TRIAL STATISTICAL ANALYSIS PLAN

c31568264-01

BI Trial No.:	1399-0013
Title:	Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design. (including Protocol Amendments No.1-2 [c29266057-03])
Investigational Product:	BI 1265162
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	18 MAR 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine transaminase
AST	Aspartate transaminase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DILI	Drug induced liver injury
$fe_{faeces,0\text{-}t2}$	fraction of (C-14)-radioactivity excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{urine,0\text{-}t2}$	fraction of (C-14)-radioactivity excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{vomit,0\text{-}t2}$	fraction of (C-14)-radioactivity excreted in vomit as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
gCV	Geometric coefficient of variation
gMean	Geometric mean
LLT	Lower level term
IQRMP	Integrated Quality and Risk Management Plan
iv	intravenous
[redacted]	[redacted]
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10th percentile

Term	Definition / description
P90	90th percentile
po	Oral
PKS	Pharmacokinetic parameter analysis set
Q1	1st quartile
Q3	3rd quartile
qd	Once daily
RAGe	Report Appendix Generator system
REP	Residual effect period
SD	Standard deviation
SOC	System organ class
TS	Treated set
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

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, randomisation.

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, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), 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

Recruitment stopped after Part 1 due to COVID-19 pandemic. Before the planned re-start of recruitment into Part 2, the study was prematurely stopped as Boehringer Ingelheim decided not to further develop the compound BI 1265162.

Consequently, only a subset of the analyses planned in the CTP will be performed, and only data from Part 1 (intravenous administration of the compound) will be analysed. For all study endpoints, listings will be provided. Tables will be provided for disposition, demography and adverse events (including one of the secondary endpoints) as well as for mass balance and PK endpoints (including the primary and all further secondary endpoints). For variables regarding medical history, concomitant medication and non-drug procedures, exposition, protocol deviations, laboratory data, vital signs and local tolerability, only listings will be provided and no descriptive analysis will be carried out.

In CTP section 7.3 the following was defined: *Important protocol deviation (iPD) categories will be specified in the Integrated Quality and Risk Management Plan, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.*
Due to SOP changes, the iPD categories are no longer available in the IQRM plan but included in an iPD specification file (3). The iPD categories originally defined in IQRM plan were transferred to the iPD specification file. Minor changes regarding the iPD categories were performed only.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following parameters will be determined:

(Part 1 & 2) Mass balance recovery of total (C-14) BI 1265162-radioactivity in urine and faeces (and vomit, if applicable). Amount of radioactivity excreted as a percentage of the administered single intravenous or oral dose of BI 1265162 (C-14) in

- *Urine - $fe_{urine,\ 0\text{-}t2}$ (fraction of (C-14)-radioactivity excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)*
- *Faeces - $fe_{faeces,\ 0\text{-}t2}$ (fraction of (C-14)-radioactivity excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)*
- *Vomit - $fe_{vomit,\ 0\text{-}t2}$ (fraction of (C-14)-radioactivity excreted in vomit as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point) - if feasible and appropriate*

The timeframe for determination of these endpoints depends on the time of discharge of each subject, based on radioactivity excretion, and is predicted to vary between 9 and 38 days after drug administration.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following parameters will be determined:

(Part 1 & 2) Assessment of the pharmacokinetics of a single intravenous or oral dose of BI 1265162 (C-14) by means of the following parameters for total (C-14) BI 1265162-radioactivity, BI 1265162 and metabolite M582 (1) in plasma:

- *$AUC_{0\text{-}tz}$ (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)*

(Part 1 & 2) Evaluation of safety and tolerability of a single intravenous or oral dose of BI 1265162 (C-14) by means of

- *Percentage of subjects with drug related adverse events (AEs) including clinically relevant findings from the physical examination*

5.3.3 Safety endpoints

Section 2.2.2.5 of the CTP:

Further safety and systemic tolerability endpoints:

- *Safety laboratory tests*
- *12-lead electrocardiogram (ECG), and*
- *Vital signs (blood pressure [BP], pulse rate [PR])*
- *Physical examination*

Additionally, local tolerability will be assessed in Part 1 with intravenous administration (see CTP section 2.2.2.4).

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, and a physical examination.*

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 investigational products, assignment of treatment and selection of doses, please see CTP, Section 4.

The study consists of 2 trial parts, Part 1 with intravenous administration and Part 2 with oral administration of the study medication. Each part follows a non-randomized, open-label, single-dose, single arm, mass balance design. It was planned that 7 healthy male subjects will enter each trial part, i.e. 14 subjects in total. Subjects will be treated with a single dose of the study medication as outlined in Table 6.1: 1 below.

Table 6.1: 1 Treatments and labels used in the analysis

Part	Treatment	Short label
1	BI 1265162 (C-14) solution for infusion, 5 mcg/mL, 50mcg, iv, qd	BI-C-14 iv
2	BI 1265162 (C-14) oral solution, 0.25 mg/mL, 5mg, po, qd	BI-C-14 po

The study was prematurely stopped after Part 1 (intravenous administration of BI 1265162 (C-14)). Therefore, all analyses will be performed for the first part only (n=7).

Section 1.2.6 of the CTP: *The Residual Effect Period (REP) of BI 1265162 is 7 days. This is the period after the last dose with measurable drug levels and/ or pharmacodynamics effects is still likely to be present.*

As the REP refers to the non-labelled BI agent but the investigational drug is radiolabelled, the definition of treatment-emergent AEs will be based on discharge from study site (see CTP Section 7.3.4). According to the study protocol, subjects will be discharged from study site at Day 9 at the earliest. In this discontinued trial, all subjects were discharged from study site at Day 9. Hence, the following study phases will be defined for the analysis of AEs:

- **Screening** (ranging from 0:00 h on day of informed consent until date/time of first administration of study medication)
- **On treatment** (ranging from the first time of administration of study medication until 0:00h on the day after discharge from study site at Day 9)
- **Follow-up (F/U)** (ranging from 0:00h on the day after discharge from study site at Day 9 until 0:00 h on the day after trial termination date)

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:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on-treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and Follow-up period will not be included in this analysis. Tables of AEs will present results by the above mentioned on-treatment phase.

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, screening and follow-up periods will 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.

Categories which are considered to be iPDs in this trial were defined in the integrated quality and risk management plan (IQRMP) prior to trial initiation. The list of iPD categories was transferred into the iPD specification file (due to changes in the SOP) (3). Within this transfer some minor adaptations were done to comply with new naming conventions and categorisations.

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).

IPDs will be identified no later than in the Report Planning Meeting. If any iPDs are identified, they are to be summarised into categories and will be captured in the decision log and in the iPD specification file (3). The iPD categories will be updated as needed. The decision on exclusion of subjects from analysis sets will be made after discussion of exceptional cases and implications for analyses.

The iPDs will be listed.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP: *Statistical analyses will be based on the following analysis sets:*

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

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects from the treated set (TS) who provide at least one pharmacokinetic endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of pharmacokinetics or due to pharmacokinetic non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Descriptive analyses of pharmacokinetic parameters will be based on the PKS.*

[…]

Plasma, urine and faeces concentration data and parameters of a subject will be included in the statistical pharmacokinetic analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of pharmacokinetics (to be decided no later than in Report Planning Meeting) or due to pharmacokinetic 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 deviations 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 and urine concentrations and/ or parameters of a subject will be considered as non-evaluable, if for example

- *Missing samples/ concentration data at important phases of pharmacokinetic disposition curve*

Plasma/urine 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.

The descriptive analysis of PK concentrations and endpoints will be based on the ADS ADPC as described in Section 7.

Table 6.3: 1 Subject sets analysed

	Subject set	
Endpoint/data description	TS	PKS
Primary endpoints		X
Safety parameters (including secondary safety endpoint)	X	
Secondary [redacted] endpoints		X
Demographic/baseline parameters	X	
Important protocol deviations	X	
Disposition	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.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035 (4)).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0012 (5) and BI-KMED-TMCP-MAN-0014 (6).

Missing baseline laboratory values will be imputed by the respective screening values.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before trial medication administration.

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.*

Trial measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 minutes for the first 4 hours after drug administration and ± 45 minutes thereafter.

According to the flow chart of the CTP, after day 9 the planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate.
The procedures are to be performed within a time window of +/- 4 hours to the planned 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

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.

Descriptive data analysis of PK endpoints and concentrations (including mass balance endpoints) will be performed by the department [redacted] at [redacted] and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (7)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (8).

The individual values of all subjects will be listed, sorted by treatment group, subject number, visit and actual treatment (if appropriate).
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, 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:

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 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.

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC and ACEXCO indicating inclusion/exclusion (ACEXC) 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 [redacted]) 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” (6) and *BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files” (9).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics for demographics are planned for this section of the report, based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of 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 should 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 trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/ or urinary excretion 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/DBLM (see Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

Section 7.3.1 of the CTP: *All parameters will be calculated and analysed descriptively.*

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoints

Section 7.3.2 of the CTP: *Secondary endpoints (...) will be assessed statistically using the same methods as described for the primary endpoints.*

7.7 EXTENT OF EXPOSURE

The date and time of drug administration will be listed for each patient.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated patients 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 with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" [BI-KMED-BDS-HTG-0041] (10) and [BI-KMED-BDS-HTG-0066] (11). All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

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:*

- *A confirmed elevation of serum potassium > upper limit of normal (ULN) in non-haemolysed blood.*
- *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 eCD. 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 (12), 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.

An overall summary of AEs (including number of patients with any AE, drug related AEs, AESIs, serious AEs and drug related serious AEs) will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and PT. The MedDRA version number will be displayed as a footnote in the respective outputs. 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 SOC and PTs will be sorted by total frequency (within SOC).

In addition, frequencies of patients with non-serious AEs that had an incidence of > 5% in at least one study part 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] (13).

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).

7.8.3 Vital signs

For vital signs (blood pressure and pulse rate), listings including change from baseline will be presented by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

Clinically relevant findings in vital signs will be reported as AEs.

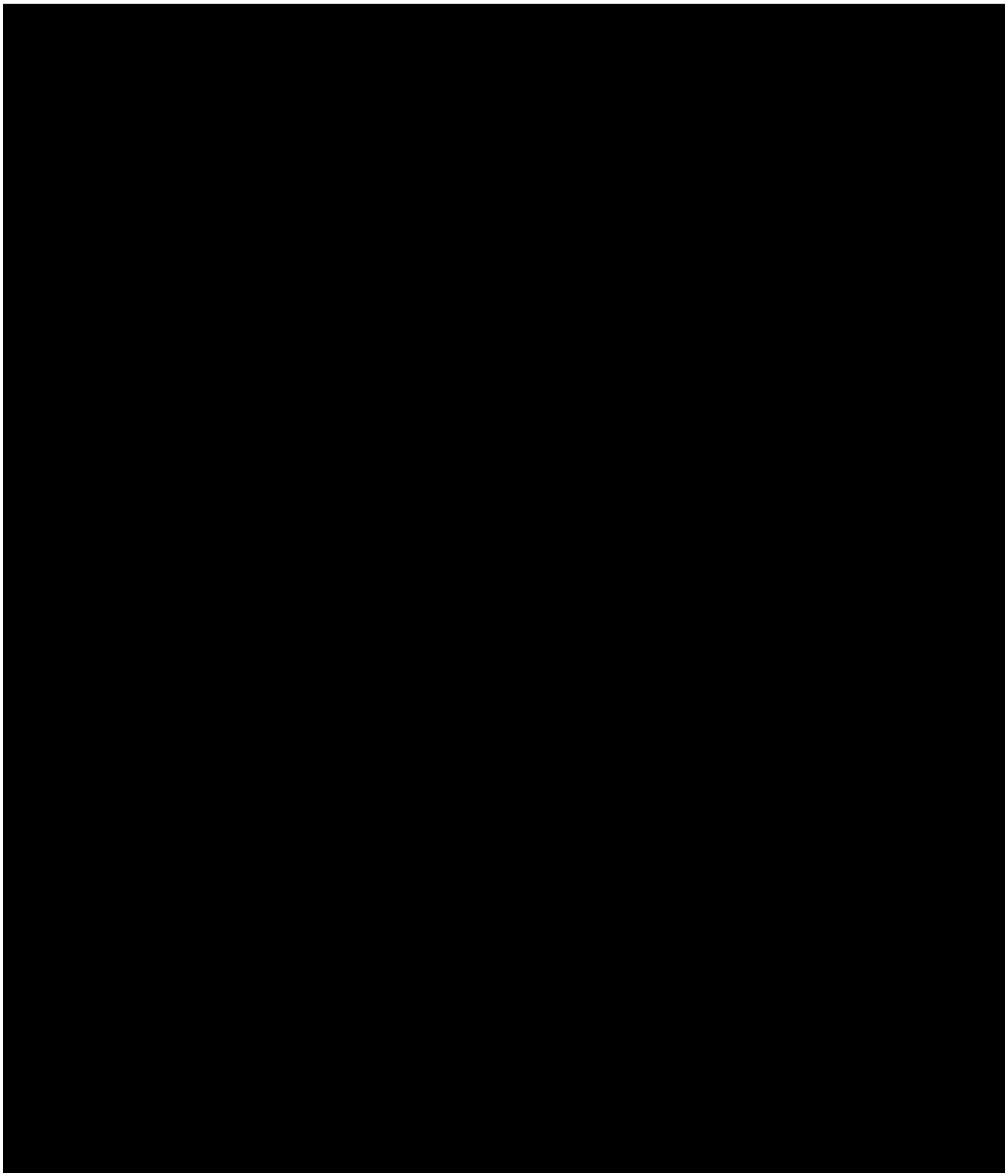
7.8.4 ECG

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

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 study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

Local tolerability
Listings of defined local adverse events will be presented for Part 1.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**18-MAR-2021**	[redacted]	None	This is the final TSAP