NOVARTIS

Clinical Development

ADPT09

CADPT09A12201 / NCT05497284

A participant- and investigator-blinded, randomized, placebo-controlled, multicenter, platform study to investigate efficacy, safety, and tolerability of various single treatments in participants with idiopathic pulmonary fibrosis

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
02-Nov-2022	Prior to DB lock	Creation of final version	N/A - First version	NA
06-Aug-2024	Prior to DB lock	Updates	Detailed baseline characteristics that will be included in the output table are included in the SAP	Section 2.3.2
06-Aug-2024	Prior to DB lock	The decision of the early termination of the study	The following analyses will not be performed, therefore removed from the SAP: 1. The pooling of the placebos from different cohorts 2. All sensitivity and supplemental analyses for the primary endpoint will not be performed, therefore removed from the SAP. 3. All the analyses on exploratory objectives and endpoints stated in Section 1.2 will not be performed, therefore removed from the SAP. 4. Planned Interim Analyses	Sections 2.1, 2.5.3, 2.5.4, 2.5.5, 2.5.6, 2.6.1.1, 2.6.1.2, 2.6.1.3, 2.8, 2.9, 2.11, 2.12, 2.13
12-Nov-2024	Prior to DB lock	Updates	Clarified previously unclear or inconsistent protocol languages	Section 2
12-Nov-2024	Prior to DB lock	Specify “On-treatment period” and “Treatment emergent AE”	The last treatment plus 30 days defined as on-treatment period and will be used as the time frame of “Treatment emergent AE”	Section 2.1.1
12-Nov-2024	Prior to DB lock	Update Protocol deviation codes exclusion of analysis sets	Detailed Protocol deviation codes provided for exclusion of analysis sets	Table 2-1
12-Nov-2024	Prior to DB lock	Consistence to the updated protocol for GAP score	GAP score will not be presented as a baseline characteristics due to lacking of the data	Section 2.3
12-Nov-2024	Prior to DB lock	Add “Direction of interest for worst case value” for biochemistry and hematology tests	Two tables added accordingly	Section 5.3
12-Nov-2024	Prior to DB lock	To be consistent using terminology	Change “Background therapy” into “standard of care”	Throughout
		Details in Progression-free survival (PFS) events	Non-elective respiratory hospitalizations defined	Section 2.6.1.1

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List of abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AWT	Airway Measures
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBL	Database Lock
DMC	Data Monitoring Committee
DMS	Document Management System
EoT	End of Treatment
CCI	[redacted]
FVC	Forced Vital Capacity
FVC%p	Forced Vital Capacity expressed in percent predicted
IA	Interim Analyses
IPF	Idiopathic Pulmonary Fibrosis
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Effect Model for Repeated Measurement
PD	Pharmacodynamic
PFS	Progression-free Survival
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
qGG	Quantitative Ground-glass
qHC	Quantitative Honeycombing
qHRCT	Quantitative High-resolution Computed Tomography
qILD	Quantitative Interstitial Lung Disease
qLF	Quantitative Lung Fibrosis
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SMQ	Standardized MedDRA Query
TFLs	Tables, Figures, Listings
TP	Trial Programmer
TS	Trial Statistician
ULOQ	Upper Limit of Quantitation

1 Introduction

This Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol (Version 05). The SAP contains detailed information to aid the production of statistics & programming input into the Clinical Study Report (CSR) for trial "CADPT09A12201".

1.1 Study design

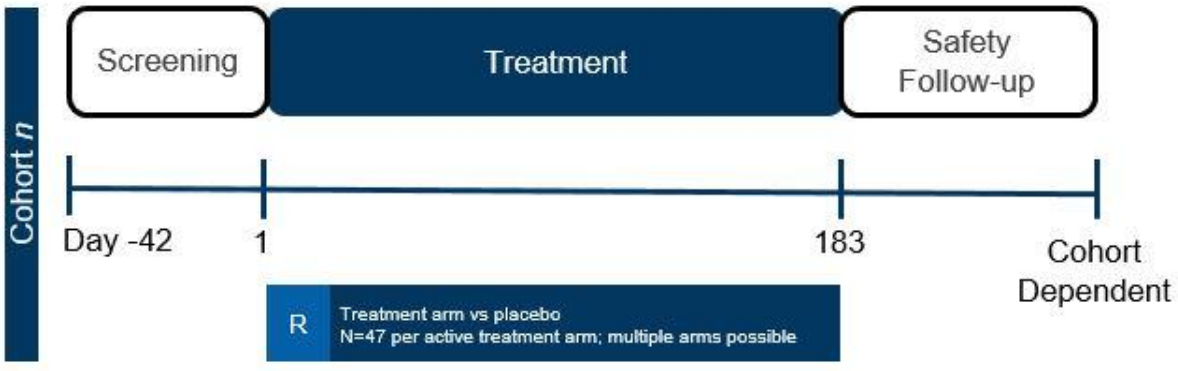
This is a randomized, placebo-controlled, participant- and investigator-blinded platform study in participants with IPF.

This study uses a platform type design to investigate "multiple targeted therapies in the context of a single disease in a perpetual manner" (Woodcock and LaVange 2017). Each investigational product and matching placebo entered the trial at a given time will be considered a unique cohort. The decision to include future cohorts is not dependent on performance of prior investigational products or cohorts. Each time a new cohort is introduced, investigational product specific information will be added to the protocol (Protocol Section 17) as a substantial amendment and submitted to Health Authorities and Ethical Committees, as required by local regulations. The cohort specific analysis will be added into an SAP amendment accordingly where necessary.

If multiple cohorts are open, participants will be allocated based on the cohort-specific eligibility criteria. Should a participant be eligible for more than one cohort, they will be randomized to any suitable cohort.

For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported upon completion of each cohort in an end of cohort report. In general, each cohort in the study will undergo similar study evaluations and assessments. Each cohort will include a screening period (Day -42 to Day -1), a treatment period of 26 weeks (Day 1 to Day 183), and a post treatment safety follow-up that is cohort specific per Protocol Section 17.

Figure 1-1 Study design



R = Randomization

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of the investigational products compared to placebo in participants with IPF	• Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in percent predicted
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of the investigational products, compared to placebo in participants with IPF	• Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in mL

• To assess the impact of the investigational products on "progression-free survival (PFS)"	• Time to progression as defined by a composite endpoint including any of the following events:
	  • Absolute reduction from baseline of ≥10% predicted in FVC
	  • Nonelective hospitalization for respiratory events
	  • Lung Transplant
	  • Death

• To assess the incidence of absolute decline in FVC ≥10% predicted	• Number of participants with absolute decline of ≥10% predicted in FVC
• To assess the impact of the investigational products on pulmonary physiology	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in DLCO absolute and percent predicted
• To assess the impact of the investigational products on exercise capacity	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in 6-minute walk distance
• To assess the impact of the investigational products on patient reported outcome	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in scores from the L-IPF (Impacts and Symptoms Modules), K-BILD, Leicester cough, and R-Scale for PF questionnaires
• To assess the safety and tolerability of the investigational products in participants with mild to moderate IPF	• Adverse Events, physical examinations, labs, ECGs, vital signs
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To assess the impact of the investigational products on disease exacerbation.	• IPF exacerbations or suspected exacerbations as determined by investigator and by using modified diagnostic criteria derived from Collard et al 2016 and exacerbations as determined by the investigator as AEs/SAEs
• To assess the impact of the investigational products on additional "progression-free survival (PFS)" analysis	• Time to progression as defined by a composite endpoint including any of the following events: Absolute reduction from baseline of ≥5% predicted in FVC Non-elective hospitalization for respiratory events Lung Transplant or Death
• To evaluate change in extent of pulmonary fibrosis quantified by HRCT scan	• Change in fibrosis from baseline to the end of treatment epoch (26 weeks of treatment) in quantitative high-resolution computed tomography (qHRCT)
• To explore the impact of the investigational products on peripheral blood biomarkers	• Change from baseline in soluble pharmacodynamic, target engagement and disease markers (may include but are not limited to: CCI [redacted] and additional protein profiling) in the peripheral blood.

Objective(s)	Endpoint(s)
• The pharmacokinetics of the investigational products after multiple doses will be assessed.	• Appropriate PK parameters will be calculated where possible using non-compartmental analysis. These may include Tmax, Cmax, AUCs. Population PK modelling may also be used for parameter estimation.
• To explore the pharmacogenetics for the potential disease association or participant stratification	• DNA analysis at baseline
• CCI [redacted]	[redacted]

1.2.1 Primary estimand(s)

Estimands are not defined since this PIIa clinical trial is not intended for registrational purposes. Novartis is of the view that there will be only a few intercurrent events for this small non-registrational study. This SAP detailed sensitivity analyses to investigate the impact of the potential intercurrent events on the primary endpoint of interest, i.e., FVC%p, but will be omitted due to the decision of early termination of the study.

2 Statistical methods

A Clinical Study Report (CSR) will be prepared following the completion of the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis Trial Statistician (TS) and Trial Programmer (TP). SAS version 9.4 or higher (SAS Institute, Cary NC) or later software will be used to perform all data analyses and to generate tables, figures, and listings.

Novartis TS and TP will be performing the interim analyses including DMC planned and/or required analyses with separate SAP detailing the planned analysis.

Descriptive statistics on continuous data will include mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum, while categorical data will be summarized as frequencies and percentages.

The cut-off date which data will be included in the analysis will be at the final Database Lock (DBL) date. All data will be considered in the analyses described hereafter.

There will be no center factor considered unless there is a strong evidence of data deviations from different centers. Planned stratification factor(s) will be included in the inferential statistical model as a covariate.

2.1.1 General definitions

Investigational treatment refers to any drug or combination of drugs or intervention administered to the study participants whose properties are being tested in the study.

The term ***'date of first administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the first time for the participants in the cohort of the study.

The term ***'date of last administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the last time in the cohort of the study.

The term ***'study day'*** refers to the Analysis Relative Day, Relative Start Day, or Relative End Day, as applicable. Day 1 is defined as the date of randomization.

For a particular date, study day will be calculated as follows:

- for dates on or after Day 1,

Study day = Assessment date – Day 1 +1

- for dates prior to Day 1,

Study day = Assessment date – Day 1.

The term ***'baseline'*** refers to the last assessment performed prior to the treatment. For spirometry data, baseline is considered as the assessment conducted in "Baseline" visit (Day 1), or the last assessment performed prior to the treatment when the assessment in the "Baseline" visit is missing.

The term '***on-treatment period***' is defined as the time between the first dose of study drug to 30 days after the last treatment visit (Day 183) if not missing or the date of last treatment visit attended in the study in case of drop-out or the death date if subject died in treatment epoch.

The term '***End of Treatment (EoT)***' refers to the last date of the on-treatment period as defined above.

The term ***'treatment-emergent adverse event'*** refers to any adverse event (AE) occurs in the "on-treatment period", started after the first dose of study treatment, or events present prior to the first dose of study treatment but increased in severity (based on preferred term (PT)).

2.2 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants who received any study drug.

The PK analysis set will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all participants with available PD data and no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as Table 2-1.

Table 2-1 Protocol deviation and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from Safety analysis in case of these PDs: • Informed consent was not obtained (INCL01) • Subject did not receive any dose of study drug (TRT10)		**Exclude subject from Safety analysis set**
Subjects are excluded from PK analysis in case of these PDs: • Informed consent was not obtained (INCL01, OTH08)		**Exclude subject from PK analysis set**
Subjects are excluded from PD analysis in case of these PDs: • Informed consent was not obtained (INCL01). • Subject did not receive any dose of study drug (TRT10) • Subject was randomized but the diagnosis of definite or probable IPF with 5 years of the screening visit is not confirmed (inclusion criteria number 3, INCL03)		**Exclude subject from PD analysis sets**
Subjects' visits may be excluded from PD analysis since the following PD occurs: • Use of prohibited medications which affect PD data (based on the list of prohibited medications provided in section 5.2 of the protocol, COMD01)		

Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to final database lock (DBL).

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics, and other baseline characteristics

2.3.1 Patient disposition

The patient disposition will be summarized by cohort and treatment group using safety set.

The number and percent of subjects screened, randomized, completed, and discontinued from the study will be summarized with reasons of discontinuation.

Screened participants, including those who completed screening and were treated, and reasons for not completing the study will be also listed by cohort and participant.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics, including smoking status, , Standard of care (Pirfenidone, Nintedanib, or No treatment), history of other respiratory diseases, history of pulmonary exacerbations, and the number of years of IPF diagnosis will be listed by cohort, treatment group, and patient using the safety analysis set.

Summary statistics will be provided by cohort and treatment group. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented when applicable.

Relevant medical history, current medical conditions at baseline (summarized by system organ class and preferred term), results of laboratory screens, drug tests and any other relevant information will be listed by cohort, treatment group and patient.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The safety analysis set will be used for the analyses.

Summary statistics will be provided for treatment compliance by treatment group.

The duration of exposure in weeks to investigational drug will be summarized by means of descriptive statistics.

The use of the standard of care medication (pirfenidone, nintedanib, or no treatment) will be summarized by treatment group.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by cohort, treatment group, epoch, and patient using safety analysis set.

2.5 Analysis supporting primary objective(s)

The primary aim of the study is to assess the efficacy of the investigational products, compared to placebo in IPF participants. This will be evaluated by assessing change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in percent predicted (FVC%p). Reduction of the decrease in change from baseline is considered a favorable outcome. The primary analysis will be conducted using PD analysis set.

2.5.1 Primary endpoint(s)

The primary endpoint of the study is change from baseline in FVC%p. It will be calculated as:

FVC%p (EoT) – FVC%p (Baseline).

2.5.2 Statistical hypothesis, model, and method of analysis

The treatment effect of the primary endpoint will be analyzed using a Bayesian random slope model to assess the difference in reduction rate (slope) between the treatment group and placebo group. The statistical model will include the intercept, time (as continuous variable), the interaction of treatment and time, the interaction of baseline FVC%p and time, and the stratification factor for the randomization, standard of care treatment with 2- categories (nintedanib and/or pirfenidone, neither) as fixed effect, and the intercept and slope of time for each participant as random effects. A robust weakly informative prior for the placebo time slope (based on 9 phase II and III studies after 2012 with total of 492 participants) will be used in the Bayesian analysis. The robustified informative prior for the change from baseline in FVC%p is

comprised of 3 components of normal distributed random variables with the following information in terms of weight (W), mean (M), and standard deviation (S):

Table 2-2 Composition of the robust weakly informative prior for the placebo tie slope

	Comp1	Comp2	Comp3
W	0.526	0.174	0.300
M	-2.93	-2.75	-3.00
S	0.865	1.837	4.754

This effectively means that we assume a placebo decline of 3% at week 26 from the baseline for the placebo group is expected. This prior belief is fixed at the design stage. Any new placebo historical data that becomes available, will not be used as part of a prior. The impact of using this placebo prior means that there would be in effect 11 more placebo participants contributing to the data analysis. A non-informative prior will be used for the rest of the parameters, assuming the change from baseline in FVC%p has a normal distribution with mean=0 and a very large SD (e.g., 1E6).

The primary summary measure of interest is the difference in FVC%p between active and placebo at week 26 derived from the Bayesian statistical model as the posterior mean estimation of the treatment effect over placebo for change from baseline FVC %p at the end of treatment (26 weeks). Statistical evidence of treatment effect will be concluded if the probability that the effect is better than placebo by 90% and there is at least 50% probability that the effect over placebo is >1.3%. No adjustments for multiplicity will be applied for this exploratory study.

2.5.3 Handling of missing values/censoring/discontinuations

If a participant who was not on standard of care at randomization initiates treatment with standard of care during the study, the subject's data collected after the initiation of standard of care will be set to missing from the primary analysis. All the missing data are considered as missing at random. No further handling will be conducted.

2.5.4 Poolability of the Placebo patients across different cohorts

Only one cohort was included due to the early termination of the study, therefore no pooling of the Placebo patients across different cohorts will be conducted.

2.5.5 Sensitivity analyses

The study will be early terminated. There will be no sensitivity analyses conducted under this situation.

2.5.6 Supplementary analyses

There will be no supplementary analyses conducted due to the early termination of the study.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

Secondary endpoints include efficacy and pharmacodynamic endpoints and safety endpoints (Table 1-1). The analyses on efficacy and pharmacodynamic endpoints will be conducted using PD analysis set. The analyses on safety endpoints will be conducted using Safety analysis set.

Analysis details will be specified in the following subsequence sections.

2.6.1.1 Efficacy and/or Pharmacodynamic endpoint(s)

Efficacy

Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in mL will be analyzed using a Mixed Effect Model for Repeated Measurement (MMRM) model. The model will include treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or neither) and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. The within subject correlation will be modeled using a repeated statement in SAS Proc Mixed with unstructured covariance matrix. In case of non-convergence the model, an alternative AR(1) covariance may be implemented.

Summary statistics of change from baseline in FVC by visit and treatment will be presented.

Progression-free survival (PFS)

- Time to event

Time to progression is defined by a composite endpoint. At the end of the treatment epoch, the Kaplan-Meier estimates of the proportion of participants who are still at the risk , along with 80% two-sided confidence intervals using Greenwood's formula, will be provided if sufficient data is available. In addition, the Kaplan-Meier estimates will be plotted against time.

The composite endpoint including ANY of the following events:

- Absolute reduction from baseline of ≥ 10% predicted in FVC
- Non-elective hospitalization for respiratory events
- Lung transplant
- Death

Non-elective respiratory hospitalizations will be defined as any unplanned inpatient hospitalizations for which the primary cause was a pulmonary condition, in the opinion of the blinded adjudicators and based on all available clinical data. Examples include, but are not limited to, the following:

- acute exacerbation of IPF (definite or suspected)
- pulmonary infection/pneumonia -pulmonary embolus
- pneumothorax
- -ulmonary aspiration
- ARDS of identifiable cause

Individual components of the composite endpoint will be summarized separately and if sufficient data is available, then further appropriate statistical analyses will be conducted.

- Progression rate

The event rates for composite endpoint and each individual components (i.e. including absolute decline of ≥10% predicted in FVC) between the treatment group and the placebo group will be compared using logistic regression model if enough the data allows.

Pulmonary physiology

To assess the impact of the IPs on pulmonary physiology, change from baseline to the end of treatment epoch (26 weeks of treatment) in DLCO and DLCO/Hb (Brian L. Graham) will be analyzed by fitting the same model of MMRM as described for the endpoint of change from baseline of FVC at 26 weeks (mL) in addition to summary statistics by treatment.

Exercise capacity

To assess the impact of the IPs on exercise capacity, change from baseline to the end of treatment epoch (26 weeks of treatment) in 6-minute walk distance (the best of the two testing results) will be analyzed by fitting the same model of MMRM as described for the endpoint of change from baseline of FVC at 26 weeks (mL)in addition to summary statistics by treatment.

2.6.1.2 Safety endpoints

All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will be summarized from initial treatment through the end of the Safety Follow-up.

The safety follow-up period will be a minimum of 30 days and may vary within each cohort. See Protocol Section 17 for details.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to dose suspension and/or discontinuation.

Any adverse events of special interest will be outlined in Protocol Section 17.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and epoch/visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by epoch, treatment, and visit/time.

12-lead ECG

All ECG data will be listed by treatment group, subject and epoch/visit/time, and abnormalities will be flagged. Summary statistics will be provided by epoch, treatment, and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and epoch/visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by epoch, treatment, and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

2.6.1.3 Patient reported outcomes

L-IPF (Impacts and Symptoms Modules), K-BILD, Leicester cough, and R-Scale for IPF questionnaires score will be reported by treatment group, patients, and epoch/visit/time. Summary statistics on the change from baseline of PRO score at the end of the treatment epoch will be provided by treatment and visit time. For continuous PRO endpoints, if data allows, the endpoints will be analyzed by fitting the same model of MMRM as described for the endpoint of change from baseline of FVC at 26 weeks (mL)in addition to summary statistics by treatment.

2.6.2 Statistical hypothesis, model, and method of analysis

Refer to Section 2.6.1.1 for the statistical hypothesis and model information for Efficacy and Pharmacodynamic secondary endpoints.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

2.6.4 Sensitivity analyses

Not applicable.

2.6.5 Supplementary analyses

Not applicable.

2.7 Safety analyses

Refer to Section 2.6.1.2 .

2.8 Pharmacokinetic endpoints

Analyses of Pharmacokinetic endpoints will not be conducted due to the early termination of the study.

2.9 PD and PK/PD analyses

Secondary efficacy and PD endpoints can be found in Section 2.6.1.1.

2.10 Patient-reported outcomes

Refer to Section 2.6.1.3 for detailed analysis.

2.11 Biomarkers

Soluble biomarker analysis will be excluded from the CSR and will be reported separately.

2.12 Other Exploratory analyses

No analyses will be conducted on the exploratory objectives/endpoints except soluble biomarkers due to the early termination of the study.

Data generated on hypothesis-free platforms may be reported separately.

2.13 Interim analysis

There will be no interim analysis due to the early termination of the study.

3 Sample size calculation

Refer to Protocol Section 12.8 and Section 17 for Details.

4 Change to protocol specified analyses

Due to the decision of the early termination of the study, the following analyses will not be performed, therefore removed from the SAP:

1. The pooling of the placebos from different cohorts
2. All sensitivity and supplemental analyses for the primary endpoint
3. All the planned CSR analyses on exploratory objectives and endpoints stated in Section 1.2
4. Planned Interim Analyses

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing element	Rule
Day, month, and year	• No imputation will be done for completely missing dates

Day, month	• If available year = year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  • Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Day	• If available month and year = month and year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  • Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date)
Day, month, and year	• Completely missing end dates (excluding. ongoing events) will be imputed by the end date of the on-treatment period*
Day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and concomitant medications with partial/missing dates will be displayed as such in the data listings.

Note: these imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.3 Concomitant medication date imputation

Refer to Table 5-1 and Table 5-2.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 or higher.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

All AEs will be reported as mapped to one of the severity levels below:

Mild = grade 1

Moderate = grade 2

Severe=grade >2 (whatever the scale).

5.3 Laboratory parameters derivations

The following table shows the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Table 5-3 Directions of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Hemoglobin	Low
Hematocrit	Low
Erythrocytes	Low
WBC	Low and high
Basophils	High
Eosinophils	High
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high

B. Chemistry	
Albumin	Low
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High
Potassium	Low and high
Magnesium	Low and high
Calcium	Low and high
LDH	High
Phosphorus	Low and high
Sodium	Low and high
CRP	High
Fibrinogen	High
HbA1c	Low and high

Vital Signs

Sitting vital signs should be within the following ranges:

- Axillary body temperature between 36.0-37.5 °C
- Systolic blood pressure, 90-139 mm Hg
- Diastolic blood pressure, 40-89 mm Hg
- Pulse rate, 40-90 bpm

ECG abnormalities

ECG abnormalities at screening or baseline:

- PR interval outside 110-200 msec
- QRS duration outside 70-120 msec
- Resting heart rate in sinus rhythm outside 40-90 bpm
- QTcF > 450 msec (male)
- QTcF > 460 msec (female)

5.4 Definition of benefit for individual endpoints

Measurement	Endpoint	Direction of benefit
Spirometry	FVC	Increase
	FVCp%	
Progression-free survival	FVCp% absolute reduction ≥ 10%	Decrease
	Non-elective hospitalization for respiratory events	Decrease

Measurement	Endpoint	Direction of benefit
	Lung transplant	Decrease
	Death	Decrease
Diffusion lung capacity	DLCO	Increase
Exercise capacity	6MWD	Increase
PRO	K-BILD	Increase
	L-IPF	Decrease
	Leicester cough	TBD
	R-scale	Decrease
HRCT	Whole lung and lobe of maximal involvement qGG, gHC, qLF, and qILD	Decrease

5.5 Statistical models

5.5.1 Analysis supporting primary objective(s)

Not applicable.

5.5.2 Analysis supporting secondary objective(s)

Not applicable.

5.6 PRO endpoints

5.6.1 K-BILD total score algorithm

A- Overview

The K-BILD is comprised of 15 items in three distinct health status domains, including breathlessness and activities (items 1, 4, 11, and 13), chest symptoms (items 2, 7, and 9), and psychological (items 3, 5, 6, 8, 10, 12, and 14) domains. A final item is used to assess the impact of the respondent's lung condition on their financial state. Rasch analysis confirmed the 15 items could be combined into a total score (12). The domain and total scores each range from 0–100, and higher scores indicate a better health status. Response options for all 15 items are on a 7-point Likert scale, ranging from 1 to 7. For each of the items, the response options vary, including: item 1 (1 = "Every time," 7 = "Never"); items 2–4, and 6–14 (1 = "All of the time," 7 = "None of the time"); item 5 (1 = "None of the time," 7 = "All of the time"); and item 15 ("A significant amount," 7 = "Not at all").

B- Scoring instruction

To score the K-BILD, the Likert response scale weightings for individual items are combined, to ensure they detect progressive change in health status. Table 5-4 shows the recoded scale weightings associated with each raw, item-level score value. Raw domain and total scores are then calculated by summing the recoded scale values provided in that table.

Table 5-4 K-BILD Response Option Weightings

Item	Response						
	1	2	3	4	5	6	7
1	0	1	2	3	4	5	6
2	0	0	1	1	2	2	3
3	0	1	2	3	4	5	6
4	0	0	1	1	2	2	3
5	0	0	1	1	1	2	2
6	0	1	2	3	4	5	6
7	0	0	1	1	2	2	3
8	0	0	1	1	2	2	3
9	0	0	1	1	1	2	2
10	0	1	2	3	4	5	6
11	0	1	2	3	4	5	6
12	0	1	2	3	4	5	6
13	0	1	2	3	4	5	6
14	0	1	2	3	4	4	5
15	0	0	1	1	1	2	2

In case of missing data, missing item scale scores will be imputed based on the average of the non-missing item scores within the domain, rounded to the nearest integer. If there is more than 50% of missing items per domain, then the domain score is set to missing. If item 15 is missing, it will be replaced by the average of all available items 1-14. If any of the domain scores are missing, the total score is set to missing.

Finally, the raw domain and total scores can be transformed to a range of 0–100 by using logit values. For each raw summed domain and total score, look up the corresponding transformed domain and total score from Table 5-5.

Table 5-5 K-BILD raw score logit transformations

Breathlessness and Activities		Chest Symptoms		Psychological		Total	
Raw Score	Transformed Score	Raw Score	Transformed Score	Raw Score	Transformed Score	Raw Score	Transformed Score
0	0	0	0	0	0	0	0
1	10.4	1	17.3	1	10.6	1	9.2
2	17.7	2	32.1	2	17.5	2	15.3
3	22.9	3	44	3	21.9	3	19.4
4	27	4	54.3	4	25.3	4	22.6
5	30.3	5	63.7	5	28	5	25.1
6	33.1	6	73.4	6	30.2	6	27.2
7	35.6	7	85.2	7	32.2	7	29
8	37.8	8	100	8	33.9	8	30.5
9	39.9			9	35.5	9	32
10	41.9			10	37	10	33.3
11	43.9			11	38.5	11	34.4
12	45.9			12	39.8	12	35.5
13	48			13	41.2	13	36.5
14	50.2			14	42.5	14	37.5
15	52.5			15	43.8	15	38.4
16	55.2			16	45.1	16	39.3
17	58.5			17	46.4	17	40.1
18	62.7			18	47.7	18	40.9
19	68.8			19	49.1	19	41.7
20	79.9			20	50.5	20	42.4
21	100			21	52	21	43.2
				22	53.5	22	43.9
				23	55.2	23	44.6
				24	56.9	24	45.2
				25	58.8	25	45.9
				26	60.8	26	46.5
				27	63	27	47.2
				28	65.5	28	47.8
				29	68.3	29	48.5

Breathlessness and Activities		Chest Symptoms		Psychological		Total	
				30	71.6	30	49.1
				31	75.6	31	49.7
				32	80.9	32	50.4
				33	88.6	33	51
				34	100	34	51.6
						35	52.2
						36	52.9
						37	53.5
						38	54.1
						39	54.8
						40	55.4
						41	56.1
						42	56.7
						43	57.4
						44	58.1
						45	58.8
						46	59.5
						47	60.2
						48	61
						49	61.8
						50	62.6
						51	63.5
						52	64.4
						53	65.3
						54	66.4
						55	67.5
						56	68.7
						57	70
						58	71.5
						59	73.2
						60	75.2
						61	77.6
						62	80.6
						63	84.6
						64	90.8
						65	100

5.6.2 L-IPF

L-IPF Impact Module

Instructions for Completing the Living with IPF (L-IPF) Impacts Module

The goal of this questionnaire is to determine how Idiopathic Pulmonary Fibrosis affects your quality of life.

Quality of life refers to your perceptions of your overall position in life in relation to:

- your goals and expectations
- your standards and values
- your concerns and judgments

Among other things, quality of life encompasses:

- your physical health (conditions/diseases, symptoms, therapies)
- your psychological state (outlook, emotional well-being)
- your level of independence
- the relationships you have with pertinent features of your environment

Reflect on your life: has Idiopathic Pulmonary Fibrosis affected your quality of life?
As you respond to the items, reflect on your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.

Items 1-15: For these items, reflect on the **last 7 days** as you consider where you are on the 0-4 scale between the two statements.

On average, over the last 7 days…

1. **How much did shortness of breath prevent you from doing things you wanted to do?**

Not at all [0] [1] [2] [3] [4] Extremely

2. **How much did fear of becoming too short of breath limit your physical exertion?**

Not at all [0] [1] [2] [3] [4] Extremely

3. **How was your stamina when you exerted physically?**

Extremely poor [0] [1] [2] [3] [4] Excellent

4. **How frustrated were you by the time it took you to complete a physical activity?**

Not at all [0] [1] [2] [3] [4] Extremely

5. **How frustrated were you by your need to rest during or after completing a physical activity?**

Not at all [0] [1] [2] [3] [4] Extremely

On average, over the last 7 days...

6. **How much did coughing embarrass you?**

Not at all [0] [1] [2] [3] [4] Extremely

7. **How much did coughing frustrate you?**

Not at all [0] [1] [2] [3] [4] Extremely

8. **How much did coughing interrupt your conversations (in person or on the phone)?**

Not at all [0] [1] [2] [3] [4] Extremely

9. **How frightening was your coughing to you?**

Not at all [0] [1] [2] [3] [4] Extremely

10. **How much was your cough a problem for you?**

Not at all [0] [1] [2] [3] [4] Extremely

11. **How much hassle or inconvenience has IPF caused you in your day-to-day life?**

None [0] [1] [2] [3] [4] A lot

12. **How much did you have to rest in the middle of doing a simple chore inside the house?**

Not at all [0] [1] [2] [3] [4] A lot

13. **How much did you have to pace yourself to make it through the day?**

Not at all [0] [1] [2] [3] [4] A lot

14. **How much time did it take to get yourself ready to leave the house?**

Very little time [0] [1] [2] [3] [4] Extremely long time

15. **How much were you forced to depend on other people to do things for you?**

Not at all [0] [1] [2] [3] [4] A lot

Symptoms Model:

Instructions for Completing the Living with IPF (L-IPF) Symptoms Module

This questionnaire is designed to assess the symptoms you may have experienced from Idiopathic Pulmonary Fibrosis (IPF) over the last 24 hours.

Keep in mind:
- you are not being asked to compare yourself to anyone else
- you are not being asked to compare how you are now with any time in the past

---

Items 1-7: The first 7 items ask about your symptoms in relation to physical activities, some of which you may not have done in the **last 24 hours.** If you did not perform an activity, we would like to know whether it was because you did not have the opportunity to do it (for example, maybe your home doesn't have stairs, so you did not walk up a flight of stairs), or whether you avoided the activity because it was too difficult.

If you did the stated activity, then reflect on the last 24 hours, and consider whether, on average, doing the activity at your usual pace or intensity level made you short of breath—and if so, how much.

Note: If you normally use oxygen when you perform a given activity, then consider your response as if you were using supplemental oxygen.

For each question, please select the box that best describes your experience.

---

1. Did you walk up one flight of stairs in the last 24 hours?

☐ Yes — How short of breath did walking up one flight of stairs make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 Extremely

☐ No — I did not walk up one flight of stairs in the last 24 hours because:

☐ A — I avoided this activity because it was too difficult to perform

☐ B — Not applicable, because I did not want or have the opportunity to do it

2. **Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?**

Not at all [0] [1] [2] [3] [4] Extremely

3. **Did you perform a grooming activity (e.g., brush teeth, shave, fix hair) in the last 24 hours?**

[Yes] How short of breath did grooming make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not perform a grooming activity in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

4. **Did you walk outside on a level surface (approximately 150 feet/45 meters, or the distance of half a typical city block) in the last 24 hours?**

[Yes] How short of breath did walking outside on a level surface make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not walk outside on a level surface in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

5. **Did you bathe or shower in the last 24 hours?**

[Yes] How short of breath did bathing or showering make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not bathe or shower in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

6. **Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?**

[Yes] How short of breath did lifting and carrying a light load a short distance make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not lift and carry a light load a short distance in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

7. **Did you become short of breath in the last 24 hours?**

[Yes] How long did it take you to recover when you became short of breath?

No time at all [0] [1] [2] [3] [4] An extremely long time

[No] Please continue to the next question

Items 8-12: These items primarily focus on your cough. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

8. **Over the last 24 hours, how often did you cough?**

Not at all [0] [1] [2] [3] [4] Constantly

If you chose "0", please skip to item 13.

9. **Over the last 24 hours, how often did you cough when you took a deep breath?**

Not at all [0] [1] [2] [3] [4] Constantly

10. **Over the last 24 hours, how often did you cough when you exerted?**

Not at all [0] [1] [2] [3] [4] Constantly

11. Over the last 24 hours, how often did you feel an annoying tickle in your throat?

Not at all [0] [1] [2] [3] [4] Constantly

12. Over the last 24 hours, how much did coughing have a negative effect on your energy?

No effect at all [0] [1] [2] [3] [4] A lot

Items 13-15: These items primarily focus on your energy level. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

13. Over the last 24 hours, how was your energy?

Extremely low [0] [1] [2] [3] [4] Excellent

14. Over the last 24 hours, of all that you wanted to get done, how much did you actually get done?

Nothing [0] [1] [2] [3] [4] Everything

15. Over the last 24 hours, how much energy did you have to do all the things you like to do?

No energy [0] [1] [2] [3] [4] A lot

Finally, we would like to ask you 5 questions about your supplemental oxygen use.

Oxygen Question 1. Do you ever use supplemental oxygen?
(Place an "X" in one box)

- ☐ Yes →→ proceed to Oxygen Question #2.
- ☐ No →→ You are finished. Skip Oxygen Questions 2-5

Oxygen Question 2. I use supplemental oxygen…
(Place an "X" in one box)

- ☐ A →→ **only when I sleep (answer Oxygen Question #3)**
- ☐ B →→ only when I perform a physical activity (such as exercising, walking or shopping) (answer Oxygen Question #4)
- ☐ C →→ **when I sleep or perform a physical activity (such as exercising, walking or shopping, but not at rest; answer Oxygen Questions #3 and #4)**
- ☐ D →→ all the time (answer Oxygen Questions #3-5)

Oxygen Question 3. When I sleep, I most often use an oxygen flow rate of ____ L/min.
(Place an "X" in one box)

☐ 0.5 ☐ 1.0 ☐ 1.5 ☐ 2.0 ☐ 2.5 ☐ 3.0 ☐ 3.5 ☐ 4.0 ☐ 4.5 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ >12

Oxygen Question 4. When I perform a physical activity (such as exercising, walking or shopping), I most often use an oxygen flow rate of ____ L/min.
(Place an "X" in one box)

☐ 0.5 ☐ 1.0 ☐ 1.5 ☐ 2.0 ☐ 2.5 ☐ 3.0 ☐ 3.5 ☐ 4.0 ☐ 4.5 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ >12

Oxygen Question 5. At rest, I most often use an oxygen flow rate of ____ L/min.
(Place an "X" in one box)

☐ 0.5 ☐ 1.0 ☐ 1.5 ☐ 2.0 ☐ 2.5 ☐ 3.0 ☐ 3.5 ☐ 4.0 ☐ 4.5 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ >12

>>The end. Thank you for taking the time to complete the L-IPF Symptoms Module.<<

For Items 16-18: Think broadly about your shortness of breath, cough and energy level over the last 7 days. Have these symptoms affected how you have felt physically? Psychologically? Have they disrupted your life? Or limited you in terms of what you would like to do or how you would like to do it? Now, please respond to Items 16-18.

On average, over the last 7 days...

16. How has shortness of breath affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

17. How much has your cough affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

18. How much has your energy level affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

For these last two, Items 19 and 20: Think broadly again about whether IPF has affected you and your quality of life over the last 7 days. Reflect on your symptoms and other aspects of your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.

On average, over the last 7 days...

19. How have you felt in terms of physical health?

Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent

20. How has your quality of life been?

Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent

>> The end. Thank you for taking the time to complete the L-IPF Impacts Module. <<

5.6.3 Leicester cough

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

☐	☐	☐	☐	☐	☐	☐
All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

☐	☐	☐	☐	☐	☐	☐
Every time	**Most times**	**Several times**	**Sometimes**	**Occasionally**	**Rarely**	**Never**

3. In the last 2 weeks, have you been tired because of your cough?

☐	☐	☐	☐	☐	☐	☐
All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**

4. In the last 2 weeks, have you felt in control of your cough?

☐	☐	☐	☐	☐	☐	☐
None of the time	**Hardly any of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

☐	☐	☐	☐	☐	☐	☐
All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**

6. In the last 2 weeks, my cough has made me feel anxious

☐	☐	☐	☐	☐	☐	☐
All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

9. In the last 2 weeks, exposure to paints or fumes has made me cough

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

10. In the last 2 weeks, has your cough disturbed your sleep?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

11. In the last 2 weeks, how many times a day have you had coughing bouts?

All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None
☐	☐	☐	☐	☐	☐	☐

12. In the last 2 weeks, my cough has made me feel frustrated

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

13. In the last 2 weeks, my cough has made me feel fed up

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

15. In the last 2 weeks, have you had a lot of energy?

None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐	☐

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

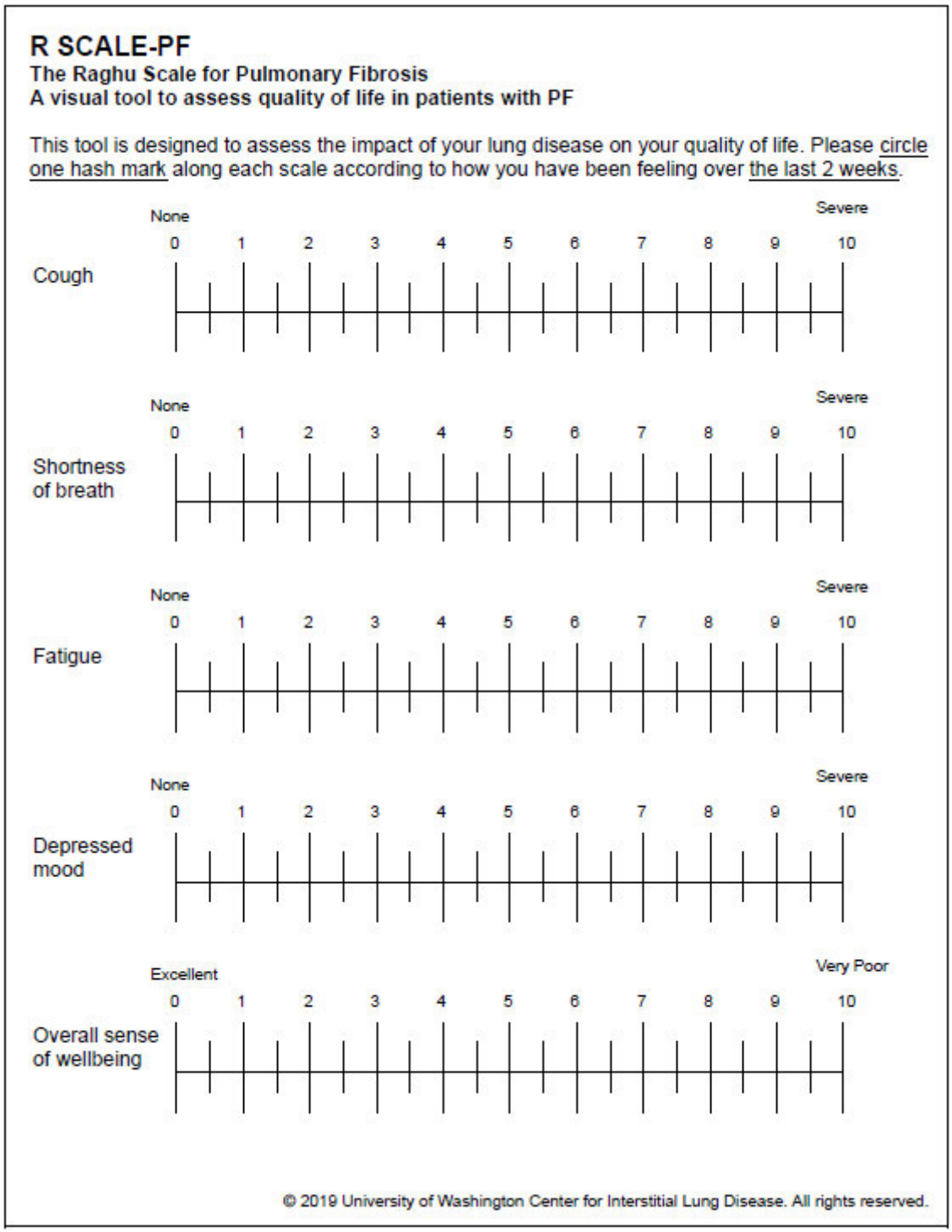
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
☐	☐	☐	☐	☐	☐	☐

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never
☐	☐	☐	☐	☐	☐	☐

Thank you for completing this questionnaire.

5.6.4 R-scale



5.7 Rule of exclusion criteria of analysis sets

Refer to Section 2.2, Table 2-1.

6 Reference

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