TRIAL STATISTICAL ANALYSIS PLAN

c31040004-01

BI Trial No.:	1199-0355
Title:	Investigating Trends in **Qua**lity of **Lif**e in Patients with Idiopathic Pulmonar**y** Fibrosis (**IPF**) Under Treatment with Nintedanib
Investigational Product(s):	Ofev®, Nintedanib
Responsible trial statistician(s):	[redacted]
Date of statistical analysis plan:	01 APR 2020 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ATC	Anatomic Therapeutic Classification System
BAL	Bronchoalveolar Lavage
BSL	Baseline
CAD	Coronary Artery Disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DL_{CO}	Diffusing Capacity for Carbon Monoxide
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
FU	Follow Up
GAD-7	Generalized Anxiety Disorder Screener Questionnaire
GAP	gender (G), age (A) and two lung physiology variables (P)
HRCT	High Resolution Computer Tomography
HRQoL	Health Related Quality of Life
ICF	Inform Consent Form
ICH	International Conference On Harmonisation
IPF	Idiopathic Pulmonary Fibrosis
LTOT	Long Term Oxygen Therapy
MedDRA	Medical Dictionary For Regulatory Activities
mMRC	modified Medical Research Council scale
MMRM	Mixed Models for Repeated Measures
PPS	Per Protocol Set
PT	Preferred Term
PD	Protocol Deviation
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
sMAQ	Simplified Medication Adherence Questionnaire
SAE	Serious Adverse Event
SOC	System Organ Class
TLC	Total Lung Capacity
ToC	Table of Contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
VAS	Visual Analogue Scale

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP). In particular, the TSAP is based on the planned analysis specification as written in CTP Section 9.7 “Data Analysis”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size. SPSS Version 24 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary objective is to evaluate the HRQoL change from baseline of IPF patients treated with nintedanib in the current clinical practice in Greece, at the time-points of 3, 6, 9 and 12 months over a 52-weeks period via SGRQ instrument.

The following surrogate endpoints will be employed to assess the objective:

- The mean change from baseline of SGRQ total score until month 3, month 6, month 9 and month 12.
- The mean change from baseline of SGRQ symptoms domain score until month 3, month 6, month 9 and month 12.
- The mean change from baseline of SGRQ activity domain score until month 3, month 6, month 9 and month 12.
- The mean change from baseline of SGRQ psycho-social impact domain score until month 3, month 6, month 9 and month 12.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

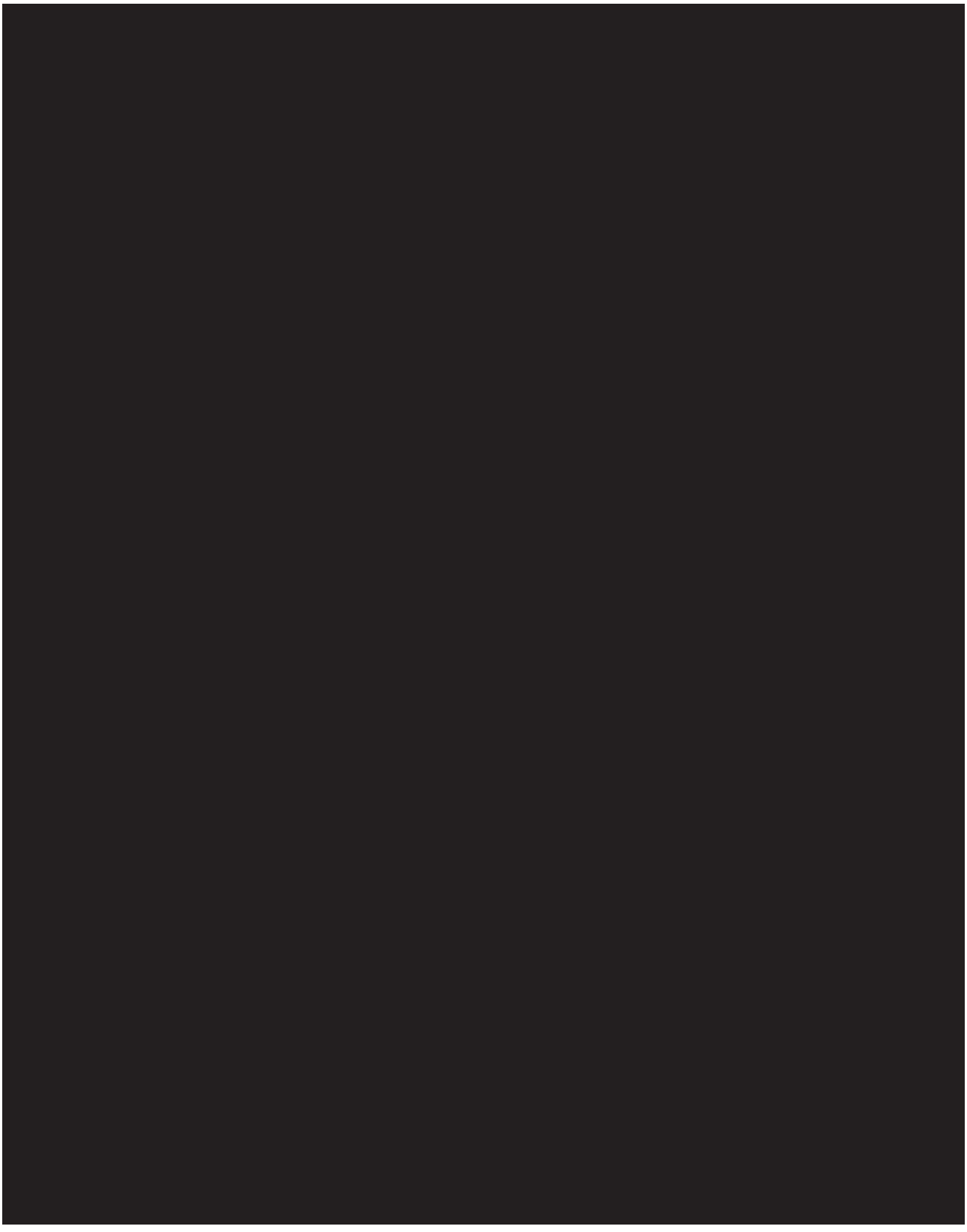
Not Applicable

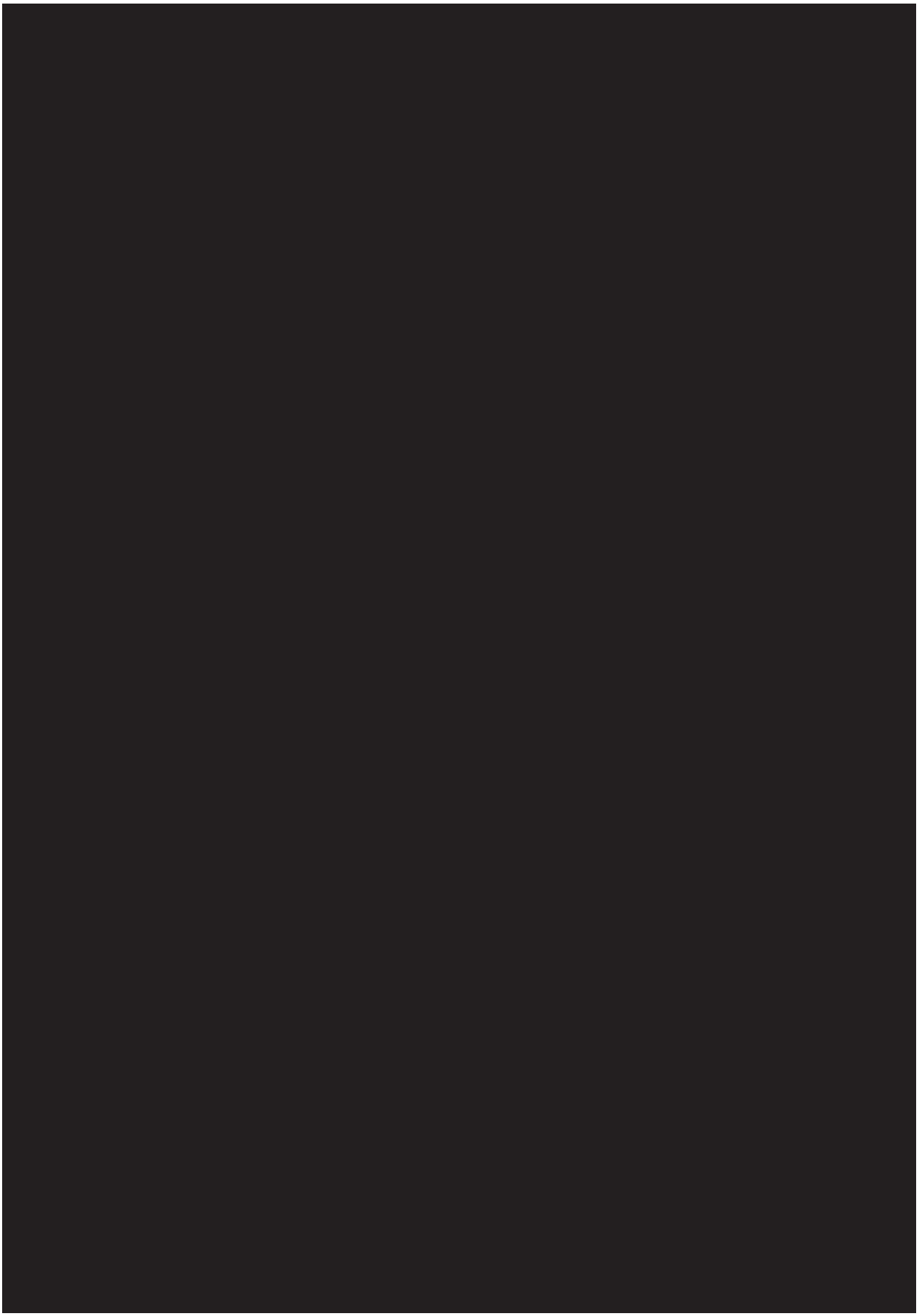
5.2.2 Secondary endpoint(s)

The following endpoints will be employed to assess the secondary study objectives:

- The mean change from baseline of mMRC questionnaire score until month 3, month 6, month 9 and month 12.
- Percentage of patients by dyspnoea severity according to mMRC questionnaire at month 3, month 6, month 9 and month 12.
- The mean change from baseline of Cough-VAS score until month 3, month 6, month 9 and month 12.
- Percentage of adhered / non- adhered patients to nintedanib treatment via SMAQ Questionnaire at month 3, month 6, month 9 and month 12.

- The mean change from baseline of GAD7 score until month 3, month 6, month 9 and month 12.
- Percentage of patients that used at least once LTOT at month 3, month 6, month 9 and month 12





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Patients enrolled in the current trial are recently diagnosed IPF patients and they have already initiated treatment with Nintedanib according to their physician's clinical decision.
No treatment intervention is relevant and therefore no special treatment assignment is under consideration.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Table 6.2:1 Important protocol deviations

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criteria not met as specified in the protocol:	The following inclusion criteria not met • Patients ≥40 years of age. • Treatment naïve patients with initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines who are initiating treatment with Nintedanib (as monotherapy for IPF) or have initiated treatment with Nintedanib (as monotherapy for IPF) within the past 7 days prior to the enrolment.* • Patients for whom the decision to prescribe therapy with Nintedanib according to the locally approved product's SmPC has already been taken prior to the study enrolment and is clearly separated from the physician's decision to include patient in the current study. * • Patients that are able to read, understand and complete the study specific questionnaires. *	PPS
	A2	Exclusion criteria met	[redacted]	PPS
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	TS, PPS
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 2 date <*Visit 2 date*>	
D		**Concomitant medication**		
	D2	Prohibited medication use	Pirfenidone taken.*	PPS
	D3	Mandatory medication not taken	Nintedanib treatment was not taken or interrupted	PPS

Category/ Code		Description	Requirements	Excluded from
			for 28 days period*	
E		**Certain Violations of procedures used to measure primary data**		
	E1	Protocol amendment / incorrect CRF, implemented after the approvals and/or PI signature	Incorrected (old) version of SGRQ questionnaire is completed after the IRB approvals*	PPS
F		**Certain Violations of time schedule to measure primary data**		
	F1	No follow-up visits performed	Only baseline visit is recorded	PPS

Note: (*) not programming activity checks. These IPV definitions in the TSAP should be made available to the Local Clinical Monitors (CMLs)/Clinical Research Associates (CRAs) to view so they know which IPVs are programmed and hence do not need to be identified at a site level on the manual PV log."

6.3 SUBJECT SETS ANALYSED

The following sets will be used for the purpose of the statistical analysis of the current trial:

Treated Set (TS): all subjects entered the trial received at least once Nintedanib during the trial. TS will be used for safety analysis. Any analysis on primary, secondary and safety endpoints will be performed in TS.

Per Protocol Set (PPS): all subjects who have completed the trial with no major protocol deviations. PPS will be used only as supportive to the TS and only in the analysis of the primary endpoint providing that the TS does not differ more than 20% from the PPS in the number of patients.

Table 6.3:1 Subject Sets Analysed

	Subject Sets	
Class of endpoint	TS	PPS
Primary endpoints	primary analysis	secondary analysis
Secondary endpoints	X	
Safety endpoints	X	
Demographic/baseline endpoints	X	

6.5 POOLING OF CENTRES

This section is not applicable because center/country will not be included in the statistical modeling.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation technique to fill in any missing values will be employed. Accordingly, the Last Observation Carried Forward technique or any other multiple imputation will not be applied.

Missing values will be differentiated from negative answers. Summary statistics will be performed only on subjects with available information (unknown data will not account in the total population for each specific variable).

For missing or incomplete AE dates or drug administration dates, or other significant dates, the BI internal procedures and guidelines (2) will be employed.

In case implausible data remain in the database once locked, then: for tables that are provided for endpoints with a large amount of implausible data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

Correction of implausible data on an individual subject case is not permitted.

In order to account for the missing values of the primary and secondary continuous endpoints, an MMRM model will be employed based on the assumption that values as missing at random.

Note: Due to incorrect translation in the Greek language of question 17 of the SGRQ instrument this specific question has been set to missing in all patients prior to the approval receipt date as mentioned in Table 9.1:1. The corrected version to be considered is the one used after the approval receipt date. No further action is to be performed to impute this data for the primary analysis of the primary

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, the last assessment / measurement observed prior to start of study medication following ICF will be assigned to baseline. Note that for some study procedures

(e.g. body weight, vital signs) this may be the value measured on the same day trial medication was started

Visit windowing will be performed as described in Table 6.7:1, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analysed using the re-calculated visits in the statistical tables. However, in the listings, all visits performed will be displayed (even if outside time-window), along with the re-calculated visit.

Table 6.7:1 Analysis Visit Windows

Analysis Visits	Target Day[1]	Analysis visit window	Group 1	Group 2
Baseline	1	<=1	<=1	<=1
FU1 3 Months	92	52-132	52-132	52-132
FU2 6 Months	183	143-213		143-213
FU3 9 Months	275	235-315		235-315
FU4 12 Months	366	326-406		326-406

[1] The baseline visit (day 1): as documented in the eCRF (after the ICF has been signed). Any assessment following this date is subject to analysis visits window.

Group 1: Eligibility criteria, Co-morbidities, Baseline information (assessment), IPF risk factors, information on IPF, Functional assessment, Questionnaires
Group 2: Symptoms, LTOT,

AEs, survival status, concomitant medication treatment with Nintedanib are excluded from analysis visit mapping window and the investigator may enter data as needed.

Post baseline: Any assessment after the baseline visit and during the follow up visits.

If after windowing of visits at baseline, two or more values fall within the same baseline interval, then the last value will be taken into account. If after windowing of post-baseline visits, two visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be picked.

7. PLANNED ANALYSIS

Continuous variables will be summarized as mean value with standard deviation (SD) and median, Q1, Q3, along with minimum and maximum values. The minimum and maximum values will have the precision of the data reported; mean, median values will have one additional decimal, whereas SD will have two additional decimals.
Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to all subjects with non missing values for the specific variable. The category missing will be displayed only if there are actually missing values. The precision of percentages will be set at one decimal points unless the resulting output indicates point to 0.0%; in that case a second decimal will be included.

Any statistical inference will be based at 2-sided level of significance of α=0.05 (i.e. 95% confidence interval will be calculated).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report based on the total population (no subgroups).

The demographic and baseline characteristics described in Section 5.4.1 will be summarized.

7.2 CONCOMITANT DISEASES AND MEDICATION

As concomitant medication is considered as any treatment received after the enrollment to the study irrespective when it was initiated (before or during the study). Concomitant medication will be presented based on ATC coding of the World Health Organization Drug Dictionary (WHO-DD) using the most recent version at the time of the database lock.

Any comorbidity reported which started prior to the study enrollment will be summarized as medical history. Separate table will summarize all comorbidities reported in the study.

7.3 TREATMENT COMPLIANCE

Treatment compliance is assessed secondary objective of the study and it is described in Section 7.5.2.4.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The SGRQ Total score and the corresponding sub domains will be calculated; it summarizes the impact of the disease on the overall health status. Scores are expressed as a percentage of

overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

The primary endpoint of SGRQ Total score and the corresponding sub domains will be summarized descriptively as continuous variables at each study visit in the TS population.

The SGRQ scores to be displayed in the above mentioned summaries will be the observed values at each visit and the absolute change from baseline at each visit.

Calculation of SGRQ score for each patient is performed on patient level based on the questionnaire manual.

Change from baseline is defined as post baseline – baseline value, assuming that both time points are non missing.

Baseline value: SGRQ following to ICF signature, see Table 6.7:1.

Post baseline value: Any SGRQ score after the baseline visit.

For the statistical inference regarding the SGRQ Total score and the corresponding sub domains, mixed models for repeated measurements model (MMRM) assuming random missingness will be fit. The dependent variable will be the SGRQ (Total score or the corresponding subdomains) at each visit. Visit, GAP_{BSL} stage, FVC_{BSL} (cut off≤70%), $DLCO_{BSL}$ (cut off <40%) and number of comorbidities (as dictated by the medical history page) will be entered as fixed factors, baseline score by visit as interaction term.

Patients will be fitted at random and an unstructured correlation matrix will be used, allowing adjustment for correlations between study visits within the study patients. The Kenward-Roger degrees of freedom approximation will be used in the model (ddfm=kr). In case of no convergence, the following steps will be considered:

- The value used in the model as tolerance in checking singularity should be changed to 10-10 (the default value is 10-12).
- Increase the number of convergence iterations to 200 (default is 100 iterations).
- Apply scoring algorithm. Request to use the Fisher scoring algorithm up to the 4th iteration. The default is 1.
- Use a simpler covariance matrix: Should none of the previous methods does not work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances. Should this also not converge, a standard Toeplitz matrix will be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) can be fitted.

Summaries of the estimated mean change from baseline of SGRQ scores until months 3, 6, 9 and 12 will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table.

Worth to note, that the response to incorrectly translated question 17 will be set to missing for any analysis mentioned above in all patients prior to the approval receipt date as mentioned in Table 9.1:1.

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoint(s)

7.5.2.1 mMRC

The secondary endpoint of mMRC score, will be summarized descriptively. The percentage of patients in each dyspnoea component of mMRC instrument will be presented in absolute and relative frequencies based on the available information at each study visit. In addition, shift tables will be provided for mMRC to compare a subject's baseline evaluation relative to the visit's observed value. For all shift tables, data will be summarized as observed, ie no imputation on missing data.
Change from baseline in mMRC score is defined as post baseline – baseline value, assuming that both time points are non missing.

For the statistical inference regarding mMRC a MMRM assuming data to be missing at random will be fit. The dependent variable will be the mMRC score at each visit. Visit, GAP_{BSL} stage, FVC_{BSL} (cut off$\leq$70%), $DLCO_{BSL}$ (cut off <40%) and number of

comorbidities (as dictated by the medical history page) will be entered as fixed factors, baseline score by visit as interaction term. Patients will be fitted at random and an unstructured correlation matrix will be used, allowing adjustment for correlations between study visits within the patients. In case of no convergence, the methods proposed at Section 7.4.1 may be introduced.
Summaries of the estimated mean change from baseline of mMRC until months 3, 6, 9 and 12 will be provided with the corresponding 95% confidence interval. Model information will be provided as footnote under the corresponding table.

7.5.2.2 Cough Visual Analogue Scale (VAS)

The secondary endpoint of cough VAS reflecting the cough burden will be summarized descriptively as continuous variables at each study visit. The VAS values to be displayed in the summaries will be the observed values at each visit and the absolute change from baseline at each visit.

Change from baseline is defined as post baseline – baseline value, assuming that both time points are non missing.

For the statistical inference regarding VAS, a mixed model for repeated measurements model (MMRM) assuming random missingness will be fitted. The dependent variable will be the VAS score at each visit. Visit, GAP_{BSL} stage, FVC_{BSL} (cut off≤70%), $DLCO_{BSL}$ (cut off <40%) and number of comorbidities (as dictated by the medical history page) will be entered as fixed factors, baseline score by visit as interaction term. Patients will be fitted at random and an unstructured correlation matrix will be used, allowing adjustment for correlations between study visits within the patients. In case of no convergence, the methods proposed at Section 7.4.1 may be introduced.
Summaries of the estimated mean change from baseline of VAS until months 3, 6, 9 and 12 will be provided with the corresponding 95% confidence interval. Model information will be provided as footnote under the corresponding table.

7.5.2.3 GAD 7

The secondary endpoint of GAD7 reflecting severity of anxiety will be summarized descriptively as continuous variables at each study visit. The GAD 7 values to be displayed in the summaries will be the observed values at each visit and the absolute change from baseline at each visit.

Change from baseline is defined as post baseline – baseline value, assuming that both time points are non missing.

GAD-7 total score for the seven items ranges from 0 to 21. Scores of 5, 10, and 15 represent cut points for mild, moderate, and severe anxiety, respectively. Frequency of patients with mild, moderate, or severe anxiety will be displayed at each visit.

For the statistical inference regarding GAD 7 score, a mixed model for repeated measurements model (MMRM) assuming random missingness will be fitted. The dependent variable will be the GAD 7 score at each visit. Visit, GAP_{BSL} stage, FVC_{BSL} (cut off≤70%), $DL_{CO\ BSL}$ (cut off ≤40%) and number of comorbidities (as dictated by the medical history

page) will be entered as fixed factors, baseline score by visit as interaction term. Patients will be fitted at random and an unstructured correlation matrix will be used, allowing adjustment for correlations between study visits within the patients. In case of no convergence, the methods proposed at Section 7.4.1 may be introduced.
Summaries of the estimated mean change from baseline of GAD 7 score until months 3, 6, 9 and 12 will be provided with the corresponding 95% confidence interval. Model information will be provided as footnote under the corresponding table.

7.5.2.4 SMAQ

The secondary endpoint of SMAQ reflecting treatment adherence will be summarized descriptively at each visit in TS. Absolute and relative frequencies of adhered / non- adhered to treatment patients will be displayed at each visit.

The questionnaire is dichotomic (yes, no), any answer in the sense of non-adherent groups, assigns patient to the non-adherent category. Thus, patient is considered non-adherent if the answers to the SMAQ questionnaire (see Table 7.5.2.4:1) are the following:
1: YES.
2: No
3: YES
4: YES
5: C, D or E
6: i) more than two days.
ii) More than four days

Table 7.5.2.4:1 SMAQ Questionnaire

1. Do you ever forget to take your medication for IPF? Y/N
2. Do you always take your medication for IPF at the indicated time? Y/N
3. Sometimes if you feel worse, do you stop taking your medication for IPF? Y/N
4. Did you miss any of your medication for IPF last weekend? Y/N
5. Think on the last week. How often did you miss to take your medication for IPF? A: Never B: 1 - 2 C: 3 - 5 D: 6 - 10 E: >10
6. i) How many days have you missed taking your medication for IPF during the past 3 months? 6. ii) How many days have you missed one of the two daily medication for IPF doses during the past 3 months?

7.5.2.5 LTOT use

The percentage of TS patients that used LTOT at each visit and the percentage of TS patients that used LTOT at least once during the study will be displayed. Percentages will be based on the number of patients with available information.

Additionally, based on the total number of visits performed from all study patients, the percentage of visits that LTOT was used will be calculated (100 x Total number of study visits that LTOT was used over the total number of study visits).

[redacted]

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

All treatment emergent adverse events recorded during the trial will be presented in listings for AEs / SAEs. Especially the Adverse Drug Reactions (ADR), these might be followed up after the study completion and until they are resolved.
As treatment emergent adverse events are considered all the AEs following ICF signature providing the patient has already received treatment with Nintedanib.
Initially, an AE overview table will be created summarizing the total number of AEs and patients with at least one: AE, SAE, SAE leading to death, SAE leading to drug discontinuation.

A separate table showing the overview of AE occurred during the study will be presented by SOC and PT. SOC terms will be sorted alphabetically; PTs will be sorted within each SOC term by decreasing frequency. In such tables if a subject reported more than one AE within the same PT or SOC, the subject will be counted only once for this PT/SOC.

AEs will be coded based on the MedDRA terminology. The existing version at the time of the database lock will be used. For further details on summarization of AE data, please refer to (3).

7.8.2 Laboratory data

No laboratory data for safety evaluation will be collected.

7.8.3 Vital signs

Systolic and Diastolic Blood pressure (mmHg), heart rate (bt/min) and weight (kg) will be summarized descriptively at each visit.

7.8.4 ECG

No ECG data for safety evaluation will be collected.

7.8.5 Others

The number and percentage of patients with IPF symptoms will be summarized at each study visit.

A separate table illustrating the number and percentage of patients with fatal event, the reason of death as well as the median survival time of the patients will be given. Survival time (in weeks) will be calculated as follows.

Survival time = (Date of death-FU – ICF date) / 7

A Kaplan Meier curves will display the survival distribution curve. Dates will be cut at the last time of follow up or death.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED.
3.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials ", current version; KMED.
4.	Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE Jr, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med; 2012 May 15 156(10):684-91 [R14-2344]
5.	Kolb M, Collard HR. Staging of idiopathic pulmonary fibrosis: past, present and future. Eur Respir Rev; 2014 Jun;23(132):220-4 [R20-0840]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**01-APR-2020**	[redacted]	None	This is the final TSAP