TRIAL STATISTICAL ANALYSIS PLAN

c35271141-01

BI Trial No.:	1424-0001
Title:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905681 administered intravenously in patients with advanced solid tumours.
Investigational Product(s):	BI 905681
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	17 JAN 2022 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary

Term	Definition / description
AE	Adverse Event
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CR	Complete Response
CRF	Case Report Form
CTC	Common Terminology Criteria
CTh	Concomitant Therapy
CTP	Clinical Trial Protocol
DBL	Databaselock
DCR	Disease Control Rate
DEC	Dose Escalation Committee
DLT	Dose Limiting Toxicity
EOT	End Of Text
EWOC	Escalation With Overdose Control
ICH	International Conference On Harmonisation
IPD	Important Protocol Deviation
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
MTDS	MTD evaluation set
OBD	Optimal Biologic Dose
OR	Objective Response
ORR	Objective Response rate
PD	Protocol Deviation
PK	Pharmacokinetics
PKS	PK set
PR	Partial Response
PT	Preferred Term
REP	Residual Effect Period
RPM	Report Planning Meeting

Term	Definition / description
ScS	Screened Set
SD	Stable Disease
STD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
ToC	Table of Contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
WHO DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per (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, and randomization.

[redacted] Version 9.4 or the latest version will be used for analyses.

R Version 4.0.1 and JAGS Version 4.3.0 or the latest versions will be used for the Bayesian Logistic Regression Model (BLRM) analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to enrollment issues, the trial will be terminated early without determination of the maximum tolerated dose (MTD)/optimal biologic dose (OBD) as per protocol. Only schedule A has been investigated in the trial. The early termination does not have an impact on the planned endpoints.

[redacted]

[redacted]

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoints of the trial are:

- The MTD/OBD of BI 905681. The MTD will be assessed based on the number of patients experiencing dose limiting toxicities (DLTs), graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, in the first cycle of treatment (first 3 weeks of treatment, MTD evaluation period). The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal to or above 33% as determined by the BLRM defined in the CTP.
- Number of patients experiencing adverse events (AEs) during the entire treatment period

5.2 SECONDARY ENDPOINT(S)

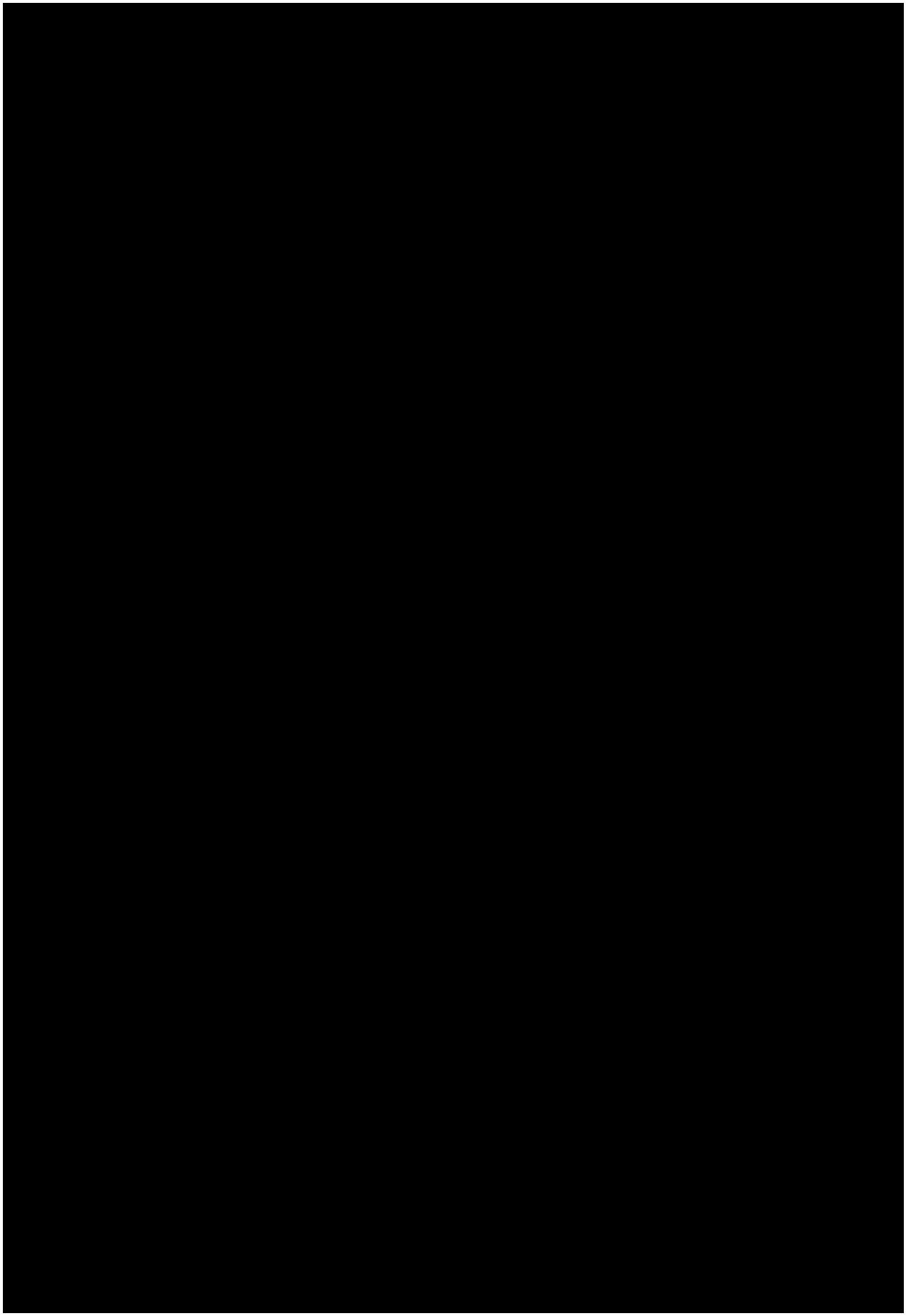
5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

The secondary endpoints of the trial are:

- The following Pharmacokinetics (PK) parameters of BI 905681 will be evaluated after the first administration of BI 905681 (if feasible), ie. in Cycle 1:
    - C_{max}: maximum measured concentration of BI 905681 in serum after first infusion
    - $AUC_{0\text{-}tz}$: area under the serum concentration-time curve over the time interval from 0 to the last measured time point (t_z)



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is an open label, non-randomized, dose escalation phase I study. The starting dose for Schedule A is BI 905681 1.0 mg/kg every three weeks. The trial has been terminated before the start of schedule B. Dose escalation decisions will be made by a Dose Escalation Committee (DEC) guided by the BLRM with escalation with overdose control (EWOC) criterion. Table 6.1: 1 shows the dose levels that were administered in Schedule A.

Table 6.1: 1 Dose levels for escalation in Schedule A

Cohort Dose Level	Proposed dose	Increment from previous dose
1	1.0 mg/kg/q3w	Starting dose
2	2.5 mg/kg/q3w	150%
3	5.0 mg/kg/q3w	100%
4	7.0 mg/kg/q3w	40%
5	8.5 mg/kg/q3w	21.4%

The data will be presented for all dose cohorts separately and in total over all dose cohorts. DLTs occurring during the MTD evaluation period (during the first treatment cycle) will be presented separately.
“Analysing treatment” will be used for reporting of treatment-emergent adverse events (AEs) and to differentiate between screening, on-treatment, and post-treatment safety data. The inequalities start date<=onset date of the AE< end date of the AE will determine whether the AE will be assigned to the “analysing treatment” or not.
The treatment periods of the trial which will be used for the reporting of AEs and safety laboratory parameters are given in Table 6.1: 2. Safety data recorded during the Residual Effect Period (REP) will be considered as on-treatment. In this trial, the REP is defined as 42 days.
If not specified otherwise, all safety tables will be based on the on-treatment period. AEs that have an onset date during the screening or post-treatment periods will be displayed in separate listings.

Table 6.1: 2 Definition of treatment periods

Analysing Treatment Period	Start Date (including)	Stop Date (excluding)
Screening	Date of informed consent	The date of first trial medication administration
On-treatment	Date of first administration of trial medication	Date of last trial medication administration + REP*, or death, +1 day whichever comes first, e.g., actual on-treatment period + REP*,
Post-treatment	Last day of on-treatment period +1 day	Date of the last contact date or death, or DBL date, whichever comes first +1 day
MTD evaluation period	Date of first administration of trial medication	Date of first administration of trial medication +21 days

*Note: A 42-day residual effect period (REP) is defined.

The initial dose of trial medication assigned at the beginning of the first treatment cycle will be used as the label of the analysing treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurements in a non-negligible way.

Important Protocol Deviations (IPDs) are stored in the DV domain template (Excel spreadsheet).

If the data show other IPDs, this table will be supplemented accordingly at Medical Quality Review Meetings (MQRMs) or Report Planning Meetings (RPMs) or through team review of the manual PD log. The final list of IPDs will be confirmed before Databaselock (DBL). No per protocol set is defined for this phase I study, but patients with an IPD will be identified and reported in the Clinical Trial Report (CTR).

6.3 SUBJECT SETS ANALYSED

The following subject sets will be defined.

- **Screened Set (ScS)**: includes all patients who have signed the informed consent form and will be used for patient disposition.

- **Treated Set (TS):** includes all patients who received at least one infusion of BI 905681. The TS is used for both efficacy and safety analyses, and for summary of demographics, baseline characteristics, disease history, and concomitant therapies.

- **MTD Evaluation Set (MTDS)**: includes all patients in the TS who were not replaced for the MTD determination. The MTD Evaluation Set is used for the primary analyses of DLTs and MTD determination. The list of replaced patients will be provided by the Clinical trial leader before DBL and documented in the decision log (2).

- **PK Analysis Set (PKS)**: The PK set includes all subjects in the TS who provide at least one observation for at least one PK endpoint without important protocol violations relevant to the evaluation of PK. The PKS is used for all pharmacokinetic analyses

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect complete data at each visit for each patient. Missing baseline laboratory values will be imputed by the respective values from the screening visit. Potential outliers will be reported and analyzed as observed. If not specified otherwise, missing data will not be imputed and remain missing. No other imputations will be performed on missing data although every effort will be made to obtain complete information on AEs, with particular emphasis on potential DLTs.

Missing or incomplete AE dates will be handled according to the Boehringer Ingelheim (BI) guideline (3). Missing data and outliers of PK data will be handled according to the BI standards (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Visit labels
Study days and visits will be labelled according to the CTP's flow chart. The visit schedule with accompanying details can also be found in the flow charts in the CTP.

Baseline definition
Unless otherwise specified, baseline is defined as the time point closest to and prior to the first administration of study treatment. Note that for some study procedures (e.g. body weight, vital signs, laboratory tests) baseline may be the measurement made on the same day the study treatment was started. In such cases these measurements will be assumed to have been taken according to the protocol, i.e. prior to the first administration of study treatment. But for some measurements, the examination time may also need to be considered, in instances where

time is recorded in addition to date. If not available, then the values reported at the screening visit will be considered.

For laboratory parameters for which not only the examination date but also the sampling time was recorded, examination time should be taken into consideration when defining baseline. That is a laboratory measurement on the same date as the first administration of study treatment is considered as baseline if and only if the examination time of this laboratory measurement is before the first administration of study treatment.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics includes: N / Mean / standard deviation [STD] / 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 only if there are actually missing values.

If needed, conversion from days to weeks, months and years will be as follows:

- Weeks=Days/7
- Months=(Days*12)/365.25
- Years=Days/365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant therapies (CTh) will be coded according to World Health Organisation Drug Dictionary (WHO DD). They will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CThs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CThs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

Summaries will be presented for previous and concomitant medications started at baseline and for concomitant therapies started after first administration of the trial medication.

7.3 TREATMENT COMPLIANCE

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

Compliance with trial medication will be based on the drug infusion/administered eCRF data and calculated as amount of drug infused/administered divided by the amount of drug to be infused/administered expressed as a percentage, see calculations below.

"Per Cycle" compliance to trial medication will be calculated as follows:

$$\frac{\text{(Amount of drug infused/administered at Cycle n)}}{\text{(Amount of drug planned to be infused/administered at Cycle n)}} \times 100.$$

Overall compliance to trial medication will be calculated as mean of the "per cycle" compliance.

The compliance will be based on the total volume infused in mL (eCRF data) compared to total volume prepared (eCRF data).

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

In order to identify the MTD of the trial, the number of patients at each dose level that had DLT during the MTD evaluation period (first three weeks for Schedule A) will be presented, excluding patients who discontinue during the first treatment cycle for reasons other than a DLT.
The BLRM as described in Section 7.1 of the CTP will be analyzed using the number of patients at each dose that had DLTs during the MTD evaluation period among the patients in the MTD set. The prior defined in Table 7.1: 1 of the CTP will be used for the analysis. The resulting posterior distribution of the DLT rates of the doses tested during the trial will be summarized using their mean, SD, 2.5% quantile, median, and 97.5% quantile. Additionally, the posterior probabilities of the DLT rate lying in the intervals [0, 0.16) (underdosing), [0.16, 0.33) (target dosing), and [0.33, 1] (overdosing) will be computed and listed for each dose. The posterior probabilities of underdosing, target dosing, and overdosing of the tested dose levels will additionally be visualized in a bar diagram that further displays which of the dose levels satisfy the EWOC criterion.

In addition, the number of patients with DLTs that occurred during the entire treatment period will be summarized at each dose level.

[redacted]

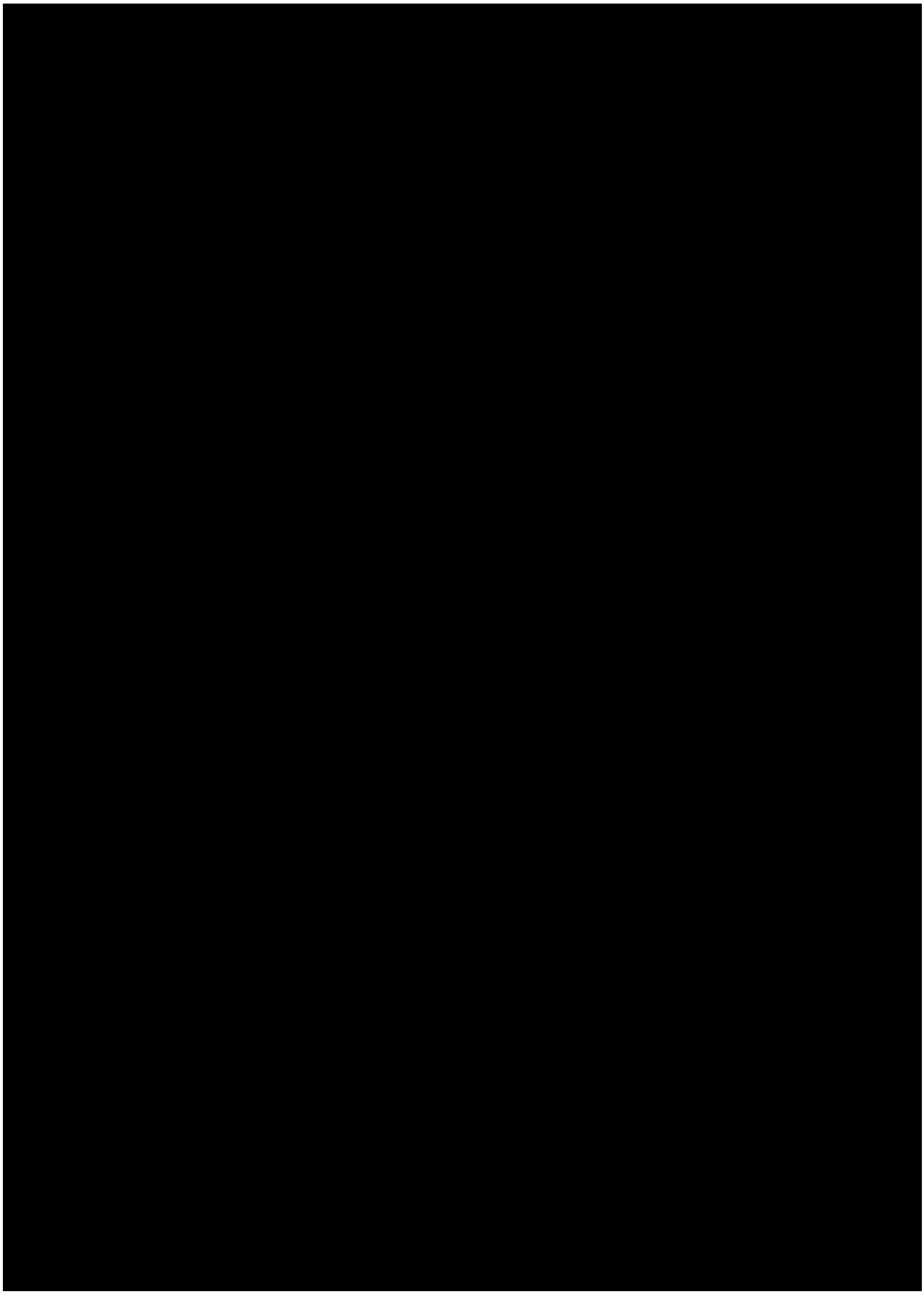
7.5 SECONDARY ENDPOINT(S)

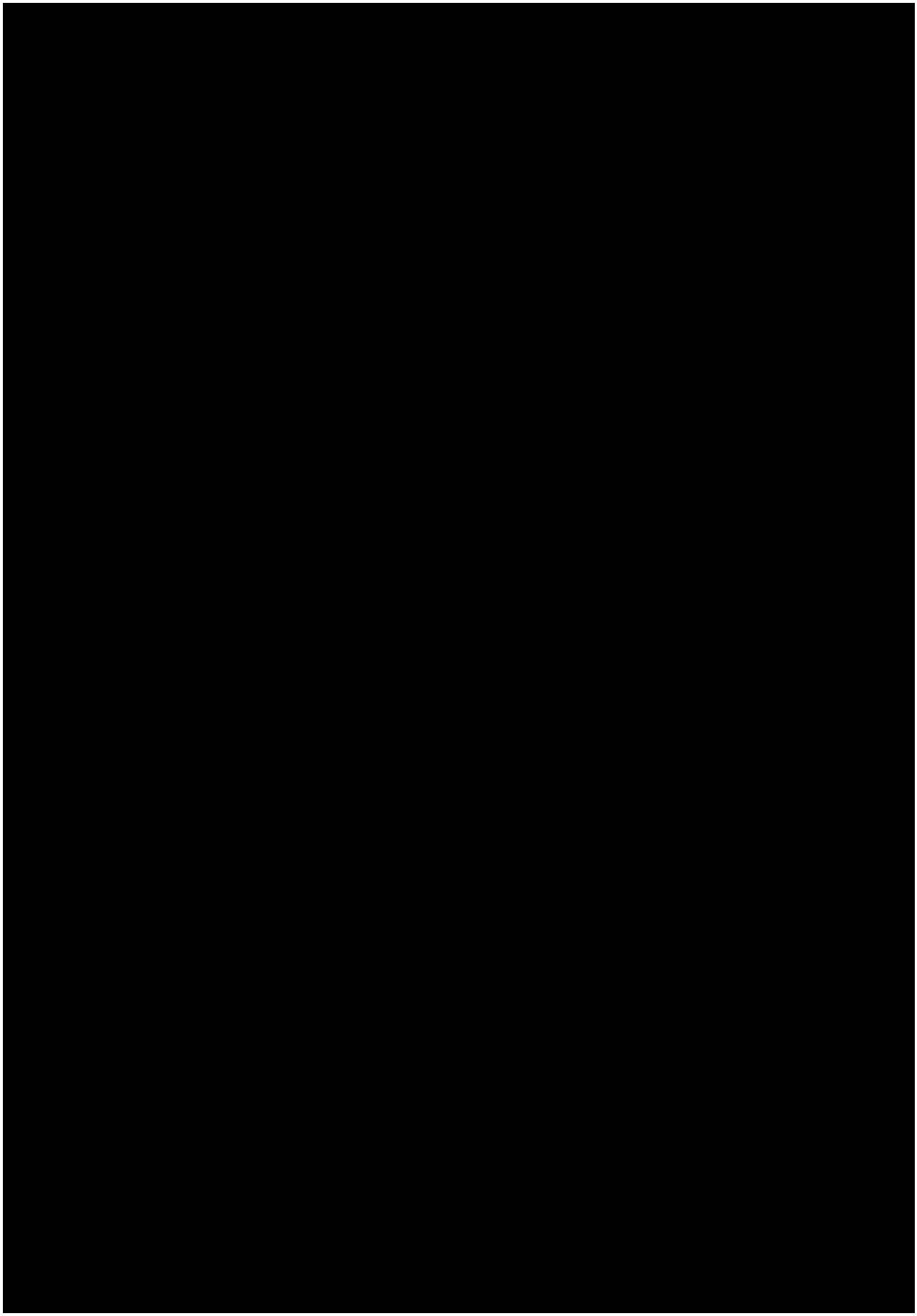
7.5.1 Key secondary endpoint(s)

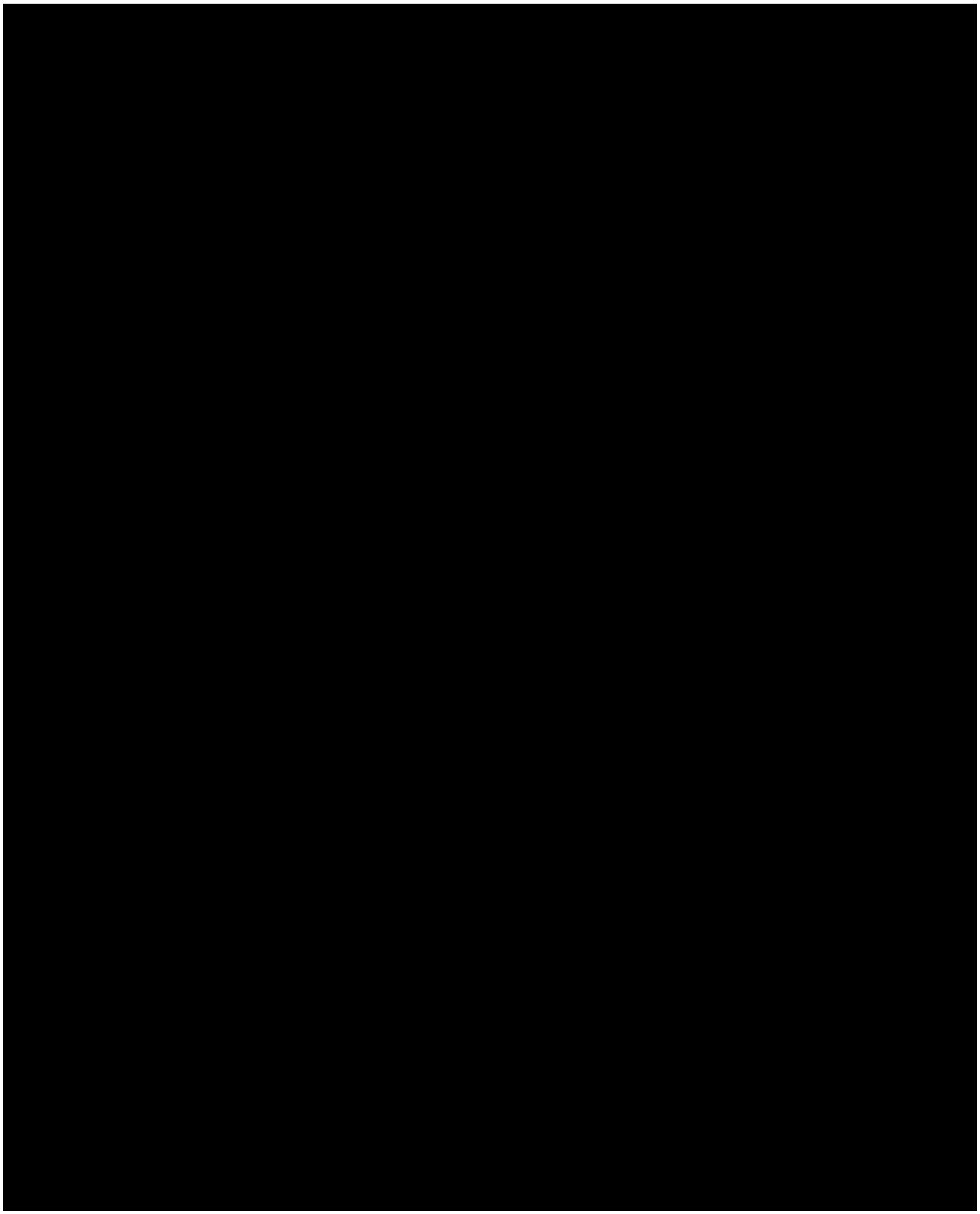
Not applicable.

7.5.2 (Other) Secondary endpoint(s)

Descriptive statistics will be presented for Cmax and $AUC_{0\text{-}tz}$. The analysis of standard PK parameters and pharmacodynamic analyses will be performed as outlined in Section 7.3.5 of the CTP, if applicable and feasible.







7.7 EXTENT OF EXPOSURE

Treatment exposure will be primarily summarized by the total on-treatment time and has been defined in Section 5.4 of this TSAP.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. In addition, some displays will be based on the MTD evaluation set and the MTD evaluation period.

7.8.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 42 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent.'

The analyses of adverse events (AE) 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. Frequency of patients with AEs will be tabulated by treatment dose, highest CTCAE grade, system organ class (SoC) and preferred term after coding according to the current version of MedDRA at the database lock. In addition, AEs will be tabulated by preferred terms only. The SoC will be sorted alphabetically. In tables displaying AEs by preferred terms, this will be sorted by descending frequency of AEs in the "Total" BI 905681 group.

Summary tables and listings of AEs, SAEs, related AEs, related SAEs, AEs of special interest, AEs leading to dose reduction, AEs leading to treatment discontinuation and AEs leading to deaths will be provided.
For the analysis of DLTs with regard to the primary endpoint see Section 7.4.1.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptively in nature and will follow standard procedures. The analysis of laboratory data will use the same "analyzing treatments" as described for AEs, except for that the baseline laboratory values will be included in the "on treatment" period. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline value will be displayed in the category "Missing CTCAE grade at baseline".
Descriptive statistics, including change from baseline, frequency of patients with transitions relative to the references range, will be provided for laboratory assessments at scheduled visits. Data collected during potential unscheduled laboratory assessments will be listed. No post-study laboratory values will be considered. CTCAE grade for applicable laboratory parameters will be calculated according to CTCAE v5.0. The following outputs will be presented:

- Baseline, last value and difference from baseline
- Worst CTCAE grade experienced during the on-treatment period
- Transitions of the CTCAE grade from baseline to the worst lab values, from baseline to the last lab values, and from the worst to last values during the on-treatment period
- Possible clinically significant laboratory values
- Transitions for laboratory values without CTCAE grade based on reference ranges

Note: For calculating the change in CTCAE grade from baseline, patients with a CTCAE grade of -9 (no CTCAE grade defined) or CTCAE grade of -5 (overlapping reference ranges) will be treated as a CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade is displayed as -9 and -5, respectively.

For Uric Acid, Hypokalemia, amylase, bicarbonate, eosinophils, glucose (high direction), INR of prothrombin time, lipase, methemoglobin, sodium (low direction) the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of -1 will be assigned. These will not be considered for laboratory analyses. In laboratory listings, the CTCAE grade is displayed as -1, respectively.

Patients with hepatic enzyme elevation will be tabulated.

7.8.3 Vital signs

Vital signs and physical examination, at Screening, baseline, during the course of the trial and at the end-of-trial evaluation will be listed with regard to possible changes compared to findings before start of treatment.

7.8.4 ECG

ECG data will be collected as described in CTP Section 5.2.4. Clinically significant findings in ECG data will be reported under “Adverse events” if applicable and will be analyzed accordingly. In addition, patients ECG assessements will be listed for all timepoints.

7.8.5 Others

Patients ophthalmologic assessments will be listed. Patients who have a bone densitometry assessment with a bone mineral decrease of >5% from baseline will be also given in a patient listing.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Not applicable.

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-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences".
3.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version.
4.	*BI-KMED-TMCP-MAN-0012:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version.
R11-1488	Kenward MG, Roger JH Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 53, 983-997, 1997.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**17-JAN-22**	[redacted]	None	This is the final TSAP