Statistical Analysis Plan

Protocol No.: INS018-055-003

Official Title of Study: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects With Idiopathic Pulmonary Fibrosis (IPF)

NCT Number: NCT05938920

Statistical Analysis Plan

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Statistical Analysis Plan: Final

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Protocol Reference: INS018-055-003
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Sponsor: InSilico Medicine Hong Kong Limited

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Glossary of Abbreviations

Abbreviation	Term
6MWD	6-Minute Walk Distance
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from time zero to dosing interval
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time with last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
BID	Bis in die (twice daily dosing)
BQL	Below Quantification Limit
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Concentration
COVID-19	Coronavirus Disease of 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
CV	Coefficient of Variation
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
ESR	Erythrocyte Sedimentation Rate
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCV	Geometric Coefficients of Variation
GGT	Gamma-glutamyl transferase
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B
HCV	Hepatitis C
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus

Abbreviation	Term
hsCRP	High sensitivity C-Reactive Protein
ICH	International Council on Harmonization
INR	International Normalized Ratio
IPF	Idiopathic Pulmonary Fibrosis
ITT	Intention to treat
LCQ	Leicester Cough Questionnaire
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantification
MAR	Missing At Random
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not At Random
NC	Not Calculated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NR	No Result
PK	Pharmacokinetics
PoC	Proof of Concept
PP	Per Protocol
PT	Preferred Term
QD	Every day
QoL	Quality of Life
QTcF	Corrected QT interval by Fridericia
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SoC	Standard of Care
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-life
TEAE	Treatment Emergent Adverse Event
t_{max}	Time at which the maximum plasma concentration occurred
TRAE	Treatment-related Adverse Event
TRSAE	Treatment-related Serious Adverse Event
TSH	Thyroid Stimulating Hormone
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman Of Childbearing Potential
λz	Terminal Elimination Rate Constant

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	26Feb2024	4.0
Protocol Amendment	28Dec2022	1.0
eCRF	14Jun2023	2.0

2. Protocol Details

2.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, proof of concept (PoC) phase IIa study evaluating safety/tolerability, pharmacokinetics (PK), and efficacy of INS018_055 orally administered at three doses, 30 mg QD or 30 mg BID or 60 mg QD (maximum 60 mg daily). Patients randomized into the study will be treated for 12 weeks.

After providing informed consent, subjects will undergo a screening visit (Visit 1) up to 30 days prior to the first day of the treatment period (Day 1, Visit 2). Subjects on standard of care (SoC) treatment for idiopathic pulmonary fibrosis (IPF) with nintedanib or pirfenidone will be eligible for study enrollment and to continue receiving their nintedanib or pirfenidone throughout the study. Eligible subjects who meet all inclusion criteria and no exclusion criteria will be assigned in a 1:1:1:1 ratio to 1 of 4 treatment arms:

- INS018_055 30 mg QD
- INS018_055 30 mg BID
- INS018_055 60 mg QD
- Placebo

A target of 15 subjects will be assigned to each treatment arm. Approximately 70 patients will be enrolled to ensure approximately 60 patients complete treatment of 12 weeks. Subjects being treated with background SoC antifibrotic therapy (nintedanib or pirfenidone) at the time of randomization will be maintained on their therapy throughout the study.

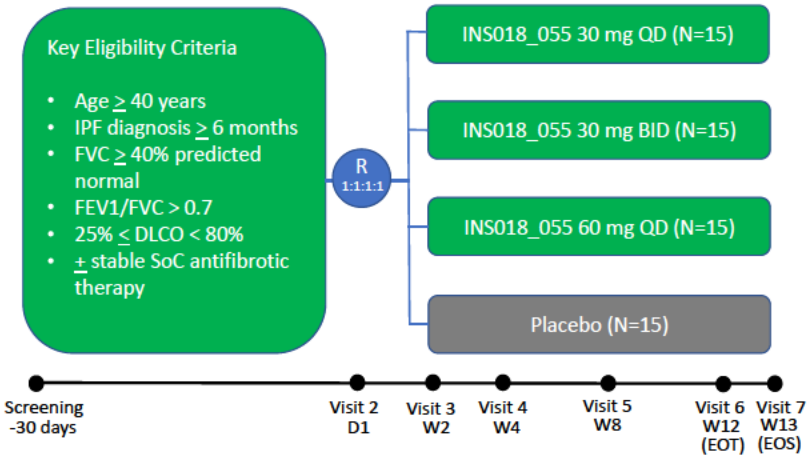
The duration of the study will be approximately 17 weeks for each subject from Visit 1 through the Visit 7 (EOS). The treatment period will include 5 visits: Study Day 1, 15 ± 3 (Week 2), 29 ± 7 (Week 4), 57 ± 7 (Week 8), and 85 ± 7 (Week 12, EOT). Subjects will return for an EOS visit approximately 1 week after completing the treatment period (Visit 7).

Following the Schedule of Study Activities, all visits [Visit 1-7 (EOS)] will include a physical exam, vital signs, weight, laboratory tests, urinalysis, medication review, assessment for adverse events (AEs), and pregnancy testing (WOCBP). During the treatment period, subjects will be also assessed for COVID-19, BMI, electrocardiogram (ECG), study drug compliance, blood sampling [PK (study drug, SoC antifibrotic therapy)], biomarker, Leicester Cough Questionnaire (LCQ), spirometry, diffuse capacity of the lungs for carbon monoxide (DLCO), 6-minute walk test (6MWD), and acute IPF exacerbations.

Safety will be assessed from Visit 1 through the follow-up visit at Week 13 (Visit 7, EOS). Efficacy assessments will occur through Week 12 (Visit 6).

Study sites will dispense INS018_055 at each study visit. Subjects will also receive placebo at each study visit to maintain blinding. Subjects will orally self-administer their assigned treatment for 12 weeks [until Week 12; Visit 6 (EOT)]. Sites will instruct subjects about treatment schedule, study diary, and return of all study medications at each visit. Sites will also follow up with patients to ensure correct self-administration. Subjects will return for a follow-up visit approximately 1 week after completing the treatment period [Visit 7; end of study (EOS)]. In case of early treatment discontinuation, subjects are expected to follow the trial schedule as per protocol.

Figure 1. Study Schema



BID = twice daily dosing, EOS = end of study; EOT = end of treatment, QD = daily dosing, R = randomized, SOC = standard of care, W = week

2.2. Study Objectives

2.2.1. Primary Objective(s)

The primary objective is to evaluate the safety and tolerability of INS018_055 orally administered for up to 12 weeks in adult subjects with IPF compared to placebo.

2.2.1.1. Estimands for the Primary Objective

Treatment: INS018_055 vs. Placebo.

Population: Patients with IPF with and without background SoC antifibrotic therapy (nintedanib or pirfenidone).

Variable: Whether patient have at least 1 treatment-emergent adverse event (TEAE).

Intercurrent Event: AE will be counted irrespective of treatment compliance, early treatment discontinuation, or use of antifibrotic or prohibited therapies (treatment policy strategy).

Population-level Summary: Percentage of patients who have at least 1 TEAE for each treatment group.

2.2.2. Secondary Objective(s)

The secondary objectives are:

- To evaluate the pharmacokinetics of INS018_055 orally administered to subjects with IPF
- To evaluate the efficacy of INS018_055 orally administered for up to 12 weeks of treatment on forced vital capacity (FVC) decline in adult subjects with IPF compared to placebo
- To evaluate the efficacy of INS018_055 orally administered for up to12 weeks of treatment to improve quality of life (QoL) and functional measures compared to placebo
- To evaluate the impact of INS018_055 orally administered on acute IPF exacerbations compared to placebo

2.2.2.1. Estimands for the Secondary Objectives

Treatment: INS018_055 vs. Placebo.

Population: Patients with IPF with and without background SoC antifibrotic therapy (nintedanib or pirfenidone).

Variable:

- Change in FVC (mL and % predicted) from Week 0 to Week 12

- Change in diffuse capacity of the lungs for carbon monoxide (DLCO % predicted) from Week 0 to Week 12
- Change in Leicester Cough Questionnaire (LCQ) from Week 0 to Week 4, 8 and 12
- Change in 6-minute walk test (6MWD) from Week 0 to Week 12

Intercurrent Event: Intercurrent events will be handled through a combination of treatment policy strategy and hypothetical strategy.

Population-level Summary: Comparison of estimated least squares means of change from baseline in FVC, DLCO, LCQ and 6MDW between active treatment group and placebo group.

2.2.3. Exploratory Objective(s)

The exploratory objective is:

- To explore the impact of oral INS018_055 on IPF biomarkers in the blood

2.3. Sample Size and Power

A sample size calculation based on statistical power considerations will not be performed. However, given an approximate sample size of 15 subjects per treatment arm, there exists a 90% probability of observing at least 1 AE if the true population rate is approximately 15%, which will be sufficient to assess the feasibility of safety parameters.

2.4. Primary Endpoint

The primary endpoint is the percentage of patients who have at least 1 TEAE.

2.5. Secondary Endpoints

The secondary endpoints are:

- PK parameters of INS018_055 and metabolites (INS018_063 and INS018_095) following the first dose on Day 1 (Visit 2) and the last dose during Week 12 (Visit 6, EOT):
  - Maximum plasma concentration (C_{max})
  - Time at which the maximum plasma concentration occurred (t_{max})
  - Area under the plasma concentration-time curve from time zero to:
    - Dosing interval τ ($AUC_{0-\tau}$)
    - Time with last measurable concentration t (AUC_{0-t})

    - Infinity (∞) ($AUC_{0-\infty}$)
  - Terminal elimination half-life ($t_{1/2}$)
  - Terminal elimination rate constant (λ_z)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V_z/F)
  - Accumulation ratio (Rac) for C_{max} and AUC
  - Trough plasma concentration (C_{trough}).
- Relative change in FVC in mL from Week 0/Visit 2 up to Week 12
- Percentage change in FVC in mL from Week 0/Visit 2 up to Week 12
- Absolute and relative change in FVC % predicted from Week 0/Visit 2 up to Week 12
- Change in Diffusion Capacity of the lung for Carbon Monoxide (DLCO) % predicted from Week 0/Visit 2 to Week 12
- Change in Leicester Cough Questionnaire (LCQ) from Week 0 to Week 4, 8 and 12
- Change in 6-Minute Walk Distance (6MWD) in meters, from Week 0 to Week 12
- Number of acute IPF exacerbations from Week 0 up to Week 12
- Number of days hospitalized for acute IPF exacerbations from Week 0 to up Week 12

2.6. Exploratory Endpoint

The exploratory endpoint is:

- Change in IPF blood biomarkers upon INS018_055 treatment from Week 0 to Weeks 2, 4, 8 and 12

3. Estimands

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of subjects targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

3.1. Estimand for the Primary Objective

The main estimand is defined through the following five attributes:

3.1.1. Treatment Condition of Interest

The primary treatment condition of interest is INS018_055 and is compared against the alternative treatment condition of placebo.

3.1.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is patients with IPF with and without background SoC antifibrotic therapy (nintedanib or pirfenidone) defined through the inclusion and exclusion criteria as part of the clinical trial protocol.

3.1.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variable to address the clinical questions is whether or not the subject have at least 1 treatment-emergent adverse event (TEAE).

3.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a treatment policy strategy. Subjects will be followed and data collected after intercurrent events will be used in the analysis.

The following intercurrent events are anticipated during the study:

- Non-compliance with the study treatment
- Early treatment discontinuation
- Use of antifibrotic or prohibited therapies

3.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the comparison of proportions of subjects who have at least 1 TEAE on INS018_055 and on placebo.

3.2. Estimands for the Secondary Efficacy Objectives

The main estimand is defined through the following five attributes:

3.2.1. Treatment Condition of Interest

The primary treatment condition of interest is INS018_055 and is compared against the alternative treatment condition of placebo.

3.2.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is patients with IPF with and without background SoC antifibrotic therapy (nintedanib or pirfenidone) defined through the inclusion and exclusion criteria as part of the clinical trial protocol.

3.2.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variables to address the clinical questions are:

- Change in FVC in mL from Week 0/Visit 2 up to Week 12
- Change in FVC % predicted from Week 0/Visit 2 up to Week 12
- Change in DLCO % predicted from Week 0/Visit 2 to Week 12
- Change in LCQ from Week 0 to Week 4, 8 and 12
- Change in 6MWD in meters, from Week 0 to Week 12

3.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a combination of treatment policy strategy and hypothetical strategy.

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 1 Handling of Intercurrent Events for the Secondary Estimand

Intercurrent event	Data collection and analysis
• Non-compliance with the study treatment • Use of antifibrotic or prohibited therapies • Early treatment discontinuation Indicators of acute IPF exacerbation	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.
• Death • Lost to follow up	For endpoints of FVC, DLCO and 6MWD, a hypothetical strategy is applied for these intercurrent events. Data collected after intercurrent events will be set as missing and will be imputed using a multiple imputation method assuming missing data are missing-at-random (MAR). For endpoint LCQ, a hypothetical strategy is applied for these intercurrent events. Analyses will be performed with MMRM analysis assuming missing at random.

3.2.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified for the above variables as follows:

- By the comparison of estimated LS means of change from baseline in FVC (mL) at Week 12 supported by the estimated difference in LS means of INS018_055 compared to placebo at Week 12.
- By the comparison of estimated LS means of change from baseline in FVC (% predicted) at Week 12 supported by the estimated difference in LS means of INS018_055 compared to placebo at Week 12.
- By the comparison of estimated LS means of change from baseline in DLCO (% predicted) at Week 12 supported by the estimated difference in LS means of INS018_055 compared to placebo at Week 12.
- By the comparison of estimated LS means of change from baseline in LCQ scores at Week 4, 8 and Week 12 supported by the estimated difference in LS means of INS018_055 compared to placebo at Week 4, 8 and Week 12.
- By the comparison of estimated LS means of change from baseline in 6MWD in meters at Week 12 supported by the estimated difference in LS means of INS018_055 compared to placebo at Week 12.

An analysis of covariance (ANCOVA)[3] model will be performed for endpoints including FVC, DLCO and 6MWD. The model will include treatment as fixed effect and baseline value as a covariate. Missing values at Week 12 will be imputed using a multiple imputation method assuming missing at random (MAR).

A Mixed Effect Repeated Measure (MMRM)[4] model assuming MAR will be performed for endpoint of LCQ. Fixed effects in the model will include treatment, visit, and baseline value as a covariates and random effects allowing for subject-specific intercepts and slopes.

3.2.6. Sensitivity Estimators for the Secondary Efficacy Estimand

A sensitivity analysis will be performed by repeating the analysis on the Per Protocol Population.

For FVC, a sensitivity analysis will be performed by repeating the analysis on population with central overread data available.

The underlying assumption of models is that missing data mechanism is MAR. Missing data not due to indicators of acute IPF exacerbation or death will be imputed based on a multiple imputation method assuming missing not at random (MNAR) framework. A sensitivity analysis under MNAR using a controlled-based jump-to reference MI method will be conducted to evaluate the robustness of efficacy results.

4. Analysis Populations

In accordance with ICH E3 and E9[5], the following analysis sets will be used for the analyses.

4.1. All Screened Population

The All Screened Population will include every subject who has signed the informed consent form. The All Screened Population will be used for summaries of disposition and the associated listing.

4.2. ITT Population

The intent-to-treat (ITT) population will include any randomized subjects. The ITT population will be used for summary of demographic and baseline characteristics. And will be used for analysis of secondary endpoints except PK analysis.

4.3. Safety Population

The safety population will include all subjects who receive at least 1 dose of study treatment.

4.4. PK Population

The PK population will include subjects who receive at least 1 dose of study treatment and have at least one measurable concentration collected postdose.

4.5. Biomarker Population

The Biomarker Population will include subjects who have pre-dose baseline value, and at least one value after treatment initiated for biomarker assessment.

4.6. SoC PK Population

The SoC PK Population will include subjects who have who receive at least 1 dose of study treatment and have at least one plasma concentration of SoC therapy.

4.7. Per Protocol Population

The Per Protocol (PP) Population will consist of all evaluable subjects in the ITT Population who do not have any major protocol deviations thought to impact the ability to assess the

effect of study treatment. PP Population are analyzed according to their randomized treatment.

Protocol deviations are defined as any change, divergence, or departure from the protocol, the principles of ICH GCP or applicable regulations. Major protocol deviations are a subset of protocol deviations which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 4.7.1 details the deviations.

4.7.1. Major Protocol Deviations Leading to Exclusion from the PP Population

Deviations from the protocol, as defined in the protocol and / or protocol deviation plan, will be documented by the study monitors and project management throughout the study period.

Only those major protocol deviations considered to impact the ability to assess the effect of study treatment will lead to complete exclusion of the subject from the PP Population. Criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock. All major protocol deviations leading to exclusion from the PP Population occurring during the study will be reviewed and approved by Sponsor prior to database lock and identified before data are unblinded.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the first day of first dose of treatment.

Day 1 is defined as first dose of treatment. Relative days on or after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of treatment for each subject will be taken from the Study Drug Administration Date and Time eCRF page. If the date in this eCRF page is missing, alternatively the date of randomization will be used.

The date of the last dose of treatment for each subject will be taken from the End of Treatment eCRF page. If the date in this eCRF page is missing, alternatively the date of End of Study will be used. If the date is missing because the subject was lost to follow-up, the date of the last visit will be used, if appropriate.

5.1.2. Screening Period/Baseline Period

For all subjects, the Screening Period is defined as the period from informed consent to the first dose of treatment. For some variables, data from more than one assessment within the Screening Period can be collected prior to the first dose of treatment.

Data collected on Day 1 (Week 0) prior to dosing will be assigned to Baseline Period.

The baseline value for a variable is therefore defined as the last non-missing value collected (from a scheduled or unscheduled visit) before the first dose of treatment, unless specifically stated otherwise.

5.1.3. Treatment Period

Data collected on Day 1 will be assigned to the Treatment Period unless the time (HH:MM) of data collection and time (HH:MM) of first dose of treatment are both recorded and the data collection time is before the time of first dose of treatment. In this case, the assessment will be assigned to the Baseline Period. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of treatment, the data collected on

Day 1 will be assigned to the Baseline Period. Adverse events collected on Day 1 prior to first does administration will be assigned to the Baseline Period. However, medications starting on Day 1, will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date / time of the first dose of treatment up to and including the date / time of the last dose of treatment.

5.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis.

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

For subjects with missing value in continuous secondary efficacy endpoints including FVC, DLCO and 6MWD, a multiple imputation using the regression method will be applied. The imputation will be performed within each treatment group assuming missing outcomes are missing at random (MAR).

For the LCQ score, the calculation of physical and psychological domain scores allows only 1 missing item, while no missing value is allowed for the calculation of social domain score. The average item score is calculated from items completed within a domain and is then used as the value for the missing items. Domain scores will not be calculated if the number of missing items is more than allowed. Calculation of total LCQ score will require all 3 non-missing domain scores, otherwise the total LCQ score will be considered as missing.

For LCQ score, missing data issues will be handled implicitly through using mixed-effects models repeated-measures (MMRM) with assumption of MAR.

To assess the sensitivity of the secondary efficacy analysis results, missing data not due to indicators of acute IPF exacerbation or death will be imputed by MI using jump-to-reference methodology assuming missing not at random (MNAR) to assess the robustness to missing at random (MAR) assumption.

Details regarding each of these analyses are provided in Section 6.6.

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication, procedure and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications and Procedures

Missing and / or incomplete dates for medications / procedures and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication/procedures or AE is “Ongoing”. AE with missing end date will be considered as “Ongoing”. Technically, this will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of: the earliest possible start date, and the date of first dose of treatment.
- The latest possible start date.
- The latest possible stop date.

For a missing / incomplete stop date the latest date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month, if month and year are available but the day is missing.
- The date of the first day of the year, if year is available but day and month are missing.
- The day of informed consent, if the date is completely missing.

The latest possible date is defined as:

- The date itself if available.
- The date of the last day of the month, if month and year are available but the day is missing.
- The date of the last day of the year, if year is available but day and month are missing.
- The date of last known date on the study for the subject plus one year, if the date is completely missing.

5.2.4. Handling of Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the quantification limit (BQL) will be set to zero in PK parameter calculation, with defined exceptions as follows:

- Any embedded BQL value (between 2 quantifiable concentrations) and BQL 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 BQL 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 BQL, the profile will be excluded from the PK analysis.
- For single dose or first dose of multiple dose phases: If a predose concentration is missing, these values may be set to zero by default.

For presentation of BQL plasma concentration in summary table, the following rules will apply:

- Values that are BQL will be set to 0 for the calculation of summary statistics.
- If an embedded BQL value is considered anomalous within the concentration time profile, this value will be excluded from the summary statistics.
- Where there is no result (NR) or nonreportable concentration values, these will be set to missing.
- If all the values are BQL , then the arithmetic mean, SD, coefficient of variation, median, min and max will be presented as 0, and the geometric mean and geometric %CV will be denoted as NC.
- If there are less than three values in the data series, only the min, max, n and n (BQL) will be presented. The other summary statistics will be denoted as not calculated (NC).
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as 0 and the geometric mean and geometric %CV will be denoted as NC.
- Out-of-window blood samples will be excluded from the calculation of descriptive statistics.

For plot of BQL plasma concentration, BQL values will be set to zero in linear-linear plots but will not be plotted in the semi-logarithmic plots.

5.2.5. Handling of Pharmacokinetic Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic 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 BQL values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive predose value(s) of first dosing greater than 5% of Cmax may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

5.2.6. Handling of Values Below the Limit of Quantification in Biomarker Analysis

BQL values in biomarker data will be set to half of the lower limit of quantification in summary tables and plots.

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those subjects with data.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

In accordance with the baseline value definition in Section 5.1.2, the absolute and percentage change from baseline will be derived as follows:

Absolute change (unit) = post-baseline value – baseline value

Percentage change (%) = [(post-baseline value– baseline value) / baseline value] × 100

All statistical comparisons will be made using two-sided tests at the α=0.05 significance level unless specifically stated otherwise. No hypothesis testing will be performed in the confirmatory sense. All the analyses will be performed in an exploratory fashion to better understand the efficacy and safety profile of INS018_055 in patients with IPF.

All laboratory test results will be received from the local laboratories. For the TFLs, the results will be summarized or presented in International System of Units (SI) units.

6.2. Subject Disposition and Data Sets Analyzed

Subject disposition will be summarized by treatment group and overall, where appropriate, for the All Screened Population. The following information will be reported:

- Number of subjects for the following categories:
  - Screened
- Number and percentage of subjects for the following categories:
  - Randomized

  - Treated
  - Not Treated
  - Complete the treatment
  - Discontinued the treatment
  - Reasons for treatment discontinuation
  - Completed the study
  - Discontinued the study
  - Reasons for study discontinuation
- Number and percentage of subjects included in each study population
- Number and percentage of subjects who met / did not meet all eligibility criteria, together with the criteria not met
- Number and percentage of subjects who failed screening prior to randomization, including the primary reason for screen failure

A subject will be regarded as having completed the study if the status recorded on the End of Study eCRF form is Complete. A subject will be considered as having discontinued the study if they have a status of study discontinuation on the End of Study eCRF form.

A listing of all subjects with their treatment and study completion status, including the respective reasons for treatment and study discontinuation, their randomization details, including first dose date and time, and actual treatment received will be presented for the All Screened Population.

A listing of all screen failed subjects with their reasons for screen failure will be presented for the All Screened Set. A separate listing of subjects who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for the All Screened Population.

A listing of all subjects included in at least one analysis set will be presented for the All Screened Population.

6.3. Protocol Deviations

All major protocol deviations leading to exclusion from the PP Population (see Section 4.7.1) will be summarized for the ITT Population by treatment group and overall. The number of unique subjects with at least one major protocol deviation which led to exclusion from the PP Population as well as the number of subjects in each major protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all subjects with one or more protocol deviations will be presented for the ITT Population.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the ITT Population by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at Baseline
- Weight (kg) at Baseline
- Body Mass Index (kg/m^2) at Baseline

Total counts and percentages of subjects will be presented for the categorical variables of:

- Age group (years):
  - <= 65
  - > 65 to <= 75
  - >75
- Sex
  - Childbearing potential
- Race
- Ethnicity

Demographic characteristics will be listed for the ITT Population.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the ITT Population by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

Standard descriptive statistics will be presented for the continuous variables of:

- FVC (actual) at Baseline
- FVC (% predicted) at Baseline
- DLCO (actual) at Baseline
- DLCO (% predicted) at Baseline
- 6MWD at Baseline
- LCQ at Baseline

Total counts and percentages of subjects will be presented for the categorical variables of:

- Smoked or used tobacco products
- Alcohol Drinking Status
- Drug Abuse Status
- Type of current standard-of-care for IPF
- HBsAg
- HBcAb
- HCV antibody
- HIV-1 antibody
- HIV-2 antibody
- Specific Treponema Pallidum Antibody
- Syphilis
- HCV RNA (qualitative)
- HBV DNA (qualitative)
- HRCT assessments
    - Type of Diagnosis
    - Histopathology Pattern

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the ITT Population.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the subject may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 27.0] (or later)] and will be presented by System Organ Class (SOC) and Preferred Term (PT). The SOCs and PTs are to be sorted by descending frequency order of system organ class, then descending frequency order of preferred term in the total column. Where SOCs or PTs tie these will be sorted alphabetically.

Medical history records will be summarized for the ITT Population by treatment group and overall as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented.

Medical history records will be listed by-subject and within-subject by medical history start date for the ITT Population.

6.4.4. Prior and Concomitant Medications / Procedures

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version March 2024 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes. The procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 27.0 (or later)] and will be presented by System Organ Class (SOC) and Preferred Term (PT).

Prior medications and concomitant medications are defined as follows:

- Historic use of anti-fibrotic therapy is defined as record with a stop date prior to screening.
- Current use of anti-fibrotic therapy is defined as record with a start date prior to EOT and a stop date on or after screening, or is ongoing at the end of the study.
- Prior medications / procedures other than anti-fibrotic therapy are those with a stop date prior to the start of the Treatment Period.
- Concomitant medications / procedures other than anti-fibrotic therapy are those with a start date on or after the start of the Treatment Period, or those with a start date before the start of the Treatment Period and either a stop date on or after the start of the Treatment Period, or are ongoing at the end of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication / procedures.

Prior and concomitant medications / procedures will be summarized separately for the ITT Population by treatment group and overall as follows:

- The number and percentage of patients with historic / current use of anti-fibrotic therapy will be presented. Patients with at least one current use of anti-fibrotic therapy will be classified as current use of anti-fibrotic therapy, otherwise will be classified as historic use of anti-fibrotic therapy.
- The number and percentage of patients with at least one prior / concomitant medication will be presented.
- The number and percentage of patients with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using descending frequency order of Anatomical Group, then descending frequency order of Therapeutic Subgroup, then descending frequency order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.
- The number and percentage of patients with at least one prior / concomitant procedure will be presented.

- The number and percentage of patients with at least one prior / concomitant procedure within each SOC and PT. The summary will be sorted by sorted by descending frequency order of SOC, then descending frequency order of PT in the total column. Where terms tie, these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the ITT Population. In the listings the relative start and stop day of prior / concomitant medication / procedures use will be calculated relative to the first dose date of treatment and will be presented for those subjects who received at least one dose of treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Treatment Compliance

Treatment compliance is defined as the number of capsules that were actually taken relative to the number of capsules that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance, assessed by capsule count, will be calculated as follows:

$$\textit{Compliance (\%)} = \frac{\textit{Number of capsules actually taken}}{\textit{Number of capsules which should have been taken as directed by the investigator}} \times 100\%$$

The calculated percentage compliance will be categorized as:

- < 80% compliance
- ≥ 80% to ≤ 120% compliance
- > 120% compliance

Compliance will be summarized for the ITT Population by treatment group as follows:

- Percent compliance will be presented by default summary statistics.
- Number and percentage of subjects within each of the compliance categories will be presented. Any subjects with missing data will be presented as part of a "Missing" category.

Treatment compliance will be listed together with exposure for the ITT Population. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy

6.6.1. Primary Efficacy Analysis

The primary efficacy endpoint is change in FVC from Week 0 up to Week 12 defined as follows:

- Absolute and relative change in FVC in mL from Week 0 up to Week 12
- Absolute and relative change in FVC % predicted from Week 0 up to Week 12

The main analysis of this endpoint will be based on the ITT population.

Observed value at Week 0 and Week 12, and the absolute and percentage changes from baseline will be summarized using standard descriptive statistics for each treatment group and overall for FVC (mL), FVC (% predicted), FEV1 (mL), FEV1 (% predicted), FEV1/FVC (actual), and FEV1/FVC (% predicted).

For spirometry results collected by local lab, the baseline values for FVC and FEV1 will be defined as the values collected at Visit 2. The predicted FVC, % predicted FVC, predicted FEV1, % predicted FEV1, predicted FEV1/FVC, and % predicted FEV1/FVC will be calculated using the Global Lung Function Initiative (GLI) 2012 spirometry prediction equations[6]. Mean value will be used when there are multiple results reported for one visit.

FVC (% predicted) = FVC (actual) / FVC (predicted) × 100

FEV1 (% predicted) = FEV1 (actual) / FEV1 (predicted) × 100

FEV1/FVC (% predicted) = FEV1/FVC (actual) / FEV1/FVC (predicted) × 100

FVC and FEV1 data confirmed by central reading will be coded as “acceptable”, “borderline acceptable” and “unacceptable”. “Unacceptable” results will not be used for analysis. Baseline measurement (Visit 2) will be the reference visit only when both FVC and FEV1 are coded as “acceptable” or “borderline acceptable” at Visit 2. Otherwise, the baseline values for FVC and FEV1 will be defined as the “acceptable” or “borderline acceptable” values collected in screening visit.

If multiple “acceptable” or “borderline acceptable” results are reported for one visit, mean values of the “acceptable” or “borderline acceptable” results will be used for data analysis.

For FEV1/FVC data, only valid records with both FVC and FEV1 are “acceptable” or “borderline acceptable” at the same time will be included in analysis. Mean value will be calculated if there are multiple valid FEV1/FVC. If Visit 2 is set as baseline but no valid result for FEV1/FVC in Visit 2, baseline FEV1/FVC will be set as missing.

For spirometry results confirmed by central lab, the predicted FVC, % predicted FVC, predicted FEV1, % predicted FEV1, predicted FEV1/FVC, and % predicted FEV1/FVC will be provided by central lab. Mean values will be used if there are multiple results reported for one visit.

Method for spirometry testing should remain the same in both baseline and Week 12. Data collected in Week 12 with different method than that used in baseline will not be included in analysis and will be set as missing.

An analysis of covariance (ANCOVA) model will be used to analyze the absolute and percentage changes from baseline in FVC (mL) and FVC (% predicted). The model will include treatment as fixed effect and baseline FVC value as a covariate. The least squares mean change from baseline with the associated standard error (SE), and the 2-sided 95% CI will be presented for each treatment group. Least squares mean differences between the INS018_055 group and placebo group, along with corresponding 2-sided 95% CIs and p-values will also be presented. No multiplicity adjustment will be performed.

To handle missing values, multiple imputation will be performed. All subjects with non-missing baseline measurement will be included. Since there is only one post-baseline visit for spirometry assessment, the missing pattern would be monotone if endpoint values are not available. The detailed steps for imputation are specified below:

1) Imputation will be done within each treatment arm assigned at randomization via SAS PROC MI with the MCMC statement. Imputation will be performed on actual values, absolute and percentage changes are calculated after the imputation.
2) For each completed dataset, the ANCOVA model specified above will be performed to compare the absolute and percentage changes from baseline to Week 12 between INS018_055 group and the placebo group.
3) The inference will be drawn using Rubin's rules via SAS PROC MIANALYZE.

6.6.2. Sensitivity for the Primary Efficacy Analyses

A sensitivity analysis to the primary analysis will be explored on the Per Protocol Population, using the same statistical methods for primary efficacy analysis. Multiple imputation will not be performed, i.e., subjects with missing value at Week 12 will be excluded from the model.

Another sensitivity analysis to the primary analysis will be performed on subjects with FVC central overread data available using the same statistical methods for primary efficacy analysis. Multiple imputation will not be performed.

The underlying assumption of the primary efficacy analysis is that missing data mechanism is MAR. To stress test the robustness of the primary analysis results, a sensitivity analysis under MNAR using a controlled-based jump-to-reference MI method will be conducted for missing data not due to indicators of acute IPF exacerbation or death. The analysis will be performed on ITT Population. The detailed steps are specified as follow.

1) For placebo patients, missing data will be imputed based on placebo group data, assuming the missing data are MAR.
2) For patients in INS018_055 groups, missing values due to indicators of acute IPF exacerbation or death will be imputed based on INS018_055 data, assuming the missing data are MAR. Missing values not due to indicators of acute IPF exacerbation or death will be imputed using the imputation model built from the placebo group, assuming the subjects with missing data in the treatment group will have a similar response profile to the subjects in the placebo group. Imputation will be performed via SAS PROC MI with the MNAR statement.
3) For each completed dataset, the ANCOVA model as specified in the primary analysis will be performed.
4) The inference will be drawn using Rubin's rules via SAS PROC MIANALYZE.

6.6.3. Secondary Efficacy Analysis

6.6.3.1. Change in DLCO (%) Predicted from Week 0 to Week 12

The predicted DLCO, % predicted DLCO, and corrected % predicted DLCO will be calculated using the GLI equation[7]. The % predicted DLCO will be calculated as DLCO (Actual) / DLCO (Predicted) × 100. Baseline measurement (Visit 2) will be the reference visit. If there is no acceptable results at baseline visit, the last acceptable result in screening visit will be used as the baseline value. If multiple acceptable results are reported for one visit, mean values of the acceptable results will be used for data analysis.

Predicted DLCO corrected for haemoglobin (Hb)[8] expressed in g x dL^{-1} can be calculated as:

Males: Predicted DLCO corrected for Hb = Predicted DLCO x [1.7Hb/(10.22+Hb)]
Females: Predicted DLCO corrected for Hb= Predicted DLCO x [1.7Hb/(9.38+Hb)]

The % predicted DLCO corrected for Hb will be calculated as DLCO (Actual) / Predicted DLCO corrected for Hb × 100.

The descriptive statistics will be provided for the actual DLCO, % predicted DLCO, % predicted DLCO corrected for Hb and changes from baseline to Week 12 by treatment group and total.

Absolute and percentage changes from baseline in DLCO (% predicted) will be analyzed using the ANCOVA model with multiple imputation as described in Section 6.6.1.

6.6.3.2. Change in LCQ from Week 0 to Week 4, Week 8 and Week 12

The LCQ is a 19-item questionnaire that examines 3 domains: physical, psychological and social. Domain score will be calculated as (sum of score from items in domain) / (number of items in domain) and the total score is calculated by adding the individual domain scores. The range for the total score on the LCQ is 3-21, and each domain score ranges from 1-7.

Domain	Number of items	Items
Physical	8	1,2,3,9,10,11,14,15
Psychological	7	4,5,6,12,13,16,17
Social	4	7,8,18,19

The LCQ tool domain-specific scores and total score at Week 0, Week 4, Week 8 and Week 12, and the changes from Week 0 to Week 4, Week 8 and Week 12 will be summarized using standard descriptive statistics for each treatment arm and total. Baseline measurement (Visit 2) will be the reference visit.

The mean value of LCQ tool domain-specific scores and total score over time will be plotted by treatment groups.

For total LCQ score, the absolute and percentage changes from baseline will be analyzed using a mixed model repeated measures (MMRM) with a random coefficient regression model. The model will include treatment, visit, treatment by visit interaction as fixed effects, baseline value as a covariate, and patient as random effect. Least squares means, their SE, 2-sided 95% CI, p value and the least squares means difference between INS018_055 and Placebo at Week 4, Week 8 and Week 12 will be presented.

6.6.3.3. Change in 6MWD from Week 0 to Week 12

Observed values in 6MWD (in meters) at Week 0 and Week 12, and change from baseline to Week 12 will be summarized using standard descriptive statistics for each treatment group. Baseline measurement (Visit 2) will be the reference visit. If there is no result at baseline visit, the last non-missing result in screening visit will be used as the baseline value.

Absolute and percentage changes from baseline in 6MWD will be analyzed using the ANCOVA model with multiple imputation as described in Section 6.6.1.

6.6.4. Sensitivity Analyses for the Secondary Efficacy Analysis

Analyses of secondary efficacy endpoints will be performed on the Per Protocol Population with observed data only.

Sensitivity analysis for the secondary efficacy variables including change from baseline in DLCO (% predicted) and change from baseline in 6MWD will be performed using the controlled-based jump-to-reference MI method described in Section 6.6.2, assuming missing not at random (MNAR) mechanism.

Sensitivity analysis for LCQ assuming MNAR mechanism will be performed as follows:

1. Intermittent missing values will be imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation will be done by treatment group via SAS PROC MI with the MCMC statement.
2. For placebo patients, missing data will be imputed based on placebo group data, assuming the missing data are MAR.
3. For patients in INS018_055 groups, missing values due to indicators of acute IPF exacerbation or death will be imputed based on INS018_055 data, assuming the missing data are MAR. Missing values not due to indicators of acute IPF exacerbation or death will be imputed using the imputation model built from the placebo group, assuming the subjects with missing data in the treatment group will have a similar response profile to the subjects in the placebo group. Imputation will be performed via SAS PROC MI with the MNAR statement.
4. Once the complete datasets are formed, the analyses for secondary efficacy endpoints specified above will be performed to each completed set.
5. Rubin's rule via SAS PROC MIANALYZE will be used to combine the analysis results in order to draw inference.

6.6.5. Subgroup Analysis

Not Applicable.

6.7. Safety

6.7.1. Extent of Exposure

Duration of exposure will be defined in week as:
Exposure (weeks) = ([date of last dose – date of first dose] + 1 – off-treatment days) / 7

Off-treatment days will be calculated as the sum of days that patient did not take any study drug.

The calculated exposure duration of exposure will be categorized as:

- less than 2 weeks
- >= 2 weeks to < 4 weeks
- >= 4 weeks to < 8 weeks
- >= 8 weeks to < 12 weeks
- >= 12 weeks

Duration of exposure will be summarized in two ways for the Safety Population by treatment group and overall.

- Descriptive statistics will be presented for duration of exposure.
- Number and percentage of patients within each of the exposure categories will be presented.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the Safety Population. Further, study treatment administration data will be listed for the Safety Population.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 27.0 or higher]. Adverse event related definitions in this study are as follows:

- TEAEs are either events with start date on or after the start of the Treatment Period and up to 17 days after EOT, or events with start date prior to the start of the Treatment Period whose severity worsens on or after the start of the Treatment Period and up to 17 days after EOT.
- Serious AEs (SAEs) will be defined as AEs regarded by the investigator as Serious Event= “Yes”.
- The relationship between an AE and study treatment is assessed as definite, probable, possible, unlikely, or unrelated. A treatment-related adverse event (TRAE) will be defined as an AE considered by the investigator as definitely, probably, or possibly related to study treatment or with unknown / missing relationship to study treatment. The most recent relationship will be used when there is multiple records for the same AE.
- The relationship between an AE and standard of care (SoC) antifibrotic therapy (nintedanib or pirfenidone) is assessed as definite, probable, possible, unlikely, unrelated, or not applicable. A SoC-related adverse event will be defined as an AE considered by the investigator as definitely, probably, or possibly related to nintedanib or pirfenidone. The most recent relationship will be used when there is multiple

records for the same AE. AE with unknown / missing relationship to nintedanib or pirfenidone will be treated as follow:

- Subjects with background SoC antifibrotic therapy, any AE with a missing relationship to nintedanib or pirfenidone will be treated as SOC-related.
- Subjects without background SoC antifibrotic therapy, the relationship should be assessed as not applicable. If subject receives SoC therapy after the last dose of treatment, any subsequent AE with a missing relationship will be treated as SOC-related.

- Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[9], version 5.0). The maximum severity will be used when there is multiple records for the same AE.
- AEs leading to discontinuation of treatment are defined as AEs where "Action Taken with Study Treatment" is indicated as "Drug Withdrawn".
- AEs leading to death are defined as AEs where "Outcome" is indicated as "Fatal", or linked to AE specified in "Death reason is Adverse Event" in "Death" Form.

In addition to the aforementioned AE types, AEs of special interest (AESIs) will be identified using the following definitions:

- Gastrointestinal: diarrhea, nausea, vomiting, clinical bleeding
- Hepatic injury. A hepatic injury is defined by the following alterations of hepatic laboratory parameters
  - An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) $\geqslant$ 3-fold ULN combined with an elevation of total bilirubin $\geqslant$ 2-fold ULN measured in the same blood draw sample, or
  - Aminotransferase (ALT, and/or AST) elevations $\geqslant$ 10-fold ULN

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the Safety Population by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:
  - TEAEs
    - TEAEs by maximum severity (CTCAE grades)
    - TEAEs with CTCAE grade ≥3
    - TEAEs leading to discontinuation of treatment
    - TEAEs leading to death
  - Treatment-emergent SAE
    - TESAEs by maximum severity (CTCAE grades)
    - TESAEs with CTCAE grade ≥3
    - TESAEs leading to discontinuation of treatment
    - TESAEs leading to death
  - AESIs

  - TRAEs
    - TRAEs by maximum severity (CTCAE grades)
    - TRAEs with CTCAE grade ≥3
    - TRAEs leading to discontinuation of treatment
    - TRAEs leading to death
  - Treatment-related SAEs (TRSAEs)
    - TRSAEs by maximum severity (CTCAE grades)
    - TRSAEs with CTCAE grade ≥3
    - TRSAEs leading to discontinuation of treatment
    - TRSAEs leading to death
  - SoC-related AEs
    - SoC-related AEs by maximum severity (CTCAE grades)
    - SoC-related AEs with CTCAE grade ≥3
    - SoC-related AEs leading to discontinuation of treatment
    - SoC-related AEs leading to death
- The number and percentage of patients reporting each AE will be summarized by SOC, PT and maximum severity (CTCAE grades) for the following types of AEs:
  - AEs
  - SAEs
- The number and percentage of patients reporting each TEAE will be summarized by SOC, PT and maximum severity (CTCAE grades) for the following types of TEAEs:
  - TEAEs
  - TRAEs
  - SoC-related TEAEs
  - Treatment-emergent SAEs (TESAEs)
  - Treatment-related SAEs (TRSAEs)
  - AESIs
- The number and percentage of patients with TEAE will be summarized by SOC, PT and relationship for the following types of TEAEs:
  - TEAEs
  - TESAEs
  - ASEIs
- The number and percentage of patients who died will be summarized by the primary reason of death

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC

or PT. TEAEs with missing severity will be included in the counts of the 'Number of Patients with at least one TEAE', 'System Organ Class' and 'Preferred Term' rows of the summary but they will not be included in the counts by severity.

Summaries by SOCs and PTs will be sorted by descending frequency order of SOC, then descending frequency order of PT in the total column. Where SOC or PT tie they will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those subjects who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of deaths
- Listing of SAEs
- Listing of AEs leading to discontinuation of treatment
- Listing of AEs leading to death
- Listing of AEs of special interest

6.7.3. Acute IPF Exacerbations

The number of acute IPF exacerbations, and number of hospitalization days for acute exacerbations from baseline up to Week 12/EOT will be summarized by treatment arm and overall for the Safety Population. Number of days hospitalized for acute IPF exacerbations will be calculated as sum of [(discharge date – admission date) + 1].

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint "Week 12/EOT".

6.7.4. Laboratory Evaluations

Data for the following laboratory tests recorded in the eCRF are to be measured at the scheduled visits indicated in the study flowchart. For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with

data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint "Week 12/EOT".

Table 2 Laboratory Tests

Hematology Test	Serum Chemistry Test	Urinalysis
• Hematocrit • Hemoglobin • RBC count • Reticulocyte count • WBC with differential ○ Eosinophils ○ Basophils ○ Monocytes ○ Lymphocytes ○ Polymorphonuclear neutrophils (segs) (if automatic differential WBC is abnormal) ○ Band neutrophils (stabs) (if automatic differential WBC is abnormal) • Platelet count • Erythrocyte sedimentation rate (ESR)	• Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • Gamma-Glutamyl transferase (GGT) • Creatine Kinase (CK) • CK-MB (if CK is elevated) • Glucose • Creatinine • Total Bilirubin • Direct and indirect Bilirubin • Total protein • High sensitivity C-Reactive Protein (hsCRP) • Blood Urea Nitrogen (BUN) • Urea • Uric acid • eGFR • Sodium • Potassium • Calcium • Chloride • Inorganic Phosphate • Albumin	• Color • Appearance • pH • Specific gravity • Glucose • Erythrocytes • Leukocytes • Protein • Urobilinogen • Urine bilirubin
Lipid Panel	**Coagulation**	**Hormone Test**
• Total cholesterol • Triglycerides • low density lipoprotein (LDL) • low density lipoprotein (HDL)	• aPTT • International Normalized Ratio (INR) • Prothrombin time • Fibrinogen	• Thyroid stimulating hormone (TSH) • fT3 • fT4

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed visit will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Population by treatment group and overall as follows:

- Observed values and change from baseline at each assessed visit for each standard continuous laboratory parameter;
- Number and percentage of patients with categorized shift (low, normal and high) values relative to the reference range at baseline compared to each post-baseline visit for each standard continuous laboratory parameter;
- Number and percentage of patients with categorized shift (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) values from baseline to each post-baseline visit for urinalysis test

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed.

The summary tables will include data from scheduled visits only, while data from unscheduled visits will not be included in summaries but will be listed.

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety Population. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low for applicable laboratory assessments.

The mean laboratory results over time will be plotted by treatment groups for Hematology, Serum Chemistry and Lipid Panel.

6.7.5. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- Systolic blood pressure (mmHg);
- Diastolic blood pressure (mmHg);
- Pulse rate (beats/min);
- Body temperature (C).

The following will be summarized by treatment group and overall for the Safety Population:

- Observed values and change from baseline at each assessed visit for each standard vital sign parameter using default summary statistics for continuous variables;
- Number and percentage of patients with categorized shift (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) values from baseline to each post-baseline visit

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint "Week 12/EOT".

A listing of all vital signs data including derived change from baseline will be provided for the Safety Population.

6.7.6. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- An overall ECG assessment classified as normal, abnormal, not clinically significant/ abnormal, clinically significant
- Heart rate (beats/min);
- RR interval (ms);
- PR interval (ms);
- QRS interval (ms);
- QT interval (ms);
- QTcF interval (ms);

The maximum post-baseline QTcF values will be classified in accordance with the ICH E14[10], Boundaries as presented in Table 3. The analysis will include all individual scheduled and unscheduled post-baseline values.

Table 3 QTcF Interval ICH E14 Boundaries

QTcF Interval	Criteria (msec)
Observed QTcF interval	<=450 ms >450 to <= 480 ms >480 to <= 500 ms >500 ms
Change from baseline in QTcF interval	<=30 ms >30 to <= 60 ms >60 ms

The ECG findings will be summarized by treatment group and overall for the Safety Population as follows:

- Observed values and change from baseline at each assessed visit for each ECG parameter using default summary statistics for continuous variables;
- Shifts from baseline of overall ECG assessment (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to each post-baseline visit
- A categorical summary of QTcF classification according to ICH E14 boundaries will be provided using counts and percentages for baseline and maximum post-baseline value.

For subjects with triplicate ECG measurements, the average of the triplicate measurements will be used in summary tables and will be listed with each of the triplicate measurements.

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint “Week 12/EOT”.
A listing of all ECG data including derived change from baseline will be provided for the Safety Population.

6.7.7. Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or AEs as appropriate and will be listed and summarized as such [See Sections 6.4.3 (Medical History) and 6.7.2 (Adverse Events)].

For each physical examination body system, the physical examination result will be summarized by treatment group and overall for the Safety Population as follows:

- Number and percentage of patients with abnormalities (abnormal, not clinically significant vs. abnormal, clinically significant) at baseline and at each assessed visit
- Number and percentage of patients with categorized shift (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) values from baseline to each post-baseline visit

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint “Week 12/EOT”.

Physical examination findings (normal/abnormal) and details of abnormalities will be listed for each patient at each assessed visit.

6.7.8. Other Safety Variables

Pregnancy test result will be listed.

6.7.9. Interim Analysis and Data Monitoring

No interim analysis will be planned for this study.

A DSMB will be established. Members of the DSMB are physicians experienced in the treatment of the disease under investigation and a statistician. The DSMB will assess safety

and tolerability during the study by evaluating entire safety data on an ongoing basis. The tasks and responsibilities of the DSMB will be specified in a DSMB charter.

6.8. Pharmacokinetic Assessments

Blood samples for plasma concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be collected at specific time points:

- Visit 2: pre-dose and post-dose (15 min, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 24 hrs prior to next dosing)
- Visits 3, 4 and 5: pre-dose
- Visit 6 (EOT): pre-dose and post-dose (15 min, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 24 hrs)

Blood samples for plasma concentrations of pirfenidone and nintedanib will be collected at the following time points:

- Visit 2: pre-dose (i.e., prior to pirfenidone or nintedanib and INS018_055 dosing, in order to get the baseline trough plasma concentration of pirfenidone or nintedanib)
- Visits 3, 4, 5, and 6 (EOT): pre-dose

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint “Week 12/EOT”.

6.8.1. Pharmacokinetic Plasma Concentration

Pharmacokinetic concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be summarized for the PK Population for each visit by treatment group and overall using protocol scheduled times and appropriate summary statistics including: n, arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric coefficient of variation (%GCV).

Trough concentration of pirfenidone and nintedanib will be summarized for the SoC PK Population for each visit by treatment group and overall using protocol scheduled times and appropriate summary statistics including: n, arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric coefficient of variation (%GCV).

For presentation of plasma concentration data in summary table, in additional to rules mentioned in section 5.2.4 and section 5.2.5, the following rules will also apply:

- Where there is no result (NR) or nonreportable concentration values, these will be set to missing.
- If there are less than three values in the data series, only the min, max, n and n (BQL) will be presented. The other summary statistics will be denoted as not calculated (NC).
- Out-of-window blood samples will be excluded from the calculation of descriptive statistics.

The arithmetic mean of concentration will be presented graphically on both linear and semi-logarithmic scales for each treatment group by visit according to the scheduled sampling time points. The +/- SD bars will only be displayed on the linear-linear scale. The arithmetic means of trough concentrations will be plotted across time by treatment arm.

For individual profiles, figures will be presented for each subject with concentration-time profiles on both linear and semi-logarithmic scales according to the actual sampling time. Overlaying individual plasma concentration-time plot and overlaying individual trough concentration-time plot will be presented. The arithmetic means of trough concentrations will be plotted across time by treatment arm. Individual plasma concentrations and trough concentrations will be presented for each subject on both linear and semi-logarithmic scales according to the actual sampling time points.

A listing of PK blood sample collection times and plasma concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be presented for all subjects for the PK Population.

A listing of trough concentration of pirfenidone and nintedanib will be presented for all subjects for the SoC PK Population.

6.8.2. Pharmacokinetic Parameters

Non-compartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin® (Version 8.3.5 or higher).

PK parameters for Week 0:

Parameter	Definition & Calculation method
C_{max} (ng/mL)	Maximum plasma concentration Observed value
t_{max} (h)	Time at which the maximum plasma concentration occurred Observed value

$AUC_{0-\infty}$ (h*ng/mL)	Area under the plasma concentration-time curve from time zero to infinity $AUC_{0-\infty}=AUC_{0-t}+C_t/\lambda_z$
$\%AUC_{extrap}$ (%)	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity $\%AUC_{extrap}=(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty} \times 100$
AUC_{0-12} (h*ng/mL) (BID group) AUC_{0-24} (h*ng/mL) (QD group)	Area under the plasma concentration-time curve from time zero to dosing interval Calculated using the trapezoidal rule (linear up log down)
AUC_{0-t} (h*ng/mL)	Area under the plasma concentration-time curve from time zero to time with last measurable concentration Calculated using the trapezoidal rule (linear up log down)
$t_{1/2}$ (h)	Terminal elimination half-life $t_{1/2}=\ln(2)/\lambda_z$
λ_z (1/h)	Terminal elimination rate constant
CL/F (L/h)	Apparent clearance (only for parent drug) $CL/F=Dose/AUC_{0-\infty}$
V_z/F (L)	Apparent volume of distribution (only for parent drug) $V_z/F=Dose/(\lambda_z \times AUC_{0-\infty})$
MR_{Cmax}, MR_{AUC}	Metabolite to parent ratio for C_{max} and AUC $MR_{Cmax}=C_{max}$ (Metabolite)/ C_{max} (Parent) $MR_{AUC}=AUC_{0-t}$ (Metabolite)/ AUC_{0-t} (Parent)

PK parameters for Week 12:

Parameter	**Definition & Calculation method**
C_{max}	Maximum plasma concentration Observed value
C_{trough}	Trough plasma concentration (including Week 2, 4, 8, 12) Observed value
t_{max}	Time at which the maximum plasma concentration occurred Observed value
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity $AUC_{0-\infty}=AUC_{0-t}+C_t/\lambda_z$
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity $\%AUC_{extrap}=(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty} \times 100$

$AUC_{0-\tau}$	Area under the plasma concentration-time curve from time zero to dosing interval Calculated using the trapezoidal rule (linear up log down)
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time with last measurable concentration Calculated using the trapezoidal rule (linear up log down)
$t_{1/2}$	Terminal elimination half-life $t_{1/2}=\ln(2)/\lambda_z$
λ_z	Terminal elimination rate constant
CL_{ss}/F	Apparent clearance (only for parent drug) $CLss/F=Dose/AUC_{0-\tau}$
V_z/F	Apparent volume of distribution (only for parent drug) $V_z/F=Dose/(\lambda_z \times AUC_{0-\tau})$
AR_{Cmax}, AR_{AUC}	Accumulation ratio for C_{max} and AUC $AR_{Cmax}=C_{max}$ (Week 12)/ C_{max} (Week 0) $AR_{AUC}=AUC_{0-\tau}$ (Week 12)/ AUC_{0-12} (Week 0) for BID group $AR_{AUC}=AUC_{0-\tau}$ (Week 12)/ AUC_{0-24} (Week 0) for QD group
MR_{Cmax}, MR_{AUC}	Metabolite to parent ratio for C_{max} and AUC $MR_{Cmax}=C_{max}$ (Metabolite)/ C_{max} (Parent) $MR_{AUC}=AUC_{0-t}$ (Metabolite)/ AUC_{0-t} (Parent)

Additional PK parameters may be determined where appropriate. The PK 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.

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}, C_{trough} and t_{max} will be the observed values obtained directly from the concentration-time profiles. For multiple peaks if any, 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.

6.8.2.1. Criteria for the Calculation of Apparent Terminal Elimination Half-Life

6.8.2.1.1. Number of Data Points

At least three data points will be included in the regression analysis and preferably should not include C_{max}.

6.8.2.1.2. Goodness of Fit

When assessing terminal elimination phases, the adjusted R^2 value will be used as a measure of the goodness of fit of the data points to determine the λ_z, the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.

Regression-based parameters will only be calculated if the adjusted R^2 value of the regression line is greater than or equal to 0.8.

6.8.2.1.3. Period of Estimation

The time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

6.8.2.2. Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- For any partial AUC determination (i.e. AUC over a dosing interval), 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.
- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported; $AUC_{0-\infty}$, CL/F and Vz/F values where the percentage extrapolation is greater than 20% will be presented but excluded from descriptive statistics.
- AUC values will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.

6.8.2.3. Presentation of PK Parameters

PK parameters will be summarized for subjects in the PK Population by treatment arm, assessed visit using descriptive statistics including: n, arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric coefficient of variation (%GCV).

All PK parameters will be listed. Regression-related PK parameters (λ_z Lower, λ_z Upper, λ_z N, R^2-adj and λ_z Span Ratio) will not be included in summary tables, but will be listed separately from other PK parameters.

For presentation of PK parameters, the following rules will apply:

- 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}.
- If there are less than three values in the data series, only the min, mean, max and n will be presented. The other summary statistics will be denoted as not calculated (NC).

6.9. Biomarker

Biomarkers associated with IPF pathology will be explored in serum or plasma. These include but are not limited to levels of MMP-7, MMP-2, MMP-9, TGF-β, IL-6. The change in IPF blood biomarkers of INS018_055 activities from baseline to Weeks 2, 4, 8 and 12/EOT will be summarized by treatment group and overall for Biomarker Population.

For subject early terminate the treatment prior to Visit 6 (Week 12), data collected in EOT visit will be summarized together with data collected in Visit 6 (Week 12) by subject who complete Visit 6 (Week 12) visit under timepoint “Week 12/EOT”.

The observed value, change from baseline and percentage change from baseline will be summarized using descriptive statistics including arithmetic mean, percent coefficient of variation (%CV), standard deviation (SD), median, minimum, and maximum values, and number of observations.

The change from baseline and percentage change from baseline will be plotted by treatment group.

7. Changes in the Conduct of the Study or Planned Analysis

Definitions for SoC PK Population is added.

Definition of PK Population is updated to include subjects who receive at least 1 dose of study treatment and have at least one measurable concentration collected postdose.

8. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Final 1.0, 04DEC2023	Final 1.0
Final 2.0, 06SEP2024	Final 2.0

Appendix 2: Example SAS Code

Secondary Efficacy Analysis – ANCOVA Model

```
proc mixed data=effdata;
class treatment;
model chg = treatment base;
lsmeans treatment /pdiff cl;
run;
```

Secondary Efficacy Analysis – MMRM Model

```
proc mixed data=effdata;
class treatment visit usubjid;
model chg = treatment visit base/ddfm=kr;
Repeated visit/ subject = usubjid type = un;
lsmeans treatment /pdiff cl;
run;
```

Multiple imputation – MCMC Statement

```
proc mi data=missdata nimpute=500 seed=1234 out=mimcmc;
mcmc impute=monotone chain=single;
var base visit1 visit2 visit3;
by treatment;
run;
```

Multiple imputation – MNAR Statement

```
proc mi data= mimcmc seed=1234 nimpute=1 out= miout;
class treatment;
monotone regression;
var base visit1 visit2 visit3;
mnar model (visit1 visit2 visit3/modelobs=(treatment='Placebo'));
run;
```

Appendix 3: Schedule of Study Activities

Trial Period	**Screening[a]**	**Treatment Period[b]**					**Follow-up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6 (EOT)**	**7 (EOS)**
Study Week		**0**	**2**	**4**	**8**	**12**	**13**
Study Day	**-30 to 0**	**1**	**15**	**29**	**57**	**85**	**92**
Visit Window (days)[c]	-	-	± 3	± 7	± 7	± 7	± 10
Informed consent[d]	X						
Demographics	X						
Medical history	X						
HRCT[e]	X						
HBV, HCV, HIV, syphilis testing[f]	X						
Height	X						
Spirometry (FEV1, FVC)[g]	X	X				X	
DLCO[h]	X	X				X	
6MWD	X	X				X	
SARS-CoV-2 testing[i]	X	X					
Assess eligibility criteria	X	X					
BMI	X	X				X	
12-lead ECG[j]	X	X		X		X	
Physical examination[k]	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Pregnancy testing[m]	X	X	X	X	X	X	X
Safety laboratory tests[n,o]	X	X	X	X	X	X	X
Urinalysis[p]	X	X	X	X	X	X	X
Adverse events[q]	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X
Randomization		X					
LCQ[r]		X		X	X	X	

Trial Period	Screening[a]	Treatment Period[b]					Follow-up
Visit Number	**1**	**2**	**3**	**4**	**5**	**6 (EOT)**	**7 (EOS)**
Study Week		**0**	**2**	**4**	**8**	**12**	**13**
Study Day	**-30 to 0**	**1**	**15**	**29**	**57**	**85**	**92**
Pharmacokinetic (PK) sampling[s]		X	X	X	X	X	
Dispense study drug		X	X	X	X		
Self-administer study drug[t]		----------X----------					
Subject study diary[u]		----------X----------					
IPF biomarker (PD) sampling (blood, pre-dose)[v]		X	X	X	X	X	
PK of SoC therapy[w]		X	X	X	X	X	
Acute IPF exacerbations[x]		X	X	X	X	X	X
Drug accountability and compliance[y]			X	X	X	X	
Completion of patient participation							X

a Screening (Visit 1) should be conducted up to 30 days prior to Visit 2 (randomization), with time allowed for central review of HRCT (performed during the screening period or within the last 12 months) or surgical lung biopsy to confirm eligibility (if HRCT is equivocal). This period may be extended up to 44 days in case of administrative issue (e.g. result from HRCT is not available). If Visit 1 cannot be performed in this extended timeframe, the patient will have to be considered a screen fail.

b Subjects who discontinue study medication will be asked to attend all study visits as originally planned in order to minimize missing data. If subject declines, all activities scheduled for the EOT visit (Visit 6) should be performed if possible. The last morning dose in the study is considered the last study dose. All subjects will be asked to return all unused medication at Visit 6/EOT.

c All efforts should be made to maintain protocol-defined visit windows. If an extenuating circumstance arises preventing this, the Sponsor and/or designee should be consulted. If the Sponsor and/or designee determines that the scientific integrity of data and patient safety would not be compromised, an out-of-window visit may be permitted.

d Informed consent must be obtained before study-related procedures are performed, including HRCT review. All AEs will be recorded from the signing of the ICF. All non-serious ongoing AEs that occurred prior to the time of first dose will be captured as medical history.

e Central review of HRCT will be performed. A historical HRCT performed within 12 months of screening (Visit 1) should be evaluated for eligibility. If an HRCT performed within the last 12 months is not available or does not meet required image acquisition specifications and the patient meets all other eligibility criteria, HRCT should be performed during the screening period.

[f] Including HBsAg, anti-HCV, hepatitis B viral load DNA, and hepatitis C viral load RNA (if applicable), anti-HIV-1, anti-HIV-2, and syphilis. Patients who are known to be hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive will undergo hepatitis B viral load DNA by PCR. Patients who are known to be hepatitis C virus (HCV) antibody positive must undergo hepatitis C viral load RNA by PCR.

[g] Spirometry results to be reviewed by site investigator to meet American Thoracic Society-European Respiratory Society criteria. Order of lung function measurements: 1. Spirometry followed by patient rest; 2. DLCO.

[h] DLCO % predicted to be corrected for hemoglobin level and conducted with equipment at each study site, carried out according to international guidelines. Order of lung function measurements: 1. Spirometry followed by patients rest; 2. DLCO.

[i] SARS-CoV-2 RT-PCR testing to be performed at screening (Visit 1), and rapid antigen test to be performed prior to randomization at Visit 2.

[j] All ECGs will be performed pre-dose.

[k] A complete physical examination will be completed at screening and symptom-specific physical examinations will be completed for other visits.

[l] Measurements of vital signs should precede blood sampling.

[m] Female with childbearing potential only: urine pregnancy test at each visit, except at Screening (Visit 1). Serum pregnancy test will be performed at screening visit.

[n] For laboratory parameters that initially do not meet eligibility requirements, a single retest within the screening period is permitted before subject is declared a screen failure.

[o] Safety laboratory parameters will be evaluated at each visit, pre-dose. This will include blood and urine. Serum chemistry analysis includes AST, ALT, AP, GGT, CK (CK-MB only if CK is elevated), glucose, creatinine, total bilirubin, direct and indirect bilirubin, total protein, hsCRP, BUN or urea, uric acid. Electrolyte analysis includes sodium, potassium, calcium, chloride, inorganic phosphate. Hematology includes hematocrit, hemoglobin, RBC count, reticulocyte count, WBC with differential (automatic WBC differential includes the relative and absolute quantification of neutrophils, eosinophils, basophils, monocytes and lymphocytes). If automatic WBC differential is abnormal, manual WBC differential is advised to include polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes and lymphocytes, platelet count, ESR. Lipid panel to include total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, albumin. Coagulation panel includes aPTT, Prothrombin time (Quick's test and INR), and fibrinogen. Hormone tests include thyroid stimulating hormone (TSH), fT3, fT4. eGFR by CKD-EPI equation.

[p] Urinalysis to include qualitative/semi-quantitative, appearance, color, pH, specific gravity, glucose, erythrocytes, leukocytes, protein, urobilinogen, urine bilirubin.

[q] Acute exacerbation will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following: Acute worsening or development of dyspnea typically for < 1 month duration, CT scan with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF, deterioration not fully explained by cardiac failure or fluid overload. [Collard 2016] Events that are clinically considered to meet the definition of acute exacerbation but fail to meet diagnostic criteria due to missing CT data should be termed "suspected acute exacerbations".

[r] The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that assesses cough related QoL. It has 3 domains (physical, psychological, and social). The total score range is 3-21, and domain scores range from 1-7; a higher score indicates a better QoL. The overall score for the LCQ for each subject is calculated by adding the individual domain scores. The LCQ will be self-administered by subjects at the indicated visits.

[s] Blood samples for plasma concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be collected at time points according shown in section 10.4 in protocol. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.

[t] Subjects will self-administer study medication. Site team will explain dosing schedule, provide study medication, and follow up with subjects.
[u] Subjects will maintain a study diary throughout study. Site team will instruct subject to record precisely the time of drug intake.
[v] Including but not limited to levels of MMP-7, MMP-2, MMP-9, TGF-beta, IL-6, TIMP-1, IL-1beta in blood samples.
[w] Blood samples for plasma concentrations of SoC therapy will be collected pre-dose (ie, prior to pirfenidone or nintedanib dosing), in order to get the trough plasma concentration of SoC therapy at Visit 2, 3, 4, 5, and 6.
[x] Investigator-reported acute IPF exacerbations to be reported in the eCRF.
[y] Collect unused previously dispensed study drug at each visit

Appendix 4: Details of GLI Equations for Predicted Value of FVC, FEV1, FEV1/FVC and DLCO

The equation for calculating predicted FVC (L), FEV1 (L) and FEV1/FVC is of the form:

$$Y = \exp(a_0 + a_1 \ln(Height) + a_2 \ln(Age) + a_3 AfrAm + a_4 NEAsia + a_5 SEAsia + a_6 Other + M_{spline})$$

Where

- Y is the predicted value
- Height is the patient's height in cm (in screening visit)
- Age is the patient's age in years (in screening visit)
- AfrAm equals to 1 if the patient's ethnic population is African American, 0 otherwise
- NEAsia equals to 1 if the patient's ethnic population is North East Asian, 0 otherwise
- SEAsia equals to 1 if the patient's ethnic population is South East Asian, 0 otherwise
- Other equals to 1 if the patient's ethnic population is Other/Mixed, 0 otherwise

The constants a_0, a_1, a_2, a_3, a_4, a_5 and a_6 depend on the patient's sex, as outlined in the table below:

	FVC		FEV1		FEV1/FVC	
	Male	Female	Male	Female	Male	Female
a_0	-11.2281	-10.4030	-10.3420	-9.6987	0.7403	0.5506
a_1	2.4135	2.2633	2.2196	2.1211	-0.1595	-0.1078
a_2	0.0865	0.0234	0.0574	-0.0270	-0.0366	-0.0544
a_3	-0.1684	-0.1555	-0.1589	-0.1484	0.0079	0.0055
a_4	-0.0405	-0.0262	-0.0351	-0.0149	0.0055	0.0088
a_5	-0.1177	-0.1516	-0.0881	-0.1208	0.0283	0.0285
a_6	-0.0825	-0.0833	-0.0708	-0.0708	0.0106	0.0106

M_{spline} can be obtained via the following lookup table based on sex and age. For ages other than those listed here, the value is derived using linear interpolation of the two nearest ages (i.e., those ages either side of the patient's actual age).

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
3	-0.0938	-0.1940	-0.1133	-0.2311	-0.0221	-0.0443
3.25	-0.0888	-0.1824	-0.1073	-0.2170	-0.0191	-0.0397

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
3.5	-0.0836	-0.1717	-0.1011	-0.2040	-0.0167	-0.0356
3.75	-0.0783	-0.1619	-0.0951	-0.1922	-0.0147	-0.0318
4	-0.0731	-0.1530	-0.0893	-0.1817	-0.0132	-0.0286
4.25	-0.0683	-0.1451	-0.0841	-0.1727	-0.0122	-0.0261
4.5	-0.0642	-0.1382	-0.0799	-0.1651	-0.0117	-0.0244
4.75	-0.0611	-0.1324	-0.0769	-0.1592	-0.0119	-0.0235
5	-0.0589	-0.1276	-0.0752	-0.1548	-0.0125	-0.0233
5.25	-0.0578	-0.1238	-0.0750	-0.1518	-0.0136	-0.0237
5.5	-0.0576	-0.1206	-0.0758	-0.1494	-0.0148	-0.0244
5.75	-0.0581	-0.1179	-0.0771	-0.1474	-0.0159	-0.0252
6	-0.0591	-0.1153	-0.0787	-0.1452	-0.0167	-0.0259
6.25	-0.0605	-0.1128	-0.0803	-0.1426	-0.0171	-0.0262
6.5	-0.0618	-0.1102	-0.0816	-0.1393	-0.0173	-0.0260
6.75	-0.0627	-0.1074	-0.0823	-0.1354	-0.0172	-0.0253
7	-0.0632	-0.1045	-0.0822	-0.1310	-0.0169	-0.0243
7.25	-0.0633	-0.1014	-0.0815	-0.1264	-0.0163	-0.0230
7.5	-0.0631	-0.0983	-0.0804	-0.1217	-0.0156	-0.0215
7.75	-0.0628	-0.0952	-0.0792	-0.1171	-0.0148	-0.0200
8	-0.0622	-0.0918	-0.0778	-0.1125	-0.0140	-0.0185
8.25	-0.0613	-0.0881	-0.0763	-0.1076	-0.0134	-0.0172
8.5	-0.0598	-0.0838	-0.0745	-0.1022	-0.0131	-0.0161
8.75	-0.0576	-0.0787	-0.0721	-0.0963	-0.0132	-0.0152
9	-0.0547	-0.0731	-0.0691	-0.0897	-0.0135	-0.0145
9.25	-0.0515	-0.0669	-0.0658	-0.0825	-0.0139	-0.0137
9.5	-0.0482	-0.0604	-0.0622	-0.0747	-0.0142	-0.0129
9.75	-0.0449	-0.0534	-0.0586	-0.0663	-0.0143	-0.0119
10	-0.0418	-0.0461	-0.0549	-0.0573	-0.0143	-0.0106
10.25	-0.0389	-0.0386	-0.0513	-0.0479	-0.0139	-0.0091
10.5	-0.0361	-0.0310	-0.0476	-0.0380	-0.0132	-0.0073
10.75	-0.0334	-0.0232	-0.0437	-0.0278	-0.0122	-0.0052
11	-0.0308	-0.0154	-0.0395	-0.0172	-0.0108	-0.0029
11.25	-0.0280	-0.0074	-0.0350	-0.0063	-0.0091	-0.0004
11.5	-0.0250	0.0006	-0.0299	0.0048	-0.0070	0.0023
11.75	-0.0217	0.0086	-0.0241	0.0161	-0.0047	0.0051
12	-0.0178	0.0166	-0.0176	0.0274	-0.0021	0.0080
12.25	-0.0134	0.0244	-0.0101	0.0386	0.0006	0.0109
12.5	-0.0083	0.0322	-0.0019	0.0496	0.0035	0.0138

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
12.75	-0.0026	0.0399	0.0071	0.0604	0.0065	0.0167
13	0.0038	0.0473	0.0169	0.0709	0.0095	0.0194
13.25	0.0108	0.0546	0.0274	0.0810	0.0126	0.0221
13.5	0.0184	0.0616	0.0384	0.0907	0.0156	0.0245
13.75	0.0263	0.0684	0.0497	0.0999	0.0186	0.0268
14	0.0346	0.0749	0.0612	0.1086	0.0215	0.0289
14.25	0.0431	0.0811	0.0728	0.1168	0.0242	0.0309
14.5	0.0518	0.0870	0.0844	0.1244	0.0268	0.0326
14.75	0.0606	0.0925	0.0958	0.1315	0.0293	0.0342
15	0.0693	0.0977	0.1068	0.1379	0.0315	0.0355
15.25	0.0779	0.1026	0.1175	0.1438	0.0336	0.0367
15.5	0.0862	0.1071	0.1276	0.1492	0.0354	0.0377
15.75	0.0943	0.1113	0.1371	0.1540	0.0370	0.0386
16	0.1020	0.1151	0.1460	0.1583	0.0385	0.0393
16.25	0.1094	0.1186	0.1542	0.1621	0.0396	0.0399
16.5	0.1163	0.1217	0.1616	0.1655	0.0406	0.0403
16.75	0.1227	0.1247	0.1684	0.1684	0.0414	0.0407
17	0.1287	0.1273	0.1744	0.1711	0.0421	0.0409
17.25	0.1342	0.1297	0.1798	0.1733	0.0425	0.0411
17.5	0.1392	0.1318	0.1845	0.1753	0.0429	0.0411
17.75	0.1437	0.1338	0.1887	0.1770	0.0431	0.0411
18	0.1478	0.1355	0.1924	0.1785	0.0432	0.0411
18.25	0.1515	0.1370	0.1956	0.1797	0.0432	0.0409
18.5	0.1548	0.1384	0.1984	0.1808	0.0431	0.0408
18.75	0.1578	0.1396	0.2008	0.1816	0.0429	0.0406
19	0.1603	0.1406	0.2029	0.1823	0.0427	0.0403
19.25	0.1625	0.1415	0.2046	0.1829	0.0424	0.0400
19.5	0.1644	0.1423	0.2060	0.1833	0.0421	0.0396
19.75	0.1659	0.1430	0.2072	0.1837	0.0418	0.0393
20	0.1672	0.1436	0.2081	0.1839	0.0414	0.0389
20.25	0.1681	0.1442	0.2087	0.1841	0.0410	0.0384
20.5	0.1689	0.1446	0.2090	0.1842	0.0406	0.0380
20.75	0.1694	0.1450	0.2092	0.1842	0.0401	0.0375
21	0.1697	0.1453	0.2091	0.1841	0.0397	0.0370
21.25	0.1698	0.1456	0.2089	0.1840	0.0392	0.0366
21.5	0.1698	0.1458	0.2084	0.1838	0.0387	0.0360
21.75	0.1696	0.1459	0.2079	0.1835	0.0382	0.0355

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
22	0.1692	0.1460	0.2071	0.1832	0.0377	0.0350
22.25	0.1687	0.1461	0.2063	0.1828	0.0372	0.0345
22.5	0.1681	0.1461	0.2053	0.1823	0.0367	0.0340
22.75	0.1674	0.1460	0.2042	0.1818	0.0362	0.0334
23	0.1665	0.1459	0.2030	0.1812	0.0357	0.0329
23.25	0.1656	0.1457	0.2016	0.1806	0.0351	0.0324
23.5	0.1646	0.1455	0.2002	0.1799	0.0346	0.0319
23.75	0.1635	0.1452	0.1987	0.1792	0.0341	0.0314
24	0.1623	0.1449	0.1970	0.1785	0.0335	0.0309
24.25	0.1611	0.1446	0.1954	0.1777	0.0330	0.0304
24.5	0.1598	0.1443	0.1936	0.1769	0.0325	0.0299
24.75	0.1585	0.1440	0.1918	0.1761	0.0319	0.0294
25	0.1571	0.1436	0.1899	0.1753	0.0314	0.0289
25.25	0.1557	0.1433	0.1880	0.1745	0.0308	0.0284
25.5	0.1542	0.1429	0.1861	0.1737	0.0303	0.0279
25.75	0.1528	0.1426	0.1841	0.1729	0.0297	0.0275
26	0.1513	0.1422	0.1821	0.1721	0.0292	0.0270
26.25	0.1498	0.1419	0.1801	0.1713	0.0287	0.0266
26.5	0.1482	0.1415	0.1781	0.1705	0.0281	0.0261
26.75	0.1467	0.1411	0.1760	0.1697	0.0276	0.0257
27	0.1451	0.1408	0.1739	0.1690	0.0271	0.0253
27.25	0.1435	0.1404	0.1718	0.1682	0.0266	0.0249
27.5	0.1419	0.1400	0.1697	0.1674	0.0261	0.0245
27.75	0.1403	0.1396	0.1677	0.1666	0.0256	0.0241
28	0.1387	0.1392	0.1656	0.1658	0.0252	0.0237
28.25	0.1371	0.1388	0.1635	0.1650	0.0247	0.0234
28.5	0.1355	0.1383	0.1615	0.1642	0.0243	0.0230
28.75	0.1339	0.1379	0.1594	0.1634	0.0238	0.0226
29	0.1323	0.1374	0.1574	0.1625	0.0234	0.0223
29.25	0.1307	0.1370	0.1554	0.1617	0.0230	0.0219
29.5	0.1291	0.1365	0.1534	0.1608	0.0225	0.0216
29.75	0.1275	0.1360	0.1514	0.1599	0.0221	0.0212
30	0.1259	0.1355	0.1495	0.1590	0.0217	0.0208
30.25	0.1243	0.1350	0.1475	0.1581	0.0214	0.0205
30.5	0.1227	0.1344	0.1455	0.1572	0.0210	0.0201
30.75	0.1211	0.1339	0.1436	0.1562	0.0206	0.0198
31	0.1195	0.1333	0.1417	0.1553	0.0202	0.0194

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
31.25	0.1179	0.1327	0.1397	0.1543	0.0199	0.0191
31.5	0.1162	0.1321	0.1378	0.1533	0.0196	0.0187
31.75	0.1146	0.1315	0.1359	0.1523	0.0192	0.0183
32	0.1130	0.1309	0.1340	0.1512	0.0189	0.0180
32.25	0.1115	0.1302	0.1321	0.1501	0.0186	0.0176
32.5	0.1099	0.1295	0.1302	0.1490	0.0182	0.0172
32.75	0.1083	0.1288	0.1283	0.1479	0.0179	0.0169
33	0.1067	0.1280	0.1265	0.1467	0.0176	0.0165
33.25	0.1052	0.1273	0.1246	0.1456	0.0173	0.0161
33.5	0.1036	0.1265	0.1227	0.1444	0.0169	0.0157
33.75	0.1021	0.1257	0.1209	0.1431	0.0166	0.0153
34	0.1006	0.1248	0.1190	0.1418	0.0163	0.0149
34.25	0.0990	0.1239	0.1172	0.1406	0.0159	0.0145
34.5	0.0975	0.1231	0.1153	0.1392	0.0156	0.0141
34.75	0.0960	0.1221	0.1135	0.1379	0.0153	0.0137
35	0.0945	0.1212	0.1116	0.1365	0.0149	0.0133
35.25	0.0930	0.1202	0.1097	0.1351	0.0146	0.0129
35.5	0.0915	0.1193	0.1078	0.1337	0.0142	0.0124
35.75	0.0900	0.1183	0.1059	0.1322	0.0139	0.0120
36	0.0885	0.1172	0.1040	0.1308	0.0135	0.0116
36.25	0.0870	0.1162	0.1021	0.1292	0.0131	0.0112
36.5	0.0856	0.1151	0.1001	0.1277	0.0127	0.0107
36.75	0.0841	0.1140	0.0982	0.1262	0.0124	0.0103
37	0.0826	0.1129	0.0962	0.1246	0.0120	0.0099
37.25	0.0811	0.1117	0.0943	0.1230	0.0116	0.0095
37.5	0.0796	0.1106	0.0923	0.1214	0.0112	0.0090
37.75	0.0781	0.1094	0.0903	0.1197	0.0108	0.0086
38	0.0765	0.1082	0.0883	0.1180	0.0105	0.0082
38.25	0.0750	0.1069	0.0863	0.1164	0.0101	0.0077
38.5	0.0735	0.1057	0.0843	0.1147	0.0097	0.0073
38.75	0.0719	0.1044	0.0823	0.1129	0.0093	0.0069
39	0.0704	0.1031	0.0803	0.1112	0.0089	0.0065
39.25	0.0688	0.1018	0.0782	0.1094	0.0085	0.0061
39.5	0.0673	0.1004	0.0762	0.1076	0.0082	0.0057
39.75	0.0657	0.0991	0.0742	0.1058	0.0078	0.0053
40	0.0641	0.0977	0.0721	0.1040	0.0074	0.0049
40.25	0.0625	0.0963	0.0700	0.1022	0.0070	0.0045

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
40.5	0.0609	0.0949	0.0680	0.1003	0.0066	0.0041
40.75	0.0593	0.0934	0.0659	0.0985	0.0063	0.0037
41	0.0577	0.0919	0.0638	0.0966	0.0059	0.0034
41.25	0.0560	0.0904	0.0617	0.0947	0.0055	0.0030
41.5	0.0544	0.0889	0.0596	0.0928	0.0052	0.0026
41.75	0.0527	0.0874	0.0575	0.0909	0.0048	0.0023
42	0.0510	0.0858	0.0554	0.0889	0.0045	0.0020
42.25	0.0494	0.0842	0.0533	0.0870	0.0041	0.0016
42.5	0.0477	0.0826	0.0511	0.0850	0.0038	0.0013
42.75	0.0460	0.0810	0.0490	0.0830	0.0034	0.0010
43	0.0443	0.0794	0.0469	0.0811	0.0031	0.0007
43.25	0.0426	0.0777	0.0448	0.0791	0.0027	0.0004
43.5	0.0408	0.0761	0.0427	0.0771	0.0024	0.0001
43.75	0.0391	0.0744	0.0406	0.0751	0.0021	-0.0002
44	0.0374	0.0727	0.0386	0.0731	0.0018	-0.0005
44.25	0.0356	0.0710	0.0365	0.0710	0.0015	-0.0007
44.5	0.0339	0.0693	0.0344	0.0690	0.0011	-0.0010
44.75	0.0322	0.0675	0.0323	0.0670	0.0008	-0.0012
45	0.0304	0.0658	0.0302	0.0650	0.0005	-0.0015
45.25	0.0286	0.0640	0.0281	0.0630	0.0002	-0.0017
45.5	0.0269	0.0622	0.0261	0.0609	0.0000	-0.0020
45.75	0.0251	0.0605	0.0240	0.0589	-0.0003	-0.0022
46	0.0233	0.0587	0.0219	0.0568	-0.0006	-0.0024
46.25	0.0215	0.0569	0.0198	0.0548	-0.0009	-0.0026
46.5	0.0197	0.0551	0.0177	0.0527	-0.0012	-0.0028
46.75	0.0178	0.0532	0.0156	0.0507	-0.0015	-0.0030
47	0.0160	0.0514	0.0135	0.0486	-0.0018	-0.0032
47.25	0.0142	0.0495	0.0114	0.0465	-0.0021	-0.0034
47.5	0.0123	0.0477	0.0093	0.0445	-0.0023	-0.0036
47.75	0.0105	0.0458	0.0072	0.0424	-0.0026	-0.0038
48	0.0086	0.0439	0.0050	0.0403	-0.0029	-0.0040
48.25	0.0068	0.0420	0.0029	0.0382	-0.0032	-0.0041
48.5	0.0049	0.0401	0.0007	0.0361	-0.0035	-0.0043
48.75	0.0030	0.0381	-0.0015	0.0339	-0.0038	-0.0045
49	0.0011	0.0362	-0.0036	0.0318	-0.0041	-0.0046
49.25	-0.0008	0.0342	-0.0058	0.0297	-0.0044	-0.0048
49.5	-0.0028	0.0323	-0.0080	0.0275	-0.0047	-0.0049

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
49.75	-0.0047	0.0303	-0.0103	0.0254	-0.0050	-0.0051
50	-0.0066	0.0283	-0.0125	0.0232	-0.0053	-0.0052
50.25	-0.0086	0.0263	-0.0147	0.0210	-0.0057	-0.0054
50.5	-0.0106	0.0243	-0.0170	0.0188	-0.0060	-0.0055
50.75	-0.0126	0.0223	-0.0193	0.0166	-0.0063	-0.0056
51	-0.0145	0.0202	-0.0216	0.0144	-0.0066	-0.0058
51.25	-0.0165	0.0182	-0.0239	0.0122	-0.0069	-0.0059
51.5	-0.0186	0.0161	-0.0262	0.0099	-0.0072	-0.0060
51.75	-0.0206	0.0140	-0.0285	0.0077	-0.0076	-0.0061
52	-0.0226	0.0119	-0.0309	0.0054	-0.0079	-0.0063
52.25	-0.0246	0.0098	-0.0332	0.0032	-0.0082	-0.0064
52.5	-0.0267	0.0077	-0.0356	0.0009	-0.0086	-0.0065
52.75	-0.0288	0.0055	-0.0380	-0.0014	-0.0089	-0.0067
53	-0.0308	0.0034	-0.0404	-0.0037	-0.0092	-0.0068
53.25	-0.0329	0.0012	-0.0428	-0.0061	-0.0096	-0.0069
53.5	-0.0350	-0.0009	-0.0453	-0.0084	-0.0099	-0.0070
53.75	-0.0371	-0.0031	-0.0478	-0.0108	-0.0103	-0.0072
54	-0.0393	-0.0053	-0.0502	-0.0131	-0.0106	-0.0073
54.25	-0.0414	-0.0075	-0.0527	-0.0155	-0.0110	-0.0074
54.5	-0.0436	-0.0098	-0.0552	-0.0179	-0.0113	-0.0075
54.75	-0.0457	-0.0120	-0.0578	-0.0203	-0.0117	-0.0077
55	-0.0479	-0.0143	-0.0603	-0.0227	-0.0120	-0.0078
55.25	-0.0501	-0.0165	-0.0629	-0.0252	-0.0124	-0.0079
55.5	-0.0523	-0.0188	-0.0654	-0.0276	-0.0127	-0.0080
55.75	-0.0545	-0.0211	-0.0680	-0.0301	-0.0131	-0.0082
56	-0.0567	-0.0234	-0.0706	-0.0326	-0.0134	-0.0083
56.25	-0.0590	-0.0257	-0.0732	-0.0350	-0.0138	-0.0084
56.5	-0.0612	-0.0281	-0.0759	-0.0375	-0.0142	-0.0085
56.75	-0.0635	-0.0304	-0.0785	-0.0401	-0.0145	-0.0087
57	-0.0658	-0.0328	-0.0812	-0.0426	-0.0149	-0.0088
57.25	-0.0681	-0.0352	-0.0839	-0.0451	-0.0152	-0.0089
57.5	-0.0704	-0.0376	-0.0866	-0.0477	-0.0156	-0.0090
57.75	-0.0727	-0.0400	-0.0893	-0.0503	-0.0160	-0.0092
58	-0.0750	-0.0424	-0.0920	-0.0529	-0.0163	-0.0093
58.25	-0.0774	-0.0449	-0.0947	-0.0555	-0.0167	-0.0094
58.5	-0.0798	-0.0473	-0.0975	-0.0581	-0.0170	-0.0095
58.75	-0.0821	-0.0498	-0.1002	-0.0607	-0.0174	-0.0097

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
59	-0.0845	-0.0523	-0.1030	-0.0634	-0.0178	-0.0098
59.25	-0.0869	-0.0548	-0.1058	-0.0660	-0.0181	-0.0099
59.5	-0.0893	-0.0573	-0.1086	-0.0687	-0.0185	-0.0100
59.75	-0.0918	-0.0598	-0.1114	-0.0714	-0.0188	-0.0102
60	-0.0942	-0.0623	-0.1143	-0.0741	-0.0192	-0.0103
60.25	-0.0967	-0.0649	-0.1171	-0.0768	-0.0195	-0.0104
60.5	-0.0991	-0.0674	-0.1199	-0.0795	-0.0199	-0.0106
60.75	-0.1016	-0.0700	-0.1228	-0.0822	-0.0203	-0.0107
61	-0.1041	-0.0726	-0.1257	-0.0850	-0.0206	-0.0109
61.25	-0.1066	-0.0751	-0.1286	-0.0878	-0.0210	-0.0110
61.5	-0.1091	-0.0777	-0.1315	-0.0905	-0.0213	-0.0112
61.75	-0.1116	-0.0804	-0.1344	-0.0933	-0.0217	-0.0113
62	-0.1141	-0.0830	-0.1373	-0.0961	-0.0220	-0.0115
62.25	-0.1166	-0.0856	-0.1402	-0.0989	-0.0224	-0.0116
62.5	-0.1191	-0.0882	-0.1431	-0.1018	-0.0227	-0.0118
62.75	-0.1217	-0.0909	-0.1461	-0.1046	-0.0231	-0.0119
63	-0.1242	-0.0936	-0.1490	-0.1075	-0.0234	-0.0121
63.25	-0.1268	-0.0962	-0.1519	-0.1103	-0.0238	-0.0123
63.5	-0.1293	-0.0989	-0.1549	-0.1132	-0.0241	-0.0124
63.75	-0.1319	-0.1016	-0.1578	-0.1161	-0.0245	-0.0126
64	-0.1344	-0.1043	-0.1608	-0.1190	-0.0248	-0.0128
64.25	-0.1370	-0.1070	-0.1638	-0.1219	-0.0252	-0.0129
64.5	-0.1395	-0.1097	-0.1667	-0.1249	-0.0255	-0.0131
64.75	-0.1421	-0.1125	-0.1697	-0.1278	-0.0259	-0.0133
65	-0.1447	-0.1152	-0.1727	-0.1308	-0.0262	-0.0135
65.25	-0.1472	-0.1180	-0.1757	-0.1338	-0.0266	-0.0136
65.5	-0.1498	-0.1207	-0.1786	-0.1368	-0.0269	-0.0138
65.75	-0.1523	-0.1235	-0.1816	-0.1398	-0.0273	-0.0140
66	-0.1549	-0.1263	-0.1846	-0.1428	-0.0276	-0.0142
66.25	-0.1575	-0.1290	-0.1876	-0.1458	-0.0280	-0.0144
66.5	-0.1600	-0.1318	-0.1906	-0.1488	-0.0283	-0.0146
66.75	-0.1626	-0.1347	-0.1936	-0.1519	-0.0287	-0.0148
67	-0.1652	-0.1375	-0.1966	-0.1550	-0.0290	-0.0150
67.25	-0.1677	-0.1403	-0.1996	-0.1580	-0.0293	-0.0151
67.5	-0.1703	-0.1431	-0.2026	-0.1611	-0.0297	-0.0153
67.75	-0.1729	-0.1460	-0.2056	-0.1642	-0.0300	-0.0155
68	-0.1754	-0.1488	-0.2086	-0.1674	-0.0304	-0.0157

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
68.25	-0.1780	-0.1517	-0.2116	-0.1705	-0.0307	-0.0159
68.5	-0.1806	-0.1545	-0.2147	-0.1736	-0.0311	-0.0161
68.75	-0.1831	-0.1574	-0.2177	-0.1768	-0.0314	-0.0163
69	-0.1857	-0.1603	-0.2207	-0.1799	-0.0318	-0.0165
69.25	-0.1882	-0.1631	-0.2237	-0.1831	-0.0321	-0.0167
69.5	-0.1908	-0.1660	-0.2267	-0.1863	-0.0325	-0.0169
69.75	-0.1933	-0.1689	-0.2298	-0.1895	-0.0328	-0.0171
70	-0.1959	-0.1718	-0.2328	-0.1926	-0.0332	-0.0173
70.25	-0.1985	-0.1747	-0.2358	-0.1958	-0.0335	-0.0175
70.5	-0.2010	-0.1776	-0.2388	-0.1991	-0.0339	-0.0177
70.75	-0.2035	-0.1806	-0.2418	-0.2023	-0.0342	-0.0179
71	-0.2061	-0.1835	-0.2449	-0.2055	-0.0346	-0.0181
71.25	-0.2086	-0.1864	-0.2479	-0.2087	-0.0349	-0.0183
71.5	-0.2112	-0.1893	-0.2509	-0.2120	-0.0352	-0.0185
71.75	-0.2137	-0.1922	-0.2539	-0.2152	-0.0356	-0.0186
72	-0.2163	-0.1952	-0.2569	-0.2184	-0.0359	-0.0188
72.25	-0.2188	-0.1981	-0.2599	-0.2217	-0.0363	-0.0190
72.5	-0.2213	-0.2010	-0.2630	-0.2249	-0.0366	-0.0192
72.75	-0.2239	-0.2040	-0.2660	-0.2282	-0.0369	-0.0194
73	-0.2264	-0.2069	-0.2690	-0.2315	-0.0373	-0.0196
73.25	-0.2289	-0.2099	-0.2720	-0.2347	-0.0376	-0.0198
73.5	-0.2314	-0.2128	-0.2750	-0.2380	-0.0379	-0.0200
73.75	-0.2340	-0.2157	-0.2780	-0.2413	-0.0382	-0.0202
74	-0.2365	-0.2187	-0.2810	-0.2445	-0.0386	-0.0204
74.25	-0.2390	-0.2216	-0.2840	-0.2478	-0.0389	-0.0206
74.5	-0.2415	-0.2246	-0.2869	-0.2511	-0.0392	-0.0207
74.75	-0.2440	-0.2275	-0.2899	-0.2543	-0.0395	-0.0209
75	-0.2465	-0.2305	-0.2929	-0.2576	-0.0399	-0.0211
75.25	-0.2490	-0.2334	-0.2959	-0.2609	-0.0402	-0.0213
75.5	-0.2515	-0.2364	-0.2989	-0.2642	-0.0405	-0.0215
75.75	-0.2540	-0.2393	-0.3018	-0.2674	-0.0408	-0.0217
76	-0.2565	-0.2422	-0.3048	-0.2707	-0.0411	-0.0218
76.25	-0.2590	-0.2452	-0.3077	-0.2740	-0.0414	-0.0220
76.5	-0.2615	-0.2481	-0.3107	-0.2773	-0.0417	-0.0222
76.75	-0.2639	-0.2510	-0.3136	-0.2805	-0.0421	-0.0224
77	-0.2664	-0.2540	-0.3166	-0.2838	-0.0424	-0.0226
77.25	-0.2689	-0.2569	-0.3195	-0.2871	-0.0427	-0.0227

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
77.5	-0.2713	-0.2598	-0.3224	-0.2903	-0.0430	-0.0229
77.75	-0.2738	-0.2627	-0.3253	-0.2936	-0.0433	-0.0231
78	-0.2762	-0.2656	-0.3282	-0.2968	-0.0436	-0.0233
78.25	-0.2787	-0.2685	-0.3311	-0.3001	-0.0439	-0.0234
78.5	-0.2811	-0.2714	-0.3340	-0.3033	-0.0442	-0.0236
78.75	-0.2835	-0.2743	-0.3369	-0.3065	-0.0445	-0.0238
79	-0.2859	-0.2772	-0.3398	-0.3098	-0.0448	-0.0240
79.25	-0.2884	-0.2801	-0.3427	-0.3130	-0.0451	-0.0241
79.5	-0.2908	-0.2830	-0.3455	-0.3162	-0.0454	-0.0243
79.75	-0.2932	-0.2859	-0.3484	-0.3194	-0.0456	-0.0245
80	-0.2956	-0.2887	-0.3512	-0.3226	-0.0459	-0.0246
80.25	-0.2980	-0.2916	-0.3541	-0.3258	-0.0462	-0.0248
80.5	-0.3004	-0.2945	-0.3569	-0.3290	-0.0465	-0.0250
80.75	-0.3027	-0.2973	-0.3597	-0.3322	-0.0468	-0.0251
81	-0.3051	-0.3001	-0.3625	-0.3354	-0.0471	-0.0253
81.25	-0.3075	-0.3030	-0.3654	-0.3386	-0.0474	-0.0254
81.5	-0.3098	-0.3058	-0.3682	-0.3417	-0.0477	-0.0256
81.75	-0.3122	-0.3086	-0.3709	-0.3449	-0.0479	-0.0258
82	-0.3146	-0.3114	-0.3737	-0.3480	-0.0482	-0.0259
82.25	-0.3169	-0.3143	-0.3765	-0.3512	-0.0485	-0.0261
82.5	-0.3192	-0.3171	-0.3793	-0.3543	-0.0488	-0.0263
82.75	-0.3216	-0.3198	-0.3820	-0.3574	-0.0491	-0.0264
83	-0.3239	-0.3226	-0.3848	-0.3606	-0.0493	-0.0266
83.25	-0.3262	-0.3254	-0.3875	-0.3637	-0.0496	-0.0267
83.5	-0.3285	-0.3282	-0.3903	-0.3668	-0.0499	-0.0269
83.75	-0.3308	-0.3309	-0.3930	-0.3699	-0.0502	-0.0270
84	-0.3331	-0.3337	-0.3957	-0.3730	-0.0504	-0.0272
84.25	-0.3354	-0.3365	-0.3984	-0.3760	-0.0507	-0.0274
84.5	-0.3377	-0.3392	-0.4011	-0.3791	-0.0510	-0.0275
84.75	-0.3400	-0.3419	-0.4038	-0.3822	-0.0512	-0.0277
85	-0.3423	-0.3447	-0.4065	-0.3852	-0.0515	-0.0278
85.25	-0.3445	-0.3474	-0.4092	-0.3883	-0.0518	-0.0280
85.5	-0.3468	-0.3501	-0.4119	-0.3913	-0.0520	-0.0281
85.75	-0.3491	-0.3528	-0.4145	-0.3944	-0.0523	-0.0283
86	-0.3513	-0.3555	-0.4172	-0.3974	-0.0526	-0.0284
86.25	-0.3535	-0.3582	-0.4198	-0.4004	-0.0528	-0.0286
86.5	-0.3558	-0.3608	-0.4225	-0.4034	-0.0531	-0.0287

	FVC		FEV1		FEV1/FVC	
Age	Male	Female	Male	Female	Male	Female
86.75	-0.3580	-0.3635	-0.4251	-0.4064	-0.0534	-0.0289
87	-0.3602	-0.3662	-0.4277	-0.4094	-0.0536	-0.0291
87.25	-0.3625	-0.3688	-0.4303	-0.4124	-0.0539	-0.0292
87.5	-0.3647	-0.3715	-0.4329	-0.4153	-0.0541	-0.0294
87.75	-0.3669	-0.3741	-0.4355	-0.4183	-0.0544	-0.0295
88	-0.3691	-0.3768	-0.4381	-0.4213	-0.0547	-0.0297
88.25	-0.3713	-0.3794	-0.4407	-0.4242	-0.0549	-0.0298
88.5	-0.3735	-0.3820	-0.4433	-0.4272	-0.0552	-0.0300
88.75	-0.3756	-0.3846	-0.4459	-0.4301	-0.0554	-0.0301
89	-0.3778	-0.3872	-0.4484	-0.4330	-0.0557	-0.0303
89.25	-0.3800	-0.3898	-0.4510	-0.4359	-0.0559	-0.0304
89.5	-0.3821	-0.3924	-0.4536	-0.4389	-0.0562	-0.0305
89.75	-0.3843	-0.3950	-0.4561	-0.4418	-0.0564	-0.0307
90	-0.3864	-0.3976	-0.4586	-0.4446	-0.0567	-0.0308
90.25	-0.3886	-0.4002	-0.4612	-0.4475	-0.0570	-0.0310
90.5	-0.3907	-0.4027	-0.4637	-0.4504	-0.0572	-0.0311
90.75	-0.3929	-0.4053	-0.4662	-0.4533	-0.0575	-0.0313
91	-0.3950	-0.4079	-0.4687	-0.4561	-0.0577	-0.0314
91.25	-0.3971	-0.4104	-0.4712	-0.4590	-0.0579	-0.0316
91.5	-0.3992	-0.4129	-0.4737	-0.4618	-0.0582	-0.0317
91.75	-0.4013	-0.4155	-0.4762	-0.4647	-0.0584	-0.0319
92	-0.4034	-0.4180	-0.4787	-0.4675	-0.0587	-0.0320
92.25	-0.4055	-0.4205	-0.4811	-0.4703	-0.0589	-0.0321
92.5	-0.4076	-0.4230	-0.4836	-0.4732	-0.0592	-0.0323
92.75	-0.4097	-0.4255	-0.4861	-0.4760	-0.0594	-0.0324
93	-0.4118	-0.4280	-0.4885	-0.4788	-0.0597	-0.0326
93.25	-0.4139	-0.4305	-0.4910	-0.4816	-0.0599	-0.0327
93.5	-0.4160	-0.4330	-0.4934	-0.4844	-0.0602	-0.0329
93.75	-0.4180	-0.4355	-0.4959	-0.4871	-0.0604	-0.0330
94	-0.4201	-0.4379	-0.4983	-0.4899	-0.0606	-0.0331
94.25	-0.4221	-0.4404	-0.5007	-0.4927	-0.0609	-0.0333
94.5	-0.4242	-0.4429	-0.5031	-0.4954	-0.0611	-0.0334
94.75	-0.4262	-0.4453	-0.5055	-0.4982	-0.0614	-0.0336
95	-0.4283	-0.4477	-0.5079	-0.5009	-0.0616	-0.0337

The regression equations and lookup tables are available in:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Xaver Baur, Graham L. Hall, Bruce H. Culver, Paul L. Enright, John L. Hankinson, Mary S.M. Ip, Jinping Zheng, Janet Stocks, the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. European Respiratory Journal Dec 2012, 40 (6) 1324-1343. Available at: https://erj.ersjournals.com/content/40/6/1324

The equation for calculating predicted DLCO (mL/min/mmHg) is of the form:

$$\mathrm{DLCO}_{predicted,male} = \exp\left(-7.034920 + 2.018368 \cdot \ln(Height) - 0.012425 \ln(Age) + M_{spline}\right)$$

$$\mathrm{DLCO}_{predicted,female} = \exp\left(-5.159451 + 1.618697 \cdot \ln(Height) - 0.015390 \ln(Age) + M_{spline}\right)$$

The following lookup table is used for determining the value of M_{spline} in the equation for calculating predicted DLCO. For ages other than those listed here, the value is derived using linear interpolation of the two nearest ages (i.e., those ages either side of the patient's actual age).

The regression equations and lookup tables are available in:
Sanja Stanojevic, Brian L. Graham, Brendan G. Cooper, Bruce R. Thompson, Kim W. Carter, Richard W. Francis, Graham L. Hall. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians European Respiratory Journal Sep 2017, 50 (3) 1700010. Available at: https://erj.ersjournals.com/content/50/3/1700010

Age	Male	Female
5	-0.11609	-0.1809
5.25	-0.11963	-0.17378
5.5	-0.12291	-0.16695
5.75	-0.12587	-0.16037
6	-0.12852	-0.15401
6.25	-0.1308	-0.14785
6.5	-0.13269	-0.14183
6.75	-0.13413	-0.13595
7	-0.1351	-0.13018

Age	Male	Female
7.25	-0.1356	-0.1245
7.5	-0.13559	-0.11891
7.75	-0.13509	-0.11339
8	-0.13407	-0.10795
8.25	-0.13256	-0.10257
8.5	-0.13055	-0.09725
8.75	-0.12808	-0.092
9	-0.12514	-0.08681
9.25	-0.12177	-0.0817

Age	Male	Female
9.5	-0.11798	-0.07665
9.75	-0.1138	-0.07168
10	-0.10924	-0.06679
10.25	-0.10435	-0.06198
10.5	-0.09914	-0.05726
10.75	-0.09365	-0.05262
11	-0.08788	-0.04808
11.25	-0.08187	-0.04362
11.5	-0.07565	-0.03927

Age	Male	Female
11.75	-0.06926	-0.03502
12	-0.06273	-0.03087
12.25	-0.0561	-0.02683
12.5	-0.04938	-0.0229
12.75	-0.0426	-0.01908
13	-0.03578	-0.01537
13.25	-0.02895	-0.01177
13.5	-0.02214	-0.00827
13.75	-0.01538	-0.00489
14	-0.00868	-0.00161
14.25	-0.00208	0.001569
14.5	0.004422	0.004642
14.75	0.010797	0.007614
15	0.017032	0.010486
15.25	0.023118	0.013261
15.5	0.029043	0.015941
15.75	0.034801	0.018529
16	0.040382	0.021027
16.25	0.045783	0.023437
16.5	0.050995	0.025762
16.75	0.056016	0.028004
17	0.060841	0.030164
17.25	0.065466	0.032246
17.5	0.069889	0.034251
17.75	0.07411	0.03618
18	0.078135	0.038035
18.25	0.081965	0.039819
18.5	0.085606	0.041531
18.75	0.089061	0.043174
19	0.092333	0.044748
19.25	0.095426	0.046257
19.5	0.098344	0.0477
19.75	0.10109	0.049079
20	0.103666	0.050395
20.25	0.106077	0.051651
20.5	0.108327	0.052846
20.75	0.11042	0.053983
21	0.112363	0.055062

Age	Male	Female
21.25	0.114159	0.056086
21.5	0.115815	0.057055
21.75	0.117334	0.057971
22	0.118721	0.058835
22.25	0.119982	0.059648
22.5	0.121119	0.060412
22.75	0.122137	0.061127
23	0.123039	0.061794
23.25	0.12383	0.062415
23.5	0.124513	0.06299
23.75	0.125091	0.063522
24	0.125569	0.06401
24.25	0.125951	0.064456
24.5	0.12624	0.064862
24.75	0.126442	0.065229
25	0.126559	0.065557
25.25	0.126595	0.065848
25.5	0.126554	0.066103
25.75	0.126439	0.066323
26	0.126254	0.066508
26.25	0.126	0.066661
26.5	0.125682	0.066781
26.75	0.125302	0.06687
27	0.124863	0.066928
27.25	0.124366	0.066956
27.5	0.123816	0.066956
27.75	0.123214	0.066927
28	0.122562	0.066871
28.25	0.121863	0.066788
28.5	0.121119	0.066679
28.75	0.120333	0.066545
29	0.119506	0.066387
29.25	0.11864	0.066204
29.5	0.117738	0.065998
29.75	0.116801	0.065769
30	0.115831	0.065518
30.25	0.11483	0.065245
30.5	0.113798	0.064952

Age	Male	Female
30.75	0.112739	0.064637
31	0.111653	0.064303
31.25	0.110542	0.063949
31.5	0.109408	0.063576
31.75	0.10825	0.063185
32	0.107072	0.062775
32.25	0.105873	0.062348
32.5	0.104656	0.061904
32.75	0.103421	0.061442
33	0.10217	0.060965
33.25	0.100903	0.060471
33.5	0.099621	0.059961
33.75	0.098326	0.059437
34	0.097018	0.058897
34.25	0.095698	0.058343
34.5	0.094367	0.057774
34.75	0.093026	0.057191
35	0.091676	0.056595
35.25	0.090317	0.055986
35.5	0.08895	0.055363
35.75	0.087576	0.054728
36	0.086195	0.05408
36.25	0.084808	0.05342
36.5	0.083417	0.052748
36.75	0.08202	0.052065
37	0.08062	0.05137
37.25	0.079216	0.050665
37.5	0.077809	0.049948
37.75	0.076399	0.049221
38	0.074987	0.048483
38.25	0.073573	0.047736
38.5	0.072157	0.046979
38.75	0.070739	0.046212
39	0.06932	0.045436
39.25	0.067899	0.044652
39.5	0.066477	0.043858
39.75	0.065054	0.043056
40	0.06363	0.042246

Age	Male	Female
40.25	0.062206	0.041427
40.5	0.060781	0.040601
40.75	0.059355	0.039767
41	0.05793	0.038926
41.25	0.056504	0.038077
41.5	0.055079	0.037222
41.75	0.053653	0.036359
42	0.052228	0.03549
42.25	0.050804	0.034614
42.5	0.04938	0.033732
42.75	0.047956	0.032844
43	0.046534	0.03195
43.25	0.045112	0.03105
43.5	0.043692	0.030144
43.75	0.042272	0.029233
44	0.040854	0.028317
44.25	0.039436	0.027396
44.5	0.038019	0.02647
44.75	0.036603	0.025539
45	0.035186	0.024603
45.25	0.03377	0.023664
45.5	0.032354	0.02272
45.75	0.030937	0.021773
46	0.02952	0.020822
46.25	0.028103	0.019867
46.5	0.026685	0.018908
46.75	0.025266	0.017947
47	0.023846	0.016982
47.25	0.022425	0.016015
47.5	0.021003	0.015044
47.75	0.019579	0.014071
48	0.018154	0.013095
48.25	0.016728	0.012117
48.5	0.0153	0.011137
48.75	0.01387	0.010154
49	0.012438	0.00917
49.25	0.011004	0.008183
49.5	0.009569	0.007195

Age	Male	Female
49.75	0.008131	0.006205
50	0.006691	0.005214
50.25	0.005248	0.004221
50.5	0.003803	0.003226
50.75	0.002356	0.002231
51	0.000906	0.001234
51.25	-0.00055	0.000236
51.5	-0.002	-0.00076
51.75	-0.00346	-0.00176
52	-0.00492	-0.00276
52.25	-0.00638	-0.00376
52.5	-0.00785	-0.00476
52.75	-0.00931	-0.00577
53	-0.01078	-0.00677
53.25	-0.01226	-0.00777
53.5	-0.01373	-0.00877
53.75	-0.01521	-0.00977
54	-0.01669	-0.01078
54.25	-0.01817	-0.01178
54.5	-0.01966	-0.01278
54.75	-0.02114	-0.01378
55	-0.02263	-0.01478
55.25	-0.02412	-0.01578
55.5	-0.02562	-0.01678
55.75	-0.02712	-0.01778
56	-0.02861	-0.01878
56.25	-0.03012	-0.01978
56.5	-0.03162	-0.02077
56.75	-0.03313	-0.02177
57	-0.03464	-0.02277
57.25	-0.03615	-0.02376
57.5	-0.03766	-0.02475
57.75	-0.03918	-0.02574
58	-0.04069	-0.02673
58.25	-0.04221	-0.02772
58.5	-0.04374	-0.02871
58.75	-0.04526	-0.0297
59	-0.04679	-0.03068

Age	Male	Female
59.25	-0.04832	-0.03167
59.5	-0.04985	-0.03265
59.75	-0.05138	-0.03363
60	-0.05292	-0.03461
60.25	-0.05445	-0.03559
60.5	-0.05599	-0.03657
60.75	-0.05753	-0.03754
61	-0.05907	-0.03851
61.25	-0.06062	-0.03948
61.5	-0.06216	-0.04045
61.75	-0.06371	-0.04142
62	-0.06525	-0.04239
62.25	-0.0668	-0.04335
62.5	-0.06835	-0.04431
62.75	-0.06989	-0.04527
63	-0.07144	-0.04623
63.25	-0.07299	-0.04719
63.5	-0.07454	-0.04814
63.75	-0.07609	-0.0491
64	-0.07764	-0.05005
64.25	-0.07919	-0.051
64.5	-0.08074	-0.05194
64.75	-0.08229	-0.05289
65	-0.08384	-0.05383
65.25	-0.08538	-0.05477
65.5	-0.08693	-0.05571
65.75	-0.08848	-0.05664
66	-0.09003	-0.05758
66.25	-0.09157	-0.05851
66.5	-0.09312	-0.05944
66.75	-0.09466	-0.06037
67	-0.09621	-0.06129
67.25	-0.09775	-0.06222
67.5	-0.09929	-0.06314
67.75	-0.10083	-0.06406
68	-0.10237	-0.06497
68.25	-0.10391	-0.06589
68.5	-0.10544	-0.0668

Age	Male	Female
68.75	-0.10698	-0.06771
69	-0.10851	-0.06861
69.25	-0.11005	-0.06952
69.5	-0.11158	-0.07042
69.75	-0.1131	-0.07132
70	-0.11463	-0.07222
70.25	-0.11616	-0.07312
70.5	-0.11768	-0.07401
70.75	-0.1192	-0.0749
71	-0.12072	-0.07579
71.25	-0.12224	-0.07668
71.5	-0.12375	-0.07756
71.75	-0.12527	-0.07844
72	-0.12678	-0.07932
72.25	-0.12829	-0.0802
72.5	-0.12979	-0.08107
72.75	-0.13129	-0.08194
73	-0.13279	-0.08281
73.25	-0.13429	-0.08368
73.5	-0.13579	-0.08455
73.75	-0.13728	-0.08541
74	-0.13877	-0.08627
74.25	-0.14026	-0.08713
74.5	-0.14174	-0.08798
74.75	-0.14322	-0.08884
75	-0.1447	-0.08969
75.25	-0.14618	-0.09054
75.5	-0.14765	-0.09138
75.75	-0.14912	-0.09223

Age	Male	Female
76	-0.15058	-0.09307
76.25	-0.15204	-0.09391
76.5	-0.1535	-0.09474
76.75	-0.15496	-0.09558
77	-0.15641	-0.09641
77.25	-0.15786	-0.09724
77.5	-0.15931	-0.09807
77.75	-0.16075	-0.09889
78	-0.16219	-0.09971
78.25	-0.16362	-0.10053
78.5	-0.16505	-0.10135
78.75	-0.16648	-0.10216
79	-0.16791	-0.10298
79.25	-0.16933	-0.10379
79.5	-0.17074	-0.1046
79.75	-0.17216	-0.1054
80	-0.17357	-0.10621
80.25	-0.17497	-0.10701
80.5	-0.17637	-0.10781
80.75	-0.17777	-0.1086
81	-0.17917	-0.1094
81.25	-0.18056	-0.11019
81.5	-0.18194	-0.11098
81.75	-0.18333	-0.11176
82	-0.18471	-0.11255
82.25	-0.18608	-0.11333
82.5	-0.18745	-0.11411
82.75	-0.18882	-0.11489
83	-0.19018	-0.11567

Age	Male	Female
83.25	-0.19154	-0.11644
83.5	-0.1929	-0.11721
83.75	-0.19425	-0.11798
84	-0.1956	-0.11875
84.25	-0.19695	-0.11951
84.5	-0.19829	-0.12028
84.75	-0.19963	-0.12104
85	-0.20096	-0.12179
85.25	-0.20229	-0.12255
85.5	-0.20362	-0.1233
85.75	-0.20494	-0.12406
86	-0.20626	-0.12481
86.25	-0.20758	-0.12555
86.5	-0.20889	-0.1263
86.75	-0.2102	-0.12704
87	-0.21151	-0.12779
87.25	-0.21281	-0.12853
87.5	-0.21411	-0.12926
87.75	-0.21541	-0.13
88	-0.2167	-0.13073
88.25	-0.21799	-0.13146
88.5	-0.21927	-0.13219
88.75	-0.22055	-0.13292
89	-0.22183	-0.13364
89.25	-0.22311	-0.13437
89.5	-0.22438	-0.13509
89.75	-0.22564	-0.13581
90	-0.22691	-0.13653

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