Trial Statistical Analysis Plan

c10844794-02

BI Trial No.:	1199.227
Title:	A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral Nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment. Including Protocol Amendments 1, 2, 3 and 4 [c03495745-05]
Investigational Product(s):	Ofev®, Nintedanib
Responsible trial statistician(s):	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	19 JUL 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse event
ALQ	Above limit of quantification
ALT	Alanine aminotransferase
AR	Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
ATS/ERS/ JRS/ALAT 2011 guideline	American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guideline on idiopathic pulmonary fibrosis treatment / 2011
BFVC	Baseline FVC
BIcMQ	Boehringer Ingelheim customized MedDRA query
BIRDS	Boehringer Ingelheim regulatory document system
BLQ	Below limit of quantification
BM	Biomarker
BRPM	Blinded report planning meeting
CNS	Central nervous system
cpm	count per million
CRF	Case Report Form
CT	Concomitant therapies
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database lock
DBLM	Database lock meeting
DILI	Drug induced liver injury
DLCO	Carbon monoxide diffusion capacity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECM	Extracellular matrix

Term	Definition / description
EMA	European Agency for the Evaluation of Medicinal Products
EOT	End of treatment
FDR	False discovery rate
FUP	Follow-up period
FVC	Forced vital capacity
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
Hb	Hemoglobin
HGNC	Human Gene Nomenclature Committee
HLT	Higher level term
HRCT	High-resolution computed tomography
ICH	International Conference on Harmonisation
IPF	Idiopathic pulmonary fibrosis
IPV	Important protocol violation
IXRS	Interactive voice/web response system
LLOQ	Lower limit of quantification
MACE	Major adverse cardiac events
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurements
MQRM	Medical Quality Review Meeting
N	Number of patients
NOA	not analysed
NOR	no valid result
NOS	no sample available
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetics set
PN	Preferred name
PT	Preferred term
PV	Pharmacovigilance

Term	Definition / description
RS	Randomized set
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SMQ	Standardised MedDRA Query
SOC	System organ class
SpO2	Oxygen saturation on pulse oximetry
TS	Treated Set
TSAP	Trial statistical analysis plan
ULOQ	Upper limit of quantification
ULN	Upper limit normal

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), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. 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, randomization.

Standard analyses on biomarkers and those on biomarker study endpoints will be described within this Statistical Analysis Plan.

SAS® Version 9.4 (or later version) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Not applicable

5. ENDPOINT(S)

Refer to Section 6.6 for missing baseline assessment.
Refer to Section 6.7 for baseline value definition.

5.1 PRIMARY ENDPOINT

The primary endpoint is the rate of change (slope) in blood CRPM from baseline to week 12.

5.2 SECONDARY ENDPOINT(S)

Secondary efficacy endpoints are described in Section 5.1.2 of CTP. Additional information is provided only on selected endpoints in the TSAP.

5.2.1 Key secondary endpoint(s)

The key secondary endpoint is the proportion of patients with disease progression as defined by absolute FVC (% predicted) decline ≥10% or death until week 52 based on in clinic supervised spirometry.

5.2.2 Secondary endpoint(s)

Secondary endpoints are the rate of change (slope) in blood C1M from baseline to week 12 and the rate of change (slope) in blood C3M from baseline to week 12.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For treatment specifications, see Section 4 of CTP.

The following trial periods will be defined: screening, post-randomisation, blinded treatment period (with sub-periods off-treatment, post-treatment and follow-up), open-label treatment period (with sub-periods off-treatment, post-treatment and follow-up) and post-study as follows:

Note: Post-treatment reflects the residual effect period.

Note: the last day of each of the following periods is excluded.

- Screening: from informed consent to randomisation
- Post-randomisation (optional): from randomisation to first randomised trial drug intake in blinded treatment period
- Blinded treatment period: from first randomised trial drug intake (or re-start of treatment if interruption) to last randomised trial drug intake (or the day before start date of interruption, if interruption) plus one day
    - Blinded off-treatment (optional): from start date of interruption to re-start of blinded treatment
    - Blinded post-treatment (optional)[a]: from the last blinded trial drug intake plus one day to last blinded trial drug intake plus 28 days plus one day or day of first open-label treatment administration (whichever occurs earlier)
    - Blinded follow-up (optional): from last blinded trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last blinded trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the blinded treatment and still continuing the trial
- Open-label treatment period: from first open label nintedanib intake (or re-start of treatment if interruption) to last open label nintedanib intake (or the day before start date of interruption, if interruption) plus one day
    - Open-label off-treatment (optional): from start date of interruption to re-start of open-label treatment
    - Open-label post-treatment (optional)[a]: from the last open-label trial drug intake plus one day to last open-label trial drug intake plus 28 days plus one day
    - Open-label follow-up (optional): from last open-label trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if

last open-label trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the open-label treatment and still continuing the trial

- Post-study: from the latest of
    - last trial drug intake plus 29 days
    - date of trial completion
    - follow-up visit
    - early end of treatment visit plus 1 day to database lock

[a] In addition, a post-treatment period of 7 days will be used for adverse event analyses to more closely reflect the period of time after the last trial drug intake when measureable drug levels or pharmacodynamic effects are still likely to be present.

In addition to the above periods, the following additional period is defined:

- Overall: Combines all available data from Blinded treatment period and Open-label treatment period.

For safety analyses, data up to the end of the blinded / open-label post-treatment period will be considered on-treatment. For on-treatment efficacy analyses, data up to the day after last trial drug intake (included) will be considered.

For efficacy analyses patients will be assigned to the treatment group they were randomised to, for safety analyses patients will be assigned to the treatment group they were treated in.

Details are provided in Table 6.1: 1.

Table 6.1: 1 Summary of analysed periods according to the type of endpoint

	Studied period	
Analysed endpoint	***Start date***	***End date*** [1]
For primary analysis (rate of change (slope) in blood CRPM from baseline to week 12)	Baseline (see Section 6.7)	Visit 5 (after time windowing, refer to Section 6.7) Data up to the day after last blinded trial drug intake (included).
For the key secondary endpoint (Proportion of patients with disease progression as defined by absolute FVC (% predicted) decline ≥10% or death until week 52)	Main analysis: Baseline (see Section 6.7) Sensitivity analysis: Visit 5 (start of open label treatment)	Visit 10 (after time windowing, refer to Section 6.7) Data up to the day after last open-label trial drug intake (included).
For secondary endpoints (rate of change (slope) in blood C1M and C3M from baseline to week 12)	Baseline (see Section 6.7)	Visit 5 (after time windowing, refer to Section 6.7) Data up to the day after last blinded trial drug intake (included).
For efficacy endpoints from week 12 to week 52 (open-label period)	Visit 5 (start of open label treatment) Note: Covariates can be measured before Visit 5.	Visit 10 (after time windowing, refer to Section 6.7) Data up to the day after last trial open-label drug intake (included).
For efficacy endpoints from baseline to week 12 (blinded period)	Baseline (see Section 6.7)	Visit 5 (after time windowing, refer to Section 6.7) Data up to the day after last blinded trial drug intake (included).

Table 6.1: 1 (continued) Summary of analysed periods according to the type of endpoint

	Studied period	
Analysed endpoint	***Start date***	***End date*** [1]
Rates of decline during blinded period	Baseline (see section 6.7)	Visit 5 (after time windowing, refer to Section 6.7) Data up to the day after last blinded trial drug intake (included).

Table 6.1: 1 (continued) Summary of analysed periods according to the type of endpoint

	Studied period	
Analysed endpoint	***Start date***	***End date*** [1]
Rates of decline during open-label period	Visit 5 (start of open label treatment) Note: Covariates can be measured before Visit 5.	Visit 10 (after time windowing, refer to Section 6.7) Data up to the day after last trial open-label drug intake (included).

Table 6.1: 1 (continued) Summary of analysed periods according to the type of endpoint

	Studied period	
Analysed endpoint	***Start date***	***End date*** [1]
AEs and laboratory data		
On-treatment period safety (AEs, laboratory data, including enzymes elevation) during blinded treatment period	Date of first trial drug intake	First day of documented intake of open-label treatment or last blinded trial drug intake plus 28 days or end of treatment, whichever occurs first
	Off-treatment periods not excluded. However, for safety listings, anything happening during a treatment interruption will be flagged as occurring during the off-treatment period (even if between [last trial drug intake; last trial blinded drug intake + 28 days])	
On-treatment period safety (AEs, laboratory data, including enzymes elevation) during open label treatment period	First day of documented intake of open-label treatment	Last open label drug intake plus 28 days or end of treatment, whichever occurs first
	Off-treatment periods not excluded. However, for safety listings, anything happening during a treatment interruption will be flagged as occurring during the off-treatment period (even if between [last trial drug intake; last trial open label drug intake + 28 days])	
On-treatment period safety (AEs, laboratory data, including enzymes elevation) during overall treatment period	Date of first trial drug intake	Last drug intake plus 28 days or end of treatment, whichever occurs first
	Off-treatment periods not excluded. However, for safety listings, anything happening during a treatment interruption will be flagged as occurring during the off-treatment period (even if between [last trial drug intake; last trial drug intake + 28 days])	

Table 6.1: 1 (continued) Summary of analysed periods according to the type of endpoint

	Studied period	
Analysed endpoint	***Start date***	***End date*** [1]
On-treatment period safety: Liver enzyme and bilirubin elevation between periods (i.e.: the elevation of bilirubin appears within 30 days of the elevation of AST and/or ALT, but in different period)	Date of first trial drug intake	Last open label drug intake plus 28 days or end of treatment, whichever occurs first
	Off-treatment periods not excluded. However, for safety listings, anything happening during a treatment interruption will be flagged as occurring during the off-treatment period (even if between [last trial drug intake; last trial open label drug intake + 28 days])	

Table 6.1: 1 (continued) Summary of analysed periods according to the type of endpoint

	Studied period	

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations. The final column describes which protocol violations will be used to exclude patients from which analysis set(s).

Table 6.2: 1 Important protocol violations (IPVs)

Category / Code		Description	Requirements / Classification	Excluded from
A		**Entrance criteria not met**		
	A1.1	Age < 40 years at Visit 1	Inclusion criterion 2 not met as specified in the protocol. Automatic IPV	None
	A1.2	No clinical diagnosis of IPF within the last 3 years from Visit 0, based upon the ATS/ERS/JRS/ALAT 2011 guideline	Inclusion criterion 3 not met as specified in the protocol. Automatic IPV	None
	A1.3	No chest high resolution computed tomography (HRCT) scan performed within 18 months of Visit 0	Inclusion criterion 4 not met as specified in the protocol. Automatic IPV	None
	A1.4	Combination of HRCT pattern and surgical lung biopsy pattern (the latter if available) as assessed by central review is not consistent with the diagnosis of IPF	Inclusion criterion 5 not met as specified in the protocol. Automatic IPV	None
	A1.5	FVC < 80% of predicted normal at visit 1	Inclusion criterion 6 not met as specified in the protocol but it was agreed during MQRM to only flag patients with FVC ≤ 0.79 Automatic IPV	None
	A2.1	ALT, AST, Total bilirubin > 1.5 fold upper limit of normal (ULN) at Visit 1	Exclusion criteria 1 or 2 met as specified in the protocol Automatic IPV	None
	A2.2	Underlying chronic liver disease (Child Pugh A, B or C hepatic impairment	Exclusion criterion 3 met as specified in the protocol Automatic IPV	None
	A2.3	Relevant airways obstruction [i.e. pre-bronchodilator FEV1/FVC < 0.70 (i.e. 70%) at Visit 1]	Exclusion criterion 4 met as specified in the protocol but it was agreed during MQRM to only flag patients with FEV1/FVC ≤ 0.65 Automatic IPV	None
	A2.4	History of myocardial infarction within 6 months of visit 1 or unstable angina within 1 month of Visit 1	Exclusion criterion 5 met as specified in the protocol (for more details refer to the protocol) Automatic IPV	None
	A2.5	Bleeding Risk	Exclusion criterion 6 met as specified in the protocol Automatic IPV	None
	A2.6	Planned major surgery during the trial participation, including lung transplantation, major abdominal or major intestinal surgery	Exclusion criterion 7 met as specified in the protocol Automatic IPV	None
	A2.7	History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1	Exclusion criterion 8 met as specified in the protocol Automatic IPV	None

Table 6.2: 1 (continued) Important protocol violations (IPVs)

Category / Code		Description	Requirements / Classification	Excluded from
	A2.8	Creatinine clearance < 30 mL/min calculated by Cockcroft–Gault formula at Visit 1	Exclusion criterion 9 met as specified in the protocol Automatic IPV	None
	A2.9	Treatment with Nintedanib, pirfenidone, azathioprine, cyclophosphamide, cyclosporine, any other investigational drug, n-acetylcysteine, prednisone/prednisolone >15 mg daily or >30 mg every 2 days OR use of other systemic corticosteroids as well as any investigational drugs within 4 weeks of Visit 2	Exclusion criterion 10 met as specified in the protocol Automatic IPV	None
	A2.10	Known hypersensitivity to nintedanib, peanut, soya or to any other components of the study medication	Exclusion criterion 11 met as specified in the protocol Automatic IPV	None
	A2.11	Prior discontinuation of nintedanib treatment due to intolerability/ adverse events considered drug related	Exclusion criterion 12 met as specified in the protocol Automatic IPV	None
	A2.12	A disease or condition which in the opinion of the investigator may interfere with testing procedures or put the patient at risk when participating in this trial	Exclusion criterion 13 met as specified in the protocol Automatic IPV	None
	A2.13	Alcohol or drug abuse which in the opinion of the treating physician would interfere with the treatment and would affect patient's ability to participate in this trial	Exclusion criterion 14 met as specified in the protocol Automatic IPV	None
	A2.14	Inability to understand and follow any study procedures such as but not limited to home spirometry, including completion of self-administered questionnaires without help	Exclusion criterion 15 met as specified in the protocol Automatic IPV	None
	A2.15	Women who are pregnant, nursing, or who plan to become pregnant while in the trial, or not willing or able to use highly effective methods of birth control	Exclusion criteria 16 and/or 17 met as specified in the protocol Automatic IPV	None
	A2.16	Acute IPF exacerbation or any respiratory tract infection in the four weeks prior to Visit 1 or during the screening period.	Exclusion criterion 18 met as specified in the protocol Automatic IPV	None
	A2.17	Participation in another trial with investigational drug/s within one month prior to Visit 1 or previous enrollment in this trial	Exclusion criterion 19 met as specified in the protocol Automatic IPV	None

Table 6.2: 1 (continued) Important protocol violations (IPVs)

Category / Code		Description	Requirements / Classification	Excluded from
B		**Informed consent**		
	B1	Informed consent not available/not done	Inclusion criterion 1 not met as specified in the protocol. Automatic IPV	All
	B2	Informed consent too late	Inclusion criterion 1 not met as specified in the protocol. Medical review during MQRM, BRPM or DBLM	None
	B3	Informed consent not given for pharmacogenetics samples (unspecified part) but blood sample drawn for testing	According to pharmacogenetics database and CRF Automatic IPV	None
	B4	Informed consent for pharmacogenetics samples (unspecified part) too late but blood sample drawn for testing	Medical review during MQRM, BRPM or DBLM	None
	B5	Informed consent not given for serum banking samples (unspecified part) but blood sample drawn for testing	According to serum banking database and CRF Automatic IPV	None
	B6	Informed consent for serum banking samples (unspecified part) too late but blood sample drawn for testing	Medical review during MQRM, BRPM or DBLM	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Wrong medication number use at any time (after Visit 2) during the trial. IPV only if medication error leads to an actual treatment switch (will be determined after unblinding). Medical review of MQRM listings	None
	C2	Randomisation not followed	Wrong medication number given leading to the patient taking treatment different from the one randomized by IXRS at time of randomisation (Visit 2). IPV only if medication error leads to an actual treatment switch. (will be determined after unblinding). Medical review of MQRM listings	None
	C3	Overall Compliance not between 80% and 120% inclusive	Medical review during MQRM	None
	C4	Medication code broken inappropriately	Except for emergency situation. Medical review of MQRM listings	None
	C5	Drug not permanently discontinued despite criteria of Section 3.3.4.1 of CTP met	Medical review of MQRM listings	None
D		**Concomitant medication**		
	D1	Patient received prohibited concomitant therapies during treatment phase	Medical review of MQRM listings	None

Table 6.2: 1 (continued) Important protocol violations (IPVs)

Category / Code		Description	Requirements / Classification	Excluded from
E		**Missing data**		
	E1	No post-baseline blood CRPM assessments up to Week 12	Automatic IPV	None
F		**Incorrect timing**		

[1]Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: BI reference document 'Protocol Violation Handling Definitions' (001-MCS-50-413_RD-01) (2)

For analyses defined in this section, the blinded and open-label period will be analyzed separately and additionally, a pooled analysis across both periods will be performed but including displays by randomized treatment.

6.3 PATIENT SETS ANALYSED

Patient sets will be used as defined in the CTP, Section 7.3.

The following table shows which patient set will be used for which class of endpoints.

Table 6.3: 1 Patient sets analysed

	Patient set	
Class of endpoint	RS	TS
Primary and key secondary endpoints		X
Secondary endpoints		X
Further endpoints		X
Safety endpoints		X
Demographic/baseline characteristics		X
Disposition	X	

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, the efficacy analyses as well as safety analyses will be evaluated by observed case analysis, i.e. using only available data without imputation.

In efficacy analyses of continuous endpoints, missing data will not be imputed. Depending on the respective endpoint, random coefficient regression or Mixed Model Repeated Measurements (MMRM) will be applied, which both analyse all available information from the observed data, using the within-patient correlation structure to provide information about the unobserved data. This method does not employ explicit imputation to handle missing data.

In the analyses of the binary endpoints, missing data will be imputed using the worst case.

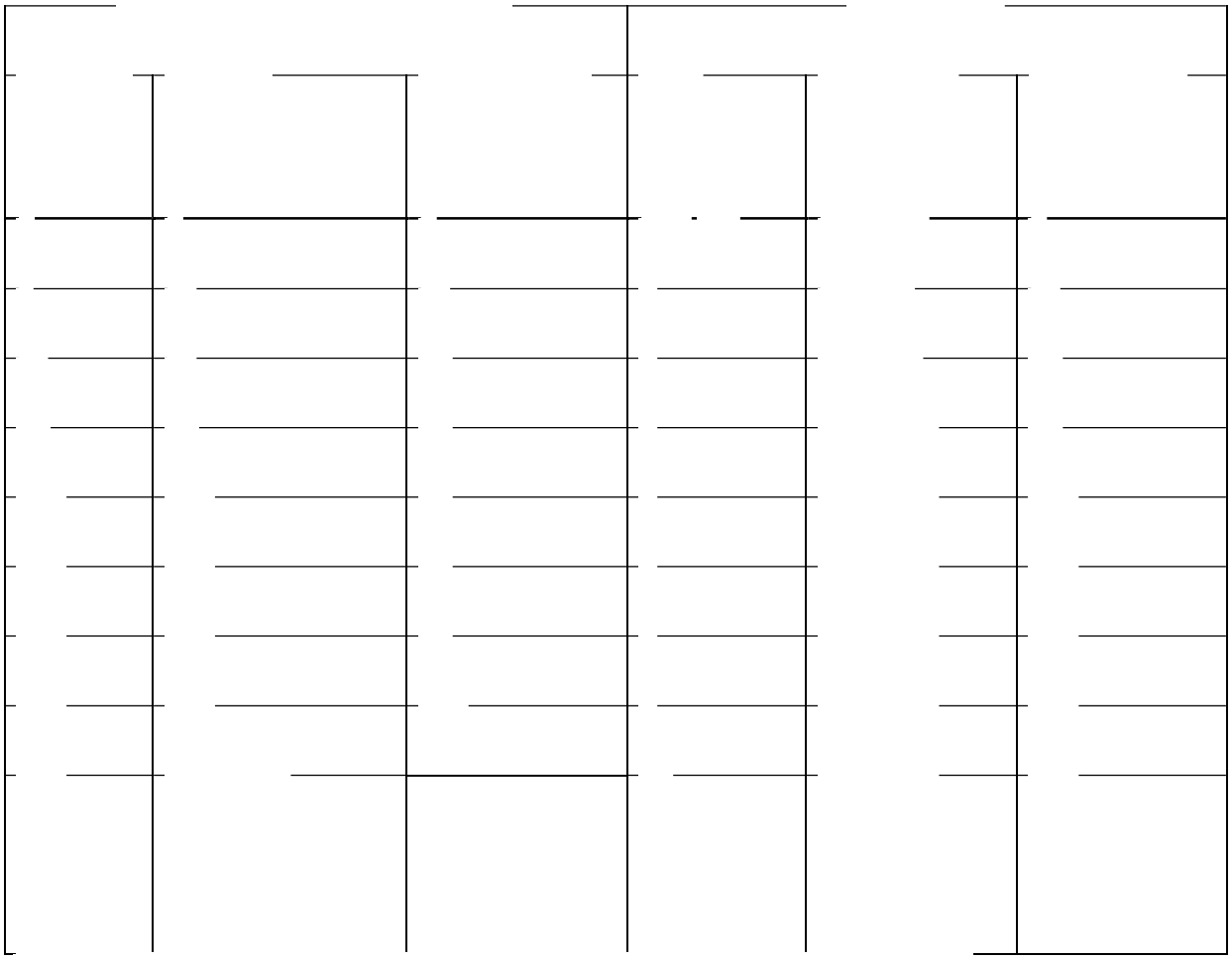
According to (001-MCS-36-472_RD-01) (6), missing biomarker data (NOS - no sample available, NOR - no valid result, NOA - not analysed) will not be imputed.
Handling of data below or above the limit of quantification:
- BLQ data will be replaced by ½ LLOQ
- ALQ data will be replaced by ULOQ, if ULOQs are available. Otherwise, ALQ data will be excluded from the analysis.

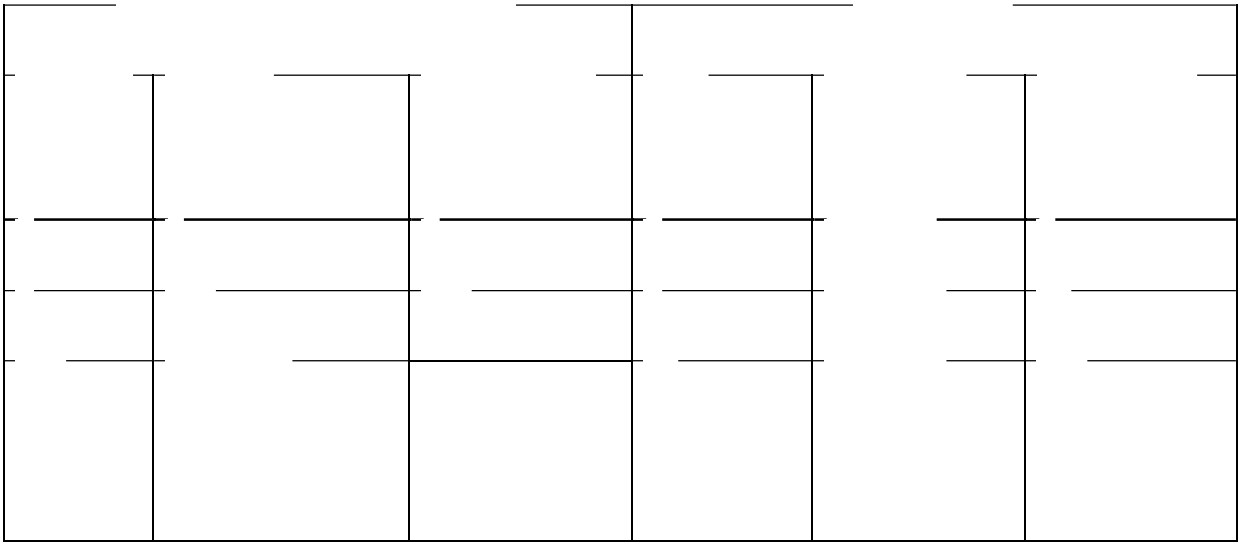
6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For an overview on planned visits refer to Flow Chart in the CTP.

As a general rule, last assessment before first trial drug intake (included) will be used as baseline. If the baseline value is missing and the screening value is available, then the baseline value will be defined as the screening value taken closest to baseline date.

A windowing will be performed as described in Tables 6.7: 1 and 6.7: 2, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analyzed 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.





If after windowing of visits at baseline, two 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. The same rules will be applied for laboratory measurements.

If after windowing of post-baseline visits, two values fall within the same interval “Follow-up”, then only the first value will be taken into account.

7. PLANNED ANALYSIS

For End of Text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max (7).

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 the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

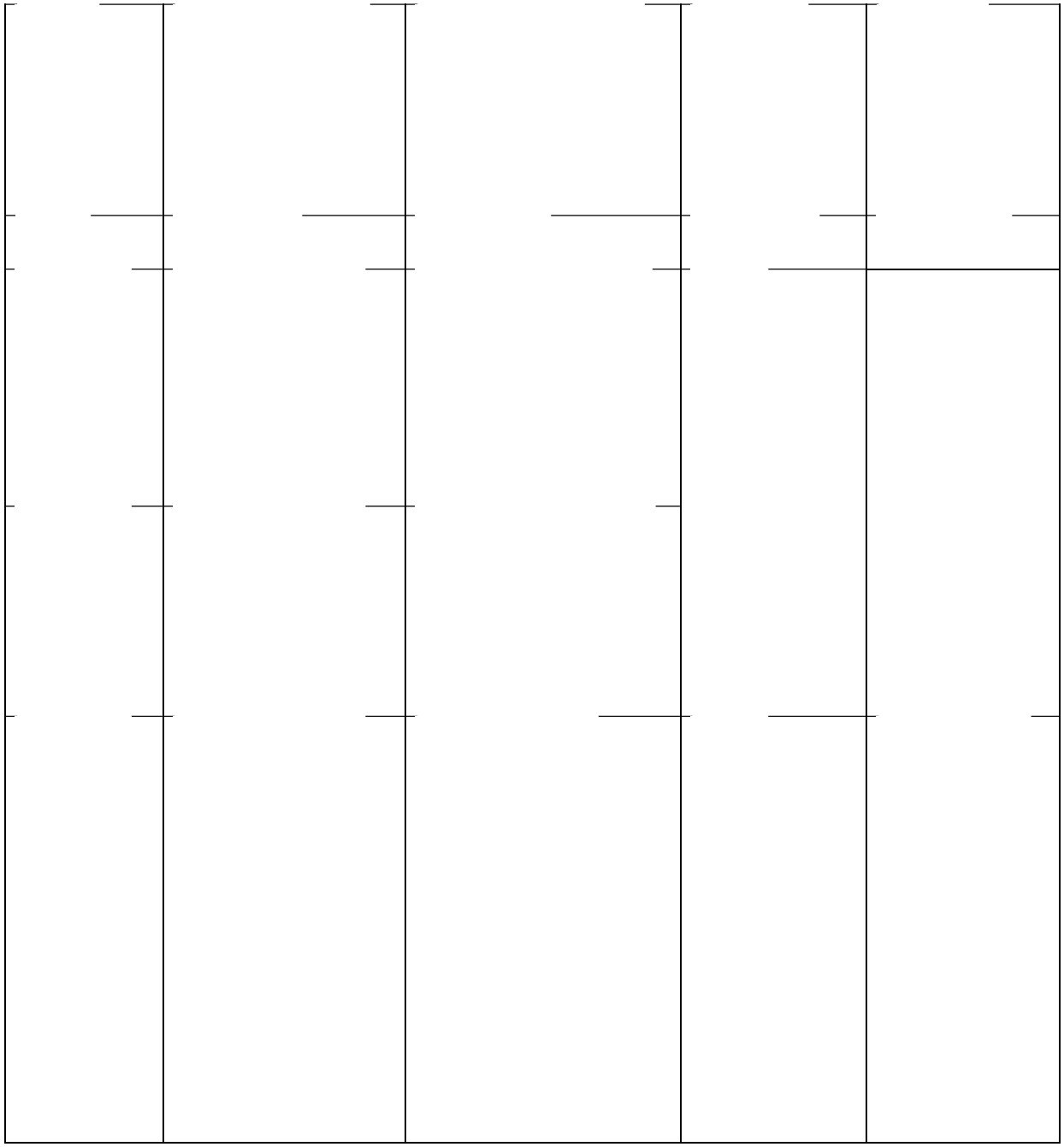
7.4.1 Primary analysis

Please refer to Section 7.3.1 of the CTP.

The primary analysis will be done on the TS.

All visits from baseline to week 12 will be included in the primary analysis, after time-windowing. Measurements after week 12 (after time windowing) are not taken into consideration for this endpoint.
Refer to Section 9.1 for SAS code specifications.

Efficacy evaluations done after lung transplant will not be used for the efficacy analyses.



7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

The key secondary endpoint is defined as the proportion of patients with disease progression as defined by absolute FVC (% predicted) decline ≥10% or death until week 52.

The following analyses are planned:

- Firstly, in order to assess the association of change in extracellular matrix (ECM) biomarker CRPM over 12 weeks with disease progression as defined by FVC decline ≥10% or death over 52 weeks, a logistic regression analysis including baseline blood

CRPM and the rate of change (slope) in blood CRPM over the first 12 weeks as covariates will be applied **for the placebo treated patients only.**
By doing this, the potential of CRPM as a prognostic biomarker is evaluated.

- Secondly, in order to assess how Nintedanib treatment during the first 12 weeks affects the association between change in extracellular matrix (ECM) biomarker CRPM over 12 weeks and disease progression, a logistic regression analysis including baseline blood CRPM, rate of change (slope) in blood CRPM over the first 12 weeks, treatment and treatment CRPM slope interaction as covariates will be applied. **The interaction term will be of primary interest within this analysis.**

- Thirdly, in order to assess whether the overall treatment regimen affects disease progression as defined by FVC decline ≥10% or death over 52 weeks, a logistic regression analysis including baseline blood CRPM and randomized treatment as covariates will be applied. **The treatment effect will be of primary interest within this analysis.**

- Fourthly, in order to assess whether rate of change (slope) in blood CRPM over the first 12 weeks to some extent explains the effect of treatment regimen on disease progression as defined by FVC decline ≥10% or death over 52 weeks, a logistic regression analysis including baseline blood CRPM, rate of change (slope) in blood CRPM over the first 12 weeks and randomized treatment as covariates will be applied. **The treatment effect will be of primary interest within this analysis.**

Patients who died or progressed in the blinded phase are not at risk in the open label period, but will be considered in the main analysis (including their progression and/or death).

The four main analyses of the key secondary endpoint outlined at the beginning of this section will be repeated by replacing CRPM by C1M and C3M, respectively.

7.5.2 Other Secondary endpoints

The following secondary endpoints are defined:

- Rate of change (slope) in blood C1M from baseline to week 12
- Rate of change (slope) in blood C3M from baseline to week 12

Please refer to Section 7.3.2 of the CTP for further details of the analysis.

This endpoint will be analyzed in a similar manner as the primary endpoint. Reasonably, baseline CRPM as covariate will be replaced by baseline C1M and C3M in these analyses.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

Unless otherwise specified, analyses of adverse events will be descriptive in nature and will be based on BI standards (10). No hypothesis testing is planned. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer to the guideline “Analysis and Presentation of Adverse Event Data from Clinical Trials” (10).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till 28 days after last drug intake (end of the residual effect period) will be assigned to the randomised treatment. Note that analysis of adverse events will be repeated considering only data until 7 days after last drug intake as treatment emergent (see also Section 6.1). Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

All adverse events occurring before first drug intake and do not deteriorate under treatment will be assigned to ‘screening’ or ‘post-randomisation’ and all adverse events occurring after last drug intake will be assigned to ‘residual effect period', ‘post-study’ or ‘follow-up’ (for listings only). Also, all AEs occurring between the start of an interruption and the end of interruption will be assigned to ‘off-treatment’ period in the listings. For details on the treatment definition, see Section 6.1.

According to ICH E3 (11), AEs classified as ‘other significant’ will include those non-serious and non-significant adverse events with

(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Blinded Report Planning Meeting.

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarized by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (11), for patients with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm), for patients with adverse events leading to dose reduction, for patients with adverse events leading to treatment discontinuation, for patients with serious adverse events , for patients with related adverse events and for patient with significant (protocol-specified) AEs (as ticked in the AE page of the CRF).

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency (within system organ class).

Specific tables will be created in order to describe diarrhoea events:

- Display of the diarrhoea specific page of the CRF

- Summary of diarrhoea events including time to onset, number and duration of episodes

- Summary of diarrhoea adverse events including seriousness, clinical consequences (dose reduction, drug discontinuation or drug interruption) and outcome

Also, a Kaplan-Meier plot of time to first diarrhoea event will be drawn by treatment.

Similar summary tables including seriousness, clinical consequences and outcome will also be presented to describe the bleeding adverse events. Depending on the number of patients having such adverse events, summary tables including time to onset, number of episodes and duration together with Kaplan-Meier plot of time to first event may also be produced.

The following adverse event groupings have been defined outside the trial protocol:

Table 7.8.1: 1 Adverse events by system using aggregated terms

System	Safety Topic	Definition (selection criteria)
Gastrointestinal	Diarrhoea	PT Diarrhoea
	Nausea	PT Nausea
	Abdominal pain	HLT 'Gastrointestinal and abdominal pains (excl oral and throat)
	Vomiting	PT Vomiting
	Pancreatitis	SMQ Acute pancreatitis (narrow)
	Gastrointestinal perforation	SMQ Gastrointestinal perforation (narrow)
Hepatobiliary	Drug-induced liver injury (DILI)	PT Drug-induced liver injury
	Hepatic disorders (broad) Drug related hepatic disorders Liver related investigations Cholestasis and jaundice of hepatic origin Hepatitis non-infectious	Table to show cumulative row for all 4 SMQs below, followed by a cumulative row for each subSMQ, followed by all PTs driving that subSMQ SMQ Drug related hepatic disorders – comprehensive search (narrow) OR SMQ Liver related investigations, signs and symptoms (broad) OR SMQ Cholestasis and jaundice of hepatic origin (narrow) OR SMQ Hepatitis, non-infectious (narrow)
	Hepatic failure	SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)
Cardiovascular	Arterial thromboembolism	SMQ Embolic and thrombotic events, arterial (narrow)
	Myocardial infarction	SMQ Myocardial infarction (narrow)
	Stroke	PV Endpoint, see Section 9.2 for included Preferred Terms

Table 7.8.1: 1 (continued) Adverse events by system using aggregated terms

System	Safety Topic	Definition (selection criteria)
	MACE	Fatal events in SOC Cardiac Fatal events in SOC Vascular Any fatal or nonfatal events in SMQ Myocardial infarction (narrow) PTs Cardiac death, Sudden death, Sudden Cardiac death Any fatal or nonfatal Stroke events as defined in respective PV Endpoint
	Cardiac failure	SMQ Cardiac failure (narrow)
	QT prolongation	SMQ Torsade de pointes/QT prolongation (narrow)
	Venous thromboembolism	SMQ Embolic and thrombotic events, venous (narrow)
	Pulmonary embolism	PT Pulmonary embolism
	DVT	PT Deep vein thrombosis
	Hypertension	SMQ Hypertension (narrow)
Metabolic	Decreased appetite	PT Decreased appetite
	Weight decreased	PTs: Weight decreased, Abnormal loss of weight
Blood	Thrombocytopenia	PTs: Thrombocytopenia, Platelet count decreased, Immune thrombocytopenic purpura
	Haematopoietic thrombocytopenia	SMQ Haematopoietic thrombocytopenia (broad)
	Neutropenia	SMQ Agranulocytosis (narrow) OR SMQ Haematopoietic leukopenia (narrow)
	Bleeding GI bleeding – oral GI bleeding – upper GI bleeding – lower GI bleeding – nonspecific Skin bleeding Respiratory bleeding CNS bleeding Urogenital bleeding Other bleeding	SMQ Haemorrhage terms (excl laboratory terms) (narrow) displayed in total and then according to categories: • Gastrointestinal – oral • Gastrointestinal – upper • Gastrointestinal – lower • Gastrointestinal – nonspecific • Skin • Respiratory • CNS • Urogenital • Other See Section 9.3 for PT lists of the bleeding subcategories.
Psychiatric	Depression	SMQ Depression (excl suicide and self-injury) (narrow)
	Suicide	SMQ Suicide/self-injury (narrow)
Renal	Renal failure	SMQ Acute renal failure (narrow)
	Proteinuria	SMQ Proteinuria (narrow)
	Glomerulonephritis	SMQ Chronic kidney disease (broad)
Cutaneous	Severe skin reactions	SMQ Severe cutaneous adverse reactions (narrow)
	Pruritus	PT Pruritus
	Rash	BIcMQ subsearch “Skin rash” (narrow)

Table 7.8.1: 1 (continued) Adverse events by system using aggregated terms

System	Safety Topic	Definition (selection criteria)
Liver laboratories	**Hepatic enzyme increased**	Following PTs: Alanine aminotransferase abnormal Alanine aminotransferase increased Aspartate aminotransferase abnormal Aspartate aminotransferase increased Hepatic enzyme abnormal Hepatic enzyme increased Hepatic function abnormal Hypertransaminasaemia Liver function test abnormal Transaminases abnormal Transaminases increased Blood alkaline phosphatase abnormal Blood alkaline phosphatase increased Gamma-glutamyltransferase abnormal Gamma-glutamyltransferase increased
	Hyperbilirubinaemia	Following PTs: Blood bilirubin abnormal Blood bilirubin increased Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice hepatocellular Bilirubin conjugated abnormal Bilirubin conjugated increased
	Alanine aminotransferase increased	Following PTs: Alanine aminotransferase increased Alanine aminotransferase abnormal
	Aspartate aminotransferase increased	Following PTs: Aspartate aminotransferase increased Aspartate aminotransferase abnormal
	Gamma-glutamyl-transferase increased	Following PTs: Gamma-glutamyltransferase increased Gamma-glutamyltransferase abnormal
	Blood alkaline phosphatase increased	Following PTs: Blood alkaline phosphatase increased Blood alkaline phosphatase abnormal

These definitions are based on MedDRA version 21.0.

For analyses defined above, the blinded and open-label period will be analyzed separately. Additionally, a pooled analysis across both periods will be performed but including displays by randomized treatment.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see DM&SM: Display and Analysis of Laboratory Data) (12).

Please refer to Section 7.3.4 of the CTP. Please refer to Section 5.4.4 for a definition of liver enzyme elevations.

Specific tables will be presented to describe liver enzyme elevations as defined in Section 5.4.4 by treatment group:

- Summary table of liver enzyme elevation including time to first onset and number of patients with liver enzyme elevation.
- Kaplan-Meier plot of time to first liver enzyme elevation (if sufficient number of events). No statistical test will be performed.
- Summary table of individual maximum liver enzyme and bilirubin elevations
- Plot of time course profile of liver enzyme for patients having liver enzyme and bilirubin elevation

7.8.3 Vital signs

Only descriptive statistics (by visit and change from baseline) are planned for this section of the report.

7.8.4 ECG

Not applicable.

7.8.5 Others

Not applicable.

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	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
3	*001-MCG-741*: "Clinical subgroup analyses for local and regional Populations in Asia - Clinical Bridging Study Waiver (BSW) and Descriptive Subgroup Analysis (SGA) Reports" , current version; IDEA for CON.
4	Jones PW, Forde Y. St George's Respiratory Questionnaire Manual. Version 2.3, 20.06.2009 [R12-2870].
5	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
6	001-MCS 36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7	*001-MCG-159_RD-03:* "Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)", current version; IDEA for CON.
8	Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley, 1987 [R12-2378].
9	Fairclough DL (2002). "Models for Longitudinal Studies II" (chapter 4), in Design and analysis of quality of life studies in clinical trial. CRC Press, p. 83-105 [R15-6302].
10	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
11	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
12	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**23-SEP-16**		None	This is the initial TSAP with necessary information for trial conduct
Final	**19-JUL-18**	(ext) /	All	This is the final TSAP