Trial Statistical Analysis Plan

c25923826-02

BI Trial No.:	1199-0340
Title:	A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) Including Protocol Amendment 1 [c21847264-02] Including Protocol Amendment 2 [c21847264-03]
Investigational Products:	Nintedanib
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1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse events of special interest
ADS	Analysis data set
ANOVA	Analysis of variance
ALT	Alanine transaminase (also called alanine aminotransferase, ALAT)
AST	Aspartate transaminase (also called aspartate aminotransferase, ASAT)
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DLCO	Carbon monoxide diffusion capacity of the lungs
ECG	Electrocardiogram
eCRF	Electronic case report form
ES	Entered set
EudraCT	European union drug regulating authorities clinical trials
EULAR	European League against Rheumatism
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
gMean	Geometric mean
gCV	Geometric coefficient of variation
Hb	Haemoglobin
HRCT	High resolution computer tomography
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
iPD	Important protocol deviation
IQRMP	Integrated quality and risk management plan

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
mRSS	modified Rodnan Skin Score
NOA	Not analysed
NOR	No valid result
NOS	No sample available
PD	Protocol deviation
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
R	Reference treatment
RAGe	Report appendix generator system
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SSc	Systemic sclerosis
T	Test treatment
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper level of normal
VAS	Visual analog scale

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 Clinical Trial Protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the CTP. 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, randomisation.

Study data will be stored in a trial database within the Medidata Rave system.

The statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and providing SAS™-based tools (e.g., macros for the analyses of adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

Pharmacokinetic (PK) parameters will be calculated using Phoenix® WinNonlin® 6.3 (or later, Pharsight Corporation, Mountain View, CA 94041-1530, USA) and/or SAS® software, version 9.4 (or later).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As compared to the CTP, the following changed in the planned analysis of this study:

For the display of adverse event data, the time intervals after residual effect periods of treatments have been renamed from 'post-treatment' to 'follow-up' (in contrast to Section 7.3.4 of the CTP).

CTP states in Section 7.3.4: *Treatment groups will be compared descriptively with regard to distribution parameters* [of laboratory data] *as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.*
This analysis was not adopted by the initial TSAP. Considering the rather sparse time points of safety laboratory sampling, and the absence of samples within the residual effect period of Microgynon® in both treatment periods (as per CTP), the value of a descriptive analysis was considered to be questionable.

CTP states in Section 2.2.1: *Pre-dose (trough) plasma concentration monitoring of steady-state nintedanib will be performed in order to assess whether ethinylestradiol and/or levonorgestrel have an influence on the exposure of nintedanib.* CTP Section 2.2.2 clarifies: *Pre-dose (trough) plasma levels concentration ($C_{pre,ss}$) of nintedanib at steady state will be assessed to prove* [nintedanib] *exposure.* This TSAP adopts the statement from Section 2.2.2.

As compared to the initial TSAP of this trial, the following changed in the planned analysis of this study:

As specified in CTP Section 5.2.10.2.1, AEs that started after the individual patient's End of Study will not be reported in the eCRF. (For an individual patient who completes the study and will participate in the roll-on Trial 1199-0225, any ongoing AE or new AE that occurs after End of Study must be reported in the roll-on trial 1199-0225.) Therefore, assignment of AEs after the End of Study examination to the "post-study" phase is not applicable. There will be no such AEs in the database and no "post-study" phase in AE analyses. The "post-study" phase defined in Table 6.1: 1 of the initial TSAP was not adopted by this final TSAP.

As specified in CTP Section 7.3.4: *All other AEs* [except for AEs from intake of Microgynon® until the end of REP of Microgynon® during Period 2] *during nintedanib treatment up to the end of the trial will be assigned to on-treatment on nintedanib.*
In Table 6.1: 1 of the initial TSAP, a nintedanib follow-up phase was defined, which is not in accordance with the definition quoted above. Therefore, the nintedanib follow-up phase was not adopted by this final TSAP and the definition of the on-treatment nintedanib phase was adapted to match the definition quoted above.

Further changes compared to the initial TSAP:

- Definition of further safety parameters of interest was added to Section 5.3.1.
- Baseline parameters were added to list of baseline characteristics in Section 5.4.1, respective analyses were added to Section 7.1.
- Definition of nintedanib treatment compliance was added to Section 5.4.2 and its presentation was specified in Section 7.3.
- Definition of nintedanib treatment exposure was revised in Section 5.4.2.
- Definition of AE analysis phases in Table 6.1: 1 and definition of AE collapsing in Section 7.8.1 were adapted to the decision that clock time will not be collected in the eCRF.
- Definition of analysis phases in Section 6.1 was restricted to AE, vital signs and laboratory data, will not be needed for spirometry.
- Table 6.2: 1 was added to specify which important PDs could potentially lead to exclusion from which analysis set.
- Definition of an enrolled set was added to Section 6.3.
- Analyses of AEs by safety topic were added to Section 7.8.1.
- Descriptive analysis of vital signs were added to Section 7.8.3.
- Presentation of pregnancy test results was added in Section 7.8.5.5.
- A few additional clarifications were added, text was adapted to the new BI standard process (e.g., use of a decision log to capture RPM decisions).

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are defined in Section 2.1.2 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable, as no key secondary endpoint was specified in the CTP.

5.2.2 Secondary endpoints

The secondary endpoint is defined in Section 2.1.3 of the CTP.

5.3.1 Safety parameters

Safety will be assessed based on the following further parameters of interest:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- Vital signs (blood pressure, pulse rate)
- Spirometry
- Clinically relevant findings from physical examination, 12-lead ECG. and echocardiography (as part of AE analysis)

Marked changes in vital signs will be defined as follows.

A marked increase is defined as:

- Systolic Blood Pressure >150 mmHg and increase >=25 mmHg above baseline
- Diastolic Blood Pressure >90 mmHg and increase >10 mmHg above baseline
- Pulse Rate >100 bpm and increase >10 bpm above baseline

A marked decrease is defined as:

- Systolic Blood Pressure <100 mmHg and decrease >10 mmHg below baseline
- Diastolic Blood Pressure <60 mmHg and decrease >10 mmHg below baseline
- Pulse Rate <60 bpm and decrease >10 bpm below baseline

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on the treatments to be administered and selection of dose, cf. Section 4 of the CTP. All patients will undergo two treatment periods in a fixed sequence.

Each patient is planned to be treated in two subsequent treatment periods. In the first treatment period, patients will receive a single dose of Microgynon® (30 mcg ethinylestradiol and 150 mcg levonorgestrel; reference treatment, R). In the second treatment period, patients will receive a single dose of Microgynon® after continuous intake of a stable dose of nintedanib (150 mg b.i.d. or 100 mg b.i.d.) for at least 10 consecutive days (test treatment, T). Nintedanib treatment will be continued for at least 14 days to approximately 28 days in this trial. The sequence of these treatment periods is fixed and the same for all patients. Microgynon® intake in the first treatment period will be at least 3 days before first nintedanib intake in the second treatment period.

For statistical analysis of AEs and vital signs, and for listings of safety laboratory, study phases are defined for each patient as described in Table 6.1: 1 and Table 6.1: 2. Note that only the date of AE onset is reported in the eCRF, but not the clock time.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs and vital signs

Study analysis phase	Label	Start (included in phase)	End (excluded from phase)
Screening	Screening	Date of informed consent	Date of first administration of study drug
On-treatment microgynon	**MIC**	Date of administration of microgynon in Treatment Period 1 I.e., the day of administration of microgynon is included in this phase.	Day of end of REP (3 days) of microgynon: Date of administration of microgynon in Treatment Period 1 + 3 days I.e., the day of end of REP is excluded from this phase. OR Date of first administration of nintedanib in Treatment Period 2 (whichever occurs first).
Follow-up microgynon	**FUP-MIC**	Date of administration of microgynon in Treatment Period 1 + 3 days	Date of first administration of nintedanib in Treatment Period 2 This phase does not exist, if start ≥ end.
On-treatment nintedanib loading phase	**Loading NIN**	Date of first administration of nintedanib in Treatment Period 2	Date of administration of microgynon in Treatment Period 2
On-treatment nintedanib plus microgynon	**NIN+MIC**	Date of administration of microgynon in Treatment Period 2 I.e., the day of administration of microgynon is included in this phase.	Day of end of REP (3 days) of microgynon: Date of administration of microgynon in Treatment Period 2 + 3 days I.e., the day of end of REP of microgynon is excluded from this phase.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs and vital signs (continued)

Study analysis phase	Label	Start (included in phase)	End (excluded from phase)
On-treatment nintedanib	**NIN**	Date of administration of microgynon in Treatment Period 2 + 3 days	Day after last contact date OR If patient is reported to continue into the 1199-0225 rollover study: Day after day of End of Treatment visit (which will be done simultaneously to End of Study visit) This phase does not exist, if start ≥ end.

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phases "MIC", "Loading NIN", "NIN+MIC", and "NIN" only. Screening and FUP-MIC will not be included in this analysis. CTR Section 15 AE displays (but not Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays) will additionally present the following totals:

- "**Total NIN**", defined as the total over on-treatment phases involving nintedanib, i.e. "Loading NIN" + "NIN+MIC" + "NIN".

- "**Total on-trt**", defined as the total over all on-treatment phases, i.e., "MIC" + "Loading NIN" + "NIN+MIC" + "NIN".

CTR Appendix 16.1.13.1.8.1 displays will present results for all study analysis phases defined in Table 6.1: 1 above, and will additionally present the following totals:

- "**Total NIN**", defined as the total over on-treatment phases involving nintedanib, i.e. "Loading NIN" + "NIN+MIC" + "NIN".

- "**Total**", defined as the total over all study analysis phases.

Table 6.1: 2 Flow chart of analysis phases for statistical analyses of safety laboratory

Study analysis phase	Label	Start (included in phase)	End (excluded from phase)
Screening	Screening	Date of informed consent	Date/time of first administration of study drug
On-treatment microgynon	**MIC**	Date/time of administration of microgynon in Treatment Period 1	Date/time of administration of microgynon in Treatment Period 1 + REP (72 h) OR Date/time of first administration of nintedanib in Treatment Period 2 (whichever occurs first).
Follow-up microgynon	**FUP-MIC**	Date/time of administration of microgynon in Treatment Period 1 + REP (72 h)	Date/time of first administration of nintedanib in Treatment Period 2
On-treatment nintedanib loading phase	**Loading NIN**	Date/time of first administration of nintedanib in Treatment Period 2	Date/time of administration of microgynon in Treatment Period 2
On-treatment nintedanib plus microgynon	**NIN+MIC**	Date/time of administration of microgynon in Treatment Period 2	Date/time of administration of microgynon in Treatment Period 2 + REP (72 h)
On-treatment nintedanib	**NIN**	Date/time of administration of microgynon in Treatment Period 2 + REP (72 h)	12:00 a.m. on day after last contact date

More details on the technical implementation of these analyses are provided in the Analysis Data Set (ADS) Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the entered set, as defined in Section 7.3 of the CTP.

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the report planning meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (PD). For definition of important PDs, and for the process of identification of these, refer to the Boehringer Ingelheim (BI) reference document "Integrated Quality and Risk Management Process" (2).

If any important PDs are identified, they are to be summarised into categories and will be captured in the decision log and DV domain specification sheet (11). Categories which are considered to be important PDs in this trial are defined in the integrated quality and risk

management plan (IQRMP). If the data show other important PDs, the definition in the IQRMP will be supplemented accordingly by the time of the RPM.

Important PDs will be summarized and listed. Table 6.2: 1 below specifies which kind of important PDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses. If the data show other important PDs, this table will be supplemented accordingly by the time of the Report Planning Meeting.

Table 6.2: 1 Handling of important PDs

PD code	PD Category & Brief Description	Excluded from which analysis set
A1.01 – A1.08	Inclusion Criteria Not Met	PKS
A2.01 – A2.26	Exclusion Criteria Violated	PKS
B1	Informed consent not available/not done	TS, PKS
B2	Informed consent too late	None
C1	Incorrect trial medication taken (i.e., deviation from the correct intended medication)	PKS
C2	Incorrect dose of trial medication taken	PKS
C3	Patient did not continuously take at least 10 consecutive days of a stable dose of nintedanib (b.i.d.) prior to the PK visit assessments in Period 2 (Visit 6)	PKS
C4	The patient missed one (or more) nintedanib capsules in the 3 days prior to or during PK profiling at Visits 6, 7, 8	PKS
D1	Prohibited medication use (cf. CTP Table 4.2.2.1:1)	PKS
D2	Improper washout of concomitant medication (cf. CTP Table 4.2.2.1:1)	PKS
G1	Incomplete intake of meal. Or non-adherence to dietary restrictions (cf. CTP Section 4.2.2.3)	PKS
G2	Treatment compliance not in accordance with protocol definition (cf. CTP section 4.3)	None

6.3 PATIENT SETS ANALYSED

All patients who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP.

The enrolled set (ENR) includes all patients who signed informed consent.

Other analysis sets are defined in Section 7.3 of the CTP. The discussion of all exceptional cases and problems and the decisions on the allocation of patients to analysis sets will be made at latest at the RPM.

Table 6.3: 1 Patient sets analysed

	Patient set			
Class of endpoint	Enrolled set (ENR)	Entered set (ES)	Treated set (TS)	PK parameter analysis set (PKS)
Important PDs		X		
Disposition	X	X	X	
Demographic/baseline characteristics			X	
Safety parameters of interest			X	
PK endpoints				X

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The reason for withdrawal (e.g. adverse events) as recorded in the electronic Case Report Form (eCRF). will be reported.

With respect to safety evaluations, it is not planned to impute missing values.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (3).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (4). Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), or BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase).

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is

defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last value prior to first administration of study drug.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (9).

The individual values of all patients will be listed by patient number and visit (if visit is applicable in the respective listing). Listings will also show treatment sequence, although all patients received treatments in the same sequence. AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For plasma concentrations as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

Moreover, the 10^{th}, 25^{th}, 75^{th} and 90^{th} percentiles will be also presented in Section 15.6.2 for the descriptive statistics of the PK parameters.

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

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 total number of patients. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

For Saint George's Respiratory Questionnaire (SGRQ), Scleroderma Health Assessment Questionnaire (SHAQ) and Scleroderma Gastrointestinal Tract Instrument (SCTC GIT 2.0), all answers will be listed.

For all other demographic and baseline characteristics, descriptive statistics are planned.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only descriptive statistics are planned for this section of the CTR. All reported diseases and medications will be summarized and listed.

A medication will be considered concomitant to study drug treatment, if it

- is ongoing at the time of first administration of study drug (Microgynon® or nintedanib) or
- starts after the time of first administration of study drug (Microgynon® or nintedanib) (see also Section 6.1).

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Nintedanib treatment compliance [%] and the assessment of whether the patient was compliant according to the protocol (yes/no, additional specification if no), will be listed as reported by the investigator in the eCRF. A footnote will explain that, in case of a treatment interruption, the compliance could be low (e.g. less than 80%) although the patient was compliant with the protocol.

Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Analysis of relative exposure on the basis of primary endpoints will be performed as defined in Section 7.3.1 of the CTP, based on the PKS.

The statistical model defined in the CTP is an analysis of variance (ANOVA) model on the logarithmic scale including "treatment" as fixed effect and "patient" as random effect.
In addition, a sensitivity analysis will be performed, using both effects as fixed effects. For

this sensitivity analysis, a statistical SAS™ raw output will be presented only (in Appendix 16.1.13.3 of the CTR).

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameters with APEXC equal to "Included", regardless of the analysis flag comment APEXCO.

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point) contains column variables ACEXC and ACEXCO indicating inclusion/exclusion (ACEXC) of a plasma concentration and an analysis flag comment (ACEXCO). Exclusion of a plasma concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE' the value will be excluded from half-life calculation only; the value is included for all other analyses.

The excluded concentration itself will be listed in the tables in Section 15 of the CTR associated with an appropriate flag.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (5).

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

Analysis of relative exposure on the basis of the secondary endpoint will be performed in the same way as for the primary endpoints.

See Section 7.4 of this TSAP for details regarding exclusion of PK parameters and plasma concentrations.

7.6.1 Safety parameters of interest

Further safety parameters of interest will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on TS.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

For analysis, multiple AE occurrence data on the electronic case report form (eCRF) will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were overlapping or adjacent (adjacency of two occurrences is given if the second occurrence started on the same day or on the day after the first occurrence ended)

For further details on summarisation of AE data, please refer to 'Handling and summarisation of adverse event data for clinical trial reports and integrated summaries' (6) [001-MCG-156 Version 5] and "Handling of missing and incomplete AE dates" (3) [001-MCG-156_RD-01].

The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs will be assigned to the screening, treatment or follow-up phases as defined in Section 6.1.

Hepatic injury and gastro-intestinal perforation are defined as protocol-specified AESIs. For details on the definition of hepatic injury see CTP Section 5.2.10.1.4.

According to ICH E3 (8), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant AEs with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or leading to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 (8).

The frequency of patients with AEs will be summarised by primary system organ class and preferred term. AEs which were considered by the investigator to be drug-related will be summarised separately. Separate tables will also be provided for patients with serious AEs (SAEs), patients with AESIs and patients with other significant AEs (according to ICH E3 (8)). The frequency of patients with AEs will also be summarised by worst common terminology criteria, primary system organ class and preferred term.

The system organ classes and preferred terms within system organ classes will be sorted by descending relative frequency.

In addition, the frequency of patients with AEs, SAEs and drug related AEs will be summarised by safety topic, subcategory and preferred term for the organ systems 'Hepatobiliary' and 'Liver laboratories'. Safety topics and subcategories are defined on project level and stored in PDMAP in the TMF (10). The most recent version of this file will be used for the analysis.

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by primary system organ class and preferred term. The frequency of patients with SAEs will also be summarised.

For disclosure of AE data in the European union drug regulating authorities clinical trials (EudraCT) register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of patients with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

Details collected in the eCRF regarding bleeding AEs and AEs of diarrhoea will be listed.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (7).

Possibly clinically significant abnormalities will be identified based on BI standard rules which are based on normalized converted lab values, i.e. on values transformed to SI units and to a standard reference range. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with possibly clinically significant abnormalities.

All individual laboratory data will be listed. Values outside the reference range will be flagged. In addition, possibly clinically significant values will be flagged in the listing.

Clinically relevant findings in laboratory data, as judged by the investigator, were to be reported as baseline conditions (if condition already existed before intake of first study drug) or as AEs (during the trial), and will be analysed as such.

7.8.3 Vital signs

Summary statistics will be presented for observed values and change from baseline.

The frequency of patients with marked changes in vital signs will be summarised according to the definitions in Section 5.3.1 of this document.

Clinically relevant abnormal findings in vital signs data, as judged by the investigator, were to be reported as baseline conditions (if condition already existed before intake of first study drug) or as AEs (during the trial) and will be analysed as such.

7.8.4 ECG

Clinically relevant abnormal findings in electrocardiogram (ECG) data, as judged by the investigator, were to be reported as baseline conditions (if condition already existed before intake of first study drug) or as AEs (during the trial) and will be analysed as such.

7.8.5 Others

7.8.5.1 Spirometry

With regard to spirometry, the highest FVC and highest FEV1 each obtained on any of three efforts which meet the criteria of the American Thoracic Society and European Respiratory Society – with preferably a maximum of five manoeuvres – were to be recorded in the eCRF.

Spirometry data (except for baseline data) will only be listed.

Clinically relevant abnormal changes in spirometry data, indicative of worsening of lung function since baseline, as judged by the investigator, were to be reported as AEs and will be analysed as part of AE analysis.

7.8.5.2 Body weight

Body weight (at screening and end of study visit) will be listed.

7.8.5.3 Physical examination

Physical examination abnormal findings were to be reported as relevant medical history/baseline condition (if condition already existed before intake of first study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.4 Doppler echocardiography

Clinically relevant abnormal findings in Doppler echocardiography were to be reported as relevant medical history/baseline condition (if condition already existed before intake of first study drug) or as AEs and will be analysed as part of AE analysis.

7.8.5.5 Pregnancy test

Pregnancy test results (as reported in the eCRF) will be listed.

8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2	*001-MCS-40-135*: “Integrated Quality and Risk Management Process”, current version; IDEA for CON
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 of Clinical Studies", current version; IDEA for CON
5	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", IDEA for CON
6	*001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", Version 5; IDEA for CON
7	*001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON
8	*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
9	*001-MCG-159:* "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10	"8-07-other-safety-topic-definition_v4.0" in PDMAP in BIRDS: http://birdslinkp.eu.boehringer.com/fdrd/drl/objectId/09000cb186bdcbc5
11	"Template Domain DV", current version; Section "Resources and Key User Emails" on ICBI homepage

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**11-OCT-2018**		None	This is the initial TSAP with necessary information for trial conduct
Final	**08-NOV-2019**		See Section 4 for a summary of changes	This is the final TSAP