STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 25 June 2019

Study Drug: TRK-250

Sponsor Reference Number: 250IPF01
[redacted] Study Number: 8376269

Clinical Phase I

Sponsor:
Toray Industries, Inc.
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Study Site:
Multiple Sites

[redacted]:

[redacted]:

1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, pharmacokinetic (PK) [redacted] analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted]

[redacted] **Date**

[redacted] **Date**

Sponsor approval:

[redacted] **Date**

2 TABLE OF CONTENTS

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

AE	adverse event
$AUC_{0\text{-tlast}}$	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
C_{max}	maximum observed plasma concentration
BID	twice daily
DL_{CO}	carbon monoxide diffusion capacity
DMC	data monitoring committee
ECG	electrocardiogram
FEV_1	Forced expiratory volume over 1 second
FVC	forced vital capacity
ICF	informed consent form
IPF	idiopathic pulmonary fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PK	pharmacokinetic
QTcB	QT interval corrected for heart rate using Bazett's method
QTcF	QT interval corrected for heart rate using Fridericia's method
SAP	Statistical Analysis Plan
SOC	system organ class
SPO_2	Oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time of maximum observed concentration

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version dated 01 June 2019), protocol amendment No. 1 (dated 17 July 2019), protocol amendment No. 2 (dated 24 July 2018) and protocol amendment No. 3 (dated 24 September 2018).

This SAP describes the planned analysis of the safety, tolerability, PK [redacted] from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK [redacted]. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Toray Industries, Inc. and [redacted]. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Toray Industries, Inc. and [redacted] and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary

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).

5.2 Secondary

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]

[redacted]

[redacted]

5.4 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]

[redacted]

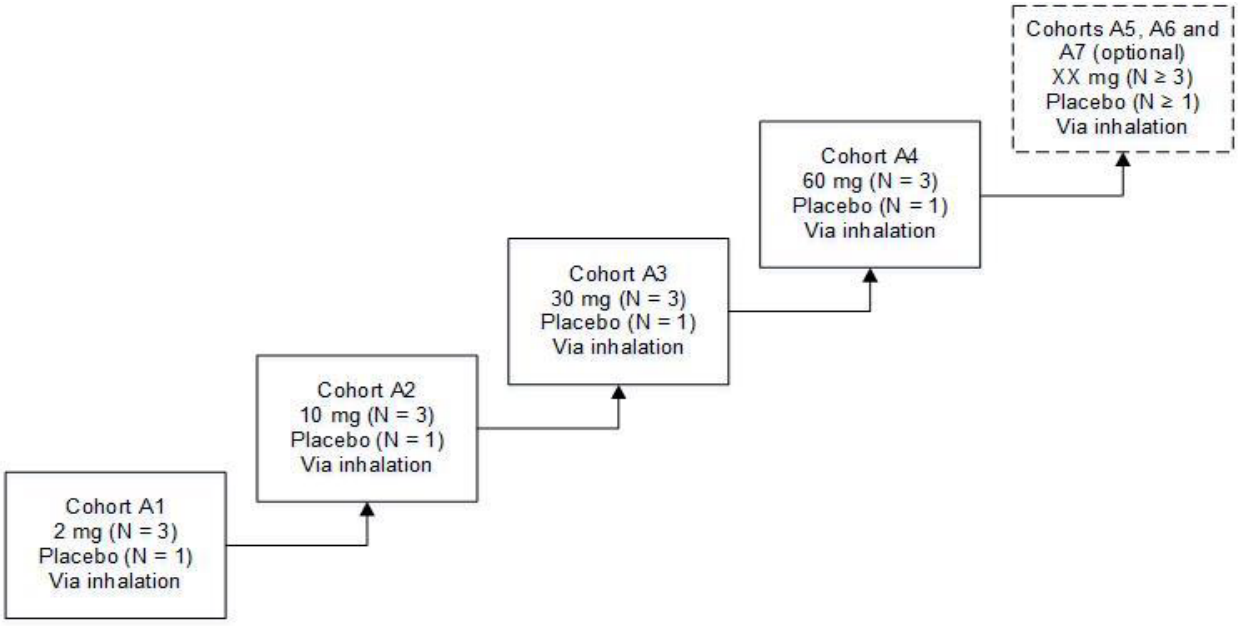
6 STUDY DESIGN

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

6.1 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.

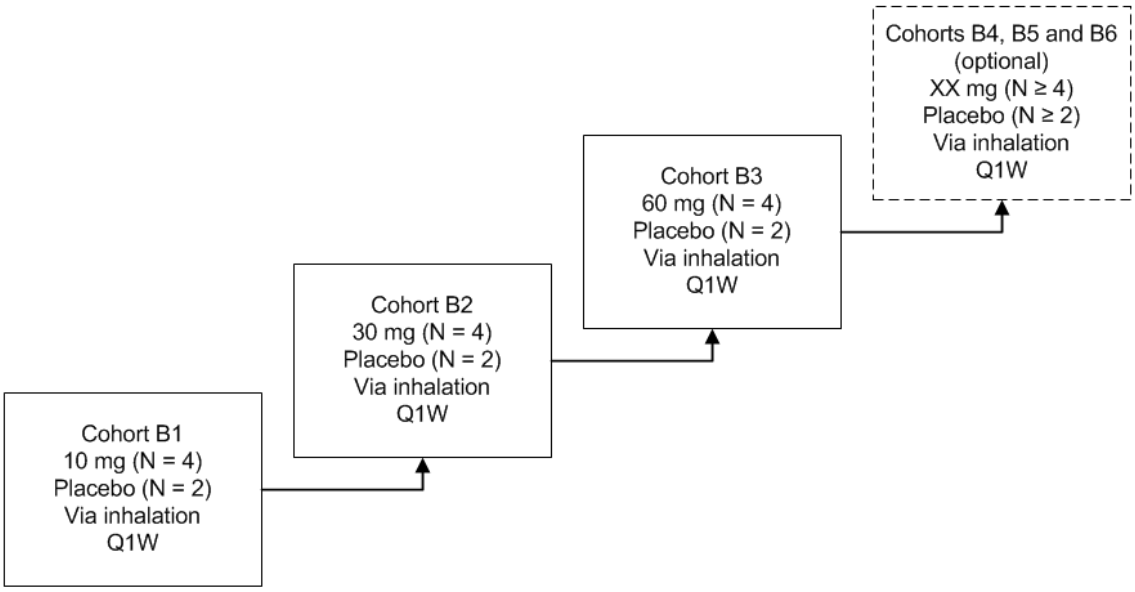
It is planned that 16 subjects will be studied in 4 cohorts (Cohorts A1 to A4), each consisting of 4 subjects. Following DMC review of the safety and tolerability data from the first 4 cohorts, up to 3 further optional cohorts (Cohorts A5 to A7) of at least 4 subjects may be added to Part A to evaluate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



6.2 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.

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.



7 TREATMENTS

The following is a list of the masked study treatment abbreviations and ordering that will be used in the Closed Report.

Part A:

Cohorts	**Treatment Order on TFLs**
Cohort A1	TRK-250 2 mg
Cohort A2	TRK-250 10 mg
Cohort A3	TRK-250 30 mg
Cohort A4	TRK-250 60 mg
Cohort A...	… mg
All Cohorts in part A	Part A Pooled placebo

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.

Part B:

Cohorts	**Treatment Order on TFLs**
Cohort B1	TRK-250 10 mg weekly
Cohort B2	TRK-250 30 mg weekly
Cohort B3	TRK-250 60 mg weekly
Cohort B…	… mg
All Cohorts in part B	Part B Pooled placebo

Up to 3 further optional cohorts (Cohorts B4 to B6) of at least 6 subjects may be added to Part B to evaluate additional doses or to further evaluate planned doses.

8 SAMPLE SIZE JUSTIFICATION

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.

9 DEFINITION OF ANALYSIS POPULATIONS

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.

The **Pharmacokinetic (PK) Population** will include all subjects who received at least 1 dose of TRK-250 and have evaluable PK data.

[redacted]

The **All Subjects Population** will consist of any subjects who signed informed consent and had study assessments recorded on the database as per the protocol.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations [redacted]

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or greater.

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). For vital signs taken in triplicate, baseline will be the median of the last 3 values taken prior to dosing. For ECGs taken in triplicate, baseline will be the mean of the last 3 values taken prior to dosing.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated, the last 3 readings are used in all subsequent calculations**.**

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. All results not taken at a scheduled timepoint for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized and listed. Subject disposition will be summarized and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following pharmacokinetic parameters will be determined where possible from the whole blood concentrations of TRK-250 using non-compartmental methods performed using Phoenix WinNonlin (Version 8.1 or higher):

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

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and T_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

10.3.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

- Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows:
    - Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
    - If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
    - If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
    - If a predose concentration is missing, these values will be set to zero.

10.3.3 Calculation of AUC

- AUC values will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive whole blood concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

- For any partial AUC determination (if required), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

10.3.4 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- PK parameter data associated with quantifiable predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

10.4 Presentation of Pharmacokinetic Data

10.4.1 Presentation of Pharmacokinetic Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a plasma or whole blood concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, it will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

10.4.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.4 Pharmacokinetic Statistical Methodology

Where data available blood concentration of TRK-250 and corresponding PK parameters will be summarized and listed. PK concentration profiles over time will be presented graphically.

[redacted]

[redacted]

10.6 Safety and Tolerability Assessments

10.6.1 Adverse Events

A pre-treatment adverse event (AE) is defined as an AE that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

All AEs will be listed. The TEAEs will be summarized by study part, treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarized by treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered having reasonable possibility relationship to the study drug.

For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

All study agent-related AEs, serious adverse events (SAE), AEs leading to withdrawal, AEs of severe intensity, life threatening and deaths will be listed separately.

10.6.2 Clinical Laboratory Parameters

All clinical chemistry, hematology data will be summarized by treatment. Changes from baseline will be calculated. Individual clinical chemistry, hematology and urinalysis listings will also be presented. In addition, all clinical chemistry, hematology and urinalysis data outside the clinical reference ranges will be summarized and listed by parameter and treatment.

10.6.3 Vital Signs

The vital signs data will be summarised by treatment, together with changes from baseline. Corresponding individual listings will also be presented.

10.6.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Bazett correction (QTcB), the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate. ECG data will be summarized and listed.

The ECG data will be summarised by treatment, together with changes from baseline.

An outlier analysis will be performed including all individual postdose measurements (not the mean data), including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF intervals will be summarised for each treatment according to the following categories: >30, >60, and ≤30 ms. All incidences of >30 and >60 ms will be flagged on the listing. In addition, the frequency of subjects with QTcB and QTcF postdose values will be summarised for each treatment, according to the following categories: >450, >480, >500, and ≤450 ms. All incidences of >450, >480, and >500 ms will be flagged on the listing.

10.6.5 Pulse Oximetry

SPO_2 data and change from baseline values will also be summarized per treatment and listed for each subject. The baseline is the last measurement before dosing.

10.6.6 Spirometry

Forced expiratory volume over 1 second (FEV_1), forced vital capacity (FVC) and their ratio will be summarized by treatment at each timepoint and listed for each individual along with their change from baseline values.

10.6.7 Carbon Monoxide Diffusion Capacity Test (DLCO)

DL_{CO} data will be summarized by treatment at each timepoint and listed for each individual along with their change from baseline values.

10.6.8 Other Assessments

All other safety assessments, [redacted] not detailed in this section will be listed but not summarized or statistically analysed.

Medical history data will be presented.

10.6.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.