Protocol

TRK-250 – A Phase I, Double-Blind, Placebo-Controlled, Single and Multiple Inhaled Dose, Safety, Tolerability, and Pharmacokinetic Study of TRK-250 in Subjects with Idiopathic Pulmonary Fibrosis

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Sponsor Reference Number: 250IPF01
[redacted]
PIND Number**:** 133065

Sponsor:
Toray Industries, Inc.
1-1, Nihonbashi-muromachi 2-chome,
Chuo-ku, Tokyo
Tokyo, 103-8666 Japan

[redacted]

Emergency Medical Contact

US: [redacted]
(this number is not to be used for submitting serious adverse event or pregnancy reports; please see Appendix 1)

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

<Name, qualification(s)>
<Institution>
<Position in organization>

Date

STUDY IDENTIFICATION

Sponsor	Toray Industries, Inc. 1-1, Nihonbashi-muromachi 2-chome Chuo-ku, Tokyo, 103-8666 Japan
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

SYNOPSIS

Title of study: TRK-250 – A Phase I, Double-Blind, Placebo-Controlled, Single and Multiple Inhaled Dose, Safety, Tolerability, and Pharmacokinetic Study of TRK-250 in Subjects with Idiopathic Pulmonary Fibrosis

Objectives:

The primary objective of the study is to assess the safety and tolerability of single and multiple inhaled doses of TRK-250 in subjects with idiopathic pulmonary fibrosis (IPF).

The secondary objective of the study is to assess the pharmacokinetics (PK) in blood following single and multiple inhaled doses of TRK-250 in subjects with IPF.

[redacted]

Endpoints:

The primary safety endpoints for this study are as follows:

- body weight
- vital signs measurements
- oxygen saturation (SpO_2) by pulse oximetry
- hematology, clinical chemistry, and urinalysis test results
- 12-lead electrocardiogram (ECG) parameters
- forced expiratory volume over 1 second (FEV_1), forced vital capacity (FVC)
- incidence and severity of adverse events (AE)

The single and multiple ascending dose PK outcome endpoints of TRK-250 are as follows (where applicable):

- area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-tlast}}$)
- maximum observed concentration (C_{max})
- time to C_{max} (T_{max})

Other PK parameters may also be added.

[redacted]

Study design:
This will be a Phase I, double-blind, randomized, placebo-controlled study conducted in 2 parts, single and multiple inhaled dose, at multiple sites.

Part A
Part A will comprise a single-dose, single-period, sequential-cohort study. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study drug administration.
It is planned that 16 subjects will be studied in 4 cohorts (Cohorts A1 to A4), each consisting of 4 subjects. Following data monitoring committee (DMC) review of the safety and tolerability data from the first 4 cohorts, up to 3 further optional cohorts (Cohorts A5 to A7) of at least 4 subjects may be added to Part A to evaluate additional doses or to further evaluate planned doses.
Investigational treatment and follow-up duration:
The first 2 subjects to be dosed in each cohort of Part A will reside at the study site from Day 1 (the day of dosing) to Day 2 (24 hours post completion of dose administration). After Investigator review of the safety data through Day 2 from the first 2 subjects, the remaining subjects in Cohort A1 may be discharged from the study site after completion of all study procedures on Day 1, returning for subsequent procedures on an outpatient basis. For subsequent cohorts, the decision of when to discharge subjects from the study site will be made by the Investigator based on the safety data through Day 2 from the first 2 subjects of the current cohort, as well as any relevant recommendations made at the previous DMC dose escalation review meeting.
All subjects will return for a Safety Follow-up visit 7 (+3) days after dosing and an Additional Follow-up visit 14 (±3) days after dosing. The timing of the Additional Follow-up visit for a cohort may be changed to a maximum of 28 (±3) days after dosing, based on emerging safety data.

[redacted]

Dose levels:
Current proposed dose levels:

- Cohort A1: 2 mg
- Cohort A2: 10 mg
- Cohort A3: 30 mg
- Cohort A4: 60 mg

[redacted]

Part B
Part B will comprise a multiple-dose, single-period, sequential-cohort study. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to initial study drug administration.
It is planned to study 18 subjects in 3 cohorts (Cohorts B1 to B3), each consisting of 6 subjects. Up to 3 further optional cohorts (Cohorts B4 to B6) of at least 6 subjects may be added to evaluate additional doses or to further evaluate planned doses.
Investigational treatment and follow-up duration:
After Screening, subjects will be dosed at the study site on Days 1, 8, 15, and 22. Subjects will return for a Safety Follow-up visit approximately 7 days after their last dose (Day 29 [+3]) and an Additional Follow-up visit approximately 14 days after the last dose (Day 36 [±3]). The timing of the Additional Follow-up visit for a cohort may be changed to a maximum of approximately 28 days after the last dose (Day 50 [±3]), based on emerging safety data.
[redacted]
Dose levels:
To be confirmed following completion of Part A. Current proposed dose levels:

- Cohort B1: 10 mg
- Cohort B2: 30 mg
- Cohort B3: 60 mg

[redacted]

Number of subjects:
Part A: 16 subjects will be studied in 4 groups (Groups A1 to A4), with the option to add up to 3 additional cohorts of at least 4 subjects at DMC recommendation.
Part B: 18 subjects will be studied in 3 groups (Groups B1 to B3), with the option to add up to 3 additional cohorts of at least 6 subjects at DMC recommendation.

Diagnosis and main criteria for inclusion:
Male and female subjects aged between 40 and 80 years (inclusive) with IPF. Subjects must have SpO_2 ≥90% at rest by pulse oximetry while breathing ambient air, FVC and FEV_1 ≥50% of predicted, ratio of FEV_1 to FVC ≥0.7, and DL_{CO} corrected for hemoglobin 30% to 79% of predicted, inclusive.

Investigational products, dose, and mode of administration:
Test product: [redacted] TRK-250 solution, formulated for inhalation via InnoSpire Go nebulizer system (Philips)
Proposed dose levels for Part A: 2, 10, 30, and 60 mg
Proposed dose levels for Part B: 10, 30, and 60 mg once weekly for 4 weeks. The dosing frequency and dosing duration for Part B will be decided on the basis of data from Part A of the study. The daily dose administered will not exceed the highest dose administered in Part A.
Administration route: inhalation

Reference product and mode of administration:
Reference product: placebo solution, formulated for inhalation via InnoSpire Go nebulizer system (Philips)
Administration route: inhalation

Duration of subject participation in the study:
Planned Screening duration: approximately 28 days.
Planned study duration (Screening to Follow-up):
Part A: planned to be no more than 7 weeks, but may be increased to a maximum of 9 weeks if the Additional Follow-up visit is delayed based on findings from the ongoing review of data by the DMC.
Part B: planned to be no more than 10 weeks, but may be increased to a maximum of 12 weeks if the Additional Follow-up visit is delayed based on findings from the ongoing review of data by the DMC.

Analysis methods:
Pharmacokinetics:
Blood samples for the analysis of TRK-250 concentrations. Pharmacokinetic parameters will be derived by noncompartmental analysis. For both study parts, the PK parameters will include $AUC_{0\text{-}tlast}$, C_{max}, and T_{max}. Other PK parameters may also be added.
[redacted]
Safety:
AE, pulse oximetry, spirometry, DL_{CO}, body weight, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis, serology), 12-lead electrocardiograms, vital sign measurements, and physical examinations.

Statistical methods:
Pharmacokinetics:
Individual blood concentrations of TRK-250 and PK parameters will be listed and summarized using descriptive statistics.
[redacted]
Safety:
Safety parameters will be listed and summarized using descriptive statistics. No inferential statistical analysis of safety data is planned.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ABCA3	adenosine triphosphate binding cassette A3
AE	adverse event(s)
ALAT	Latin American Thoracic Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
$AUC_{0\text{-}24h}$	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0\text{-}tlast}$	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
CRF	Case Report Form(s)
CRO	Contract Research Organization
CSA	clinical study agreement
DL_{CO}	carbon monoxide diffusion capacity
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	forced expiratory volume over 1 second
FLP	full length product
FVC	forced vital capacity
FVC%pred	percent of predicted forced vital capacity
GCP	Good Clinical Practice
GLI	Global Lung Initiative
GLP	Good Laboratory Practice
HEPA	high efficiency particulate air
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
IC_{50}	concentration that reduces effect by 50%
ICF	Informed Consent Form

ICH	International Council for Harmonisation
IMP	investigational medicinal product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IUD	intrauterine device
IxRS	interactive voice/web response system
JRS	Japanese Respiratory Society
LC-FD	liquid chromatography with fluorescence detection
LC/MS-HRAM	liquid chromatography/mass spectrometry-high resolution accurate mass
LLOQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
NOAEL	no-observed-adverse-effect level
[redacted]	[redacted]
PK	pharmacokinetic(s)
QTcB	QT interval corrected for heart rate using Bazett's method
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
siRNA	small, interfering ribonucleic acid
SLB	surgical lung biopsy(ies)
SOP	standard operating procedure(s)
SP-A2	surfactant protein A2
SP-C	surfactant protein C
SpO_2	oxygen saturation
TGF-β1	transforming growth factor-beta 1
T_{max}	time of maximum observed concentration
TMF	Trial Master File
UIP	usual interstitial pneumonia
ULN	upper limit of normal
WCBP	women of childbearing potential

1. INTRODUCTION

1.1. Overview

Interstitial pulmonary fibrosis (IPF) is one of the interstitial pneumonias, known also as cryptogenic fibrosing alveolitis. The condition is also identified as usual interstitial pneumonia (UIP), the term given its appearance on high-resolution computed tomography (HRCT) scans of the lung and histopathologic examination of surgical lung biopsies (SLB).[1]

Toray Industries, Inc. (Toray), is developing TRK-250 for the potential treatment of IPF.

An international, professional society (American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association [ATS/ERS/JRS/ALAT]) statement defines IPF as a specific lung disorder of adults, of unknown cause, characterized by progressive dyspnea, associated with poor prognosis, resulting from progressive fibrosing interstitial pneumonia of unknown cause.[2] Criteria for the diagnosis of IPF detailed in this publication are adopted as criteria central to establishing subject eligibility for this clinical trial.

The etiology of IPF remains undetermined. Risk factors have been identified, including:

- cigarette smoking and atmospheric pollutants
- viral infection
- chronic aspiration
- drugs

Genetic predisposition seems to play a role in some cases of IPF.[3] Mutations in surfactant proteins A2 (SP-A2) and C (SP-C) as well as in adenosine triphosphate binding cassette A3 (ABCA3) genes appear to be involved in cases of familial IPF. A genetic abnormality in the promoter of the gene encoding mucin 5B (MUC5B) has been identified in about one third of individuals with familial and sporadic IPF; the abnormality is only found in about 9% of individuals without clinical evidence of IPF. Telomerase gene mutations (TERT, TERC, DKC1, TINF2) that cause shortened telomeres have been identified in about one quarter of sporadic and more than one third of familial IPF cases. Still, the interplay of all risk factors remains poorly understood, more so in sporadic IPF cases.

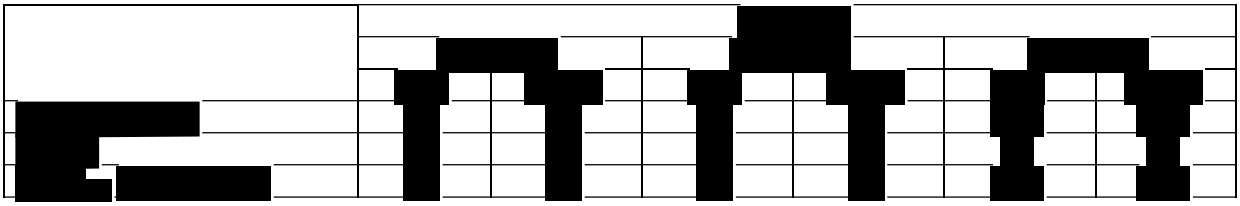
A central role for transforming growth factor-beta 1 (TGF-β1) has been documented for decades in fibrosis in many organs, in airway remodeling, and in IPF.[4] TRK-250 is a small, interfering ribonucleic acid (siRNA) molecule that targets the TGF-β1 guide sequence. TRK-250 aims to inhibit the progression of pulmonary fibrosis and, thus, slow the decline in lung function, by selectively targeting TGF-β1 messenger ribonucleic acid (mRNA) and thereby suppressing the expression of TGF-β1 protein, a key growth factor involved in lung fibrosis, at the gene expression level.[5] TRK-250 employs a proprietary nucleic acid platform that synthesizes 2 complementary single oligoribonucleotide strands. The 2 strands of oligoribonucleotides are linked by a proline derivative and a second proline derivative terminated with guanine completes the sequence. TRK-250 is formulated as a solution for inhalation, supporting direct administration to the lung.

This trial will be the first time that TRK-250 is administered to humans.

[redacted]

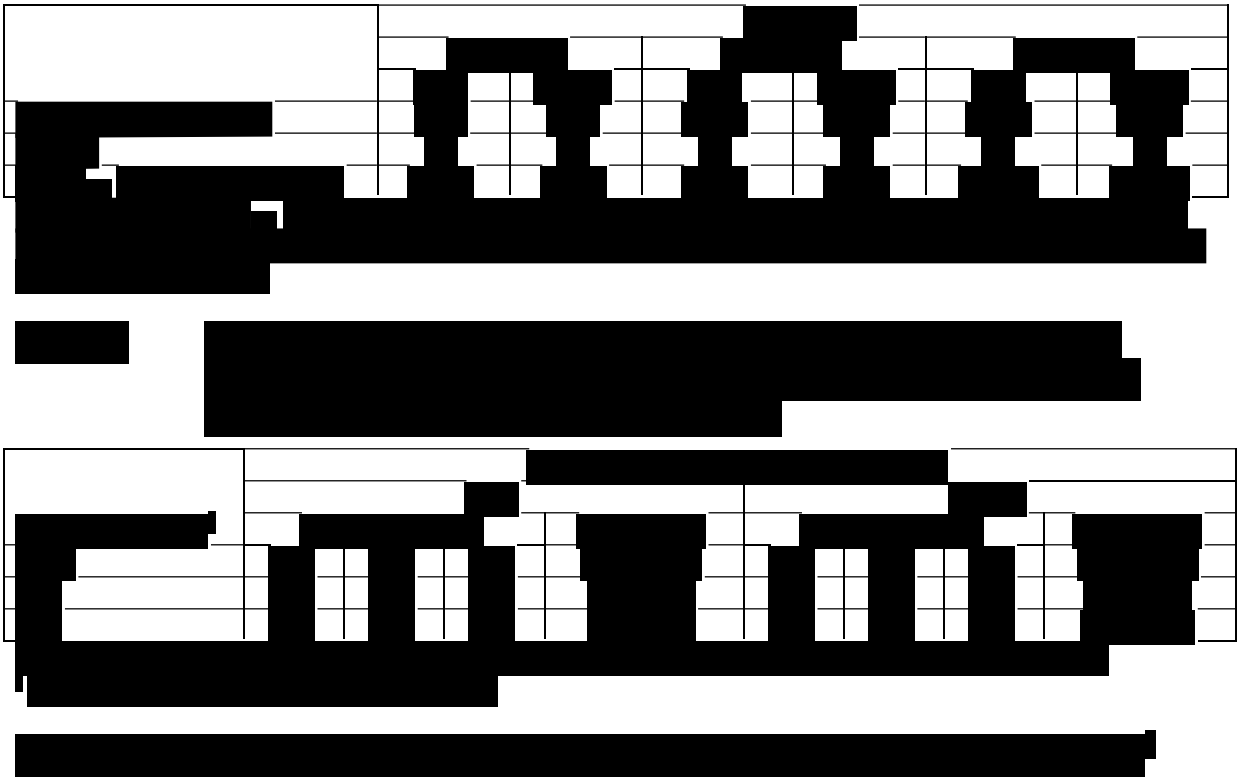
[redacted]

[redacted]



[redacted]

[redacted]



[redacted]

[redacted]

1.6. Summary of Clinical Experience

TRK-250 has not previously been administered to humans.

1.7. Study Rationale

The principal aim of this study is to obtain safety and tolerability data when TRK-250 is administered by inhalation as single and multiple doses to subjects with IPF. A sequential-cohort, ascending-dose design has been chosen to optimize safety since Part A of the study will be the first time TRK-250 is administered to humans.

Conducting the study in subjects with IPF was considered necessary due to the paucity of data concerning administration of siRNA, in general, and TRK-250, specifically, to healthy subjects; a perception shared by regulatory authorities.

Inhaled administration has been chosen for the study since this is the intended route of clinical administration.

PK blood sampling is included in this trial design. This should advance understanding of the potential for inhaled TRK-250 to have off-target effects.

Once-weekly dosing frequency has been selected for Part B because 4 once-weekly intratracheal doses of TRK-250 were shown to be pharmacologically active in a human TGF-β1 [redacted] model.

Based on the nonclinical data, the duration of treatment in each part of this trial is considered adequate to achieve the study's objectives.

This study will be double blind and placebo controlled to avoid bias in the collection and evaluation of data. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

Ongoing review of safety and tolerability data will be performed before deciding to proceed to the next dose escalation. [redacted]

1.8. Benefit-Risk Assessment

Subjects with IPF in the current study are not expected to gain significant, long-term health benefits (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures.

Although there is no evidence from nonclinical studies of bronchoconstriction following inhalation of TRK-250, subjects will have spirometry performed to assess for this important safety finding in this trial.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple inhaled doses of TRK-250 in subjects with IPF.

The secondary objective of the study is to assess the PK in blood following single and multiple inhaled doses of TRK-250 in subjects with IPF.

[redacted]

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- body weight
- vital signs measurements

- oxygen saturation (SpO_2) by pulse oximetry
- hematology, clinical chemistry, and urinalysis test results
- 12-lead electrocardiogram (ECG) parameters
- forced expiratory volume over 1 second (FEV_1), forced vital capacity (FVC)
- incidence and severity of adverse events (AE)

2.2.2. Secondary Endpoints

The single and multiple ascending dose PK outcome endpoints of TRK-250 are as follows (where applicable):

- AUC from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-}tlast}$)
- C_{max}
- T_{max}

Other PK parameters may also be added.

[redacted]

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled study conducted in 2 parts, single and multiple inhaled dose, at multiple sites.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, single-period, sequential-cohort study. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study drug administration.

The total duration of study participation for each subject (from Screening through Additional Follow-up visit) is planned to be no more than 7 weeks but may be increased to a maximum

of 9 weeks if the Additional Follow-up visit is delayed based on findings from the ongoing review of data by the data monitoring committee (DMC).

It is planned that 16 subjects will be studied in 4 cohorts (Cohorts A1 to A4), each consisting of 4 subjects. Following DMC review of the safety and tolerability data from the first 4 cohorts, up to 3 further optional cohorts (Cohorts A5 to A7) of at least 4 subjects may be added to Part A to evaluate additional doses or to further evaluate planned doses.

All subjects will return for a Safety Follow-up visit 7 (+3) days after dosing and an Additional Follow-up visit 14 (±3) days after dosing. The timing of the Additional Follow-up visit for a cohort may be changed to a maximum of 28 (±3) days after dosing, based on emerging safety data.

In each of Cohorts A1 to A4, 3 subjects will receive TRK-250 and 1 subject will receive placebo. All doses will be administered in accordance with a randomization schedule on the morning of Day 1. Each subject will receive only a single dose of TRK-250 or placebo during the study.

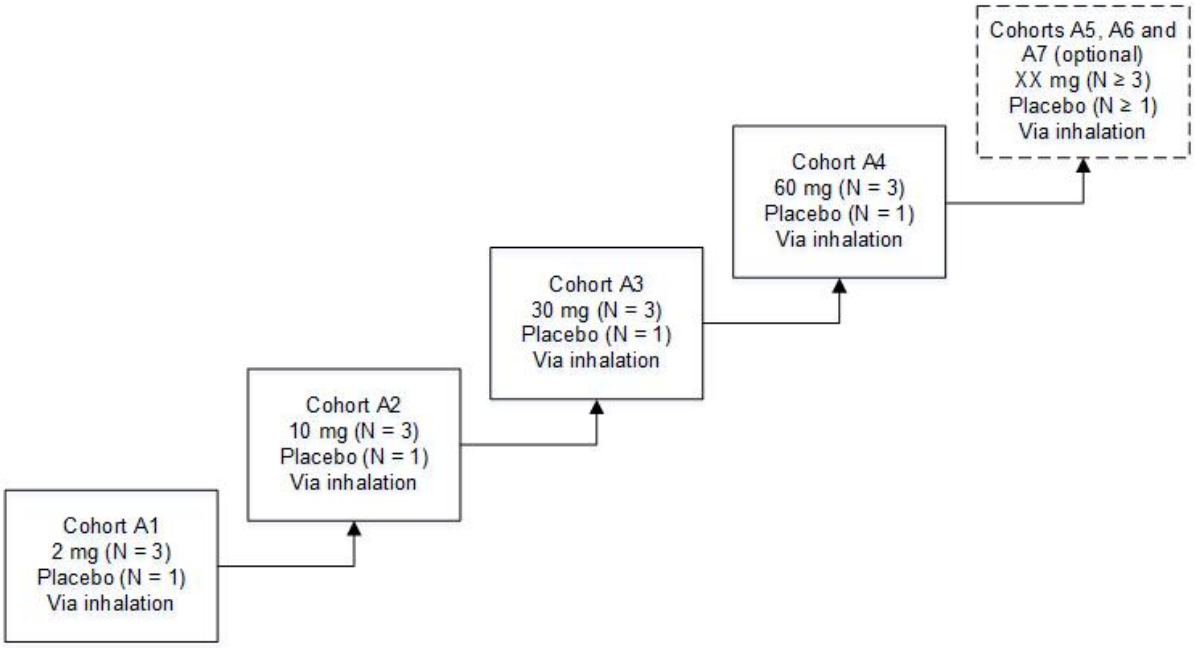
- Cohort A1: 2 mg
- Cohort A2: 10 mg
- Cohort A3: 30 mg
- Cohort A4: 60 mg

[redacted]

[redacted] pharmacologically active dose levels (ie, when the escalated dose will be ≥34.7 mg).

An overview of the study design and the planned dose levels are shown in Figure 1.

Figure 1: Study Schematic (Part A)



3.1.2. Part B

Part B will comprise a multiple-dose, single-period, sequential-cohort study. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to initial study drug administration.

The total duration of study participation for each subject (from Screening through Safety Follow-up visit) is planned to be no more than 10 weeks but may be increased to a maximum of 12 weeks if the Additional Follow-up visit is delayed based on findings from the ongoing review of data by the DMC.

[redacted]

[redacted]

All subjects will return for a Safety Follow-up visit approximately 7 days after their last dose (Day 29 [+3]) and an Additional Follow-up visit approximately 14 days after the last dose (Day 36 [±3]). The timing of the Additional Follow-up visit for a cohort may be changed to a maximum of approximately 28 days after the last dose (Day 50 [±3]), based on emerging safety data.

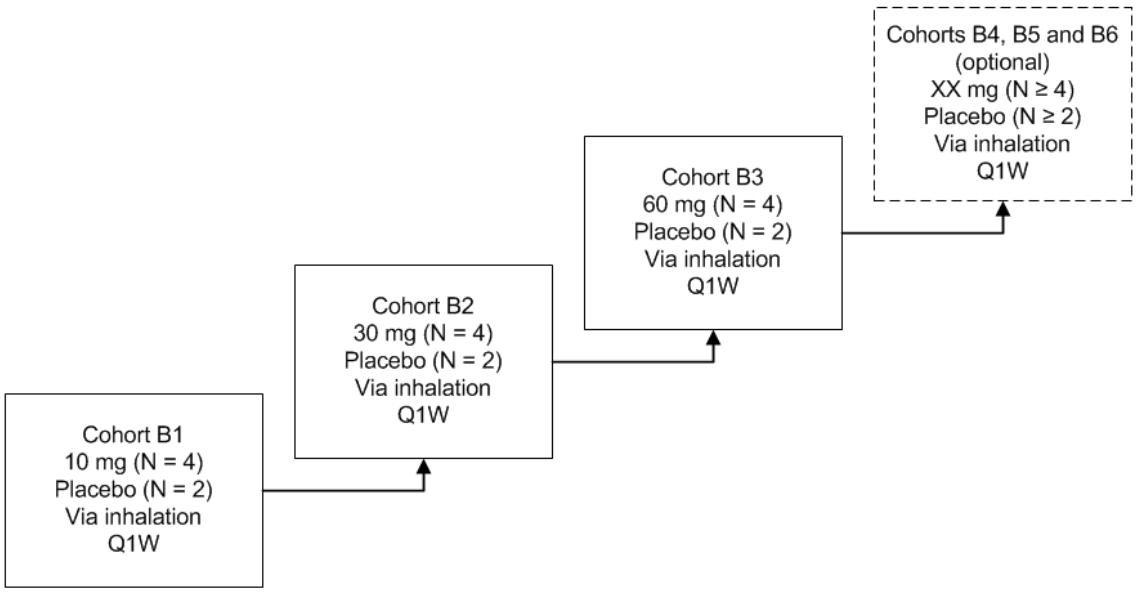
In each of Cohorts B1 to B3, 4 subjects will receive TRK-250 and 2 subjects will receive placebo. Doses will be administered on the morning of Days 1, 8, 15, and 22 in accordance with a randomization schedule. Each subject will receive 4 once-weekly doses of TRK-250 or placebo during the study. [redacted]

[redacted]

- Cohort B1: 10 mg
- Cohort B2: 30 mg
- Cohort B3: 60 mg

[redacted] shown in Figure 2.

Figure 2: Study Schematic (Part B)



A Schedule of Assessments is presented in Appendix 5.

3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of randomization occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last protocol-specified assessment, whether scheduled or unscheduled.

3.3. Additional Cohorts

Following review of the safety and tolerability data from the planned dose cohorts, the DMC may recommend additional dose cohorts to be added to the study. Up to 3 further cohorts of at least 4 subjects [redacted] may be included in Part A, and up to 3 further cohorts of at least 6 subjects [redacted] may be included in Part B. If the dose escalation stopping criteria have not been met, the doses administered in the additional cohorts may exceed the proposed highest doses shown in Table 4; [redacted]

The Sponsor is responsible for making the final decision whether to add any additional cohorts if recommended by the DMC. The decision will be documented in the Trial Master File (TMF), and the Institutional Review Board (IRB) will be notified of the changes.

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-cohort, ascending-dose design has been chosen for safety reasons because TRK-250 is in the early stages of clinical development, with Part A of

the study being the first time it will be administered to humans. Inhaled doses have been chosen for both parts of the study since this is the intended clinical route of administration.

[redacted]

This study will be double blind and placebo controlled to avoid bias in the collection and evaluation of data. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

[redacted]

3.4.1. Dose Interval

[redacted]

- [redacted]
- [redacted]

[redacted]

3.5. Selection of Doses in the Study

[redacted]

[redacted]

[redacted]

The proposed IMP dose levels for Parts A and B are shown in Table 4.

Table 4: Proposed IMP Dose Levels for Parts A and B

Study Part	Cohort	Treatment
Part A	A1	2 mg TRK-250 or placebo
	A2	10 mg TRK-250 or placebo
	A3	30 mg TRK-250 or placebo
	A4	60 mg TRK-250 or placebo
	Optional Cohorts A5, A6, and A7	XX mg TRK-250 or placebo
Part B	B1	10 mg TRK-250 or placebo Q1W
	B2	30 mg TRK-250 or placebo Q1W
	B3	60 mg TRK-250 or placebo Q1W
	Optional Cohorts B4, B5, and B6	XX mg TRK-250 or placebo Q1W

Abbreviations: IMP = investigational medicinal product; Q1W = once weekly.

For Part B of the study, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. The weekly dose of TRK-250 administered during this part of the study will not exceed the maximum well-tolerated dose level studied in Part A.

[redacted]

[redacted]

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria, at the Screening visit unless otherwise stated:

1. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.
2. Male or female between 40 and 80 years of age, inclusive, at Screening.
    a. Women of childbearing potential (WCBP) and all male subjects will agree to use contraception (refer to Section 6.5) throughout enrollment (ie, from signing the ICF to the last protocol-specified assessment, whether scheduled or unscheduled).
3. Clinical, radiographic, and (when available) histologic features consistent with IPF within 5 years prior to Screening, confirmed using ATS/ERS/JRS/ALAT statement[2] for the diagnosis of IPF in effect at the time of this trial's initiation.

a. Interpretation of HRCT and, if performed, SLB must be confirmed by central over-reader (see Section 7.1.10.1 and Section 7.1.10.2).

b. HRCT performed within 12 months prior to the initiation of Screening that is determined to be of suitable quality by the central over-reader will be used to confirm subject eligibility.

4. SpO_2 ≥90% at rest by pulse oximetry while breathing ambient air.
5. FVC ≥50% of predicted.
6. FEV_1 ≥50% of predicted.
7. Ratio of FEV_1 to FVC ≥0.7.
8. DL_{CO} corrected for hemoglobin 30% to 79% of predicted, inclusive.
9. Life expectancy of at least 12 months.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria on or before Day 1, as applicable:

1. Serious or uncontrolled medical, surgical, or psychiatric disease that in the opinion of the Investigator would compromise subject safety.
2. History of acute exacerbation of IPF or respiratory tract infection within 3 months prior to Screening.
3. Planned surgery during the study (Day 1 to Additional Follow-up Visit).
4. History of malignant tumor within 5 years prior to Screening (with the exception of treated squamous and basal cell skin cancers and treated Stage 0/*in situ* cervical cancer).
5. History of emphysema or clinically significant respiratory diseases (other than IPF), as determined by the Investigator.
6. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator.
7. Pregnant or planning to become pregnant during enrollment.
8. Breastfeeding or planning to breastfeed during enrollment.
9. History of alcoholism or drug/chemical abuse within 2 years prior to Day 1.
10. Alcohol consumption >21 units per week for males and >14 units per week for females within 30 days prior to Screening. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine. Eligible subjects must have agreed not to exceed this limit until the end of the subject's enrollment.
11. Positive urine drugs of abuse at Screening for substance or metabolite of substance that was not prescribed and that remains positive on repeat testing.
12. Positive hepatitis panel (positive for either hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody) and/or positive human immunodeficiency

virus test. Subjects whose results are compatible with prior immunization and not infection may be included at the discretion of the Investigator.

13. Participation in a clinical study involving administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, prior to Day 1.
14. Use or intend to use any medications/products known to alter TRK-250 absorption, metabolism, or elimination processes within 30 days prior to Day 1 and for the remainder of enrollment, unless deemed acceptable by the Investigator.
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Day 1 and for the remainder of enrollment, unless deemed acceptable by the Investigator.
16. Consumption in any form of tobacco- or nicotine-containing products, excluding over-the-counter or prescription nicotine replacement products approved for marketing by the FDA, within 3 months prior to Day 1.
17. Receipt of blood products within 3 months prior to Day 1.
18. Donation of blood, plasma, or platelets within 6 weeks prior to Day 1.
19. Unable to perform spirometry or to inhale study drug properly, in the opinion of the Investigator. In particular, subjects whose cough may impede proper study treatment, in the opinion of the Investigator, should be excluded.
20. Poor peripheral venous access.
21. Have previously received TRK-250.
22. A subject who, in the opinion of the Investigator, should not participate in this study.
23. Findings that are diagnostic of an alternative condition other than UIP on surgical lung biopsy, HRCT imaging, transbronchial lung biopsy, or BAL.
24. Other known causes of interstitial lung disease (eg, drug toxicities, environmental exposures, connective tissue diseases).
25. End-stage fibrotic disease expected to require organ transplantation within 6 months.
26. Taking a systemic corticosteroid, cytotoxic therapy (eg, chlorambucil, azathioprine, cyclophosphamide, or methotrexate), vasodilator therapy for pulmonary hypertension (eg, bosentan), or unapproved treatment for IPF (eg, interferon-gamma, penicillamine, cyclosporine, mycophenolate, or N-acetylcysteine) within 4 weeks prior to Screening.
    a. Treatment with pirfenidone (Esbriet®) or nintedanib (Ofev®), though not both concurrently, is permitted, provided that the subject has been on a stable dose for at least 4 weeks prior to Screening and it is anticipated the dose will remain unchanged throughout enrollment (ie, from signing the ICF to the last protocol-specified assessment, whether scheduled or unscheduled).
27. Has received an investigational therapy within 5 half-lives of the agent or 6 months prior to Screening, whichever is longer.

4.3. Subject Number and Identification

Subjects will be assigned a subject number prior to the first dosing occasion at the time of their randomization. Assignment of subject numbers will be in ascending order.

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion post randomization that is clinically relevant and affects subject safety as determined by the Investigator.
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator.
- any clinically relevant sign or symptom that, in the opinion of the Investigator, warrants subject withdrawal.

If a subject is withdrawn, the Sponsor and [redacted] will be notified by the Investigator and the date and reason(s) for the withdrawal will be documented in the subject's Case Report Form (CRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, including the Additional Follow-up visit assessments, if possible (Appendix 5). Other procedures may be performed at the Investigator's or Sponsor's discretion. If the subject is in-house, the Safety Follow-up procedures should be performed before the subject is discharged from the clinic, if possible. The Investigator may also request that the subject return for a separate follow-up visit to complete the Safety Follow-up procedures. Any withdrawn subject who completes the Safety Follow-up procedures should be invited to attend for a separate follow-up visit to complete the procedures scheduled for the Additional Follow-up visit; this additional visit should be performed approximately 1 week after the Safety Follow-up procedures. All withdrawn subjects will be followed until resolution of all their AE or until the unresolved AE are judged by the Investigator to have stabilized.

Subjects who are withdrawn for reasons not related to study drug, including randomized subjects who never receive study drug, may be replaced following discussion between the Investigator and the Sponsor to ensure the required number of subjects complete each cohort. Subjects withdrawn as a result of an AE thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator or Sponsor if any of the following criteria are met:

- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancellation of drug development

- the DMC recommends discontinuation of the study due to safety concerns.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

The IMP [redacted] will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis. The IMP will be provided as a clear and sterile solution, formulated for inhalation via InnoSpire Go nebulizer system (Philips). [redacted]

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations and packaged together with the diluent as kit boxes. Study treatment (IMP or placebo) will be prepared for administration by qualified site personnel in accordance with Table 5.

Table 5: Preparation of TRK-250 Doses for Nebulization

Dose	2 mg (or Placebo)	10 mg (or Placebo)	30 mg (or Placebo)	60 mg (or Placebo)
[redacted]				

5.2. Study Treatment Administration

Each dose of TRK-250 and placebo will be administered by oral inhalation using InnoSpire Go. Measures to protect against secondary exposure will be employed as described in Section 5.2.1.

Study treatment must be administered by blinded site personnel.

Subjects will be administered the study treatment in a sitting position. All doses will be administered irrespective of fasting status.

Subjects must be instructed not to disclose to anyone whether the study treatment is associated with a taste or odor.

Prior to administering study drug, the Investigator should passively observe the subject's cough character and frequency to establish a "qualitative" baseline. The subject should be asked to rate informally her/his shortness of breath (eg, on a scale of 0 to 10 or none, mild, moderate, or severe).

After starting study drug administration and for roughly 30 minutes afterwards, the Investigator should continue to passively observe the subject for change in character and/or

frequency of cough. Special attention should be given to assessing whether the subject's cough may impede proper study treatment.

The same informal self-assessment should be performed for chest tightness. A substantial fraction of patients experience no change in cough or chest tightness during methacholine or histamine challenge even with ≥20% decline in FEV_1, but a change in cough and/or chest tightness are good and early indicators of worsening bronchoconstriction.

5.2.1. Secondary Exposure Protection Measures

Study treatment may be administered in a negative pressure enclosure or in proximity to a portable high efficiency particulate air (HEPA) filtration system intended for healthcare in accordance with local standard operating procedures (SOP) and/or study documents.

[redacted]

5.3. Randomization

Randomization to placebo/active will be performed using an interactive voice/web response system (IxRS) randomization service. Investigators must register the subject for the IxRS system in sequence of the screening completion and dispense study drug to each subject per the code allocated by IxRS. This unique drug code will not be changed throughout the study.

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to TRK-250.
- The Investigator and other site personnel not involved in the preparation of study treatment will remain blinded to study treatment randomization.
- Respiratory protection must be used (as described in Section 5.2.1) during study treatment administration to prevent site personnel from detecting any taste or odor of the study treatment.
- Subjects must be instructed not to disclose to anyone whether study treatment is associated with a taste or odor.
- Interim bioanalytical data will be provided in a blinded manner.

The IxRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the Investigator, it is in the subject's best interest to know the study treatment assignment. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and CRF, as appropriate.

5.5. Treatment Compliance

To ensure treatment compliance, all doses of study treatment will be administered under the supervision of suitably qualified site personnel.

5.6. Drug Accountability

The Investigator will maintain an accurate record of receipt of study supplies. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by [redacted] or the Sponsor on request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to [redacted] (or designee) or may be destroyed at the study site in accordance with [redacted] or the Sponsor's written instructions and local SOP.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

6.1.1. Restricted Concomitant Therapies

Subjects should be instructed to withhold for at least 4 hours before planned study visits **any** short-acting bronchodilator therapy (beta-agonist or anticholinergic agents). Withheld doses may be taken after the spirometry session scheduled to occur within 30 minutes after completion of study treatment administration.

Each subject will refrain from use of any new prescription or nonprescription medications during enrollment until the last planned or unscheduled study visit, unless clinically indicated to safeguard the subject's safety or well-being.

Either pirfenidone or nintedanib must have been taken at a stable dose for at least 4 weeks prior to Screening and should be continued at the same dose throughout a subject's enrollment (ie, from signing the ICF to the last protocol-specified assessment, whether scheduled or unscheduled). Dose adjustment in accordance with the prescribing information is permitted if clinically indicated.

All other therapies are permitted concomitant therapies. All prescription medications should be continued at the same dose throughout a subject's enrollment (ie, from signing the ICF to the last protocol-specified assessment, whether scheduled or unscheduled), unless a change is clinically indicated to safeguard the subject's safety or well-being. Consistent compliance and dosing of inhaled therapies is particularly important.

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data and in the relevant CRF.

6.1.2. Prohibited Concomitant Therapies

Taking pirfenidone and nintedanib simultaneously is prohibited for subjects enrolled in this study.

Taking a systemic corticosteroid, cytotoxic therapy (eg, chlorambucil, azathioprine, cyclophosphamide, or methotrexate), vasodilator therapy for pulmonary hypertension (eg, bosentan), unapproved treatment for IPF (eg, interferon-gamma, penicillamine, cyclosporine, mycophenolate, or N-acetylcysteine), or any other investigational treatment is prohibited for subjects enrolled in this study.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests.

On the days with PK assessments (Day 1 for Part A and Days 1 and 22 for Part B), meals will be identical for each cohort.

Water will be freely available at all times.

Consumption of alcohol >21 units per week for males and >14 units per week for females is not permitted within 30 days prior to Screening until the end of the subject's enrollment. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.

6.3. Smoking

Subjects may not consume in any form tobacco- or nicotine-containing products, excluding over-the-counter or prescription nicotine replacement products approved for marketing by the FDA, within 3 months prior to Day 1 until the end of the subject's enrollment.

6.4. Blood Donation

Subjects must not donate blood, plasma, or platelets from 6 weeks prior to Day 1 until 56 days after the end of the subject's enrollment.

6.5. Contraception

Women who are not of childbearing potential will not be required to use contraception. Women not of childbearing potential are defined as:

- permanently sterile due to hysterectomy or bilateral oophorectomy confirmed by history, or
- postmenopausal, defined as at least 12 months postcessation of menses without an alternative medical cause, confirmed by a Screening blood follicle-stimulating hormone level >40 mIU/mL.

Subjects who are WCBP must be willing to use a highly effective method of birth control (ie, contraceptive measure with a failure rate of <1% per year) in conjunction with male barrier contraception (ie, male condom with spermicide) from the time of signing the ICF until 90 days after the last dose of study treatment. The highly effective method of contraception should be started at least 1 menstrual cycle prior to the first dose of study drug. Highly effective methods of contraception are:

- intrauterine device (IUD; eg, Mirena®). Steel or copper IUDs are not acceptable.
- established use of oral, implantable, transdermal, or injectable hormonal method of contraception associated with inhibition of ovulation.
- male sterilization (performed at least 90 days prior to the Screening visit), with verbal confirmation of surgical success (for female subjects on the study, the vasectomized male partner should be the sole partner for that subject).
- bilateral salpingectomy, tubal ligation, or tubal occlusion (performed at least 90 days prior to the Screening visit).

Male subjects will be surgically sterile for at least 90 days prior to Screening or will be required to use a male condom with spermicide from Day 1 until 90 days after the last dose of study drug when sexually active with female partners of childbearing potential. Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the last dose of study drug. Male subjects are required to refrain from donation of sperm from Day 1 until 90 days after the last dose of study drug.

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and coital withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active she/he must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes heterosexually active, they must agree to use contraception as described above.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood sampling
- spirometry
- any other procedures [redacted] (ECGs will be scheduled before vital signs measurements).

Spirometry should preferably be performed before DL_{CO} at timepoints where both assessments are required (but see Section 7.1.8).

[redacted]

7.1. Safety and Tolerability Assessments

7.1.1. Adverse Events

AE definitions, assignment of seriousness, severity, and causality, and procedures for reporting SAE are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AE occurring at any other time during the study.

All nonserious AE, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study drug until study completion. SAE will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, seriousness, and severity will be documented, together with an Investigator's opinion of the relationship to study drug.

SAE will be followed up until the subject's status reverts to baseline, the AE is determined by the Investigator to be irreversible, or death of the subject. Non-serious AE will be followed up until resolution or the AE is determined by the Investigator to be irreversible. This will be completed at the Investigator's discretion. If not possible to follow up an SAE or AE, appropriate reasons should be provided.

7.1.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 5. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more

detailed assessment of clinical laboratory safety evaluations is required. Maximum blood volumes that will be collected in this study for clinical laboratory evaluations and other blood collections are listed in Appendix 3.

Subjects will be asked to provide a urine sample for drugs of abuse screen at Screening. For all WCBP, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 5.

An Investigator will perform a clinical assessment of all Screening clinical laboratory data.

7.1.3. Vital Signs

Blood pressure, pulse rate, respiratory rate, and oral body temperature will be assessed with the subject sitting at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. Oral body temperature will be measured singly.

7.1.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value >500 ms
- QTcF change from the baseline (Day 1 predose) is >60 ms.

If repeated, the repeat values will be used for data analysis.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator will perform a clinical assessment of each 12-lead ECG.

The ECG machine will compute the PR and QT intervals, QTc, QRS duration, and heart rate. The QT interval corrected for heart rate using Bazett's method (QTcB) and QTcF will also be calculated. A common set of reference ranges will be applied to all the preceding ECG parameters at all sites.

7.1.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 5.

Full physical examination will include the following body systems: general appearance, eyes/ears/nose/throat/head/neck, chest and lungs (including inspection of the thorax for scars

consistent with SLB at Screening), cardiovascular, abdomen, musculoskeletal, lymphatic, dermatologic, neurologic, psychiatric, and extremities.

7.1.6. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 5.

7.1.7. Pulse Oximetry

Pulse oximetry will be performed with the subject sitting at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5.

The Screening assessment will be conducted while the subject is breathing ambient air.

If the subject's subsequent status requires supplemental oxygen by nasal prongs/cannula, the initial SpO_2 measurement should be obtained with the subject breathing the currently prescribed oxygen supplementation. Using clinical judgement to assure the subject's safety and well-being, an attempt should be made to obtain SpO_2 with the subject breathing oxygen at 2 L/minute by nasal prongs/cannula for 5 minutes (less time if desaturation is rapid and clinically significant). Then, an attempt should be made to obtain SpO_2 with the subject breathing ambient air for 5 minutes, again using clinical judgement to assure the subject's safety and well-being.

7.1.8. Spirometry

Spirometry testing will be conducted to measure FVC, FEV_1, and FEV_1/FVC at the times indicated in the Schedule of Assessments in Appendix 5.

Spirometry will be performed and interpreted in accordance with published guidelines.[9,10] Spirometry predicted values will be calculated using Global Lung Initiative (GLI) 2012 equations.[11]

At any study visit when performance of both spirometry and DL_{CO} are planned, the preferred order is for spirometry to be performed before DL_{CO}. If this should not be feasible, the rationale must be well documented in source records. Whatever order of testing is implemented at Day 1 is the order of testing to be used at every subsequent study visit.

A subject may only proceed to Day 1 when Screening spirometry is determined to be adequate by the central over-reader. If Screening spirometry is determined to be inadequate by the central over-reader, the subject must return for repeat testing at the earliest feasible date. If the subject reaches the end of the Screening window (see Appendix 5) without documentation of adequate spirometry as determined by the central over-reader, the subject will fail Screening and may rescreen once.

Baseline spirometry values are those obtained at Day 1. In the event that Day 1 spirometry is determined not to be adequate by the central over-reader and the subject has received study treatment, baseline spirometry values are those obtained at Screening.

When planning repeat spirometry, the turnaround time required for central over-read (see the vendor's study manual) should be taken into consideration. When repeating either spirometry or DL_{CO} determined to be inadequate by the central over-reader, only the inadequate modality (spirometry and/or DL_{CO}) needs to be repeated.

Spirometry may only be performed on subjects in this study by site personnel certified as competent to perform the assessments. Whenever possible, all spirometry on a single subject should be performed:

- at the same time of day (±2 hours) as for the initial session (ie, Screening)
- on the same equipment
- by the same site personnel
- under the same conditions, including the order in which spirometry and DL_{CO} assessments at the same timepoint are performed

Spirometry tests will be performed in accordance with bronchodilator restrictions specified in Section 6.1.1.

At study visits when study treatment is to be administered, the following schedule of spirometry assessments (forced expiratory maneuvers) is recommended:

- a minimum of 3, maximum of 6 maneuvers within 60 minutes predose
- preferably 3 but a minimum of 2 maneuvers as soon as feasible but within 15 minutes after completion of dose administration
- preferably 3 but a minimum of 2 maneuvers at 30 ± 5 minutes after completion of dose administration
- preferably 3 but a minimum of 2 maneuvers at 60 ± 10 minutes after completion of dose administration
- preferably 3 but a minimum of 2 maneuvers at 90 ± 15 minutes after completion of dose administration

The maximum number of forced expiratory maneuvers in any day should not exceed 16. The minimum number of maneuvers at study visits when study treatment is to be administered should be 11 but it is acknowledged this may be too taxing for an individual with IPF. The Investigator should use clinical judgement to balance the safe monitoring of the subject for possible bronchoconstriction following study treatment against the burden of this testing. Greater emphasis should be placed on proper assessment closer to the time when treatment is completed than at later times. In the absence of evidence of bronchoconstriction and if the subject is not able to perform the schedule of assessments proposed above, the Investigator may alter the timing of postdose spirometry sessions, ie, spread them out over a longer interval, or may reduce the number of postdose spirometry sessions. The Investigator may not alter the specified predose spirometry assessment. At every postdose spirometry session, a minimum of 2 forced expiratory maneuvers must be attempted.

If the Investigator implements changes to the proposed postdose spirometry assessments, the rationale must be documented in detail in source records.

If the Investigator determines it is necessary to alter postdose spirometry, the decision applies only to the current visit. At all subsequent study visits, efforts to implement the proposed schedule of assessments should be renewed.

Clinical judgement is also foreseen to predicate how to perform assessments when postdose bronchoconstriction is suspected. In this circumstance, the number and timing of forced expiratory maneuvers is to be determined by the Investigator. Ideally, there should be a final assessment demonstrating resolution of bronchoconstriction, ie, FEV_1 and FVC decline <12% from predose values.

Detailed spirometry testing instructions will be provided to sites in a separate document.

7.1.9. Carbon Monoxide Diffusion Capacity Test

In order to assess pulmonary gas exchange in subjects, testing will be conducted to measure DL_{CO} at the times indicated in the Schedule of Assessments in Appendix 5.

DL_{CO} will be performed and interpreted in accordance with published guidelines.[12] DL_{CO} predicted values will be calculated using GLI 2017 equations.[13]

A subject may only proceed to Day 1 when Screening DL_{CO} is determined to be adequate by the central over-reader. If Screening DL_{CO} is determined to be inadequate by the central over-reader, the subject must return for repeat testing at the earliest feasible date. If the subject reaches the end of the Screening window (see Appendix 5) without documentation of adequate DL_{CO} as determined by the central over-reader, the subject will fail Screening and may rescreen once.

Baseline DL_{CO} values are those obtained at Day 1. In the event that Day 1 DL_{CO} is determined not to be adequate by the central over-reader and the subject has received study treatment, baseline DL_{CO} values are those obtained at Screening.

When planning repeat DL_{CO}, the turnaround time required for central over-read (see the vendor's study manual) should be taken into consideration. When repeating either spirometry or DL_{CO} determined to be inadequate by the central over-reader, only the inadequate modality (spirometry and/or DL_{CO}) needs to be repeated.

Testing for DL_{CO} may only be performed on subjects in this study by site personnel certified as competent to perform the assessments. Whenever possible, all DL_{CO} on a single subject should be performed:

- at the same time of day (±2 hours) as for the initial session (ie, Screening)
- on the same equipment
- by the same site personnel
- under the same conditions, including the order in which spirometry and DL_{CO} assessments at the same timepoint are performed

DL_{CO} will be performed in accordance with bronchodilator restrictions specified in Section 6.1.1.

DL_{CO} will be corrected for hemoglobin. Hemoglobin may be measured locally within 7 days before the DL_{CO} measurement. Alternatively, the hemoglobin value reported by the central laboratory obtained at the study visit during which DL_{CO} was performed may be used.

Detailed DL_{CO} testing instructions will be provided to sites in a separate document.

7.1.10. Diagnosis of IPF

The diagnosis of IPF will be confirmed using ATS/ERS/JRS/ALAT consensus criteria.[2] The consensus criteria are modified with regard to HRCT confirmation of UIP as follows.

7.1.10.1. High-Resolution Computed Tomography

HRCT assessment will be conducted for Screening purposes only, as part of confirming the diagnosis of UIP/IPF (see Schedule of Assessments in Appendix 5). HRCT must qualify based on Table 4 in ATS/ERS/JRS/ALAT statement for the diagnosis of IPF.[2]

If the most recent historical HRCT was performed more than 12 months prior to the initiation of Screening, OR if the HRCT performed within 12 months prior to the initiation of Screening is determined not of suitable quality by the central over-reader, the imaging study must be repeated during Screening. Any HRCT used to establish subject eligibility must undergo central interpretation. Details of the central over-read vendor will be provided to study sites in a separate document.

7.1.10.2. Surgical Lung Biopsy

Site personnel are expected to confirm at Screening whether the subject has undergone SLB by: detailed review of the medical record; focused questioning when obtaining the medical history; and physical examination focused on detection of scars suggestive of SLB.

If SLB has been performed, efforts to obtain these slides must be initiated immediately. Once the slides are in the site's possession, they must be handled per the central over-reader's instructions with special attention to obscuring all identifying information. Then, the slides will be submitted to the independent, central over-read vendor. Details of the central over-read vendor will be provided to study sites in a separate document.

SLB will be interpreted on the basis of Table 5 in Raghu et al. 2011.[2] For the purposes of this trial, the column labeled Possible UIP Pattern will be considered synonymous with Nonclassifiable Fibrosis as discussed in the ATS/ERS/JRS/ALAT statement's text under UIP Pattern: Histopathology Features; see Section 7.1.10.3.

7.1.10.3. Combined Eligibility Criteria

Table 6 adds the preceding refinements to Table 6 in the ATS/ERS/JRS/ALAT statement.[2]

Table 6: Diagnosis of IPF

	Histopathological Pattern				
HRCT Pattern	**Not Available**	**UIP**	**Probable UIP**	**Possible UIP/ Nonclassifiable Fibrosis**	**Not UIP**
UIP	ELIGIBLE	ELIGIBLE	ELIGIBLE	ELIGIBLE	NOT Eligible
Possible UIP	NOT Eligible	ELIGIBLE	ELIGIBLE	NOT Eligible	NOT Eligible
Inconsistent with UIP Pattern	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

Abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

7.1.11. Emergency Sponsor Contact

In a medical emergency, a qualified healthcare provider will attend to the subject's immediate clinical management, including administration of medical intervention according to the Standard of Care. The healthcare provider may speak with a [redacted] Project Physician who is knowledgeable about the details of this trial by contacting the [redacted] 24-Hour Call Center.

United States: [redacted]

7.2. Pharmacokinetic Assessments

7.2.1. Pharmacokinetic Sample Collection and Processing

Blood samples for PK analysis will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 5. Changes to the scheduled times of PK assessments may be proposed based on emerging PK data. Final determination for revision of the PK schedule will be the responsibility of the Sponsor and the decision will be documented in the TMF.

Samples taken from subjects who received placebo will not be analyzed.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.2.2. Pharmacokinetic Analytical Methodology

Blood concentrations of TRK-250 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

[redacted]

[redacted]

[redacted]

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (TRK-250 or placebo) and have at least 1 postdose safety assessment.

8.2.2. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of TRK-250 and have evaluable PK data.

[redacted]

8.3. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No inferential statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.4. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual blood concentration data, using commercial software such as Phoenix® WinNonlin®. Blood concentrations of TRK-250 and PK parameters will be listed and summarized using descriptive statistics.

[redacted]

8.6. Interim Analysis

Between each dose escalation, the DMC will review all available safety data to ensure it is safe to proceed with the planned dose escalation, and also to make recommendations on the escalation to a higher exposure dosing regimen, progression to Part B, and dosing regimen to be used in Part B. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PK data, where available, may also be reviewed in terms of dose escalation. These analyses will be performed with soft locked (not hard locked) data.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug in humans, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significant affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator will make a determination of the relationship of the AE to the study drug using a two-category system according to the following guidelines:

- **No reasonable possibility**: Evidence exists that the AE has a clear etiology other than the study treatment.
- **Reasonable possibility**: A temporal relationship exists between the AE onset and administration of the study treatment and cannot be readily explained by other etiologies (eg, the subject's clinical state, concomitant therapies).

In the causality assessment of the AE, in cases when the Investigator assesses that there is no reasonable possibility of a relationship between the AE and study treatment, other obvious suspected cause(s) of the event (eg, pre-existing condition, underlying disease, intercurrent illness, concomitant medication, study participation, study procedures, wash-out periods) should be provided.

Follow-up of Adverse Events

Serious adverse events (SAE) will be followed up until the subject's status reverts to baseline, the AE is determined by the Investigator to be irreversible, or death of the subject. Non-serious AE will be followed up until resolution or the AE is determined by the Investigator to be irreversible. This will be completed at the Investigator's discretion. If not possible to follow up an SAE or AE, appropriate reasons should be provided.

Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (IMP) (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

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

The investigator should notify the Sponsor or pharmacovigilance provider assigned by the Sponsor of any death or SAE that he/she may become aware of occurring at any time after a subject has discontinued or terminated study participation and that may reasonably be related to this study.

Definition of Life-Threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AE and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

If an SAE occurs, the Investigators will take appropriate action immediately and will strive to identify the causes of the event.

All SAE, irrespective of their causality, will be notified by the Investigator to the pharmacovigilance provider assigned by the Sponsor and the Medical Monitor in writing using the "Serious Adverse Event Report Form" (eg, by email or facsimile) within 24 hours of when an SAE is first recognized or reported.

Email: [redacted]

Fax: [redacted]

The provided information shall contain as much detail regarding the event as is available at the time. Investigators shall not wait to receive additional information to fully document the event, before notifying the SAE at the initial notification. Subsequently, a full written report of the SAE will be sent to the pharmacovigilance provider and Medical Monitor within 3 working days of the original notification. Further follow-up reports will be provided when new information becomes available. Where applicable, information from relevant hospital records or autopsy reports should be obtained, if possible, and provided to the pharmacovigilance provider assigned by the Sponsor and the Medical Monitor.

Food and Drug Administration (FDA)-reportable SAE will be reported to FDA by the pharmacovigilance provider on behalf of the Sponsor using FDA Form 3500A or equivalent within the timeframe required by the FDA.

The responsible Institutional Review Board (IRB) will be notified of any FDA-reportable SAE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

Pregnancy

Pregnancy in itself is not considered an AE, unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are considered AE, and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy, such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly, would meet the criteria of an SAE and therefore should be reported as an SAE. Elective abortions without complications should not be handled as an AE.

All pregnancies (even if suspected) must be reported on the appropriate CRF page (Pregnancy Form) within 24 hours of the time that the investigator became aware of the

pregnancy (or suspected pregnancy). In any case, each pregnancy should be followed until its termination (either by birth of a child or abortion) and the CRF Pregnancy Form should be updated.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Potassium Sodium Total bilirubin[a] Total CO_2 (measured as bicarbonate) Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology[b]:	**Drug screen[c]:**	**Hormone panel - women only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids	Follicle-stimulating hormone (postmenopausal women only)[b] Pregnancy test (human chorionic gonadotropin)[c]

[a] Direct bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at Screening.
[c] Blood pregnancy testing will be performed at Screening and Safety Follow-up visit and urine pregnancy testing will be performed at Day 1 predose in women of childbearing potential only. If there is doubt over the accuracy of a positive urine pregnancy test result, a blood pregnancy test must be obtained through the central laboratory to confirm the result. A local blood pregnancy test may also be performed if considered to be in the best interest of the subject (eg, travel planning).

Appendix 3: Total Blood Volume

The maximum blood volume to be withdrawn per subject (Part A or Part B), including all scheduled blood draws and any unscheduled blood draws that may be needed for subject safety, will not exceed [redacted] mL.

Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with site personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in Case Report Forms (CRF), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on CRF unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- A Study Monitor will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on a CRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's CRF data in accordance with the Data Management Plan.

A CRF must be completed for each subject who signs an ICF and undergoes any screening procedures, according to the CRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the CRF to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the CRF and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the CRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the CRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

If the Investigator expects to participate in the publication of data generated from this site, he or she must obtain prior approval of the Sponsor before submission for publication or presentation.

Appendix 5: Schedule of Assessments

Table 1: Schedule of Assessments – Part A (Single Dose)

Study Epoch	**Screening**	**Treatment**			**Follow-up**	
Study Procedures	**Screening**	**Day 1 predose**	**Day 1 dosing & postdose**	**Days 2 & 3**	**Safety Follow-up**	**Additional Follow-up**
Study Day (Window)	**-28 to -1**	**1**	**1**	**2 & 3**	**7 (+3)**	**14 (±3)**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographic data[a]	X					
Medical history	X	X[b]				
Body weight and height	X				X[c]	
Oral body temperature	X	X[d]	X	X	X	X
Blood pressure and pulse rate	X	X[d]	X[e]	X	X	X
SpO_2	X	X[d]	X[e]	X	X	X
Physical examination	X	X	X[f]	X[f]	X[f]	X[f]
Pregnancy test[g]	X	X			X	
Follicle-stimulating hormone[h]	X					
12-lead ECG	X	X	X[i]	X	X	
HRCT	X[j]					
Spirometry[k]	X	X[l]	X[l]	X	X	X
Carbon monoxide diffusion capacity[k]	X	X[d]		X	X	X
Clinical chemistry and hematology	X	X		Day 3 only	X	
Serology	X					
Urine drugs of abuse screen[m]	X					
[redacted]		[redacted]	[redacted]	[redacted]		
Nonresidential visit	X			Day 3 only	X	X
Study treatment administration			X			
Adverse event recording		X	X	X	X	X
[redacted]		[redacted]				
Pharmacokinetic blood sampling		X	X[o]			
[redacted]		[redacted]			[redacted]	[redacted]

Note, where multiple assessments are required at a single timepoint, the following order of procedures should be used: blood sampling, spirometry, other procedures (ECGs should be scheduled before vital signs measurements). See also footnote k.
Note, timing of safety and pharmacokinetic assessments may be changed based upon findings from previous cohorts.
Abbreviations: ECG = electrocardiogram; HRCT = high-resolution computed tomography; SpO_2 = oxygen saturation.

[a] To include smoking history.
[b] Interim medical history.
[c] Height measured only at Screening.
[d] Within 60 minutes prior to dosing.
[e] 1 hour and 2 hours after completion of dose administration.
[f] Symptom-directed physical examination.
[g] In women of childbearing potential. Blood pregnancy test will be performed at Screening and Safety Follow-up; urine pregnancy test will be performed at Day 1. If the Day 1 pregnancy test is positive, dosing of that subject should not proceed. If there is doubt over the accuracy of a positive urine pregnancy test result, a blood pregnancy test must be obtained through the central laboratory to confirm the result. A local blood pregnancy test may also be performed if considered to be in the best interest of the subject (eg, travel planning). If the local test is negative and there are no other clinical findings suggestive of pregnancy, the subject may be dosed.
[h] In postmenopausal women (at least 12 months postcessation of menses without an alternative medical cause) only, to confirm postmenopausal status. Confirmation of postmenopausal status requires level >40 mIU/mL in addition to appropriate history (refer to Section 6.5).
[i] 2 hours after completion of dose administration.
[j] If the most recent historical HRCT was performed more than 12 months prior to the initiation of Screening OR if the HRCT performed within 12 months prior to the initiation of Screening is determined not to be of suitable quality by the central over-reader, the imaging study must be repeated during Screening. Any HRCT used to establish subject eligibility must undergo central interpretation.
[k] Spirometry should preferably be performed before carbon monoxide diffusion capacity assessments at timepoints where both assessments are required, but if not feasible, the rationale should be documented in source records and the order of testing implemented on Day 1 should be used at every subsequent study visit.
[l] Completion of a minimum of 3, maximum of 6 forced expiratory maneuvers within 60 minutes predose. Preferably 3 but a minimum of 2 maneuvers as soon as feasible but within 15 minutes after completion of dose administration and at 30 ± 5 minutes, 60 ± 10 minutes, and 90 ± 15 minutes after completion of dose administration (up to a maximum of 16 forced expiratory maneuvers per day).
[m] Exclusionary only if positive for a drug or metabolite of a drug that has not been prescribed and that remains positive on repeat testing.
[redacted]
[o] Within 5 minutes after completion of dose administration and 10, 30, and 60 minutes after completion of dose administration, to assay for parent drug (TRK-250). PK sampling times are given as targets to be achieved within reasonable limits (eg, ±10%).

Table 2: Schedule of Assessments – Part B (Multiple Dose)

Study Epoch	**Screening**	**Treatment**		**Follow-up**	
Study Procedures	**Screening**	**Days 1, 8, 15 & 22 predose**	**Days 1, 8, 15 & 22 dosing & postdose**	**Safety Follow-up**	**Additional Follow-up**
Study Day (Window)	**-28 to -1**	**1, 8 (+1), 15 (+1) & 22 (+1) (≥7 days between doses)**		**29 (+3)**	**36 (±3)**
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographic data[a]	X				
Medical history	X	X[b]			
Body weight and height	X			X[c]	
Oral body temperature	X	X[d]	X	X	X
Blood pressure and pulse rate	X	X[d]	X[e]	X	X
SpO_2	X	X[d]	X[e]	X	X
Physical examination	X	X	X[f]	X[f]	X[f]
Pregnancy test[g]	X	Day 1 predose only		X	
Follicle-stimulating hormone[h]	X				
12-lead ECG	X	X	X[i]	X	
HRCT	X[j]				
Spirometry[k]	X	X[l]	X[l]	X	X
Carbon monoxide diffusion capacity[k]	X	X[d]		X	X
Clinical chemistry and hematology	X	X		X	
Serology	X				
Urine drugs of abuse screen[m]	X				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study treatment administration			X		
Adverse event recording		X	X	X	X
[redacted]		[redacted]			
Pharmacokinetic blood sampling		Days 1 & 22	Days 1 & 22[n]		
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	[redacted]

Study Epoch	Screening	Treatment		Follow-up	
Study Procedures	**Screening**	**Days 1, 8, 15 & 22 predose**	**Days 1, 8, 15 & 22 dosing & postdose**	**Safety Follow-up**	**Additional Follow-up**
Study Day (Window)	**-28 to -1**	**1, 8 (+1), 15 (+1) & 22 (+1) (≥7 days between doses)**		**29 (+3)**	**36 (±3)**
[redacted]					

Note, where multiple assessments are required at a single timepoint, the following order of procedures should be used: blood sampling, spirometry, other procedures (ECGs should be scheduled before vital signs measurements). [redacted]. See also footnote k.
Note, timing of safety and pharmacokinetic assessments may be changed based upon findings from previous cohorts.
Abbreviations: [redacted] DL_{CO} = carbon monoxide diffusion capacity; ECG = electrocardiogram; HRCT = high-resolution computed tomography; [redacted] SpO_2 = oxygen saturation.

[a] To include smoking history.
[b] Interim medical history.
[c] Height measured only at Screening.
[d] Within 60 minutes prior to dosing.
[e] 1 hour and 2 hours after completion of dose administration.
[f] Symptom-directed physical examination.
[g] In women of childbearing potential. Blood pregnancy test will be performed at Screening and Safety Follow-up; urine pregnancy test will be performed at Day 1. If the Day 1 pregnancy test is positive, dosing of that subject should not proceed. If there is doubt over the accuracy of a positive urine pregnancy test result, a blood pregnancy test must be obtained through the central laboratory to confirm the result. A local blood pregnancy test may also be performed if considered to be in the best interest of the subject (eg, travel planning). If the local test is negative and there are no other clinical findings suggestive of pregnancy, the subject may be dosed.
[h] In postmenopausal women (at least 12 months postcessation of menses without an alternative medical cause) only, to confirm postmenopausal status. Confirmation of postmenopausal status requires level >40 mIU/mL in addition to appropriate history (refer to Section 6.5).
[i] 2 hours after completion of dose administration.
[j] If the most recent historical HRCT was performed more than 12 months prior to the initiation of Screening OR if the HRCT performed within 12 months prior to the initiation of Screening is determined not to be of suitable quality by the central over-reader, the imaging study must be repeated during Screening. Any HRCT used to establish subject eligibility must undergo central interpretation.
[k] Spirometry should preferably be performed before DL_{CO} at timepoints where both assessments are required, but if not feasible, the rationale should be documented in source records and the order of testing implemented on Day 1 should be used at every subsequent study visit.
[l] Completion of a minimum of 3, maximum of 6 forced expiratory maneuvers within 60 minutes predose. Preferably 3 but a minimum of 2 maneuvers as soon as feasible but within 15 minutes after completion of dose administration and at 30 ± 5 minutes, 60 ± 10 minutes, and 90 ± 15 minutes after completion of dose administration (up to a maximum of 16 forced expiratory maneuvers per day).
[m] Exclusionary only if positive for a drug or metabolite of a drug that has not been prescribed and that remains positive on repeat testing.
[n] Within 5 minutes after completion of dose administration and 10, 30, and 60 minutes after completion of dose administration, to assay for parent drug (TRK-250). PK sampling times are given as targets to be achieved within reasonable limits (eg, ±10%).
[redacted]
[p] To avoid artifacts in any subsequent spirometry or DL_{CO} assessments, [redacted]
[redacted]
[r] The Day 1 sample must be taken prior to administration of any study treatment. Although it is preferred that the Day 15 sample is taken predose, this is not mandatory.