmacokinetic plasma samples will be transferred with accompanying documentation to:

Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc.  
8609 Cross Park Drive  
Austin, Texas 78754  
Telephone: 512.834.7766

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## **APPENDIX 2 PHARMACOKINETIC URINE SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS**

### **A. Collection and Processing**

<b>Processing Instructions</b>	
<b>Note</b>	A more detailed description of urine sample preparation requirements will be provided by the analytical laboratory. The method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the investigator site file.
<b>2</b>	<b>PART A:</b> A urine sample will be collected predose (spot collection). A 24-hour urine collection will begin after dose administration.
	<b>PART B:</b> A urine sample will be collected predose (spot collection). A 24-hour urine collection will begin after the first dose administration on Day 1.

### **B. Labeling of aliquot tubes**

1. Labels will contain at least the following information:
  - a) Sponsor study number
  - b) Subject identification
  - c) Study Part; sampling time
  - d) Aliquot number (1 or 2)

### **C. Shipment**

1. The samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. The second set of samples will be shipped after the bioanalytical laboratory confirms receipt of the first set of samples.
2. Samples will be packaged into separate containers and sorted by subject.
3. Prior to shipment, the samples will be appropriately packed in a cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours.
4. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment. Expected samples that are not present will be identified.

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5. All frozen pharmacokinetic urine samples will be transferred with accompanying documentation to:

Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc.  
8609 Cross Park Drive  
Austin, Texas 78754  
Telephone: 512.834.7766

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### **APPENDIX 3 BUFFY COAT SAMPLE COLLECTION, PROCESSING, AND SHIPMENT INSTRUCTIONS**

A more detailed description of buffy coat sample preparation requirements may be provided by the analytical laboratory. If such a description is provided, the method of sample preparation provided by the laboratory shall supersede those provided in this protocol and appropriate documentation shall be placed in the investigator site file.

#### **EQUIPMENT AND MATERIALS:**

BD Vacutainer® Blood Collection Set (BD Cat#367352)

BD Vacutainer Cell preparation tube (CPT) with sodium citrate (BD Cat#362761)

Pasteur Pipettes

15ml conical tubes

1 x PBS with 0.5% v/v Phosphatase inhibitor cocktail (Sigma #P0044)

Centrifuge – capable of producing ~10,000 x g

#### **PROCEDURES:**

##### **A) Collection of Blood in BD Vacutainer® CPT with sodium citrate (cat# 362761)**

NOTE: Gloves should be worn for venipuncture procedure.

1. Open the blood collection needle package (BD Cat#367352) but do not remove needle shield.
2. Insert blood collection tube (BD Vacutainer CPT with sodium citrate; Cat#362761) into holder. (Do not puncture the diaphragm of the stopper of CPT tube).
3. Select site for venipuncture.
4. Apply tourniquet. Prepare venipuncture site with an appropriate antiseptic.
5. Remove needle shield. Perform venipuncture with patient's arm in a downward position and tube stopper uppermost. This reduces the risk of backflow of any anticoagulant into the patient's circulation.
6. Push the CPT tube onto needle of the holder, puncturing diaphragm of stopper.
7. Remove tourniquet as soon as blood appears in the tube.
8. Draw ~8 ml of blood in the BD Vacutainer CPT, remove the tube from the holder.
9. If a multiple sample needle is being used, remove the tube and place a new tube into the holder.
10. If the second tube does not draw, remove needle and discard in appropriate disposal device. Repeat procedure from step 1.

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11. Remove needle from vein. Apply pressure to puncture site with dry, sterile gauze until bleeding stops.
12. Apply bandage, if desired.
13. After collection, dispose of needle using an appropriate disposal device. Do not reshield.
14. Invert the blood-filled tube 8 to 10 times to mix anticoagulant additive with blood. Do not shake. Vigorous mixing can cause hemolysis.

**B) Isolation of Buffy Coat Cells (Peripheral Blood Mononuclear Cells (PBMCs))**

1. Centrifuge the sample tubes at 1500 x g for 20 minutes at 18-25 °C. (Note: It is critical to centrifuge the sample tubes within 5 minutes, as waiting for a longer period of time may cause red blood cell lysis as well as affect the phosphorylation state of protein)
2. After centrifugation, the buffy coat of mononuclear cells will be visible just under the plasma layer. Aspirate approximately half of the plasma without disturbing the buffy coat cell layer using a Pasteur pipette. Collect buffy coat cell layer with a Pasteur pipette and transfer to a 15 mL size conical centrifuge tube with cap. (6-8 ml of blood will give a yield of ~3ml of buffy coat)
3. Add 10 ml of 1 x PBS containing 0.5% Phosphatase Inhibitor cocktail (Sigma; Cat#P0044). Mix cells by inverting tube 5 times.
4. Centrifuge for 15 minutes at 300 RCF. Aspirate as much supernatant as possible without disturbing cell pellet.
5. Immediately after step 4 (within 1 minutes), freeze on dry ice, then store the cell pellet at -80°C until shipped.
6. Ship on Dry Ice (a sufficient amount to last at least 4 days) by overnight courier to Sponsor after full cohort collection complete. Communicate with sponsor before shipment to pre-arrange shipment date.

All frozen pharmacokinetic buffy coat samples will be transferred with accompanying documentation to:

Attn: Ravikumar Sitapara, Ph.D.  
Pulmokine Inc.  
7 University Place, Room B127B  
Rensselaer NY 12144  
Phone: 518-472-0952

**APPENDIX 4     PART B: MAD TWICE DAILY (BID) DOSING**

The Safety Review Committee will review the safety data (including local irritation) and pharmacokinetic data from the SAD protocol (Part A) to determine the starting dose for the first MAD cohort and if the first cohort of the MAD protocol should be dosed QD (once daily), BID (twice daily; once every 12 hours), or TID (three times daily; 6 hours between each dose for a given day of dosing).

If the decision is made to start dosing in the MAD protocol at BID, then the Safety Review Committee will review the safety data (including local irritation) and PK data from the first MAD cohort to determine if BID dosing should continue, if dosing should be reduced to QD, or if dosing should be increased to TID for the next cohort.

**Blood Sampling, Processing and Shipment**

A total of 180 mL (30 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.

In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 353.5 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.

Blood samples collected up to and including 24 hours postdose within  $\pm 2$  minutes of scheduled time will not be considered deviations. Blood samples collected after 24 hours through 48 hours after the last dose within  $\pm 5$  minutes of scheduled time will not be considered deviations. Blood samples collected after 48 hours postdose after the last dose within  $\pm 10$  minutes of scheduled time will not be considered deviations.

**Table 8     Total Amount of Blood to be Collected for Testing in Part B (BID Dosing)**

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	25	25
Clinical labs during study (check-in, Days 2, 4, 7, 9, and 14)	6	15	90
Clinical labs end-of-study	1	15	15
Platelet aggregation	3	6.5	19.5
Buffy coat samples	3	8	24
Pharmacokinetic analysis	30	6	180
Total			353.5

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**Table 9 Part B Events Schedule (BID)**

Part B - BID	Study Day(s)																								
	-28 to -1	-1		1													2		3 to 6	7	8	9	10	14	35
Procedure	Screening	Check-in	Pre-dose	0 hr	3/5 min	10 min	20 min	1 hr	2 hr	4 hr	8 hr	10 hr	12 hr	16 hr	20 hr	23 hr	24 hr	36 hr							
Informed consent	X																								
Demographics and smoking history	X																								
Medical and medication histories	X																								
Concomitant medication review	X																						X	X	X
Vital signs and pulse oximetry <sup>a</sup>	X		X			X		X		X	X		X	X			X		X	X	X	X	X	X	X
Physical examination <sup>b</sup>	X		X														X		X <sup>b</sup>	X		X		X	X
12-lead ECG <sup>c</sup>	X		X				X		X	X	X						X			X		X		X	X
Chest X-ray	X																					X			X <sup>d</sup>
Pulmonary function tests <sup>e</sup>	X	X						X		X	X					X			X	X				X	X
PPD <sup>f</sup>	X																								
TSH	X																								X

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Part B - BID	Study Day(s)																									
	-28 to -1	-1		1													2		3 to 6	7	8	9	1 0	1 4	3 5	
Procedure	Screening	Check -in	Pre- dose	0 hr	3/5 mi n	10 mi n	20 mi n	1 hr	2 hr	4 hr	8 hr	1 0 hr	1 2 hr	1 6 hr	2 0 hr	23 hr	2 4 hr	36 hr								
HIV, hepatitis B and C	X																									
Fasting lipid panel	X																					X				
Serum chemistry <sup>g</sup>	X	X															X			X	X		X		X	X
Hematology <sup>g</sup>	X	X															X			X	X		X		X	X
Urinalysis <sup>g</sup>	X	X															X			X	X		X		X	X
Coagulation (PT, PTT, INR) <sup>g</sup>	X	X															X			X	X		X		X	X
Platelet aggregation <sup>h</sup>			X			X															X					
Buffy coat <sup>i</sup>			X			X															X					
FSH (postmenopausal female subjects)	X																									
Pregnancy (females subjects only)	X	X																							X	X
Urine drug/alcohol/cotinine screens	X	X																								
Meals <sup>j</sup>		X			X													X	X	X	X					

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Part B - BID	Study Day(s)																										
	-28 to -1	-1		1													2		3 to 6	7	8	9	1 0	1 4	3 5		
Procedure	Screening	Check -in	Pre- dose	0 hr	3/5 mi n	10 mi n	20 mi n	1 hr	2 hr	4 hr	8 hr	1 0 hr	1 2 hr	1 6 hr	2 0 hr	23 hr	2 4 hr	36 hr									
Dose inhalation training		X	X														X										
Dose administration				X									X				X		X	X							
Blood collection for PK analysis <sup>k</sup>			X		X												X		X	X	X	X	X	X	X	X	
Urine collection for PK analysis <sup>l</sup>			X		X															X							
Confinement <sup>m</sup>		X				X														X	X	X	X				
Outpatient visits <sup>n</sup>	X																						X	X	X		
Adverse event assessment <sup>o</sup>				<div></div> X <div></div>																							

BUN = blood urea nitrogen; CR = creatinine; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PPD = positive purified protein derivative skin test; PT = prothrombin time; PTT = partial thromboplastin time; T<sub>max</sub> = time of maximum concentration; TSH = thyroid stimulating hormone

- a: A full set of vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at screening, predose on Day 1, and at the end-of-the study visit on Day 35. Blood pressure, pulse rate, and pulse oximetry will be measured on Day 1 and Day 7 (times relative to the first dose of the day) at 10 minutes and 1, 4, 8, 12, 16, and 24 hours postdose, daily (predose) on Days 3-6 and 7-9, and at the outpatient visits on Day 10 and 14. At the screening visit, each subject will have blood pressure measured in both arms. If

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there is no significant difference (i.e., greater than 15 mmHg) between the systolic blood pressure in each arm at screening, then at other times the subject may have blood pressure measured in one arm.

- b: Physical examinations will be conducted for all subjects at screening, before the first dose on Day 1, and on Days 2, 4, 7, 9, 14, and 35.
- c: All subjects will have ECGs performed at screening and at the following times on Day 1 and Day 7 (times relative to the first dose of the day): predose, 20 minutes postdose, 2, 4, 8, and 24 hours postdose, Day 9 (prior to check-out), Day 14, and at the end of the study.
- d: Chest x-ray will be performed on Day 35 if clinically indicated as determined by the Investigator.
- e: Pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) using spirometry will be performed at screening, check-in, at 1, 4, 8, and 23 hours after administration of the first and last morning doses (Day 1 and Day 7), at least 1 hour after the first dose on Day 4, on Day 14, and at the end of the study (Day 35). Repeat spirometry will be allowed at the Investigator's discretion.
- f: PPD test to be read 48-72 hours after placement.
- g: Safety labs (chemistry, hematology, coagulation, and urinalysis) will be collected at the following time points: screening, check-in, Day 2, Day 4, Day 7, Day 9, Day 14 and Day 35 (end of study)
- h: To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.
- i: To be performed before the first dose of the day on Day 1 and 5 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.
- j: Optional meals may be provided the day of check-in. Subjects will fast overnight for at least 10-hours before the first dose of each day. After the morning dose on Day 1 and Day 7, no food will be allowed until 4 hours postdose. On other dosing days (Days 2–6), no food will be allowed for at least 1 hour after the morning dose. Subjects will nothing to eat for at least 2 hours before the second dose of each day and for at least 1 hour after the second dose.

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- k: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, and on Day 8, Day 9, Day 10, Day 14, and Day 35 (total of 30 samples). Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.
- l: Urine samples for pharmacokinetic analysis will be collected on Day 1 and Day 7 (times relative to the first dose of the day) predose (spot collection) and for the first 24 hours after dosing.
- m: Subjects will remain in the research center for observation until 48 hours after the last dose (Day 9).
- n: Subjects will return to the clinical research site for a safety evaluation and PK blood draws on Days 10, 14, and 35.
- o: Subjects will be monitored for adverse events from the beginning of confinement until the end-of-study visit.

## **APPENDIX 5     PART B: MAD THREE TIMES DAILY (TID) DOSING**

The Safety Review Committee will review the safety data (including local irritation) and pharmacokinetic data from the SAD protocol (Part A) to determine the starting dose for the first MAD cohort, and if the first cohort of the MAD protocol should be dosed QD (once daily), BID (twice daily; once every 12 hours), or TID (three times daily; 6 hours between each dose).

If the decision is made to start dosing in the MAD protocol at TID, then the Safety Review Committee will review the safety data (including local irritation) and PK data from the first MAD cohort to determine if TID dosing should continue, if dosing should be reduced to BID or QD for the next cohort. Similarly, if the starting dose in the MAD protocol is BID, then the Safety Review Committee will review the safety data (including local irritation) and PK data from the first MAD cohort to determine if BID dosing should continue, or if dosing should be changed to QD or TID for the next cohort.

### **Blood Sampling, Processing and Shipment**

A total of 180 mL (30 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.

In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 353.5 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.

Blood samples collected up to and including 24 hours postdose within  $\pm 2$  minutes of scheduled time will not be considered deviations. Blood samples collected after 24 hours through 48 hours after the last dose within  $\pm 5$  minutes of scheduled time will not be considered deviations. Blood samples collected after 48 hours postdose after the last dose within  $\pm 10$  minutes of scheduled time will not be considered deviations.

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Table 10 Total Amount of Blood to be Collected for Testing in Part B (TID Dosing)

Reason for Collection	Number of Samples	Volume per Sample (mL)	Total Volume (mL)
Clinical labs at screening	1	25	25
Clinical labs during study (check-in, Days 2, 4, 7, 9, and 14)	6	15	90
Clinical labs end-of-study	1	15	15
Platelet aggregation	3	6.5	19.5
Buffy coat samples	3	8	24
Pharmacokinetic analysis	30	6	180
Total			353.5

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**Table 11 Part B Events Schedule (TID Dosing)**

Part B - TID	Study Day(s)																										
	-28 to -1	-1		1															2	3 to 6	7	8	9	10	14	35	
Procedure	Screening	Check-in	Pre-dose	0 h	3/5 min	10 m	20 m	1 h	2 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	20 h	23 h	24 h	36 h							
Informed consent	X																										
Demographics and smoking history	X																										
Medical and medication histories	X																										
Concomitant medication review	X																								X	X	X
Vital signs and pulse oximetry <sup>a</sup>	X		X			X		X	X	X					X	X			X		X	X	X	X	X	X	X
Physical examination <sup>b</sup>	X		X															X		X <sup>b</sup>	X		X		X	X	
12-lead ECG <sup>c</sup>	X		X				X		X	X								X			X	X			X	X	
Chest X-ray	X																							X		X <sup>d</sup>	
Pulmonary function tests <sup>e</sup>	X	X						X			X						X			X	X				X	X	
PPD <sup>f</sup>	X																										
TSH	X																									X	
HIV, hepatitis B and C	X																										

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Part B - TID	Study Day(s)																										
	-28 to -1	-1		1															2		3 to 6	7	8	9	10	14	35
Procedure	Screening	Check-in	Pre-dose	0 h	3/5 min	10 m	20 m	1 h	2 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	20 h	23 h	24 h	36 h							
Fasting lipid panel	X																								X		
Serum chemistry <sup>g</sup>	X	X																	X		X	X		X		X	X
Hematology <sup>g</sup>	X	X																	X		X	X		X		X	X
Urinalysis <sup>g</sup>	X	X																	X		X	X		X		X	X
Coagulation (PT, PTT, INR) <sup>g</sup>	X	X																	X		X	X		X		X	X
Platelet aggregation <sup>h</sup>			X			X																X					
Buffy coat <sup>i</sup>			X			X																X					
FSH (postmenopausal female subjects)	X																										
Pregnancy (females subjects only)	X	X																								X	X
Urine drug/alcohol/cotinine screens	X	X																									
Meals <sup>j</sup>		X			X														X		X	X	X				
Dose inhalation training		X	X																X								
Dose administration				X								X			X				tid		tid	tid					
Blood collection for PK analysis <sup>k</sup>			X		X														X		X	X	X	X	X	X	X

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Part B - TID	Study Day(s)																				
	-28 to -1	-1		1														2	3 to 6	7	8
Procedure	Screening	Check-in	Pre-dose	0 h	3/5 min	10 m	20 m	1 h	2 h	4 h	5 h	6 h	8 h	10 h	12 h	16 h	20 h	23 h	24 h	36 h	
Urine collection for PK analysis <sup>l</sup>			X		X														X		
Confinement <sup>m</sup>		X				X												X	X	X	X
Outpatient visits <sup>n</sup>	X																				X
Adverse event assessment <sup>o</sup>			← X →																		

BUN = blood urea nitrogen; CR = creatinine; ECG = electrocardiogram; FSH = follicle-stimulating hormone; h = hour; HIV = human immunodeficiency virus; INR = international normalized ratio; m = minute; PK = pharmacokinetic; PPD = positive purified protein derivative skin test; PT = prothrombin time; PTT = partial thromboplastin time; T<sub>max</sub> = time of maximum concentration; tid = three doses per day; each dose will be separated by 6 hours; TSH = thyroid stimulating hormone

- A full set of vital signs (blood pressure, pulse rate, respiration rate, temperature, and pulse oximetry) will be measured at screening, predose on Day 1, and at the end-of-the study visit on Day 35. Blood pressure, pulse rate, and pulse oximetry will be measured on Day 1 and Day 7 (times relative to the first dose of the day) at 10 minutes and 1, 4, 8, 12, 16, and 24 hours postdose, daily (predose) on Days 3-6 and 7-9, and at the outpatient visits on Day 10 and 14. At the screening visit, each subject will have blood pressure measured in both arms. If there is no significant difference (i.e., greater than 15 mmHg) between the systolic blood pressure in each arm at screening, then at other times the subject may have blood pressure measured in one arm.
- Physical examinations will be conducted for all subjects at screening, before the first dose on Day 1, and on Days 2, 4, 7, 9, 14, and 35.

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- c) All subjects will have ECGs performed at screening and at the following times on Day 1 and Day 7 (times relative to the first dose of the day): predose, 20 minutes postdose, 2, 4, 8, and 24 hours postdose, Day 9 (prior to check-out), Day 14, and at the end of the study.
- d) Chest x-ray will be performed on Day 35 if clinically indicated as determined by the Investigator.
- e) Pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be performed at screening, check-in, and at 1 hour after the first morning dose on Day 1, Day 4, and Day 7, at least 1 hour before second dose on Day 1 and Day 7, 23 hours after the first morning dose on Day 1 and Day 7, on Day 14 and at the end of the study (Day 35). Repeat spirometry will be allowed at the Investigator's discretion.
- f) PPD test to be read 48-72 hours after placement.
- g) Safety labs (chemistry, hematology, coagulation, and urinalysis) will be collected at the following time points: screening, check-in, Day 2, Day 4, Day 7, Day 9, Day 14 and Day 35 (end of study).
- h) To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.
- i) To be performed before the first dose of the day on Day 1 and 5 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.
- j) Optional meals may be provided the day of check-in. Subjects will fast overnight for at least 10-hours before the first dose of each day. On Day 1 and Day 7, no food will be allowed until 4 hours after the first dose of the day. On other dosing days (Days 2–6), no food will be allowed for at least 1 hour after the first dose of the day. Subjects will fast for at least 1.5 hours before the second and third doses of each day.
- k) Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. An additional blood sample will be collected on Day 2 (12 hours after the 3<sup>rd</sup> dose on Day 1). Blood samples will also be collected before the first dose on Days 2-6, and on Day 8 (6 hours and 12 hours after the 3<sup>rd</sup> dose on Day 7), Day 9, Day 10, Day 14 and Day 35 (total of 30 samples). Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.

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- l) Urine samples for pharmacokinetic analysis will be collected on Day 1 and Day 7 (times relative to the first dose of the day) predose (spot collection) and for the first 24 hours after dosing.
- m) Subjects will remain in the research center for observation until 48 hours after the last dose (Day 9).
- n) Subjects will return to the clinical research site for a safety evaluation and PK blood draws on Days 10, 14, and 35.
- o) Subjects will be monitored for adverse events from the beginning of confinement until the end-of-study visit.

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## APPENDIX 6 SUMMARY OF CHANGES

The purpose of this protocol amendment (protocol version.5.3, dated 31 July 2018) is to make the following revisions to protocol version 5.0 dated 29 Jun 2018:

The primary purposes of this amendment are to:

- Revise the sample collection times for buffy coat and platelet aggregation in Part B of the study
- Clarify that blood samples will be collected for PK analysis on Day 7 (predose) and on Day 9 during Part B of the study
- Add a PK blood sample collection on Day 2 (predose) and Day 8 (12 hours after the third dose on Day 7) of Part 2, TID dosing
- Clarify timing of dose inhalation training on Table 11

This amendment also incorporates the following change from clarification letter 6 dated 12 Jul 2018:

- Clarify the pharmacokinetic sample collection window

The sections of protocol version 5.0 affected by the protocol revisions are noted in the following table.

Section Number	Section Title	Description of Change (s)
3.2	Part B	<p>From:</p> <p>Blood samples for pharmacokinetic evaluation will be obtained before the first dose of the day on Day 1 and at selected times through 36 hours after the first dose on Day 1, before the first dose on Days 3-6, through 36 hours after the first dose on Day 7, and on Day 10, Day 14, and Day 35.</p> <p>For QD dosing, a total of 33 pharmacokinetic blood samples will be collected from each subject in Part B.</p> <p>For BID dosing, a total of 29 pharmacokinetic blood samples will be collected from each subject in Part B.</p> <p>For TID dosing, a total of 27 pharmacokinetic blood samples will be collected from each subject in Part B.</p> <p>To:</p> <p>Blood samples for pharmacokinetic evaluation will be obtained before the first dose of the day on Day 1 <b>and Day 7</b> and at selected times through 36 hours after the first dose on Day 1, before the first dose on Days 3-6, through 36 hours after the first dose on Day 7, and on <b>Day</b></p>

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Section Number	Section Title	Description of Change (s)
		<p><b>9, Day 10, Day 14, and Day 35.</b></p> <p>For QD dosing, a total of <b>34</b> pharmacokinetic blood samples will be collected from each subject in Part B.</p> <p>For BID dosing, a total of <b>30</b> pharmacokinetic blood samples will be collected from each subject in Part B.</p> <p>For TID dosing, a total of <b>30</b> pharmacokinetic blood samples will be collected from each subject in Part B.</p>
5.7	Blood Sampling, Processing and Shipment	<p><i>The following applies to QD dosing, Change from:</i></p> <p>A total of 192 mL (32 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.</p> <p>In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 365.5 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.</p> <p>Blood samples collected up to and including 24 hours postdose within <math>\pm 2</math> minutes of scheduled time will not be considered deviations. Blood samples collected after 24 hours through 48 hours after the last dose within <math>\pm 5</math> minutes of scheduled time will not be considered deviations. Blood samples collected after 48 hours postdose after the last dose within <math>\pm 10</math> minutes of scheduled time will not be considered deviations.</p> <p>To:</p> <p>A total of <b>204 mL (34 x 6 mL samples)</b> will be collected from each subject in Part B for pharmacokinetic analysis.</p> <p>In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately <b>377.5 mL</b>. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.</p> <p>Blood samples collected up to and including 24 hours postdose within <math>\pm 2</math> minutes of scheduled time will not be considered deviations. Blood samples collected after 24 hours through 48 hours after the last dose within <math>\pm 5</math> minutes of scheduled time will not be considered deviations, <b>with the following exception: when blood collection is scheduled for the same time as dose administration (at times other than the first dose administration) samples collected</b></p>

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Section Number	Section Title	Description of Change (s)																
		<b>within -5 minutes of scheduled time will not be considered deviations.</b> Blood samples collected after 48 hours postdose after the last dose within ± 10 minutes of scheduled time will not be considered deviations.																
5.7	Table 5, Total Amount of Blood to be Collected for Testing in Part B (QD)	<div><div>From:</div><table><tr><td>Pharmacokinetic analysis</td><td>32</td><td>6</td><td>192</td></tr><tr><td colspan="3">Total</td><td>365.5</td></tr></table><div>To:</div><table><tr><td>Pharmacokinetic analysis</td><td>34</td><td>6</td><td>204</td></tr><tr><td colspan="3">Total</td><td>377.5</td></tr></table></div>	Pharmacokinetic analysis	32	6	192	Total			365.5	Pharmacokinetic analysis	34	6	204	Total			377.5
Pharmacokinetic analysis	32	6	192															
Total			365.5															
Pharmacokinetic analysis	34	6	204															
Total			377.5															
12	Table 7 Part B Events Schedule (Once Daily [QD] Dosing) <u>Footnotes “h” and “i”</u>	<div>Footnotes “h” and “i”, Change from:</div> <div><div>h: To be performed on Day 1 predose and 10 minutes postdose (or Tmax, based on analysis from previous cohort) and on Day 7 at 10 minutes postdose (or Tmax, based on analysis from previous cohort).</div><div>i: To be performed on Day 1 predose and 10 minutes postdose (or Tmax, based on analysis from previous cohort) and on Day 7 at 10 minutes postdose (or Tmax, based on analysis from previous cohort).</div><div>To:</div><div><div>h: To be performed on Day 1 predose and <b>5 minutes</b> postdose (or Tmax, based on analysis from previous cohort); and on Day 7 at 10 minutes postdose (or Tmax, based on analysis from previous cohort).</div><div>To be performed on Day 1 predose and <b>5 minutes</b> postdose (or Tmax, based on analysis from previous cohort) and on Day 7 at <b>5 minutes</b> postdose (or Tmax, based on analysis from previous cohort).</div></div></div>																

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Section Number	Section Title	Description of Change (s)
12	Table 7 Part B Events Schedule (Once Daily [QD] Dosing)	<p><i>Footnote “j”, change from:</i></p> <p>Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose on Day 1) and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on Day 10, Day 14, and Day 35. For multi-dose administrations, the 1-minute blood collection will be performed after dosing procedures are complete. Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.</p> <p><i>To:</i></p> <p>Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 <b>and Day 7</b>, and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on <b>Day 8, Day 9</b>, Day 10, Day 14, and Day 35 (<b>total of 34 samples</b>). For multi-dose administrations, the <b>3-minute</b> blood collection will be performed after dosing procedures are complete. Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.</p>
Appendix 1	Pharmacokinetic Blood Sample Collection, Processing, And Shipment Instructions	<p><i>Part B, Row 2B, change from:</i></p> <p>If QD dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose on Day 1) and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on Day 10, Day 14, and Day 35 (total 32 samples).</p> <p>For multi-capsule administrations (if required to achieve the dose), the 3-minute blood collection will be performed after inhalation procedures for a given dose are complete.</p> <p>If BID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, Day 10, Day 14, and Day 35 (total of 29 samples).</p> <p>If TID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and</p>

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		<p>Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. Blood samples will also be collected before the first dose on Days 3-6, and on Day 10, Day 14 and Day 35 (total of 27 samples).</p> <p><i>To:</i></p> <p>If QD dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose on Day 1 <b>and Day 7</b>) and at the following times: Day 1 and Day 7 at 3, 10, 20, 30, and 40 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after dosing; predose on Days 3-6, and on <b>Day 9</b>, Day 10, Day 14, and Day 35 (total <b>34 samples</b>).</p> <p>If BID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, <b>and on Day 8, Day 9</b>, Day 10, Day 14, and Day 35 (total of <b>30 samples</b>).</p> <p>If TID dosing: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. <b>An additional sample will be obtained on Day 2 (12 hours after the 3<sup>rd</sup> dose on Day 1).</b> Blood samples will also be collected before the first dose on <b>Days 2-6</b>, and on <b>Day 8 (6 hours and 12 hours after the 3<sup>rd</sup> dose on Day 7)</b>, Day 9, Day 10, Day 14 and Day 35 (total of <b>30 samples</b>).</p> <p><b>For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.</b></p>
Appendix 1	Part B Sample Collection Summary	<p><i>Change the number of time points per period from 32 to 34 if QD.</i></p> <p><i>Change the number of time points per period from 29 to 30 if BID.</i></p> <p><i>Change number of time points per period from 27 to 30 if TID.</i></p>
Appendix 4	Part B: MAD Twice Daily (BID) Dosing	<p><b>Blood Sample Processing and Shipment, Change from:</b></p> <p>A total of 174 mL (29 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.</p> <p>In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 347.5 mL. Additional blood</p>

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Section Number	Section Title	Description of Change (s)																
		may be collected if necessary for repeat laboratory evaluations or AE follow up. <b>To:</b> A total of <b>180 mL (30 x 6 mL samples)</b> will be collected from each subject in Part B for pharmacokinetic analysis.  In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately <b>353.5 mL</b> . Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.																
Appendix 4	Part B: MAD Twice Daily (BID) Dosing	<i>Total Amount of Blood to be Collected for Testing in Part B (BID Dosing), change from:</i> <table><tr><td>Pharmacokinetic analysis</td><td>29</td><td>6</td><td>174</td></tr><tr><td colspan="3">Total</td><td>347.5</td></tr></table> <b>To:</b> <table><tr><td>Pharmacokinetic analysis</td><td><b>30</b></td><td>6</td><td><b>180</b></td></tr><tr><td colspan="3">Total</td><td><b>353.5</b></td></tr></table>	Pharmacokinetic analysis	29	6	174	Total			347.5	Pharmacokinetic analysis	<b>30</b>	6	<b>180</b>	Total			<b>353.5</b>
Pharmacokinetic analysis	29	6	174															
Total			347.5															
Pharmacokinetic analysis	<b>30</b>	6	<b>180</b>															
Total			<b>353.5</b>															
Appendix 4	Part B Events Schedule (BID)	<b>Footnotes “h”, “I”, and “k”, change from:</b>  h: To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.  i: To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.  <b>k:</b> Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, Day 10, Day 14, and Day 35 (total of 29 samples). Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.  <b>To:</b>  h: To be performed before the first dose of the day on Day 1 and <b>5</b>																

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		<p><b>minutes</b> after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1; <b>and 5 minutes after the first dose on Day 7.</b></p> <p>i: To be performed before the first dose of the day on Day 1 and <b>5 minutes</b> after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.</p> <p><b>k:</b> Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7 and at the following times after each dose (2 per day) on Day 1 and Day 7: 3 and 30 minutes and 2, 8, and 12 hours. Blood samples will also be collected before the first dose on Days 3-6, <b>and on Day 8, Day 9, Day 10, Day 14, and Day 35 (total of 30 samples).</b> Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration</p>
Appendix 5	Part B: MAD Three Times Daily (TID) Dosing	<p><i>Blood Sampling, Processing, and Shipment, change from:</i></p> <p>A total of 162 mL (27 x 6 mL samples) will be collected from each subject in Part B for pharmacokinetic analysis.</p> <p>In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately 335.5 mL. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.</p> <p><i>To:</i></p> <p>A total of <b>180 mL (30 x 6 mL samples)</b> will be collected from each subject in Part B for pharmacokinetic analysis.</p> <p>In addition, approximately 173.5 mL of blood will be collected for laboratory evaluations. The total volume of blood collected from each subject will not exceed approximately <b>353.5 mL</b>. Additional blood may be collected if necessary for repeat laboratory evaluations or AE follow up.</p>

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Section Number	Section Title	Description of Change (s)			
Appendix 5	Part B: MAD Three Times Daily (TID) Dosing	Total Amount of Blood to be Collected for Testing in Part B (TID Dosing), change from:			
		Pharmacokinetic analysis	27	6	162
		Total			335.5
		To:			
		Pharmacokinetic analysis	30	6	180
Total			353.5		
Appendix 5	Part B: MAD Three Times Daily (TID) Dosing	Table 11, Dose Inhalation Training			
		Place “X” under 24 hours			
		Footnotes “h”, “I”, and “k”, change from:			
		h: To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.			
		i: To be performed before the first dose of the day on Day 1 and 10 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.			
		k: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. Blood samples will also be collected before the first dose on Days 3-6, and on Day 10, Day 14 and Day 35 (total of 27 samples). Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.			
		To:			
		h: To be performed before the first dose of the day on Day 1 and 5 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1; and 5 minutes after the first dose on Day 7.			
		i: To be performed before the first dose of the day on Day 1 and 5 minutes after the first dose of the day (or Tmax, based on analysis from previous cohort) on Day 1 and Day 7.			
		k: Blood samples for pharmacokinetic evaluation will be obtained prior to the first dose administration (predose) on Day 1 and Day 7, and at the following times after each dose (3 per day) on Day 1 and Day 7: 3 and 40 minutes and 6 hours. An additional sample			

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		<b>will be obtained on Day 2 (12 hours after the 3<sup>rd</sup> dose on Day 1).</b> Blood samples will also be collected before the first dose on <b>Days 2-6</b> , and on <b>Day 8 (6 hours and 12 hours after the 3<sup>rd</sup> dose on Day 7), Day 9, Day 10, Day 14 and Day 35 (total of 30 samples).</b> Exception: For multi-capsule administrations (if required to achieve the dose), the first postdose blood collection will be performed 5 minutes after the start of study treatment administration.