Trial Statistical Analysis Plan

c11290811-03

BI Trial No.:	1199.36
Title:	INSTAGE™: A 24-week, double-blind, randomized, parallelgroup study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment Including Protocol Amendment 2 [c03484701-03]
Investigational Product(s):	Nintedanib (Ofev®)
Responsible trial statistician(s):	Phone : Fax :
Date of statistical analysis plan:	24 MAY 2018 SIGNED
Version:	Final version

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical classification system
bid	bis in die (twice daily dosing)
BRPM	Blinded report planning meeting
BMS	Biomarker analysis set
cpm	counts per million
CT	Concomitant Therapies
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic Blood Pressure
DLCO	Carbon Monoxide Diffusion Capacity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual

Term	Definition / description
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
ECG	Electrocardiogram
ECHO	Echocardiogram
EF	Ejection Fraction
EMA	European Medicines Agency
EOT	End of Treatment
FAS	Full analysis set
FDR	False Discovery Rate
FVC	Forced Vital Capacity
FUP	Follow-Up
Hb	Hemoglobin
HGNC	HUGO Gene Nomenclature Committee
HRCT	High-resolution Computed Tomography
HUGO	Human Genome Organisation
ICH	International Conference on Harmonisation
IHSS	Idiopathic Hypertrophic Subaortic Stenosis
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IU	International Units
Kco	Carbon Monoxide Transfer Coefficient
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at Random
MI	Multiple Imputation
MMRM	Mixed Effects Model for Repeated Measures
MQRM	Medical Quality Review Meeting
O*C	Oracle Clinical
PaCO2	Partial Pressure of Carbon Dioxide
PAH	Pulmonary Arterial Hypertension
PK	Pharmacokinetics
PKS	Pharmacokinetics set

Term	Definition / description
PN	Preferred name
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
REP	Residual effect period
RPKM	Read counts per million
SA	Statistical analysis
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standardised MedDRA query
SpO2	Oxygen Saturation
SOC	System organ class
SSC	Special Search Category
TCM	Trial Clinical Monitor
TESS	Treatment emergent signs and symptoms
tid	ter in die (3 times a day)
TMW	Trial Medical Writer
ToC	Table of contents
TPM	Transcripts per million
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper Limit of Normal
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
VA	Alveolar Volume

3. INTRODUCTION

As per International Conference on Harmonisation (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.

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

Analyses of differential gene expression will be performed using R version 3.0.2 or later (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. weblink R-project.org) in conjunction with limma package version 3.18.13 or later (Smyth GK, Limma: linear models for microarray data, Bioinformatics and Computational Biology Solutions Using R and Bioconductor 397-420, 2005).

5. ENDPOINTS

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 change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 12. Refer to the St George's Respiratory Questionnaire (SGRQ) manual (2) for calculations of SGRQ scores.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Secondary endpoints

The secondary endpoints are defined in Section 5.1.2 of the CTP and are:

- Change from baseline in dyspnea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at week 12.
  The questionnaire should be scored as a simple sum of all items.

- Change from baseline in SGRQ total score at week 24.

- Change from baseline in dyspnea using UCSD SOBQ at week 24.
  The questionnaire should be scored as a simple sum of all items.

- Percentage of patients with on-treatment Serious Adverse Events (SAE) from baseline to week 24.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

The following trial periods will be defined: screening, post-randomisation, treatment period, off-treatment, residual effect period, follow-up and post-study as follows:

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 treatment period
- 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
- Off-treatment (optional): from start date of interruption to re-start of treatment
- Residual effect period (optional): from the last trial drug intake plus one day to last trial drug intake plus 28 days plus one day
- Follow-up (optional): from last trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last trial drug intake took place more than 28 days before trial completion, or for patients having prematurely discontinued the 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

For safety analyses, data up to 28 days after last trial drug intake (included) 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 safety and efficacy analyses, patients will be assigned to the treatment group they were randomised to.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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

Table 6.2: 1 Important protocol violations

Category	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 6 years before Visit 1, based upon the ATS/ERS/JRS/ALAT 2011 guideline	Inclusion criterion 3 not met as specified in the protocol. Automatic IPV	None
A1.3	Combination of HRCT pattern and surgical lung biopsy pattern (the latter if available) as assessed by the investigator is not consistent with the diagnosis of IPF as assessed by the investigator based on a HRCT scan performed within 18 months of visit 1	Inclusion criterion 4 not met as specified in the protocol. Automatic IPV	None
A1.4	DLCO (corrected for Hb) > 35% predicted of normal at visit 1	Inclusion criterion 5 not met as specified in the protocol. Automatic IPV	None
A2.1	Previous enrolment in this trial	Exclusion criterion 1 met as specified in the protocol Automatic IPV	None
A2.2	ALT, AST, Total bilirubin > 1.5 fold upper limit of normal (ULN) at Visit 1	Exclusion criteria 2 or 3 met as specified in the protocol Automatic IPV	None
A2.3	Relevant airways obstruction [i.e. pre-bronchodilator FEV1/FVC < 0.7 at Visit 1]	Exclusion criterion 4 met as specified in the protocol 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

Table 6.2: 1 Important protocol violations (cont'd)

Category	Description	Requirements / Classification	Excluded from
A	**Entrance criteria not met**		
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
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	Presence of aortic stenosis (AS) per investigator judgement at visit 1	Exclusion criterion 10 met as specified in the protocol Automatic IPV	None
A2.10	Severe chronic heart failure: defined by left ventricular ejection fraction (EF) < 25% per investigator judgement at visit 1	Exclusion criterion 11 met as specified in the protocol Automatic IPV	None
A2.11	Presence of idiopathic hypertrophic subaortic stenosis (IHSS) per investigator judgement at visit 1	Exclusion criterion 12 met as specified in the protocol Automatic IPV	None
A2.12	Second-degree or third-degree atrioventricular (AV) block on electrocardiogram (ECG) per investigator judgement at visit 1	Exclusion criterion 13 met as specified in the protocol Automatic IPV	None
A2.13	Hypotension (systolic blood pressure [SBP] < 100 mm Hg or diastolic blood pressure [DBP] < 50 mm Hg) (symptomatic orthostatic hypotension) at visit 1	Exclusion criterion 14 met as specified in the protocol Automatic IPV	None
A2.14	Uncontrolled systemic hypertension (SBP > 180 mmHg; DBP > 100 mmHg) at visit 1	Exclusion criterion 15 met as specified in the protocol Automatic IPV	None
A2.15	Known penile deformities or conditions (e.g., sickle cell anemia, multiple myeloma, leukemia) that may predispose to priapism	Exclusion criterion 16 met as specified in the protocol Automatic IPV	None
A2.16	Retinitis pigmentosa	Exclusion criterion 17 met as specified in the protocol Automatic IPV	None
A2.17	History of vision loss	Exclusion criterion 18 met as specified in the protocol Automatic IPV	None
A2.18	History of nonarteritic ischemic optic neuropathy	Exclusion criterion 19 met as specified in the protocol Automatic IPV	None

Table 6.2: 1 Important protocol violations (cont'd)

Category	Description	Requirements / Classification	Excluded from
A	**Entrance criteria not met**		
A2.19	Veno-occlusive disease	Exclusion criterion 20 met as specified in the protocol Automatic IPV	None
A2.20	History of acute IPF exacerbation or respiratory infection within 8 weeks of visit 2	Exclusion criterion 21 met as specified in the protocol Automatic IPV	None
A2.21	Treatment with nitrates, n-acetylcysteine, pirfenidone, azathioprine, cyclophosphamide, cyclosporine, prednisone >15 mg daily or >30 mg every 2 days OR equivalent dose of other oral corticosteroids as well as any investigational drug within 4 weeks of visit 2	Exclusion criterion 22 met as specified in the protocol Automatic IPV	None
A2.22	Treatment with prostaglandins (e.g., epoprostenol, treprostinil), endothelin-1 antagonists (e.g., bosentan, sitaxsentan, ambrisentan), phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, vardenafil) or a stimulator of guanylatcyclase (e.g., riociguat) within 4 weeks of visit 2	Exclusion criterion 23 met as specified in the protocol Automatic IPV	None
A2.23	Treatment with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir within 4 weeks of visit 2	Exclusion criterion 24 met as specified in the protocol Automatic IPV	None
A2.24	Supplementation with L-arginine and concurrent use of grapefruit juice or St John's wort within 4 weeks of visit 2	Exclusion criterion 25 met as specified in the protocol Automatic IPV	None
A2.25	Treatment with the reduced dose of nintedanib (100 mg bid) within 4 weeks of visit 2	Exclusion criterion 26 met as specified in the protocol Automatic IPV	None
A2.26	Permanent discontinuation of nintedanib in the past due to adverse events considered drug-related	Exclusion criterion 27 met as specified in the protocol Automatic IPV	None
A2.27	Known hypersensitivity or intolerance to nintedanib, sildenafil, galactose, peanut or soya or any other components of the study medication	Exclusion criterion 28 met as specified in the protocol Automatic IPV	None
A2.28	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 29 met as specified in the protocol Automatic IPV	None

Table 6.2: 1 Important protocol violations (cont'd)

Category	Description	Requirements / Classification	Excluded from
A	**Entrance criteria not met**		
A2.29	Alcohol or drug abuse which in the opinion of the treating physician would interfere with the treatment	Exclusion criterion 30 met as specified in the protocol Automatic IPV	None
A2.30	Women who are pregnant, nursing, or who plan to become pregnant while in the trial, or who are of childbearing potential and not willing or able to use highly effective methods of birth control	Exclusion criteria 31 and 32 met as specified in the protocol Automatic IPV	None
A2.31	Inability to understand and follow any study procedures such as but not limited to completion of self-administered questionnaires without help	Exclusion criterion 33 met as specified in the protocol Automatic IPV	None
A2.32	Underlying chronic liver disease (Child Pugh A, B or C hepatic impairment)	Exclusion criterion 34 met as specified in the protocol Automatic IPV	None
B	**Informed consent**		
B1	Informed consent not available/not done	Inclusion criterion 1 met as specified in the protocol Automatic IPV	None
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 pharmacogenetics sample collected and analyzed	According to pharmacogenetics database and CRF Automatic IPV	None
B4	Informed consent too late for pharmacogenetics samples (unspecified part) but pharmacogenetics sample collected and analyzed	Medical review during MQRM, BRPM or DBLM	None
B5	Informed consent not given for serum banking samples (unspecified part) but serum banking sample collected and analyzed	According to serum banking database and CRF Automatic IPV	None
B6	Informed consent too late for serum banking samples (unspecified part) but serum banking sample collected and analyzed	Medical review during MQRM, BRPM or DBLM	None

Table 6.2: 1 Important protocol violations (cont'd)

Category	Description	Requirements / Classification	Excluded from
C	**Trial medication and randomization**		
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	Randomization not followed	Wrong medication number given leading to the patient taking treatment different from the one randomized by IXRS at time of randomization (Visit 2). IPV only if medication error leads to an actual treatment switch. (to be determined after unblinding). Medical review of MQRM listings	None
C3	Wrong stratum selected during randomization	Wrong stratum selected in IXRS during randomization (Visit 2) Medical review of MQRM listings	None
C5	Medication code broken inappropriately	Except for emergency situation. Medical review of MQRM listings	None
C6	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 with any of the trial drugs	Medical review of MQRM listings	None
E	**Missing data**		
E1	No possible to calculate post-baseline SGRQ total score up to Week 24 and patient not died or withdrew consent before scheduled visit 3	Automatic IPV	None
E2	Not possible to calculate baseline SGRQ total score	Automatic IPV	None
E3	Serious non-compliance potentially affecting primary endpoint	Review of PVs escalated from Quality Management tool "GEM" during MQRM or BPRM	None

6.3 PATIENT SETS ANALYSED

Patient sets will be used as defined in the CTP, Section 7.

Additionally the Biomarker analysis set (BMS) includes all subjects in the treated set who have analysable data (observed or imputed) in at least one serum/plasma derived protein biomarker (see Section 5.3.4.1) and will be used for the respective analysis.

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

Table 6.3: 1 Patient sets analyzed

	Patient Set	
Class of endpoint	TS	BMS
Primary and key secondary endpoints	X	
Secondary endpoints	X	
Further endpoints	X	
Safety endpoints	X	
Demographic/baseline characteristics	X	
Biomarkers[1]	X	X

[1] Analyses of soluble biomarkers will be performed on the BMS.
Transcriptome profiling will be performed on the TS.

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6 “Handling of missing data and outliers”.

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.

Data of treated subjects who failed to complete all stages of the study (subjects who withdraw consent or are removed from the trial) will be reported as far as data are available. It is not planned to impute missing values.

For the SGRQ, the SGRQ manual (2) allows for 25% of missing data per component (i.e. 2 questions for symptoms, 6 questions for impacts and 4 questions for activities), the rules defined in the SGRQ manual will be used to derive the SGRQ.

Additionally the responses to questions 5 and 6 will be made consistent to the extent that if the answer to question 5 is 5 (none of the time) and the answer to question 6 is non-missing (i.e., length of worst attack specified), then question 6 will be set to missing.
Therefore scores will be calculated ignoring that item. In this case, the missing response to question 6 will not be included in the count of missing questions for the symptoms component.

If SOBQ is not completely answered, the missing questions will not be imputed, and the score will be set to missing.

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 table 6.7:1 to table 6.7: 6 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.

All visits, regardless whether study treatment is ongoing or not, and EOT visit are classified according to the time windowing rules. EOT is the day of the last trial drug administration (nintedanib and sildenalfil/placebo).

Visits recorded as FUP visits will be classified according to the time windowing as given in the table for time windowing and will not keep their labeling “FUP”, unless they fulfill the conditions for the last category in the table.

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.

For visits of patients who continue to attend the scheduled study visits after early EOT visit the same rules apply as given above.

Table 6.7: 2 Time windowing rules for SGRQ, UCSD SOBQ, EQ-5D, Resting SpO_2

Time window of actual day [1]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
1	1	1	2	Baseline	1
2	57	56	3	4 weeks	29
58	127	69	5	12 weeks	85
128	No limit		7	24 weeks	169

[1] First trial drug intake date is taken into account as a reference to calculate time windows

7. PLANNED ANALYSIS

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

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 as the last category only if there are actually missing values.

7.4 PRIMARY ENDPOINT

Please refer to Section 7.3.1 of the CTP.

7.4.1 Primary analysis

The primary analysis will be done on the TS in observed cases including observations after premature discontinuation of treatment.

All visits from baseline to week 12 will be included in the primary analysis, after time-windowing. Measurements after week 12 are not taken into consideration for this endpoint.

A patient is considered as having signs indicative of right heart dysfunction if at least one of the conditions presence of right ventricular dilatation, paradoxical septum motion, right atrium enlargement, right ventricular systolic dysfunction, or right ventricular hypertrophy is met.

If the null hypothesis of no difference in the mean change from baseline in SGRQ total score at week 12 between nintedanib co-administered with sildenafil compared to treatment with nintedanib alone is rejected at the two-sided alpha level of 5%, the secondary endpoints UCSD SOBQ at week 12, SGRQ total score at week 24, and UCSD SOBQ at week 24 are tested hierarchically as described in Section 7.2 of the CTP.

As defined in Section 7.3.1 of the CTP, change from baseline in SGRQ total score at week 12 will be analysed using REML based MMRM. The model will include fixed effect for treatment, visit and presence of any echocardiographic signs indicative of right heart dysfunction (as described in Section 5.4.1.4), baseline SGRQ total score as a covariate and treatment-by-visit and baseline-by visit as interaction terms. Baseline SGRQ total score will be measured at visit 2. No imputation is planned if this assessment is not available for a patient. An unstructured (co)variance matrix will be used to model the within-patient measurements. In case there is a lack of convergence, a Compound Symmetry (co)variance matrix will be used. The Roger-Kenward approximation will be used to estimate denominator degrees of freedom. Data collected after visit 5 (planned 12 weeks after start of study treatment) will not be used for this analysis. Analyses will be implemented using SAS® Version 9.4 or higher. The primary treatment comparisons will be the contrast between treatments at 12 weeks.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Not applicable.

7.5.2 Secondary endpoints

The analysis will be performed as defined in Section 7.3.2 of the CTP.

The variable 'signs indicative of right heart dysfunction' (yes/no) is derived as described for the primary endpoint.

For SGRQ total score and UCSD SOBQ, a graph of the mean total score change from baseline (± SEM) over time for each treatment group will be displayed. The same graph will be performed on adjusted mean changes from baseline.
Descriptive statistics for SGRQ total score and subscores as well as SOBQ over time and change from baseline will be displayed.

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 (6). 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” (6).

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 until 28 days after last drug intake (end of the residual effect period) will be assigned to the randomised treatment. 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 (7), AEs classified as ‘other significant’ will include those non-serious and non-significant adverse events which

- represents a marked hematological or other laboratory abnormality;
- led to an intervention, including withdrawal of drug treatment, dose reduction (‘action taken = discontinuation’ or ‘action taken = reduced’ for any of the study treatments), or significant additional concomitant therapy.

An overall summary of adverse events will be presented.

Separate tables will be provided for

- patients with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm)
- patients with investigator defined drug related adverse events
- patients with serious adverse events
- patients with investigator defined drug related serious adverse events
- patients with other significant adverse events according to ICH E3 (7)
- patient with adverse events of special interest (AESI) (as defined in the CTP Section 5.3.6.1).
- patients with adverse events leading to death
- patients with adverse events leading to temporary or permanent dose reduction of nintedanib
- patients with adverse events leading to permanent dose reduction of nintedanib
- patients with adverse events leading to interruption of nintedanib
- patients with adverse events leading to interruption of sildenafil/placebo
- patients with adverse events leading to premature discontinuation of nintedanib only,
- patients with adverse events leading to premature discontinuation of sildenafil/placebo only,
- patients with adverse events leading to permanent discontinuation of nintendanib and sildenafil/placebo

These AE tables will be displayed in total and by subgroup presence (yes/no) of signs indicative of right heart dysfunction.

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency in oral nintedanib coadministered with oral sildenafil treatment arm (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.

Specific 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 may also be produced.

In addition, the number of treatment emergent MACE events will be displayed including result of adjudication overall and by presence (yes/no) of signs indicative of right heart dysfunction.

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)
Gastro-intestinal	Diarrhoea	PT Diarrhoea
	Nausea	PT Nausea
	Vomiting	PT Vomiting
	Abdominal pain	HLT 'Gastrointestinal and abdominal pains (excl oral and throat)
	Pancreatitis	SMQ Acute pancreatitis (narrow)
	Gastrointestinal perforation	SMQ Gastrointestinal perforation (narrow)
Hepato-biliary	Drug-induced liver injury (DILI)	PT Drug-induced liver injury
	Hepatic disorders combined	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)
Cardio-vascular	Arterial thromboembolism	SMQ Embolic and thrombotic events, arterial (narrow)
	Myocardial infarction	SMQ Myocardial infarction (narrow)

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

System	Safety Topic	Definition (selection criteria)
Cardio-vascular	Stroke	Pharmacovigilance Endpoint Stroke PTs (see list in ADS Plan)
	Haemorrhagic stroke	SMQ Haemorrhagic central nervous system vascular conditions (narrow)
	Ischaemic stroke	SMQ Ischaemic central nervous system vascular conditions (narrow)
	Stroke (broad)	SMQ Haemorrhagic central nervous system vascular conditions (narrow) OR SMQ Ischaemic central nervous system vascular conditions (narrow)
	MACE	Fatal events in SOC Cardiac OR Fatal events in SOC Vascular OR Any fatal or nonfatal events in SMQ Myocardial infarction (narrow) OR PTs Cardiac death, Sudden death, Sudden Cardiac death OR Any fatal or nonfatal events as defined in PV Endpoint Stroke PTs
	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

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

System	Safety Topic	Definition (selection criteria)
Blood	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 (see list in ADS Plan): • Gastrointestinal – oral • Gastrointestinal – upper • Gastrointestinal – lower • Gastrointestinal – nonspecific • Skin • Respiratory • CNS • Urogenital • Other
	Thrombocytopenia	PTs: Thrombocytopenia, Platelet count decreased, Immune thrombocytopenic purpura
	Haematopoietic thrombocytopenia	SMQ Haematopoietic thrombocytopenia (broad)
	Neutropenia	SMQ Agranulocytosis (narrow) OR SMQ Haematopoietic leukopenia (narrow)
Renal	Renal failure	SMQ Acute renal failure (narrow)
	Proteinuria	SMQ Proteinuria (narrow)
	Glomerulonephritis (broad) Glomerulonephritis (narrow)	SMQ Chronic kidney disease (broad) HLT Glomerulonephritis and nephrotic syndrome
Psychiatric	Depression	SMQ Depression (excl suicide and self-injury) (narrow)
	Suicide	SMQ Suicide/self-injury (narrow)

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

System	Safety Topic	Definition (selection criteria)
Cutaneous	Rash	BIcMQ Skin rash (narrow): Exfoliative rash Mucocutaneous rash Rash Rash erythematous Rash follicular Rash generalized Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papular Rash papulosquamous Rash pruritic Rash pustular Rash rubelliform Rash scarlatiniform Rash vesicular Symmetrical drug-related itertriginous and flexural exanthema Vascular access site bruising
	Pruritus	PT Pruritus
	Severe skin reactions	SMQ Severe cutaneous adverse reactions (narrow)
Liver laboratories	Hepatic enzyme increased	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

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

System	Safety Topic	Definition (selection criteria)
Liver laboratories	Hyperbilirubinaemia	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	Alanine aminotransferase increased Alanine aminotransferase abnormal
	Aspartate aminotransferase increased	Aspartate aminotransferase increased Aspartate aminotransferase abnormal
	Gamma-glutamyl-transferase increased	Gamma-glutamyltransferase increased Gamma-glutamyltransferase abnormal
	Blood alkaline phosphatase increased	Blood alkaline phosphatase increased Blood alkaline phosphatase abnormal

For definitons of Pharmacovigilance Endpoint **Stroke** PTs and for **SMQ haemorrhage** term categorization see ADS plan.

All these definitions are based on MedDRA version 20.1. Note that changes to these definitions due to MedDRA updates will not trigger a TSAP update. Updated definitions are maintained in BIRDS under Human Pharma/nintedanib/Clinical/substance level/Project Data Management and Statistics/Section 4 Database.

The most recent version effective at DBL date will be used for trial reporting.

Frequencies and percentages of patients with AEs within system and within safety topic according to aggregated terms will be presented by treatment arm. The data will be displayed according to the order given in Table 7.8.1: 1.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8).

Please refer to Section 7.3.4 of the CTP.

Kaplan-Meier plot for time to first liver enzyme elevation will be presented and displayed by treatment (if sufficient number of events).

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. The time to event will be censored at EOT + 28 days. The Kaplan-Meier plots will present the time period until 24 weeks + 28 days.
- 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, relevant ECG findings are recorded as baseline condition or AEs.

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	Jones PW, Forde Y. St George's Respiratory Questionnaire Manual. Version 2.3, 20.06.2009 [R12-2870]
3	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4	001-MCS-36-472_RD-01: Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses
5	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
7	*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
8	*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	**17-OCT-16**		None	This is the initial TSAP with necessary information for trial conduct.
Final	**21 FEB 2018**		None	This is the final TSAP
Final	**24 MAY 2018**		None	Updated TSAP after BRPM comments in April 2018.