TRIAL STATISTICAL ANALYSIS PLAN

c40875946-01

BI Trial No.:	1305-0033
Title:	The effect of multiple oral doses of BI 1015550 on metabolism of midazolam administered orally in healthy male subjects (open-label, two-period fixed sequence design trial) Revised protocol #02 [c38906736-02]
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	16 JAN 2023 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse Event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
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
BI	Boehringer Ingelheim
C-SSRS	Columbia-Suicide Severity Rating Scale
CARE	Clinical data analysis and reporting environment
CDR	Clinical Data Repository
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
[redacted]	[redacted]
COVID	Coronavirus disease
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EudraCT	European union drug regulating authorities clinical trials
ICH	International Conference On Harmonisation
iPD	Important protocol deviations
MedDRA	Medical Dictionary For Regulatory Activities
HADS	Hospital Anxiety and Depression Scale
IPD	Important protocol deviations
PKS	Pharmacokinetic parameter analysis set

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Term	Definition / description
PK	Pharmacokinetic(s)
Pharmacokinetic(s)	Pharmacokinetic(s)
RAGe	Report appendix generator
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SDL	Subject data Listing
SIB	Suicidal Ideation and Behavior
SOC	System Organ Class
TS	Treated set
ULN	Upper limit of normal range
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan

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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 revised CTP, and to include detailed procedures for executing the statistical analysis of the primary variables and other data.

This TSAP assumes familiarity with the CTP and its 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 revised 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 as collected in the eCRF will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

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).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 8.1.1 or higher, [redacted].

Status of TSAP

This is the final approved TSAP for the final analysis.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

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5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Primary endpoints are PK endpoints of midazolam, as defined in **Section 2.1.2 of the CTP**.

- *AUC0-tz (area under the concentration-time curve of the analyte* [midazolam] *in plasma over the time interval from 0 to the last quantifiable data point)*
- *Cmax (maximum measured concentration of the analyte* [midazolam] *in plasma)*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Secondary endpoint is PK endpoint of midazolam, as defined in **Section 2.1.3 of the CTP**.

- *AUC0-∞ (area under the concentration-time curve of the analyte* [midazolam] *in plasma over the time interval from 0 extrapolated to infinity)*

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5.4 OTHER VARIABLE(S)

5.4.1 Demographic and other baseline characteristics

CTP Section 5.2.1 *At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy […].*

Body mass index will be calculated as weight [kg] / height $[m]^2$.

5.4.2 Treatment compliance and treatment exposure

Treatment compliance will not be analysed as a specific endpoint, **cf. Section 4.3 of the CTP**.

Treatment exposure to midazolam is defined as the number of doses and total dose of midazolam per subject by period and over both periods.

Treatment exposure to BI 1015550 is defined as the number of doses and total dose of BI 1015550 per subject.

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, and selection of dose, **cf. Section 4 of the CTP**. For information of overall trial design, **cf. Section 3.1 of the CTP.**

This is a two-period trial with fixed sequence R-T. In trial period R (Reference Treatment Period) subjects will receive midazolam alone (Reference treatment (R)) whereas in trial period T (Test Treatment Period) midazolam plus BI 1015550 (Test treatment (T)) will be administered.

In trial period R, each subject will receive:

- 2 mg midazolam administered as oral solution in fasted state on Day 1 of Visit 2

In trial period T, each subject will receive:

- Multiple doses of 18 mg BI 1015550 administered bid (morning and evening dose) for 13 days (Day -13 to Day -1 of Visit 3) as tablets.
- 18 mg BI 1015550 as tablet combined with 2 mg midazolam administered as oral solution in the morning on Day 1 of Visit 3.

Morning doses are in fasted state. For the evening doses no special fasting requirement applies.

CTP Section 1.2.3: *The Residual Effect Period (REP) of BI 1015550* [redacted]*. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present. The residual effect period of midazolam is 12 hours.*

For statistical analysis of AEs, the following analysis phases are defined for each subject. Analysis phases for active treatments are defined separately for Period R and Period T.

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Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening[1]	**Screening**	Date of informed consent	Date/time of administration of midazolam
On treatment	**midazolam**	Date/time of first administration of midazolam	Date/time of first administration of midazolam + REP (12 hours)
Follow-up	**F/U midazolam**	Date/time of first administration of midazolam + REP (12 hours)	Date/time of first administration of BI 1015550 or 12:00 a m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI**	Date/time of first administration of BI 1015550	Date/time of administration of midazolam (second dose on Visit 3) or date/time of last administration of BI 1015550 + REP (7 days * 24 hours) or 12:00 a m. on day after subject's trial termination date, whichever occurs earlier.
On treatment	**BI + midazolam**	Date/time of administration of midazolam at Day 1, Visit 3	Date/time of administration of midazolam (second dose on Visit 3) + REP (12 h)
On treatment	**BI**	Date/time of administration of midazolam (Visit 3) + REP (12 h)	Date/time of last administration of BI 1015550 + REP (7 days * 24 h) or 12:00 a m. on day after subject's trial termination date, whichever occurs earlier.
Follow-up	**F/U BI**	Date/time of last administration of BI 1015550 + REP (7 days * 24 h)	12:00 a m. on day after trial termination date

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data and vital signs.

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8. will present results for the on-treatment phase only defined in Table 6.1: 1. Screening will not be included in this analysis.

All AEs will be listed, based on the "actual treatment" defined in these tables.

In AE tables in CTR Section 15.3 (but not in displays for ClinicalTrials.gov or EudraCT), the following totals will be provided in addition:

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- "Total midazolam", defined as the total over all on-treatment phases involving midazolam
- "Total BI", defined as the total over all on-treatment phases involving BI
- "Total on-trt", defined as the total over all on-treatment phases involving BI and midazolam

Safety laboratory data, vital signs, and PK parameters will be analysed with clear differentiation between baseline (cf. Section 6.7) and post-baseline. Follow-up laboratory measurements will be listed, but will not be used in descriptive summaries. Of note, no distinction will be made between on- or off-treatment assessments of a post-baseline visit in the by-visit-summaries of vital signs.

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

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 PD (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2) and the DV domain template.

If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain template. If the data show other iPDs, the definition in the DV domain template will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. Which kind of iPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM.

Non-important COVID-19 related PDs will only be listed.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYSED

The treated set (TS) and pharmacokinetic parameter analysis set (PKS) will be used as defined in the **CTP, Section 7.2.1.1**.

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Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	Treated set	PKS
Disposition	X	
iPDs	X	
Primary endpoints		X
Secondary endpoints		X
[redacted]		
[redacted]		[redacted]
Safety parameters	X	
Demographic/baseline characteristics, concomitant diseases, concomitant medications and concomitant procedures	X	
Treatment 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

CTP Section 3.3.4: *If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.*

CTP Section 7.3.1: *It is not planned to impute missing values for safety parameters*.

One exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

CTP Section 7.3.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

Missing data and outliers of PK data are handled according to BI standards (4) and (5).

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[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The last non-missing value determined prior to BI 1015550 administration will be defined as baseline.

[redacted]

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

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7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment, subject number and visit (if visit is applicable in the respective listing). 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 (SDL) 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

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

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 respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

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7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation - Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant to a dose group, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

CTP Section 7.2.5: *Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods*.

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint (cf. Section 5.4.2). Any deviations from complete intake will be addressed in the RPM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

Relative bioavailability of midazolam under steady state exposure of BI 1015550 (Test) compared with midazolam alone (Reference) will be evaluated as defined in the CTP for the primary endpoints specified in Section 5.1.

CTP Section 7.2.2:

The statistical model used for the analysis of the primary endpoints 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 sources of variation: treatment. The effect 'subjects' will be considered as random, whereas the treatment effect will be considered as fixed. The model is described by the following equation:

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y_{km} $= \mu + \tau_k + s_m + e_{km}$, *where*
y_{km} = *logarithm of response measured on subject m receiving treatment k,*
μ = *the overall mean,*
s_m = *the effect associated with the* m^{th} *subject, m=1,2,…,n*
τ_k = *the* k^{th} *treatment effect, k = 1, 2*
e_{km} = *the random error associated with the* m^{th} *subject who received treatment k,*

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) 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.

CTP Section 7.2.1.2 *Descriptive and inferential statistics of PK parameters will be based on the PKS.*

Exclusion of PK parameters

The ADS ADPP 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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEX equal to "Included".

CTP Section 7.2.1.2: *Plasma* [redacted] *concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the* [descriptive summary as well as the] *statistical analyses.*

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEX or 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 only; the value is included for all other analyses. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

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Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

[redacted]

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable.

7.5.2 (Other) Secondary endpoint(s)

7.5.2.1 Secondary endpoint analysis

CTP Section 7.2.3: *The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints* [see Section 7.4.1 and Section 7.4.2]

[redacted]

[redacted]

[redacted]

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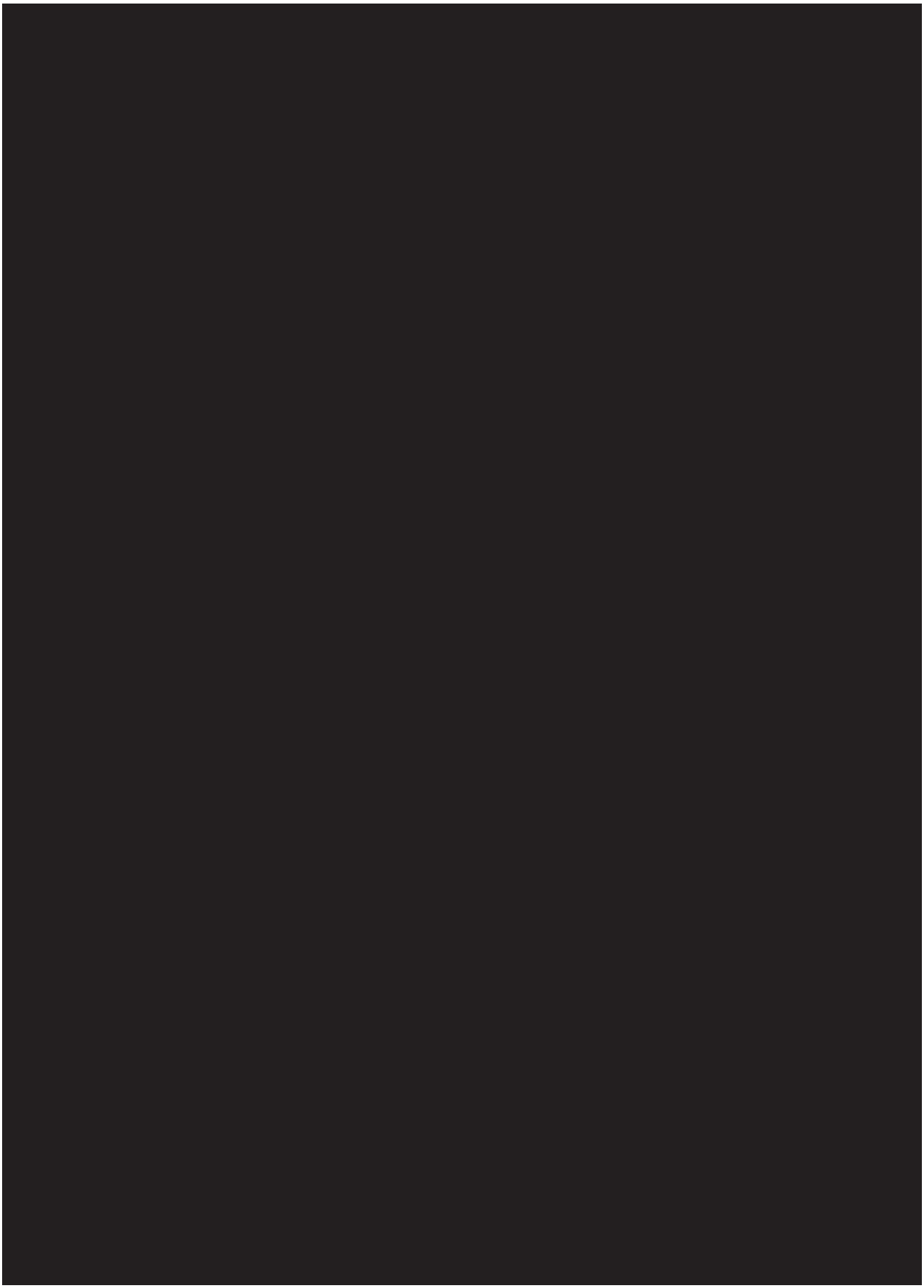

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7.6.3 Safety parameters

Safety endpoints and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

Descriptive statistics of exposure of BI 1015550 and midazolam are planned for this section of the report. These will be based on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS and will be descriptive in nature, **cf. Section 7.2.5 of the CTP**.

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 subjects with AEs and not on the number of AEs.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

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. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of adverse events of special interest (AESI).

CTP Section 5.2.6.1.4: *The following are considered as AESIs:*

- *Potential severe DILI*

  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up 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 in samples drawn within 30 days of each other, or*

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○ *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

• *Vasculitis events*
In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels.

• *Serious infections, opportunistic or mycobacterium tuberculosis infections*
[refer to CTP Section 5.2.6.1.4 for the complete list of terms]

• *New onset of severe depression, defined as HADS subscore >14*
• *New onset of severe anxiety, defined as HADS subscore >14*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not. According to ICH E3 (8), 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).

The frequency of subjects with AEs will be summarised by treatment, primary SOC 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 subjects with SAEs and subjects with AESIs. AEs will also be summarized by maximum intensity.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

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

For disclosure of AE data in the 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 summarized.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (9).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

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Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Unscheduled measurements of laboratory 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. Descriptive statistics 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).

Clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Possibly clinically significant laboratory values will be listed in Section 15.4.1. of the CTR

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate and body temperature) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, 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). If the time of measurement is missing for a scheduled measurement, the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).

If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in ECG 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. No separate listing or analysis of ECG data will be prepared.

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7.8.5 Others

7.8.5.1 Physical examination

Physical findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Body weight

Descriptive statistics of body weight over time and for the difference from baseline (see Section 6.7) will be provided.

7.8.5.3 Assessment of suicidal ideation and behavior (SIB) based on C-SSRS

Suicidality monitoring will be performed as described in Section 5.2.5.1 of the CTP, results will be listed.

Findings may also be reported as AEs as described in the CTP Section 5.2.6.2.3.

7.8.5.4 Assessment of anxiety and depression based on HADS

Results of Hospital Anxiety and Depression Scale (HADS) will be listed only. For details of the questionnaire, cf CTP Section 5.2.5.2.

Findings may also be reported as AEs as described in the CTP Section 5.2.6.1.4 and 5.2.6.2.3.

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8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database at trial initiation.

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9. 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-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; KMED
3	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*KM Asset BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED
5	*KM Asset BI-KMED-TMCP-MAN-0010:* "Description of Analytical Transfer Files, PK/PD Data Files and ADA files", current version; KMED
6	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7	*KM Asset BI-KMED-BDS-HTG-0066:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
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	*KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED

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11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	16 JAN 2023	[redacted]	None	This is the final TSAP