STATISTICAL ANALYSIS PLAN

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 1.0

DATE: 16 Aug 2018

NCT NUMBER: NCT03473236

Statistical Analysis Plan

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 1.0

Issue Date: 16 August-2018

Author: Gillian Green, BSc, MSc

Kathryn Roupe, Ph.D.

Previous Versions

Not Applicable

Biostatistical Operations: SAP and/or TFL Shell Approval

Study name: 4004002

Sponsor: Gossamer Bio Inc

SAP Version being approved: PK10571 SAP V1.0

TFL Shell version being approved: (PK 10571 Listing Shells V1.0/PK10571 v1.0 Table Shells V1.0)

The SAP / TFL Shells identified above have been reviewed and approved by:

Author: [redacted]

Position: Statistician

Author's signature: DocuSigned by: [redacted]

WCT reviewer: [redacted]

Position: [redacted]

Reviewer's signature: DocuSigned by: [redacted] **Date:**

WCT reviewer: [redacted]

Position: Principal Statistician

Reviewer's signature: DocuSigned by: [redacted]

The SAP and TFL shells above has been reviewed and approved by the sponsor:

Name of Approver: [redacted]

Position: Senior Director

Author's signature: DocuSigned by: [redacted]

Name of Approver: [redacted]

Position: Senior Director Biostatistics

Reviewer's signature: DocuSigned by: [redacted]

DocuSign SECURED

Certificate Of Completion

Envelope Id: EEFEF1BAA5A14B2D943DD7DE45B0F909
Subject: Please DocuSign: PK10571_TFL_Approval.doc
Source Envelope:
Document Pages: 2
Certificate Pages: 6
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Signatures: 5
Initials: 0

Status: Completed

Envelope Originator:
[redacted]
3800 Paramount Parkway
Suite 400
Morrisville, NC 27560
[redacted]
[redacted]

Record Tracking

Status: Original
16-Aug-2018 | 16:23:30

Holder: [redacted]
[redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] [redacted] Statistician Worldwide Clinical Trials Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 7DF9CE89-266B-41ED-B88E-4F56BB2A9EB1 [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 16-Aug-2018 | 16:25:11 Viewed: 16-Aug-2018 | 16:25:45 Signed: 16-Aug-2018 | 16:26:34
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Principal Statistician Worldwide Clinical Trials Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: EC063864-7B26-426C-8091-53E5DD89E0D7 [redacted] Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 17-Aug-2018 | 14:08:17 Viewed: 17-Aug-2018 | 14:10:07 Signed: 17-Aug-2018 | 14:10:51
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 6AD53DA3-636B-483C-9AA0-59A6EB458A6C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Aug-2018 | 14:08:17 Viewed: 17-Aug-2018 | 17:58:00 Signed: 17-Aug-2018 | 17:59:26
Electronic Record and Signature Disclosure: Accepted: 17-Aug-2018 | 17:58:00 ID: 824de041-5c37-4f86-b39c-23cc520cc681		
[redacted] [redacted] Pharmacokineticist, Principal Research Scientist Worldwide Clinical Trials Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: A2103069-EADE-42BA-87CC-9685DDF4E5A1 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 16-Aug-2018 | 16:26:34 Resent: 17-Aug-2018 | 14:07:45 Viewed: 17-Aug-2018 | 15:41:17 Signed: 17-Aug-2018 | 15:42:09
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 30399B56-D45C-409C-8032-AFF795FFB819 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Aug-2018 | 14:08:17 Viewed: 22-Aug-2018 | 00:41:41 Signed: 22-Aug-2018 | 00:42:49
Electronic Record and Signature Disclosure: Accepted: 27-Jun-2018 | 05:45:39 ID: c02e1bb7-17fa-4c1b-9eb2-3be37bade041		

In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17-Aug-2018 | 14:08:17
Certified Delivered	Security Checked	22-Aug-2018 | 00:41:41
Signing Complete	Security Checked	22-Aug-2018 | 00:42:49
Completed	Security Checked	22-Aug-2018 | 00:42:49

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

From time to time, Worldwide Clinical Trials (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign, Inc. (DocuSign) electronic signing system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies
At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after signing. If you wish for us to send you paper copies of any such documents from our office to you, you should contact the originator of the document.

Withdrawing your consent
If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind
If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of a DocuSign envelope instead of signing it. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically
Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures

electronically from us.

How to contact Worldwide Clinical Trials
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows.

To advise Worldwide Clinical Trials of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to the originator of your document and in the body of such request you must state: your previous e-mail address and your new e-mail address.
In addition, you must notify DocuSign, Inc. to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in the DocuSign system.

To request paper copies from Worldwide Clinical Trials
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send an e-mail to the originator of the document and in the body of such request you must state your e-mail address, full name, postal address, and telephone number.

To withdraw your consent with Worldwide Clinical Trials
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

1. decline to sign a document from within your DocuSign session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
2. send an e-mail to the originator of your document and in the body of such request you must state your e-mail, full name, postal address, and telephone number.

Required hardware and software

Operating Systems	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution	800 x 600 minimum
Enabled Security Settings	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically
To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I agree' box, I confirm that:

- **I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC CONSUMER DISCLOSURES document; and**
- **I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and**
- **My electronic signature is the legally binding equivalent of my handwritten signature; and**
- **Until or unless I notify Worldwide Clinical Trials as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by Worldwide Clinical Trials during the course of my relationship with you.**

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale

Table of Contents

1. INTRODUCTION

This document details the planned statistical analyses for the Gossamer Bio Inc., protocol "*4004002*" study titled "A Phase 1A Single Ascending Dose and Multiple Ascending Dose Double-Blind, Placebo-Controlled, Randomized Trial of Oral Inhalation PK10571 in Healthy Adult Subjects".

The proposed analyses are based on the contents of the final version of the protocol (dated 29-June-2018, version 5.0).

This project has two parts

Part A (SAD)

Subjects will receive either PK10571 starting dose of [redacted] fine particle dose (FPD), PK10571 dose of [redacted] FPD, PK10571 dose of [redacted] FPD, PK10571 dose of [redacted] FPD, or placebo. An optional fifth cohort of up to [redacted] FPD may be added. Part A will enroll up to 40 subjects; 8 subjects per cohort in a parallel design. 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.

Subjects will receive one of the treatments listed in Table 1 in randomized fashion.

Table 1 Part A: Planned Doses for Cohorts 1, to 5

Cohort	Test Formulation Dose	Placebo
1 -	PK10571 [redacted] FPD (n= 6)	Placebo (n=2)
2 -	PK10571 [redacted] FPD (n=6)	Placebo (n=2)
3 -	PK10571 [redacted] FPD (n=6)	Placebo (n=2)
4-	PK10571 [redacted] FPD (n=6)	Placebo (n=2)
5-	PK10571 up to [redacted] FPD (n=6)	Placebo (n=2)
FPD = fine particle dose; n = number of subjects Note: Cohort 5 is optional		

Part B (MAD)

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 up to 3 cohorts of 8 subjects each in a parallel design.

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 initial dose for Part B will be determined after review of the safety and pharmacokinetic data from Part A.

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

Subjects will receive one of the treatments listed below in randomized fashion.

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

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

n = number of subjects
Note: Each subject will receive a dosing according to the assigned treatment 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.

2. STUDY 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 [redacted] 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 [redacted] in healthy adult subjects (Part B)
- To evaluate the bioavailability of PK10571 following single- and multiple-dose regimens

- [redacted]

3. ENDPOINTS

3.1. Primary Endpoint

The safety endpoints are the incidence of treatment-emergent events (TEAEs), physical examination findings, and changes in vital signs, pulmonary function and electrocardiogram (ECG) measurements.

Pharmacokinetic (PK) endpoints are the summary of the pharmacokinetic parameters (e.g. C_{max}, AUC_{last}, and AUC_{inf}) for PK10571 across treatments, dose-linearity assessment and steady state assessment (after multiple dosing) [redacted]

4. SAMPLE SIZE

Forty subjects will be dosed in Part A of this study.

Twenty-four 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.

5. RANDOMIZATION

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.

For both the SAD and MAD parts 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.

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.

6. PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1. Analysis Population

The populations for Part A and Part B will be tabulated both separately and overall.

6.1.1. Safety Population

The Safety Population is defined as all subjects who received any study drug.

6.1.2. PK Population

The PK population is defined as all subjects who received active study drug and have at least one quantifiable postdose concentration.

6.2. Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1. Age

Age at date of first dose will be calculated in SAS. To ensure age is correctly derived across all timepoints including leap days the following logic is to be used.

```
age = floor ((intck('month', birthdate,date) - (day(date) < day(birthdate))) / 12);
```

Note: Date = Date of first dose of study drug.
This logic will calculate the age in years relative to date of Birth and date of first dose of study drug.

6.2.2. Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.3. Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug in both Part A and Part B.

6.2.4. Early Terminations Assessments

End-of-study (EoS) procedures will be performed on Day 11 of Part A and on Day 35 of Part B. Early Termination (ET) will be included with (EoS) tabulations.

6.2.5. Duration/Study Day/Time

Study day will be calculated as the number of days from first dose of study drug for both Part A and Part B.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose.

6.2.6. Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates; however, in the rare case that an adverse event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not, then a conservative approach will be taken, and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the eCRF.

6.2.7. Exposure to Study Drug

Exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

6.2.8. Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.9. Unscheduled Visits

Only scheduled values will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.10. Concentration-Time Data

PART A:

Blood samples for pharmacokinetic analysis of PK10571 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 as specified by the protocol amendment. For [redacted], two blood samples were collected at 1 and 5 minutes, instead of one blood sample at 3 minutes, prior to the protocol amendment. For [redacted] and above, the 3-minute sample was collected after the protocol amendment.

PART 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 3rd 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 3rd 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.

For summarization of the concentration-time data, concentrations below the limit of quantitation (BLQ) will be set to zero. Mean concentration-time profiles will be created for SAD (all cohorts), SAD male vs. female (all cohorts), MAD (all cohorts), MAD male vs. female (all cohorts), and MAD (Day 1 vs. Day 7) for each cohort. Mean concentration-time profiles will be created using nominal time. All subject concentration-time plots (all subjects in one plot for each cohort, SAD and MAD) will be created using actual time. Individual subject plots (one subject per plot) will be created for MAD (Day 1 vs. Day 7) using actual time.

For time points occurring before 1.00 hour, nominal time will be presented to 3 significant figures (i.e.: 0.0167, 0.050, 0.083, 0.167, 0.333, 0.500, and 0.667 hours postdose). After 0.667 h, time will be presented as 2 decimal places (i.e.: 1.00, 2.00, 4.00, 8.00, 12.00, 24.00, 36.00, and 48.00 hours postdose).

6.2.11. PK Parameters

Concentration-time data for PK10571 will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3 or higher, Certara, L.P.)[1].

During the pharmacokinetic analysis, concentrations that were BLQ up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing". Actual sample times will be used in the pharmacokinetic analysis.

The following PK parameters will be calculated for PK10571 for single ascending dose (SAD, Part A):

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data, reported to 3 significant figures C_{max} will be presented with and without weight-adjustment. Weight adjustment will be calculated as C_{max} x body weight in kg/70.
T_{max}	Time of the maximum plasma concentrations, reported to 2 decimal places
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data, reported to 3 significant figures

Parameter	Definition
T_{last}	Time of last quantifiable plasma concentration, reported to 3 significant figures
AUC_{0-24}	Area under the plasma concentration-time curve from time-zero to 24 hours postdose, reported to 3 significant figures AUC_{0-24} will be presented with and without weight-adjustment. Weight adjustment will be calculated as AUC_{0-24} x body weight in kg/70.
AUC_{last}	Area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration (C_{last}), as calculated by the linear trapezoidal method, reported to 3 significant figures AUC_{last} will be presented with and without weight-adjustment. Weight adjustment will be calculated as AUC_{last} x body weight in kg/70.
AUC_{inf}	Area under the plasma concentration-time curve from the time of dosing extrapolated to infinity, reported to 3 significant figures and calculated as: $AUC_{0-inf} = AUC_{0-last} + C_{last}/\lambda z$, where λz is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve AUC_{inf} will be presented with and without weight-adjustment. Weight adjustment will be calculated as AUC_{inf} x body weight in kg/70.
λ_z (K_{el}, Lambda z)	Apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve, reported to 3 significant figures
$T_{½}$	The observed terminal elimination half-life, reported to 3 significant figures and calculated as: $T_{½} = \ln(2)/\lambda_z$
CL/F	The apparent total plasma clearance after an inhaled dose, reported to 3 significant figures and calculated as:

Parameter	Definition
	$CL/F=Dose/AUC_{0\text{-}inf}$, where F is the bioavailability CL/F will be presented with and without weight-adjustment. Weight adjustment will be calculated as CL/F x 70/body weight in kg.
V_z/F	The apparent volume of distribution after an inhaled dose, reported to 3 significant figures and calculated as: $V_z/F=Dose/(AUC_{inf} \times \lambda_z)$, where F is the bioavailability Vz/F will be presented with and without weight-adjustment. Weight adjustment will be calculated as Vz/F x 70/body weight in kg.

The following PK parameters will be calculated for PK10571 for multiple ascending dose on Days 1 and 7, unless specified otherwise (MAD, Part B):

Parameter	Definition
C_{max}	Maximum plasma concentration, determined directly from individual concentration-time data, presented to 3 significant figures C_{max} will be presented with and without weight-adjustment. Weight adjustment will be calculated as C_{max} x body weight in kg/70.
T_{max}	Time of the maximum plasma concentrations, presented to 3 significant figures
C_{last}	Last quantifiable plasma concentration determined directly from individual concentration-time data, presented to 3 significant figures
T_{last}	Time of last quantifiable plasma concentration, presented to 3 significant figures
$AUC_{0\text{-}24}$	Area under the plasma concentration-time curve for time zero to 24 hours postdose, presented to 3 significant figures

Parameter	Definition
	AUC_{0-24} will be presented with and without weight-adjustment. Weight adjustment will be calculated as AUC_{0-24} x body weight in kg/70.
Cavg,ss	Average concentration at steady state, calculated as AUC_{0-24}/24 h (Day 7 only), presented to 3 significant figures
CLss/F	Apparent clearance at steady state (Day 7 only), presented to 3 significant figures and calculated as: CLss/F=Total daily dose/AUC_{0-24}, where F is the bioavailability. CLss/F will be presented with and without weight-adjustment. Weight adjustment will be calculated as CLss/F x 70/body weight in kg.
V_z/F	Apparent volume of distribution in the terminal phase (Day 7 only), presented to 3 significant figures Vz/F will be presented with and without weight-adjustment. Weight adjustment will be calculated as Vz/F x 70/body weight in kg.
Rac	Accumulation ratio during multiple dosing; presented to 3 significant figures and calculated as: RAC=AUC_{0-24} Day 7/AUC_{0-24} Day 1
λ_z (K_{el} , Lambda z)	Apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve (Day 7 only), presented to 3 significant figures
$T_{½}$	The observed terminal elimination half-life, presented to 3 significant figures and calculated as: $T_{½} = \ln(2)/\lambda_z$ (Day 7 only)

No value for λ_z and other λ_z-related parameters (AUC_{inf}, $T_{1/2}$, etc.) will be reported if λ_z cannot be estimated.

PK concentration data will be summarized by study part, treatment, and day (for MAD study part) at each nominal sample time. PK parameter data will be summarized by study part, treatment, and day (for MAD study part). PK parameter data will also be stratified by sex and for males and females combined. PK parameter tables will include columns for baseline BMI, FEV1, and FVC.

6.3. Conventions

All clinical summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[2].

Summaries of the clinical data will be presented by treatment group. In addition, disposition, demographic, and baseline summaries will include an overall column that consists of all subjects.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 6.3 or higher) or SAS (Version 9.4 or higher).

Treatment group labels will be displayed as follows:

Cohort	Test Formulation
1	Placebo
	PK10571 [redacted] FPD
2	Placebo
	PK10571 [redacted] FPD
3	Placebo
	PK10571 [redacted] FPD
4	Placebo
	PK10571 [redacted] FPD
5	Placebo
	PK10571 up to [redacted] FPD
FPD = fine particle dose; Placebos will be grouped within summary tables	

Cohort	Test Formulation
1	Placebo
	PK10571 initial dose
2	Placebo
	PK10571 mid dose*
3	Placebo
	PK10571 high dose*

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. Placebos will be grouped together within summary tables.

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

The initial (lower) dose for Part B will be determined after review of the safety and pharmacokinetic data from Part A.

The data from the lower dose cohort will be analyzed before deciding whether to proceed with the higher dose cohorts.

Listings will be sorted in the following order: treatment, subject, parameter, and visit unless otherwise stated. All data will be listed.

For clinical data, continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

PK data (concentration-time data and PK parameters) will be summarized by (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%). In addition, the geometric mean and geometric CV% will be reported for all PK parameters except T_{max}. T_{max} will be presented as median, minimum, and maximum.

Baseline values for FEV1, FVC, and BMI, defined as the values obtained prior to and closest in time to the first dose, will also be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%).

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless

otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1. Decimal Places

Decimal places for derived data described in section 6.2.10 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer (for example, day, month, year and number of days) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

For PK data, individual concentrations will be reported to 3 significant figures and individual PK parameters will be reported to the precision as stated in Section 6.2.10. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, and geometric mean will be reported to the same precision as for individual data. CV% and geometric CV% will be reported to 2 decimal places; p-values will be reported to 4 decimal places. Percent ratios of the geometric least squares means and associated 95% confidence intervals will be reported to 2 decimal places.

6.4. Subject Disposition

Subject disposition will be summarized as follows for each part:

- The number of subjects who were consented, who were randomized, and who are in each analysis population will be summarized by treatment group and overall. The number of early termination and the reasons for terminations will be tabulated by treatment group and overall.

6.5. Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2.

6.6. Baseline Comparability

The comparability of treatment with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by treatment for the following variables based on the Safety Population.

6.7. Demography

Demography will be tabulated by treatment and overall for each part.

- Age at time of first dose
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Native Hawaiian or Other Pacific Islander
  - Multiple
- Height (cm)
- Body weight (kg)
- BMI (kg/m^2)

Where multiple races have been selected these will be summarized as multiple on the Demographic table, but each race will be listed individually. Social history will be listed.

The following baseline social history summary will also be presented by treatment and overall. Listings will also be provided.

- Tobacco Use frequency (never, former, current).
- Alcohol Use frequency (never, former, current).

6.8. Medical History

Separate listings of previous and ongoing conditions at screening will be presented for the Safety Population. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term.

6.9. Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Population. Prior medications are defined as all medications starting before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug and will be coded using the WHODrug dictionary.

6.10. Exposure to Study Drug

For Part B, extent of exposure (number of days of exposure to study drug) will be presented by treatment for the Safety Population. All dosing information will be listed.

6.11. Pharmacokinetic and Statistical Analyses

Pharmacokinetic analyses are outlined below. Other exploratory analyses may be conducted as well.

Statistical Comparison: Single Dose (Day 1, Reference) and Multiple Dosing (Day 7, Test): Part B

Comparison of the log-transformed pharmacokinetic parameters C_{max} and AUC_{0-24} for PK10571 across study days (Day 7 vs. Day 1) will be performed using an ANOVA model and the two one-sided t-tests procedure. The ANOVA model will include factors for subject, day, and cohort. The ratios of the geometric means and 95% confidence intervals will be reported. Statistical analyses will be performed using appropriate software, e.g., Phoenix™ WinNonlin® (Version 6.3 or higher, Certara L.P.) and/or SAS® (Version 9.3 or higher, SAS Institute Inc.).

SAS code will be of the form:

[redacted]

Assessment of Dose-proportionality: Power Model

The relationship between dose and exposure parameters will be examined graphically for Part A (C_{max}, AUC_{last}, AUC_{0-24}, and AUC_{inf}) and Part B (C_{max} and AUC_{0-24}, Days 1 and Day 7).

Evaluation of dose proportionality will be explored using power analysis.

To assess dose proportionality, the pharmacokinetic parameters after drug administration will be compared across each dose level.

Statistical analyses will be done using a power model with mixed effects (Smith, 2000)[3] of the following general form:

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon,$$

where

PK is the pharmacokinetic parameter tested (e.g., C_{max} or AUC),

$\ln(\beta_0)$ is the y-intercept,

β_1 is the slope (a value of $\beta 1 \approx 1$ indicates linearity), and

ε is an error term.

The estimate of slope, $\beta 1$ will be reported along with the corresponding 2-sided 95% CIs. As this is an exploratory analysis, if the 95% CI of β_1 includes 1 and/or the estimate of β_1 is relatively close to 1, PK data may appear to be dose proportional.

The SAS code will be of the form:

[redacted]

The Attainment of Steady-State:

The attainment of steady-state will be assessed by visual inspection of trough concentrations, and statistical assessment. For statistical assessment, linear regression of the individual trough concentrations on Days 3-7 vs time will be conducted, and the slope, 95% CI of the slope, and p-value will be estimated. If the 95% CI of the slope includes 0 and/or the estimate of slope is relatively close to 0, steady-state may appear to be reached.

Exploratory Analyses: Scatterplots

To assess relationships between PK10571 PK parameters and baseline characteristics, scatterplots will be created as outlined below.

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug in both Part A and Part B.

Scatterplots for Part A (SAD) (y-axis vs x-axis)

- C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs baseline FVC.
- C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs baseline FEV1.
- C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs. body size (baseline body weight and BMI).
- C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs gender. C_{max} and AUC values will be presented with and without weight-adjustment.
- CL/F and V_z/F vs baseline FVC.
- CL/F and V_z/F vs baseline FEV1.
- CL/F and V_z/F vs. body size (baseline body weight and BMI).
- CL/F and V_z/F (with and without weight-adjustment) vs gender.

Scatterplots for Part B (MAD):

- C_{max}, AUC_{0-24}, and $T_{½}$ vs baseline FVC.
- C_{max}, AUC_{0-24}, and $T_{½}$ vs baseline FEV1.
- C_{max}, AUC_{0-24}, and $T_{½}$ vs body size (baseline body weight and BMI).
- C_{max}, AUC_{0-24}, and $T_{½}$ vs gender. C_{max} and AUC values will be presented with and without weight-adjustment.
- CLss/F and V_z/F vs baseline FVC.
- CLss/F and V_z/F vs baseline FEV1.
- CLss/F and V_z/F vs body size (baseline body weight and BMI).
- CLss/F and V_z/F (with and without weight-adjustment) vs gender.

For all the scatterplots, different symbols will be used for different dose cohorts. For MAD, $T_{½}$, CLss/F, and V_z/F values are for Day 7 only.

For C_{max} and AUC: weight-adjusted PK parameter = PK parameter × body weight in kg/70.

For CL and V: weight-adjusted PK parameter = PK parameter × 70/body weight in kg.

6.12. Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

6.12.1. Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug and before EoS/ET visit.
- Any pre-existing condition that has worsened in severity on or after the first dose of study drug and before the EoS/ET visit.

A treatment-related AE is defined as an AE as being related or possibly related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

The following tables will be presented for AEs:

- Overall incidence of TEAEs, severe TEAEs, treatment-related TEAEs, SAEs, and TEAEs leading to early termination.
- Incidence of TEAEs by system organ class and preferred term
- Incidence of treatment-related TEAE by system organ class and preferred term,
- Incidence of Serious TEAEs by system organ class and preferred term
- Incidence of TEAEs by maximum severity and system organ class and preferred term
- Incidence of treatment-related TEAEs by maximum severity and system organ class and preferred term
- Incidence of TEAEs by relationship to study drug and system organ class and preferred term
- Incidence of TEAEs by system organ class and preferred term, combining all placebo subjects in a single treatment group and all drug-treated subjects in a single treatment group, for SAD, MAD, and both SAD and MAD combined
- Listing of TEAEs leading to early termination
- Listing of Serious TEAEs (presented in the Table section of the appendices)

- Listing of Deaths (presented in the Table section of the appendices)

System organ class will be presented in descending order of overall frequency and then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within system organ class.

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and/or most related occurrence for tabulations by severity and by relationship to the study drug.

All AEs will be listed.

6.12.2. Laboratory Data

For Part A and Part B, the following analysis will be undertaken separately. Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment and visit for each hematology (including coagulation), urinalysis, and serum chemistry (including fasting lipid panel and fasting glucose) parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

All laboratory data, will be listed for example:

- Serology testing: hepatitis B, hepatitis C, and HIV
- Urine drug, alcohol, and cotinine screen tests.
- Serum pregnancy tests (all female subjects)
- FSH tests (female subjects claiming post-menopausal status)

6.12.3. Vital Signs

For Part A and Part B, the following will be presented separately. Descriptive statistics for observed values and changes from baseline to post dose assessments in the following vital signs will be presented by treatment at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Pulse oximetry (%)

All vital sign data will be listed.

6.12.4. Pulmonary Function Test

For Part A and Part B, the following will be presented separately. Descriptive statistics for observed values and changes from baseline to post dose assessments in the following pulmonary function tests (FEV1 and FVC; best of 3 reproducible maneuvers) will be tabulated by treatment. All pulmonary function test data will be listed.

The details of exploratory analysis are shown in Section 6.11. All statistical output will be listed and figures produced for the scatter plots.

6.12.5. Electrocardiogram Data

For Part A and Part B, the following will be presented separately. Descriptive statistics for observed values and changes from baseline to post dose assessments in the following ECG quantitative variables will be tabulated by treatment at each visit:

- Heart rate (bpm)
- PR interval (msec)
- RR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTc interval (msec)
- QTc interval (msec) [Bazett's formula - QTcB]
- QTc interval (msec) [Fridericia's formula - QTcF]

- Note: Bazett's formula is QTcB=QT/$\sqrt{(RR)}$, Fredericia's formula is QTcF=QT/$\sqrt[3]{(RR)}$

Shift tables in relation to the overall interpretation (Normal, Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) from baseline to each follow-up visit will be presented.

All ECG data, including details of any abnormalities, will be listed.

6.12.6. Physical Examination

For Part A and Part B, all data, including details of clinically significant findings, will be listed.

6.12.7. Other Safety Analysis

For Part A and Part B, chest X-ray details will be listed only. Purified protein derivative (PPD) skin test and thyroid-stimulating hormone (TSH) tests will be listed only with serology testing.

If available buffy coat will be tabulated by treatment and listed, including change from baseline.

7. SAFETY REVIEW COMMITTEE

The bioanalytical laboratory and pharmacokineticist will be unblinded to allow for analysis and presentation for the assessment by the safety review committee between cohorts. The data presented to the safety review committee will not contain subject-level identifiers in order to maintain the blind of the participants of the safety review unless there is a study emergency. Only the bioanalytical lab and pharmacokineticist will be unblinded for data preparation.

Interim pharmacokinetic analysis will include:

Blinded Concentration vs. Time Table (summary statistics) stratified by Cohort (SAD) and Cohort and Day (MAD)

Mean Concentration vs. Time Profile comparing doses (SAD and MAD) and Days 1 and 7 (MAD)

Mean concentration vs. Time profiles comparing Gender within each Cohort

Blinded PK parameters (summary statistics) stratified by Cohort (SAD) and Cohort and Day (MAD).

Blinded PK parameters (summary statistics) stratified by Cohort and Gender (SAD) and Cohort, Day, and Gender (MAD).

Scatterplots for Part A (SAD):

C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs. baseline FVC

C_{max}, AUC_{0-24}, AUC_{last}, AUC_{inf}, and $T_{½}$ vs. baseline FEV1

Scatterplots for Part B (MAD):

C_{max}, AUC_{0-24}, and $T_{½}$ vs. baseline FVC

C_{max}, AUC_{0-24}, and $T_{½}$ vs. baseline FEV1

8. CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes planned to protocol analysis.

9. REFERENCES

1. Phoenix™ WinNonlin® (Version 6.3, Certara L.P.)
2. SAS Institute Inc. The SAS System, Version 9.4. Cary, NC, SAS Institute Inc.
3. Smith et. al. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality, Pharmaceutical Research Vol. 17, No. 10, 2000

APPENDIX 1 : LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Note: Table, Figure, and Listing numbers/titles are subject to change after final analysis.

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1a	Subject Disposition, (SAD) – Randomized Subjects	IP	
14.1.1.1b	Subject Disposition, (MAD) – Randomized Subjects	IP	
14.1.2	**Demographics**		
14.1.2.1a	Demographics (SAD) - Safety Population	IP	
14.1.2.1b	Demographics (MAD) - Safety Population	IP	
14.1.3	**Baseline Characteristics**		
14.2	**Efficacy Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1a	Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (SAD) – Safety Population	IP	
14.3.1.1b	Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (MAD) – Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.2a	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (SAD) – Safety Population	IP	
14.3.1.2b	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (MAD) – Safety Population	IP	
14.3.1.3a	Adverse Events, Treatment Related, Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (SAD) – Safety Population	IP	
14.3.1.3b	Adverse Events, Treatment Related, Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (MAD) – Safety Population	IP	
14.3.1.4a	Adverse Events, Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (SAD) – Safety Population	IP	
14.3.1.3.4b	Adverse Events, Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term (MAD) – Safety Population	IP	
14.3.1.5a	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum Severity (SAD) – Safety Population	IP	
14.3.1.5b	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class, Preferred Term and Maximum Severity (MAD) – Safety Population	IP	
14.3.1.6a	Adverse Events, Treatment Related Treatment Emergent Adverse Events by Primary System Organ Class Preferred Term and Maximum Severity (SAD) – Safety Population	IP	
14.3.1.6b	Adverse Events, Treatment Related Treatment Emergent Adverse Events by Primary System	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Organ Class Preferred Term and Maximum Severity (MAD) – Safety Population		
14.3.1.7a	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class and Relationship to Study Drug (SAD) - Safety Population	IP	
14.3.1.7b	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class and Relationship to Study Drug (MAD) - Safety Population	IP	
14.3.1.8	Adverse Events, Treatment Emergent Adverse Events by Primary System Organ Class by Study Part and Study Drug -Safety Population	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	SAE Listing – Safety Population	IP	
14.3.2.2	Deaths, Listing – Safety Population	IP	
14.3.2.3	Listing of Early Termination –Safety Population	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
	Not Applicable		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Laboratory, Listing of Clinically Significant Values – Safety Population	IP	
14.3.5	**Extent of Exposure, Dosage Information, and Compliance**		
14.3.5.1b	Extent of Exposure – Safety Population	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1a	Vital Signs, Change from Baseline (SAD) – Safety Population	IP	
14.3.6.1b	Vital Signs, Change from Baseline (MAD) – Safety Population	IP	
14.3.7	**Other Safety**		
14.3.7.1a	Hematology Data, Change from Baseline (SAD) – Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.1b	Hematology Data, Change from Baseline (MAD) – Safety Population	IP	
14.3.7.2a	Hematology Data, Normal Range Shifts (SAD)– Safety Population	IP	
14.3.7.2b	Hematology Data, Normal Range Shifts (MAD) – Safety Population	IP	
14.3.7.3a	Serum Chemistry Data, Change from Baseline (SAD) – Safety Population	IP	
14.3.7.3b	Serum Chemistry Data, Change from Baseline (MAD) – Safety Population	IP	
14.3.7.4a	Serum Chemistry Data, Normal Range Shifts (SAD) – Safety Population	IP	
14.3.7.4b	Serum Chemistry Data, Normal Range Shifts (MAD)– Safety Population	IP	
14.3.7.5a	Urinalysis Data, Change from Baseline (SAD)– Safety Population	IP	
14.3.7.5b	Urinalysis Data, Change from Baseline (MAD)– Safety Population	IP	
14.3.7.6a	Urinalysis Data, Normal Range Shifts (SAD)– Safety Population	IP	
14.3.7.6b	Urinalysis Data, Normal Range Shifts (MAD) – Safety Population	IP	
14.3.7.7a	Platelet Aggregation Data, Change from Baseline (SAD) – Safety Population	IP	
14.3.7.7b	Platelet Aggregation Data, Change from Baseline (MAD) – Safety Population	IP	
14.3.7.8a	Platelet Aggregation Data, Normal Range Shifts (SAD) – Safety Population	IP	
14.3.7.8b	Platelet Aggregation Data, Normal Range Shifts (MAD) – Safety Population	IP	
14.3.7.9a	ECG Data, Change from Baseline (SAD) – Safety Population		
14.3.7.9b	ECG Data, Change from Baseline (MAD) – Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.10a	ECG Data, Overall Interpretation (SAD) – Safety Population	IP	
14.3.7.10b	ECG Data, Overall Interpretation (MAD)– Safety Population	IP	
14.3.7.11a	Pulmonary Function, Change from Baseline (SAD) -Safety Population	IP	
14.3.7.11b	Pulmonary Function, Change from Baseline (MAD) -Safety Population	IP	
14.3.8	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) Part A		
14.4.2	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) Part A - Stratified by Sex		
14.4.3	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 Part B		
14.4.4	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 Part B – Stratified by Sex		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.4.5	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 Part B		
14.4.6	Descriptive Statistics for Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 Part B – Stratified by Sex		
14.4.7	Descriptive Statistics for Trough Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Part B		
14.4.8	Descriptive Statistics for Trough Concentration-Time Data of PK10571 in Plasma after Administration of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Part B – Stratified by Sex		
14.4.9	Plasma Pharmacokinetic Parameters of PK10571 after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) Part A		
14.4.10	Plasma Pharmacokinetic Parameters of PK10571 after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) Part A – Stratified by Sex		
14.4.11	Plasma Pharmacokinetic Parameters of PK10571 after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 Part B		
14.4.12	Plasma Pharmacokinetic Parameters of PK10571 after Administrations of xx mg FPD (Cohort 1), xx		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 Part B – Stratified by Sex		
14.4.13	Plasma Pharmacokinetic Parameters of PK10571 after of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 Part B		
14.4.14	Plasma Pharmacokinetic Parameters of PK10571 after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 Part B – Stratified by Sex		
14.4.15	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of PK10571 Comparing xx mg FPD on Day 7 vs. xx mg FPD on Day 1 (Cohort 1)		
14.4.16	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of PK10571 Comparing xx mg FPD on Day 7 vs. xx mg FPD on Day 1 (Cohort 2)		
14.4.17	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of PK10571 Comparing xx mg FPD on Day 7 vs. xx mg FPD on Day 1 (Cohort 3)		
14.4.18	Dose Proportionality Assessment of PK10571 (Part A)		
14.4.19	Dose Proportionality Assessment of PK10571 for Day 1 and Day 7 (Part B)		

Note: Buffy coat analysis is exploratory and may not be undertaken; in such case, the tables will be blank with the note analysis no longer required.

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Mean Plasma PK10571 Concentration-time Data after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) (Part A) on Linear and Semi-logarithmic Scales		
14.4.2	Mean Plasma PK10571 Concentration-time Data after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 (Part B) on Linear and Semi-logarithmic Scales		
14.4.3	Mean Plasma PK10571 Concentration-time Data after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.4	Mean Plasma PK10571 Concentration-time Data after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), [redacted] FPD (Cohort 5) (Part A) Males vs. Females on Linear and Semi-logarithmic Scales		
14.4.5	Mean Plasma PK10571 Concentration-time Data after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 (Part B) Males vs. Females on Linear and Semi-logarithmic Scales		
14.4.6	Mean Plasma PK10571 Concentration-time Data after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 7 (Part B) Males vs. Females on Linear and Semi-logarithmic Scales		
14.4.7	Mean Plasma PK10571 Concentration-time Data after Administrations of xx mg FPD (Cohort 1) on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.8	Mean Plasma PK10571 Concentration-time Data after Administration of xx mg FPD (Cohort 2) on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.9	Mean Plasma PK10571 Concentration-time Data after Administration of xx mg FPD (Cohort 3) on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.10	Plasma PK10571 Concentration-time Profiles for All Subjects after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) (Part A) on Linear and Semi-logarithmic Scales		
14.4.11	Plasma PK10571 Concentration-time Profiles for All Subjects after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2), and xx mg FPD (Cohort 3) on Day 1 (Part B) on Linear and Semi-logarithmic Scales		
14.4.12	Plasma PK10571 Concentration-time Profiles for All Subjects after Administrations of xx mg FPD (Cohort 1), xx mg FPD (Cohort 2) and xx mg FPD (Cohort 3) on Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.13	Plasma PK10571 Concentration-time Data for Individual Subjects after xx mg FPD (Cohort 1), on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.14	Plasma PK10571 Concentration-time Data for Individual Subjects after xx mg FPD (Cohort 2), on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		
14.4.15	Plasma PK10571 Concentration-time Data for Individual Subjects after xx mg FPD (Cohort 3), on Day 1 and Day 7 (Part B) on Linear and Semi-logarithmic Scales		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.16	Plasma Concentration-Time Profiles for PK10571 with Linear Regression for Estimating the Terminal Elimination Rate		
14.4.17	Scatter Plot for PK Parameters Vs Baseline FEV1 by Cohort (SAD)		
14.4.18	Scatter Plot for Vs PK Parameters Baseline FVC by Cohort (SAD)		
14.4.19	Scatter Plot for PK Parameters Vs Body Size by Cohort (SAD)		
14.4.20	Scatter Plot for PK Parameters Vs Gender by Cohort (SAD)		
14.4.21	Scatter Plot for PK Parameters Vs Baseline FEV1 by Cohort (MAD)		
14.4.22	Scatter Plot for PK Parameters Vs Baseline FVC by Cohort (MAD)		
14.4.23	Scatter Plot for PK Parameters Vs Body Size by Cohort (MAD)		
14.4.24	Scatter Plot for PK Parameters Vs Gender by Cohort (MAD)		

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition – Randomized Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Population	IP	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Populations –Safety Population	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Population	IP	
16.2.4.2	Previous Medical History – Safety Population	IP	
16.2.4.3	Ongoing Medical History – Safety Population	IP	
16.2.4.4	Social History – Safety Population	IP	
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1	PK Sampling Times – Safety Population	IP	
16.2.5.2	Dose Exposure – Safety Population	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	PK10571 Plasma Concentration-Time Data Listing by Subject (Part A)		
16.2.6.2	PK10571 Plasma Concentration-Time Data Listing by Subject (Part B)		
16.2.6.3	Plasma Terminal Elimination Rate of PK10571 for Individual Subjects after Single Dose Administrations of [redacted] FPD (Cohort 1), [redacted] FPD (Cohort 2), [redacted] FPD (Cohort 3), [redacted] FPD (Cohort 4), and [redacted] FPD (Cohort 5) (Part A)		
16.2.6.4	Plasma Terminal Elimination Rate of PK10571 for Individual Subjects after xx mg FPD (Cohort 1) on Days 1 and 7 (Part B)		
16.2.6.5	Plasma Terminal Elimination Rate of PK10571 for Individual Subjects after xx mg FPD (Cohort 2) on Days 1 and 7 (Part B)		
16.2.6.6	Plasma Terminal Elimination Rate of PK10571 for Individual Subjects after xx mg FPD (Cohort 3) on Days 1 and 7 (Part B)		
16.2.6.7	PK Output text		

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.8	SAS Output for Part B Day 7 vs Day 1 Comparison (Cohort 1)		
16.2.6.9	SAS Output for Part B Day 7 vs Day 1 Comparison (Cohort 2)		
16.2.6.10	SAS Output for Part B Day 7 vs Day 1 Comparison (Cohort 3)		
16.2.6.11	SAS Output-Dose Proportionality Assessment Part A		
16.2.6.12	SAS Output-Dose Proportionality Assessment Part B Day 1		
16.2.6.13	SAS Output-Dose Proportionality Assessment Part B Day 7		
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Population	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data – Safety Population	IP	
16.2.8.2	Serum Chemistry Data – Safety Population	IP	
16.2.8.3	Urinalysis Data – Safety Population	IP	
16.2.8.4	Urine Drug, Cotinine and Alcohol Screen – Safety Population	IP	
16.2.8.5	Serology, PPD and TSH Data – Safety Population	IP	
16.2.8.6	Pregnancy Test and FSH Data – Safety Population	IP	
16.2.8.7	Buffy Coat and Platelet Aggregation Data – Safety Population	IP	
16.2.8.8	Physical Examination Data – Safety Population	IP	
16.2.8.9	Vital Signs Data – Safety Population	IP	
16.2.8.10	ECG Data – Safety Population	IP	
16.2.8.11	Chest X-ray – Safety Population	IP	
16.2.8.12	Prior and Concomitant Medications – Safety Population	IP	
16.2.8.13	Pulmonary Function Data– Safety Population	IP	
16.2.8.14	SAS Mean Difference Output	IP	

Signature:

Email: cpeterson@gossamerbio.com