TRIAL STATISTICAL ANALYSIS PLAN

c39368660-02

BI Trial No.:	1199-0452 ([redacted] Trial No. QSC204583)
Title:	A Phase I study for formulation selection and subsequent optimization of two different oral formulations of Nintedanib in healthy male subjects (open-label, randomised, single-dose study in three parts)
Investigational Products:	Nintedanib
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	28 FEB 2023 SIGNED
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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
b.i.d.	Bis in die: twice per day
BMI	Body mass index
C_{24}	Concentration of the analyte in plasma 24 h after the (first) dose
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma within the 24h dosing interval
CV	Arithmetic Coefficient of Variation
DILI	Drug induced liver injury
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
IR	Immediate release
Max	Maximum
Min	Minimum
MR	Modified release
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PKS	PK parameter analysis set
Q1	1^{st} quartile
Q3	3^{rd} quartile
QD	Quaque die, once daily
R	Reference treatment
RAGe	Report Appendix Generator system

Term	Definition / description
SD	Standard Deviation
T	Test treatment
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of 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 trial statistical analysis plan (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.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, [redacted]).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The trial was prematurely terminated during recruitment of subjects in trial part 1 since the first analysis of part 1 was not as expected and further development has stopped.

Consequently, only data from trial part 1 (n=7/15 for cohort 1, n=14/15 for cohort 2) will be analysed. For part 1, all analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for Nintedanib:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 [first dose] extrapolated to infinity which includes also the second Nintedanib dose of the day)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for Nintedanib:

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma within the 24h dosing interval)*
- *C_{24} (concentration of the analyte in plasma 24 h after the (first) dose)*

5.3 FURTHER ENDPOINTS

[redacted]

[redacted]

Safety and tolerability endpoints

Section 2.2.2.2 of the CTP:

Safety and tolerability of Nintedanib will be assessed based on:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

5.4 OTHER VARIABLES

Section 5.2.1 of the CTP:
At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests (including drug screening), and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight.

Age [years] will be determined as the difference between year of informed consent and year of birth.

BMI will be calculated as weight [kg] / (0.01 * height [cm])^2.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Sections 3 and 4.

The study was originally planned to consist of up to three trial parts aiming to assess and optimize different modified release (MR) formulations of oral Nintedanib.

Section 3.1 of the CTP:
The study will be performed in healthy male subjects as an open-label, randomised, single-dose study in up to three trial parts in order to compare each of the test treatments (MR1, MR2, MRX) to the respective reference treatment R. The subjects will be randomly allocated to three treatment sequences in trial part 1 and 2 (Latin square design) and two sequences in trial part 3 (optional)*. There will be a washout period of at least 14 days between the treatments, i.e. the morning dose in the preceding treatment period and the morning dose in the following treatment period are separated by at least 14 days.*

Each trial part was planned as a randomised crossover trial, details are provided below:

In trial part 1, it was planned to assign 30 healthy male subjects to two parallel groups (trial part 1A and 1B, each n=15). In each parallel group, subjects were randomised to one of three treatment sequences:

Trial part 1A (Cohort 1):
R / MR1-1 / MR1-2
MR1-2 / R / MR1-1
MR1-1 / MR1-2 / R

Trial part 1B (Cohort 2):
R / MR2-1 / MR2-2
MR2-2 / R / MR2-1
MR2-1 / MR2-2 / R

For details of dosage and formulation see Table 6.1: 1 below:

Table 6.1: 1 Treatments and labels used in the analysis – Part 1

Trial Part	Cohort	Treatment		Short label
1A / 1B	1 / 2	C / F	Ofev® [redacted] mg soft capsules (IR)*, [redacted] mg (1 capsule) twice per day (b.i.d.)	R
1A	1	A	Nintedanib MR1[1], Prototype 1 Tablet (MR1-1), [redacted] mg (1 tablet) as single dose	MR1-1
1A	1	B	Nintedanib MR1[1], Prototype 2 Tablet (MR1-2), [redacted] mg (1 tablet) as single dose	MR1-2
1B	2	D	Nintedanib MR2[2], Prototype 1 Tablet (MR2-1), [redacted] mg (1 tablet) as single dose	MR2-1
1B	2	E	Nintedanib MR2[2], Prototype 2 Tablet (MR2-2), [redacted] mg (1 tablet) as single dose	MR2-2

* Immediate Release
[1] MR1 = Monolithic Nintedanib Modified Release Prototype Tablet
[2] MR2 = Polyox Nintedanib Modified Release Prototype Tablet

If the trial was to be continued with trial part 2, it was planned to assign 15 healthy male subjects to the three treatment sequences:

R / MRX-1 / MRX-2
MRX-2 / R / MRX-1
MRX-1 / MRX-2 / R

If the trial was to be continued with trial part 3, it was planned to assign 14 healthy male subjects to the two treatment sequences:

R / MRX-5, MRX-5 / R

The trial was prematurely terminated during trial part 1 (see Section 4). General definitions, analysis definitions and description of the statistical analysis in the following sections of this document refer to the analysis of trial part 1 only.

Section 1.2.5 of the CTP:
The Residual Effect Period (REP) is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For this trial using 1 day treatment of [redacted] to (potentially) [redacted] mg Nintedanib in healthy male volunteers, a REP of 14 days is used, i.e. the individual subject's end of trial is on day 15 following dosing at the earliest and the washout between periods is at least 2 weeks (see CTP *Flow Chart).*

Based on this, the following study phases will be defined for the analysis of adverse events (AEs):

- **Screening**
  - Ranging from 0:00h on day of informed consent until administration time of first drug administration in treatment period 1.
- **On treatment** (labelled **(**in Part 1): "**R**", "**MR1-1**", "**MR1-2**", "**MR2-1**", "**MR2-2**")
  - Ranging from the administration time of first respective drug administration in this period until 14 days (12 AM on day 14) thereafter OR until next drug administration of the following period, whatever occurs first.
- **Follow-up** (labelled "**F/U R**", "**F/U MRX-Y**", with X=1,2, Y=1,2))
  - Ranging from 14 days (12 AM on day 14) after administration time of first drug administration of that period until the next drug administration of the following period OR until trial termination, whatever occurs first.

Section 7.3.4 of the CTP:
Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

The following AE displays will be provided in the report:

In Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays, the on treatment phase will be analysed (labelled with the short label of the study treatment). The screening and follow-up phases will not be included in this analysis.

The following totals will be provided in addition for Section 15.3:

- a total over all on treatment phases from cohort 1 **("Total Cohort 1")**
- a total over all on treatment phases from cohort 2 **("Total Cohort 2")**
- a total over all on treatment phases from trial part 1 **("Total")**

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included and no totals will be provided.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects. Consistency check listings (for identification of deviations of 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, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of

important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

Section 7.3 of the CTP:
*Important protocol deviation (*iPD*) categories will be suggested in the DV domain sheet,* iPDs *will be identified no later than in the Report Planning Meeting, and the* iPD *categories will be updated as needed.*

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) (3) and in the decision log (4). The iPD specification file will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:

Statistical analyses for each crossover part will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.*

(…)

Pharmacokinetics

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject experiences emesis at any time during the labelled dosing interval.*
- *A predose concentration is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Table 6.3: 1 Subject sets analysed

	Subject analysis set	
Class of endpoint	TS	PKS
Analyses of PK endpoints		X
Disposition	X	
Demographic/baseline parameters	X	
Important protocol deviations	X	
Exposure	X	

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.5.

Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (5).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (6) and BI-KMED-TMCP-MAN-0014 (7).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before drug administration in each treatment period.

Section 6.1 of the CTP:
Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, the end of trial examination, and measurements and assessments scheduled to occur 'before' trial medication administration in the morning of Day 1 are provided in the CTP *Flow Chart.*

If not stated otherwise in the CTP *Flow Chart, the general acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.*

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- *The pre-dose urine sample will be the first void of the day or a sample collected ≤3 h before dosing*
- *Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time*

Adherence to time windows will be checked via the consistency check listings at the RPM.

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

7. PLANNED ANALYSIS

Each of the three possible trial parts was planned to be analysed separately. Cohort 1 and cohort 2 of trial part 1 will be presented in one table, but the reference group will be stratified to R (Cohort 1) and R (Cohort 2).

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.4 and Section 7.5.2) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK endpoints and concentrations will be performed by the department of Translational Medicine and Clinical Pharmacology (TMCP) at BI and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (8)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number and visit. The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

For analyte concentrations and PK parameters, the following descriptive statistics will additionally be calculated:

Nobs	number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical to 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 available in the CRF and will display the number of observations in a category, as well as the percentage (%). Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in brackets (e.g. (mg)).

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters only if they are not flagged for exclusion, that is APEX is equal to "Included".

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a 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/time interval. 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in *BI-KMED-TMCP-MAN-0014* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (7) and *BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files" (10).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a “No” in the respective column.

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

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP:
Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY ENDPOINTS

The relative bioavailability of several MR formulations of Nintedanib compared to Ofev® IR will be investigated on the basis of the primary PK endpoint $AUC_{0-\infty}$ (see Section 5.1).

Each of the crossover parts will be analysed separately.

7.4.1 Primary analysis of the primary endpoints

Section 7.3.1 of the CTP:
The statistical model used for the analysis of the primary endpoint will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment*

k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2,(3),

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., n_i

π_j = the j^{th} period effect, j = 1, 2, (3),

τ_k = the k^{th} treatment effect, k = 1, 2, (3),

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoint (see Section 5.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

The implementation for this analysis will be accomplished by using the CSD macros based on PKS. The following SAS code can be used:

```
PROC MIXED DATA=indata METHOD=REML;
        CLASS subject treatment sequence period;
        MODEL logpk = treatment sequence period / DDFM=KR;
        RANDOM subject(sequence);
        LSMEANS treatment / PDIFF CL ALPHA=0.1;
RUN;
```

7.5 SECONDARY ENDPOINTS

The relative bioavailability of several MR formulations of Nintedanib compared to Ofev® IR will also be investigated on the basis of the secondary PK endpoint $AUC_{0\text{-}tz}$, C_{max} and C_{24} (see Section 5.2.2).

Each of the crossover parts will be analysed separately.

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 (Other) Secondary endpoints

Section 7.3.2 of the CTP:
The secondary endpoints (refer to Section 5.2.2) will be calculated according to the relevant internal BI procedures and will be assessed statistically using the same methods as described for the primary endpoint.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

AEs will be coded using MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (11) and [BI-KMED-BDS-HTG-0066] (12) will be applied.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', 'on-treatment' or 'follow-up' phases as defined in Section 6.1. The 'on-treatment' and 'follow-up' AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.6.1.4 of the CTP:
The following are considered as AESIs:

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

According to ICH E3 (13), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious

adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary system organ class (SOC) and preferred term (PT).

The system organ classes will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC).

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (14). Analyses will be based on normalised values.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data including change from baseline will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). In the listing the change from baseline will also be displayed.

For vital signs, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point). Time courses of vital signs presenting means and standard deviations per time point and treatment group will be provided.

Clinically relevant findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as AEs (when they occurred during treatment), and will be analysed as such.

No separate ECG listing will be provided.

7.8.5 Others

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of trial drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released for interim analysis as specified in the CTP Section 4.1.5.

The treatment information will be loaded into the trial database after completion of enrolment for the respective trial parts, i.e. the randomisation has been completed.

9. 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-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
4.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
5.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
6.	*BI-KMED-TMCP-MAN-0012:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
7.	*BI-KMED-TMCP-MAN-0014:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED.
8.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
9.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, KMED.
10.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
12.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, KMED.
13.	*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, EMA webpage.
14.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**25-AUG-2022**	[redacted]	None	This is the final TSAP
2	**28-FEB-2023**		Sections 4, 6.1, 7, 7.8.3	Update of cohort labels, description of premature trial termination, figures for vital signs added