Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44020208-01**
BI Trial No.:	**1402-0019**
Title:	An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects (Revised Protocol including Amendments 1-3 [c41232811-04])
Investigational Product:	BI 1358894
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Date of statistical analysis plan:	19 MAR 2024
Version:	1.0

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http: //glossary

Term	Definition / description
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
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BMI	Body mass index
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
$C_{min,ss}$	Minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
COC	Combined oral contraceptives
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic Coefficient of Variation
DBL	Data base lock
DILI	Drug induced liver injury
DRSP	Drospirenone
EE	Ethinylestradiol
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
Q1	1st quartile
Q3	3rd quartile
REP	Residual effect period

Term	Definition / description
RPM	Report Planning Meeting
RAGe	Report Appendix Generator system
SD	Standard Deviation
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).

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

This trial has been prematurely terminated during the run-in period as Boehringer Ingelheim decided not to continue with trial execution due to strategic reasons. None of the subjects has started with treatment period 1. Therefore, not all analyses as planned in the CTP will be performed. For all study endpoints listings will be provided. Tables will only be provided for adverse events (AEs). For variables regarding disposition, demography, medical history, concomitant medication and non-drug procedures, exposition, protocol deviations, laboratory data, vital signs and C-SSRS suicidality, only listings will be provided and no descriptive analysis will be carried out. An additional analysis set, the Entered set, will be defined as a base for the disposition listings.
The descriptive and model-based analysis of pharmacokinetic endpoints will not be performed as well, in line with the CTP no PK samples were collected in the run-in period.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

This section is not applicable as no plasma concentrations are collected since the trial has been prematurely terminated. The primary endpoints originally defined in the CTP were:

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for ethinylestradiol and drospirenone:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

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

5.2.2 Secondary endpoints

This section is not applicable as no plasma concentrations are collected since the trial has been prematurely terminated. The secondary endpoint originally defined in the CTP was:

- *$C_{min,ss}$ (minimum concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

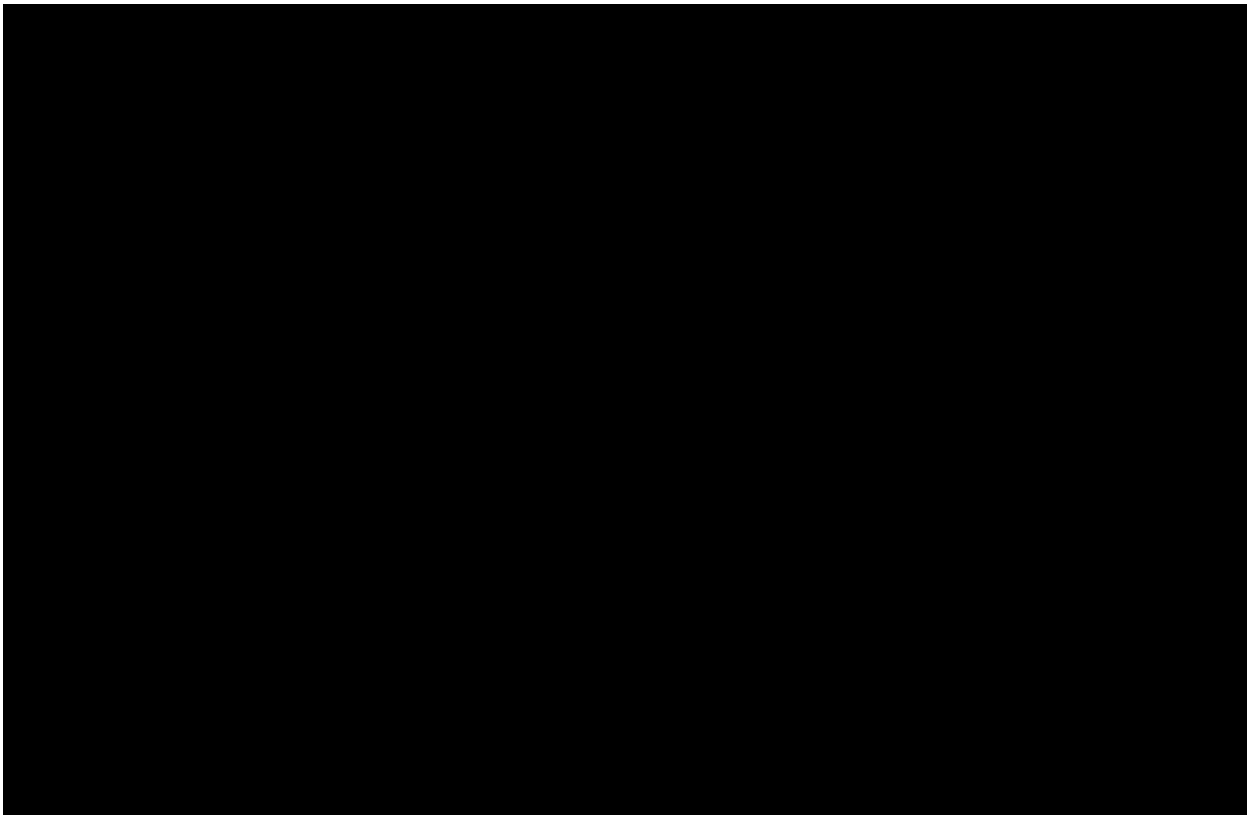
5.3 FURTHER ENDPOINTS

Safety and tolerability endpoints

Section 2.2.2.3 of the CTP:

Safety and tolerability of BI 1358894 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)*
- *Suicidality assessment (C-SSRS)*



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.

This is a Phase I trial in healthy female subjects between 18 and 35 years of age. A total of 32 subjects was planned to be entered to the trial.

Section 3.1 of the CTP:

The trial will be performed as a non-randomised, open-label, two-period, fixed sequence trial with run-in period in healthy female subjects in order to compare the test treatment (T) to the reference treatment (R).

Reference (R): one tablet of Yasmin® q.d. after a continental breakfast on Days 1-21 in Period 1.

Test (T): one tablet of Yasmin® q.d. + one tablet of BI 1358894 25 mg q.d. + two tablets of BI 1358894 50 mg q.d. after a continental breakfast on Days 1-21 in Period 2.

The Reference Treatment will always be followed by the Test Treatment in a fixed sequence. There will be no wash-out period between the treatments.

All subjects will undergo a run-in period that starts between Day -56 and Day -28. In this period, the subjects will take one tablet of Yasmin® daily until Day -8.In the last 7 days of each treatment period (i.e., Day 22 to Day 28) and the run-in period (i.e.Day -7 to Day -1) no treatment will be given in order to induce bleeding.

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

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	Yasmin tablet (30ug Ethinylestradiol + 3mg Drospirenone), qd	COC
T	BI 1358894, 1*25 + 2*50mg tablet + Yasmin tablet (30ug Ethinylestradiol + 3mg Drospirenone), qd	BI+COC

The study was prematurely terminated after the run-in period, with n=28 subject treated in the run-in period. Therefore, all analyses will be performed for the run-in period only.

Section 1.2.3 of the CTP:
Based on an effective half-life of 50-70 hours, the Residual Effect Period (REP) of BI 1358894 is 17 days. This is the period after the last dose during which relevant drug levels and/or pharmacodynamic effects are still likely to be present.
The REP of ethinylestradiol is 5 days based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 20 h, or 4.2 days, rounded to 5 days).
The REP of drospirenone is 9 days based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 40 h, or 8.3 days, rounded up to 9 days).

Overall, the REP of 17 days will be considered for evaluation of adverse events in the trial.

The study was prematurely terminated after run-in period. Therefore, the subjects received combined oral contraceptives (COC), but none of the subjects was treated with BI 1358894. Consequently, the REP of ethinylestradiol and drospirenone was 9 days.

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

- **Screening**
  - Ranging from 0:00h on day of informed consent until time of first administration of COC.
- **On treatment (labelled "COC (run-in)")**
  - Ranging from the time of first administration of COC until last administration of COC plus 9 days (216 h) thereafter OR until trial termination (0:00 h on the day after trial termination), whatever occurs first.
- **Follow-up (labelled "Follow-up (run-in)")**
  - Ranging from the end of REP until trial termination (0:00 h on the day after trial termination).

Section 7.2.5 of the CTP:
Note that AEs occurring after the last per protocol contact but entered before 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 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.
- 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 prior to Data base lock (DBL). 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).

Important protocol deviation (iPD) categories are pre-specified in the iPD specification file (DV domain) (3). IPDs will be identified no later than DBL, 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). Both documents will be stored within the TMF in EDMS.

The iPDs will be summarized and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable.

6.4 SUBJECT SETS ANALYSED

Section 7.2.1.1 of the CTP:

Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.*

The study was prematurely terminated after run-in period. No PK parameter values were assessed. Therefore, the pharmacokinetic parameter analysis set as defined in the CTP is not applicable.

An additional analysis set will be defined for listings of disposition:

- Entered set (ES): The entered set includes all subjects who were entered to the trial.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.3:

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last measurement before first administration of COC.

Section 6.1 of the CTP:
Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the CTP *Flow Chart.*
Study measurements and assessments scheduled to occur 'before' trial medication administration are to be performed and completed within a 2 h-period prior to the trial drug administration.

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

If scheduled in the CTP *Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.*

During the run-in period, administration of Yasmin® tablets must be done by the subjects at home. The subjects are advised to take Yasmin® tablets with a cup of water at the same time each day, approximately between 06.00 and 10.00 am local time.

Adherence to time windows will be checked via the consistency check listings prior to DBL.

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

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.3 and 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

The study was prematurely terminated after run-in period. Therefore, in 15.3 and 15.4 only AEs will be presented. In addition, no descriptive data analysis of PK endpoints and concentrations will be performed.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (6)).

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only listings are planned for this section of the report, based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only listings are planned for this section of the report, based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the version defined in the decision log (4) of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

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

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.

7.3 TREATMENT COMPLIANCE

Only listings are planned for this section of the report, based on the TS.

It is not intended to list the compliance separately.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The study was prematurely terminated after run-in period. No PK parameter values were assessed. Therefore, no primary or secondary endpoint analyses will be performed.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

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

7.6 FURTHER OBJECTIVE ANALYSIS

Pharmacokinetic endpoints

The study was prematurely terminated after run-in period. No PK parameter values were assessed. Therefore, no descriptive analyses of PK endpoints will be performed.

Safety endpoints

For a description of the analysis of safety and tolerability, please refer to Section 7.8.

7.7 EXTENT OF EXPOSURE

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" (7) and "Analysis and Presentation of AE data from clinical trials" (8) 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. 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:

- *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 aminotransferase) and/or ALT (alanine aminotransferase) ≥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*

  - *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 (9), 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 events

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 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 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 descending 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 primary SOC and PT.

7.8.2 Laboratory data

Only listings will be provided for laboratory data and will be based on BI standards as presented in “Handling, Display and Analysis of Laboratory Data” (10). 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.

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 (prior to DBL).

7.8.3 Vital signs

Only listings will be presented for vital signs (blood pressure and pulse rate). The change from baseline will also be displayed.

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

Clinically relevant abnormal findings will be reported as adverse events.
No separate listing or analysis of continuous ECG monitoring will be prepared.

7.9 OTHER ANALYSIS

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.

Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality assessment with the C-SSRS will be assessed as additional safety parameter, measured at screening and at the end of study, due to the premature termination of trial. The results will be listed only. If applicable, the following sentence will be sufficient: No subjects with suicidal ideation, suicidal behaviour, or self-injurious behaviour without suicidal intent.

[redacted]

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Not applicable due to open label fashion of the trial as described in the CTP section 4.1.5.

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-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
8.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of AE data from clinical trials", current version, KMED.
9.	*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.
10.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.

[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**19-Mar-24**	[redacted]	None	This is the final TSAP.