TRIAL STATISTICAL ANALYSIS PLAN

c31207422-01

BI Trial No.:	1371-0008
Title:	Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma (singleblind, randomised, placebo-controlled, parallel group design). (including Protocol Amendments No.1-5 [c21616656-06])
Investigational Product:	BI 894416
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	10 FEB 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
website: glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
[redacted]	[redacted]
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BLQ	Below limit of quantification
BMI	Body mass index
BMS	Biomarker Set
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CSD	Company standard displays
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
ECGPCS	ECG Pharmacokinetic Concentration Set
FEF 25-75	Forced Expiratory Flow at 25-75%
[redacted]	[redacted]
FEV1	Forced Expiratory Volume (Pressure) in 1 second
[redacted]	[redacted]
[redacted]	[redacted]
FVC	Forced (expiratory) Vital Capacity
gCV	Geometric Coefficient of Variation

Term	Definition / description
gMean	Geometric Mean
LI	Linearity Index
LLOQ	Lower limit of quantification
LLT	Lower Level Term
IQRMP	Integrated Quality and Risk Management Plan
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PEF	Peak Expiratory Flow
PKS	PK parameter analysis set
Q1	1^{st} quartile
Q3	3^{rd} quartile
RAGe	Report Appendix Generator system
RV	Residual Volume
SD	Standard Deviation
sd	Single dose
SVC	Slow Vital Capacity
[redacted]	[redacted]
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 endpoints 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).

[redacted]

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

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

In addition, an enrolled set (ES) and an ECG pharmacokinetic concentration set (ECGPCS) have been introduced. The ECGPCS is used for the ECG exposure response analysis.

Additionally, the linearity index will be determined in the MRD part (see section 7.6 for details).

In CTP Section 7.5.1 it is stated that it is not planned to impute missing values for safety parameters. Nevertheless, according to BI standards, missing or incomplete AE dates as well as missing baseline laboratory parameters will be imputed. Standards for ECG endpoint calculations are also applied (refer to section 6.6 for details).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Section 2.1.2 of the CTP: *Primary endpoint to assess safety and tolerability of BI 894416 is the percentage of patients with drug-related adverse events.*

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

Section 2.1.3 of the CTP:

Efficacy Endpoints: (for lung function and small airway assessment) from MRD part:

- Airway resistence (*Raw*) *after 7 days of* t.i.d. *treatment*

Pharmacokinetic Endpoints for BI 894416:

SRD part:

- $AUC_{0-\infty}$ *(area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*
- C_{max} *(maximum measured concentration of the analyte in plasma)*

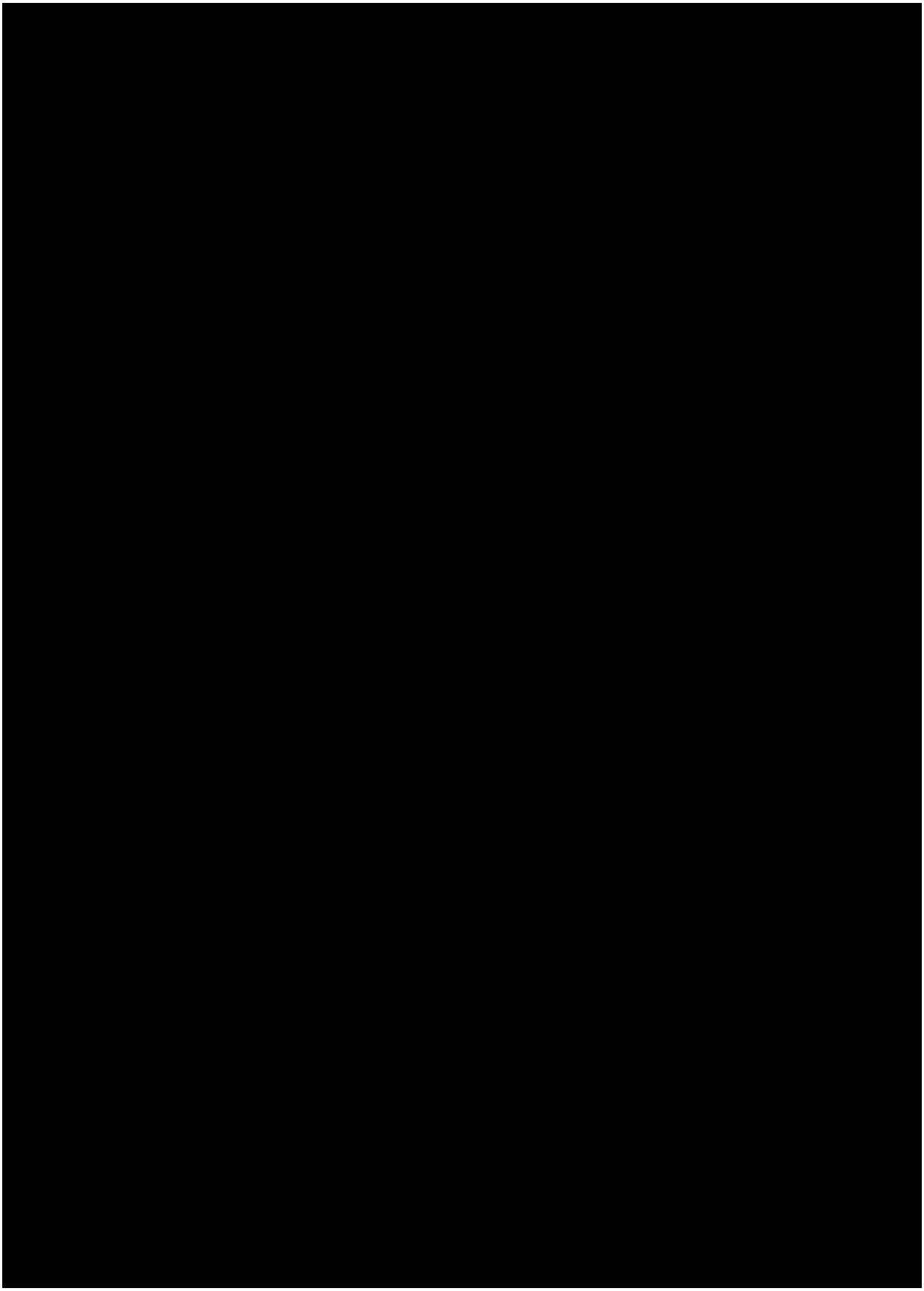
MRD part:

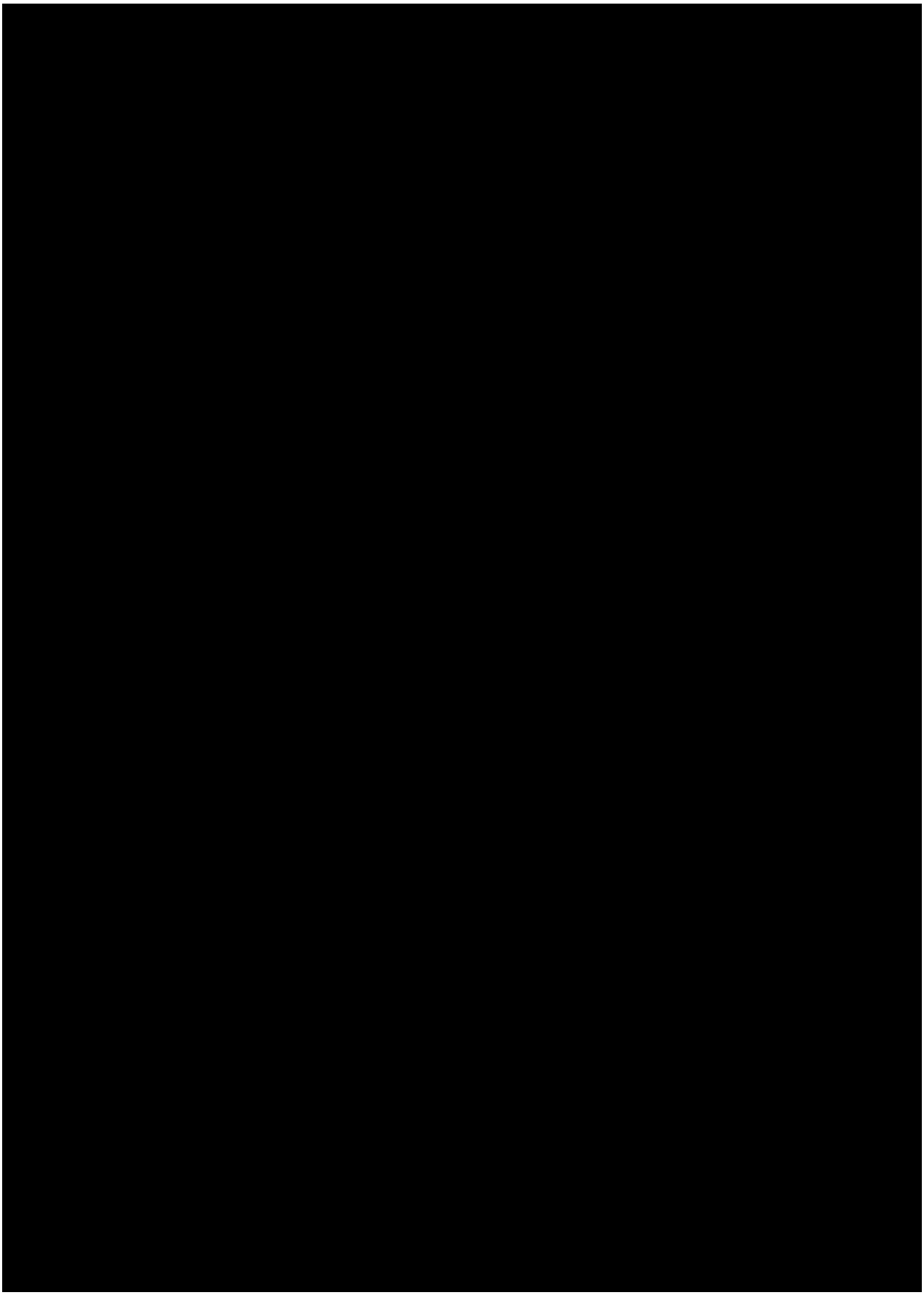
After the first dose:

- AUC_{0-8} *(area under the concentration-time curve of the analyte in plasma over the time interval 0 to 8h)*
- C_{max} *(maximum measured concentration of the analyte in plasma)*

After the last dose:

- $AUC_{\tau,ss}$ *(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)*





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatments and selection of doses, please see CTP, Section 4.

The study will be performed as randomised, placebo-controlled, single-blind, parallel group study with two parts (SRD part and MRD part) in patients with mild asthma.

If not otherwise stated, the two trial parts (SRD and MRD) will be evaluated separately.

It is planned that 50 patients will be treated with a single dose of BI 894416 or Placebo in the SRD part of the trial and 50 patients will be treated up to 7 days with tid dosing and 2 days with qd dosing of BI 894416 or Placebo in the MRD part of the trial. Both trial parts consist of 5 dose groups comprising a planned number of 10 patients per group (8 on active treatment, 2 on Placebo).

Table 6.1: 1 Labels for treatments for use in the CTR – SRD part

Dose group	Sort order	Treatment		Short label
	1	P[+]	Matching Placebo tablet q.d.	Placebo sd
1	2	A	75 mg BI 894416 tablet q.d.	BI 75mg sd
2	3	B	125 mg BI 894416 tablet q.d.	BI 125mg sd
5	4	K	170 mg BI 894416 tablet q.d.	BI 170mg sd
3	*5*	*C*	*175 mg BI 894416 tablet q.d.*	*BI 175mg sd*
4	*6*	*D**	*225 mg BI 894416 tablet q.d.*	*BI 225mg sd*

*The dosage may be reduced to a dose >175 mg and <225 mg in case that preliminary PK analysis predict that a dose lower than 225 mg is needed to not exceed the limits of exposure
[+]The placebo group in the safety evaluation will consist of all patients treated with placebo, regardless of the dose group in which they were treated.

The SRD part was stopped after dose group BI 170mg single dose (sd) as exposure limits outlined in the CTP were reached. Dose groups BI 175mg sd and BI 225mg sd were not performed.

Table 6.1: 2 Labels for treatments for use in the CTR – MRD part

Dose group	Sort order	Treatment		Short label
	1	R+	Matching Placebo tablet t.i.d.	Placebo tid
1	2	F	10 mg BI 894416 tablet t.i.d.	BI 10mg tid
2	3	G	25 mg BI 894416 tablet t.i.d.	BI 25mg tid
3	4	H	50 mg BI 894416 tablet t.i.d.	BI 50mg tid
5	5	L	60 mg BI 894416 tablet t.i.d.	BI 60mg tid
4	*6*	*I**	*70 mg BI 894416 tablet t.i.d.*	*BI 70mg tid*

+The placebo group in the safety evaluation will consist of all patients treated with placebo, regardless of the dose group in which they were treated.
*The dosage may be reduced to a dose >50 and <70 mg tid in case that preliminary PK analysis predict that a dose lower than 70 mg tid is needed to not exceed the limits of exposure (CTP Section 4.1.2) or to not exceed the exposure covered by the SRD part of the trial with predicted gMean $C_{max,ss}$ and $AUC_{0-24,ss}$ values.

With CTP version 5.0, an interim dose group (dose group 5) of 60 mg tid is inserted between dose group 3 and 4. Dose group BI 70mg tid was not performed.

Section 1.2.2 of the CTP: *…the individual patient's end of trial is 14 days following last dosing with BI 894416 or placebo at the earliest.*
All AEs reported between administration of BI 894416 and the individual patient's end of trial will be counted as on-treatment AEs.

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until first administration time of study drug (BI 894416 or Placebo))
- **On treatment**
  - **BI/Placebo treatment** (separately for each treatment, ranging from the time of first administration of BI 894416/Placebo until 0:00h (midnight) on the day after trial completion date)

The following AE displays will be provided in the report:

Section 15.3 (separately for SRD and MRD part) and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only but combined for SRD and MRD part) 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 will not be included in this analysis.
The following totals will be provided in section 15.3 in addition:

- a total over all on-treatment phases ("**Total**")
- a total over all on-treatment phases involving BI 894416 ("**BI Total**")

The following totals will be provided in section 16.1.13.1.8 in addition:

- a total over all on-treatment phases ("**Total**")
- a total over all on-treatment phases ("**Total - SRD part**")
- a total over all on-treatment phases ("**Total - MRD part**")
- a total over all on-treatment phases involving BI 894416 ("**BI Total**")
- a total over all on-treatment phases involving BI 894416 ("**BI Total – SRD part**")
- a total over all on-treatment phases involving BI 894416 ("**BI Total – MRD part**")

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays the screening period will be included and no totals will be provided.

Tables of vital signs and laboratory values will present results by the above mentioned on-treatment phase.

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 patients.

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

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 and database lock meeting (RPM/DBLM). 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).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes and decision log as well as an accompanying Excel spreadsheet (3). Categories which are considered to be iPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other iPDs, the definition in the IQRMP will be supplemented accordingly by the time of the Report Planning Meeting.

The iPDs will be summarised and listed.

Table 6.2: 1 below specifies which kind of iPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of patients from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
iPD B1	Informed consent not available/not done	All
iPD B2	Informed consent too late	None
iPD B3	Wrong informed consent form signed	All
iPD A	In-/Exclusion Criteria Not Met	PKS, BMS, ECGPCS
iPD C1	Incorrect trial medication taken	PKS, BMS, ECGPCS
iPD C2	Randomisation not followed	PKS, BMS, ECGPCS
iPD C3	Wrong dosage schedule	PKS, BMS, ECGPCS
iPD C4	Incorrect intake of trial medication	PKS, BMS, ECGPCS
iPD D1	Prohibited medication use	PKS, BMS, ECGPCS
iPD D2	Improper washout of concomitant medication	PKS, BMS, ECGPCS
iPD E1	Certain violations of procedures used to measure primary or secondary data	PKS, BMS, ECGPCS
iPD F1	Certain violations of time schedule used to measure primary or secondary data	PKS, BMS, ECGPCS
iPD G1	PDs affecting efficacy, safety and rights	PKS, BMS, ECGPCS
iPD G2	Certain deviations of time schedule with respect to nutrition	PKS, BMS, ECGPCS
iPD Q1	Missed examination	PKS, BMS, ECGPCS
iPD Q2	Missed visit	PKS, BMS, ECGPCS
iPD Q3	Drug shipment	PKS, BMS, ECGPCS

6.3 SUBJECT SETS ANALYSED

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

- Enrolled Set (ES):
  This subject set includes all patients who were enrolled in the study regardless of whether they were treated or not. The ES is used for the disposition table / listing.

- *Treated set (TS): The treated set includes all patients who were randomised and treated with at least one dose of study drug. The treatment assignment will be*

determined based on the first treatment the patients received. The treated set will be used for safety analyses.

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

- [redacted]

- ECG Pharmacokinetic Concentration Set (ECGPCS):
  This subject set includes all patients from the TS who provide at least one pair of a valid drug plasma concentration of BI 894416 and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analyses. For placebo patients, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the RPM before data base lock.
  All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS.

Pharmacokinetics

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

Relevant protocol deviations may be

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

- *Incorrect dose of trial medication taken*

- *Use of restricted medications*

Plasma and urine concentrations and/or parameters of a patient will be considered as nonevaluable, if for example

- *The patient experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the patients experiencing emesis),*

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

Plasma/urine concentration data and parameters of a patient which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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

[redacted]

Table 6.3: 1 Subject sets analysed

	Subject set				
Class of endpoint	ES	TS	PKS	BMS	ECGPCS
Analysis of PK endpoints			X		
[redacted]				[redacted]	
ECG endpoints and plasma concentrations used in exposure-response analysis					X
Safety parameters		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/[redacted] data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

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

Unscheduled measurements of laboratory data or vital signs 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. Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles. If all cardiac cycles of an ECG are missing, no imputation will be done.

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on-treatment QTc/QT intervals into “no new onset” / “new onset” categories, a missing value is obtained only in case that
(i) all on-treatment values are missing and
(ii) the baseline value is less than or equal to 500 msec, or missing.
If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as ‘no new onset’. If baseline is missing and the maximum on-treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a ‘new onset’ in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as ‘no new onset’. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

For placebo patients the missing plasma concentration values will be replaced by 0 for the exposure response analysis. For patients on active drug, missing plasma concentration values with ‘BLQ’ in the comment field will not be replaced.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of BI 894416 (SRD part: value at V3, ptm -3:00, MRD part: value at V3, ptms -17:00, -1:00, -0.05).

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 Charts.*

If Screening Visit is performed on Day -3 (within 76 hours) prior to administration of trial drug, the ambulatory Visit 2 can be omitted.

Study 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 (including blank values for PK and biomarkers).

In the SRD part, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on Day 1 and ± 90 min on Day 2.

The acceptable deviation from the scheduled time for neurological tests in the SRD part is ± 45 min on Day 1 and ± 90 min on Day 2.

Starting from 48 h post administration a time window of ±120 min will be allowed for all study activities (incl. PK and biomarker sampling) in the SRD part.

In the MRD part, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration on Day 1

and Day 9, ± 30 min thereafter on Day 1 and Day 9, ± 90 min on Day 2 and on Day 10 and ± 120 min from Day 11 onwards.

The acceptable deviation from the scheduled time for neurological tests in MRD part is ± 4 min on Day 1, and ± 90 min on Day 2.

From Day 3 until Day 8 and from 48 h post last administration on Day 9 a time window of ± 120 min will be allowed for all study activities (incl. PK and biomarker sampling) in the MRD part, except PK samples taken pre dose on Days 5, 7 and 8. Pre dose PK samples are taken within a time window of 15 min prior to drug administration.

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

If Visit 2 is omitted because Visit 1 was performed within 76 hours prior to the trial drug administration, the Visit 1 ECG data were transferred as Visit 2 data.

There will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in the Table 6.7: 1 and the Table 6.7:2 below:

Table 6.7: 1 Time schedule of 12-lead ECG recordings – SRD part

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -3		Screening	NA
2	-3 to -1	-72:00	Pre-treatment	All three ECGs of the triplicate
		-71:45	Pre-treatment	All three ECGs of the triplicate
		-71:30 (separated by at least 15minutes)	Pre-treatment	All three ECGs of the triplicate
3	1	-3:00	Baseline	All three ECGs of the triplicate
		0:30	On treatment	first single ECG of the triplicate
		1:00	On treatment	first single ECG of the triplicate
		1:30	On treatment	first single ECG of the triplicate
		2:00	On treatment	first single ECG of the triplicate
		2:30	On treatment	first single ECG of the triplicate
		3:00	On treatment	first single ECG of the triplicate
		4:00	On treatment	first single ECG of the triplicate
		6:00	On treatment	first single ECG of the triplicate
		8:00	On treatment	first single ECG of the triplicate
		12:00	On treatment	first single ECG of the triplicate
	2	24:00	On treatment	first single ECG of the triplicate
		34:00	On treatment	NA
4	3	48:00	On treatment	NA
5	4	72:00	On treatment	NA
8	15-17		End of trial examination	NA

At Visit 1 single ECGs will be recorded.
At Visit 2 and Visit 3 (up to planned time 24:00h) triplicate ECGs will be recorded. For the four pre-dose triplicate ECGs all three single ECGs will be evaluated. For the other triplicate ECGs only the first single ECG will be evaluated.
At Visit 3 (planned time 34:00h) and Visits 4-8, single ECGs will be recorded.

Table 6.7: 2 Time schedule of 12-lead ECG recordings – MRD part

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -3		Screening	NA
3	-1	-17:00	Pre-treatment	All three ECGs of the triplicate
		-16:45	Pre-treatment	All three ECGs of the triplicate
		-16:30 (separated by at least 15minutes)	Pre-treatment	All three ECGs of the triplicate
		-1:00	Baseline	All three ECGs of the triplicate
3	1	0:30	On treatment	first single ECG of the triplicate
		1:00	On treatment	first single ECG of the triplicate
		1:30	On treatment	first single ECG of the triplicate
		2:00	On treatment	first single ECG of the triplicate
		2:30	On treatment	first single ECG of the triplicate
		3:00	On treatment	first single ECG of the triplicate
		4:00	On treatment	first single ECG of the triplicate
		6:00	On treatment	first single ECG of the triplicate
		8:00	On treatment	first single ECG of the triplicate
		12:00	On treatment	first single ECG of the triplicate
	2	24:00	On treatment	first single ECG of the triplicate
	2	34:00	On treatment	NA
	3	47:00, 56:00, 58:00	On-treatment	NA
	4	70:30, 80:00	On-treatment	NA
	5	104:00	On-treatment	NA
	6	128:00	On treatment	NA
	7	152:00	On treatment	NA
	8	176:00	On treatment	NA
	9	191:55	On treatment	first single ECG of the triplicate
		192:30	On treatment	first single ECG of the triplicate
		193:00	On treatment	first single ECG of the triplicate
		193:30	On treatment	first single ECG of the triplicate
		194:00	On treatment	first single ECG of the triplicate
		194:30	On treatment	first single ECG of the triplicate
		195:00	On treatment	first single ECG of the triplicate
		196:00	On treatment	first single ECG of the triplicate
		198:00	On treatment	first single ECG of the triplicate

Table 6.7: 2 Time schedule of 12-lead ECG recordings – MRD part - continued

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
		200:00	On treatment	first single ECG of the triplicate
		204:00	On treatment	first single ECG of the triplicate
	10	216:00	On treatment	first single ECG of the triplicate
4	11	240:00	On treatment	NA
5	12	264:00	On treatment	NA
6	13	288:00	On treatment	NA
7	16	-	On treatment	NA
8	23-30	-	On treatment	NA

For the four pre-dose triplicate ECGs all three single ECGs will be evaluated. For the other triplicate ECGs only the first single ECG will be evaluated.

Section 5.2.5.1 of the CTP: *Central ECG lab evaluation will be performed (during the study and/or after the study) for the first of three replicate ECGs per time point. For baseline, all three ECGs of the triplicate ECG on Day 1 pre-dose will be evaluated. For the three triplicate ECGs on Day -3 to -1 all ECGs will be evaluated. This will include the determination of cardiac QRSaxis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor.*

For the exposure response analyses, pairs of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g. HR change from baseline and the plasma concentration measured at planned time 1:00 will build one pair.
Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded from the analysis will be decided no later than at the RPM. This critical time deviation depends on the PK properties. When plasma concentrations are expected to change only little around a given time point, the acceptable time deviation between ECG recording and PK blood sampling may be bigger.

7. PLANNED ANALYSIS

In general, the two trial parts (SRD and MRD) will be evaluated separately if not stated otherwise.

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

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

Descriptive data analysis of PK parameters and concentrations will be performed by the department [redacted] and will be presented in Section 15.6 of the CTR.

Descriptive data analysis of gene expression data will also be performed by the department [redacted]

Descriptive data analysis of the efficacy endpoints will be performed by [redacted] and will be presented in Section 15.2 of the CTR and in Appendix 16.2.6.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations (7).

The individual values of all patients will be listed, sorted by dose group, patient number, and visit.
The listings will be included in Appendix 16.2 of the CTR.

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

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

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

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 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 (%) for each dose group. Percentages will be rounded to one decimal place and will be based on all patients in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

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

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables APEXC and APEXCO 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 or 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 (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (11).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The data will be summarised by dose group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded using the 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. Patients 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/biomarker analysis will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured sample concentrations 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 (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 894416.

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.

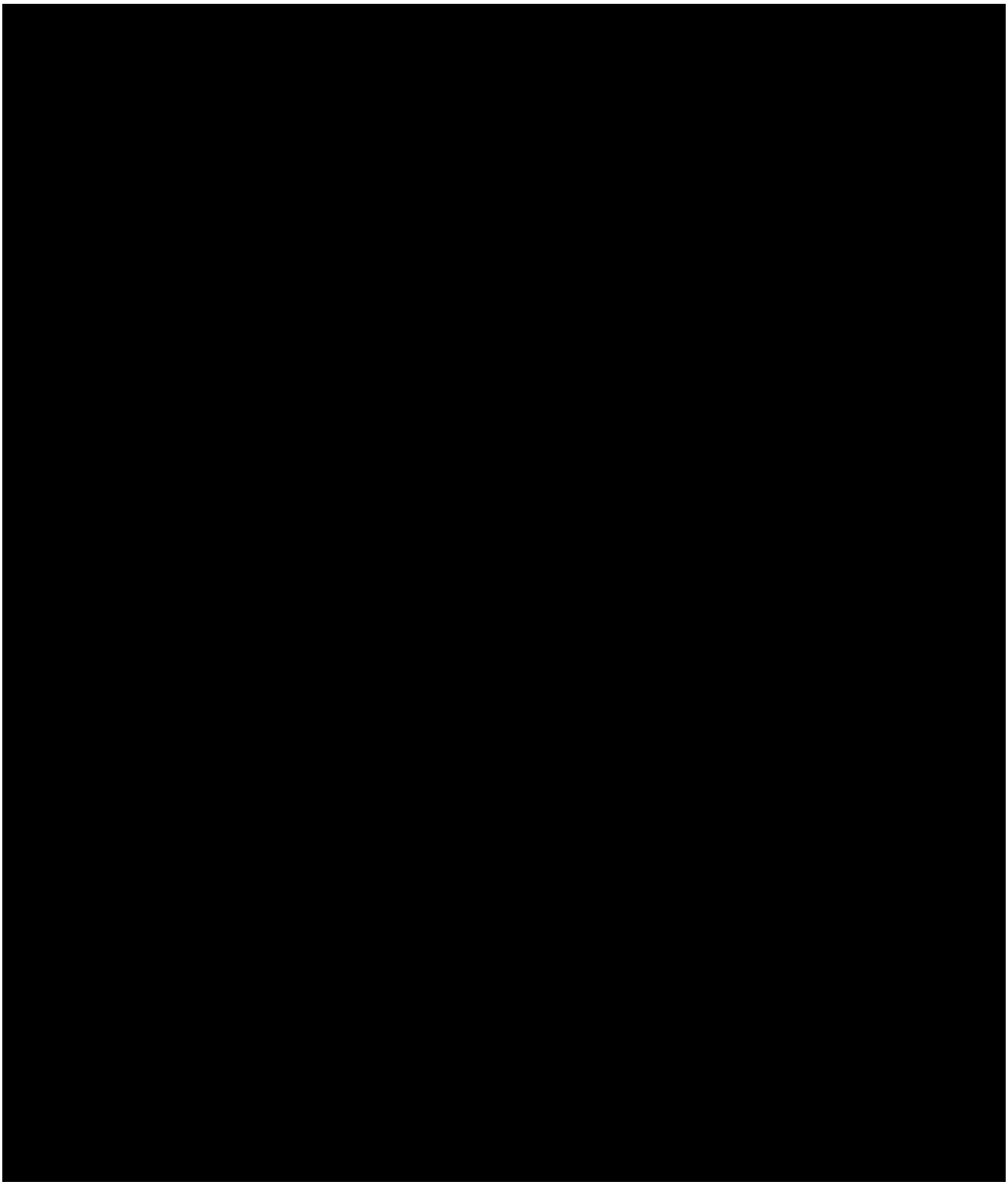
7.5.2 Secondary endpoints

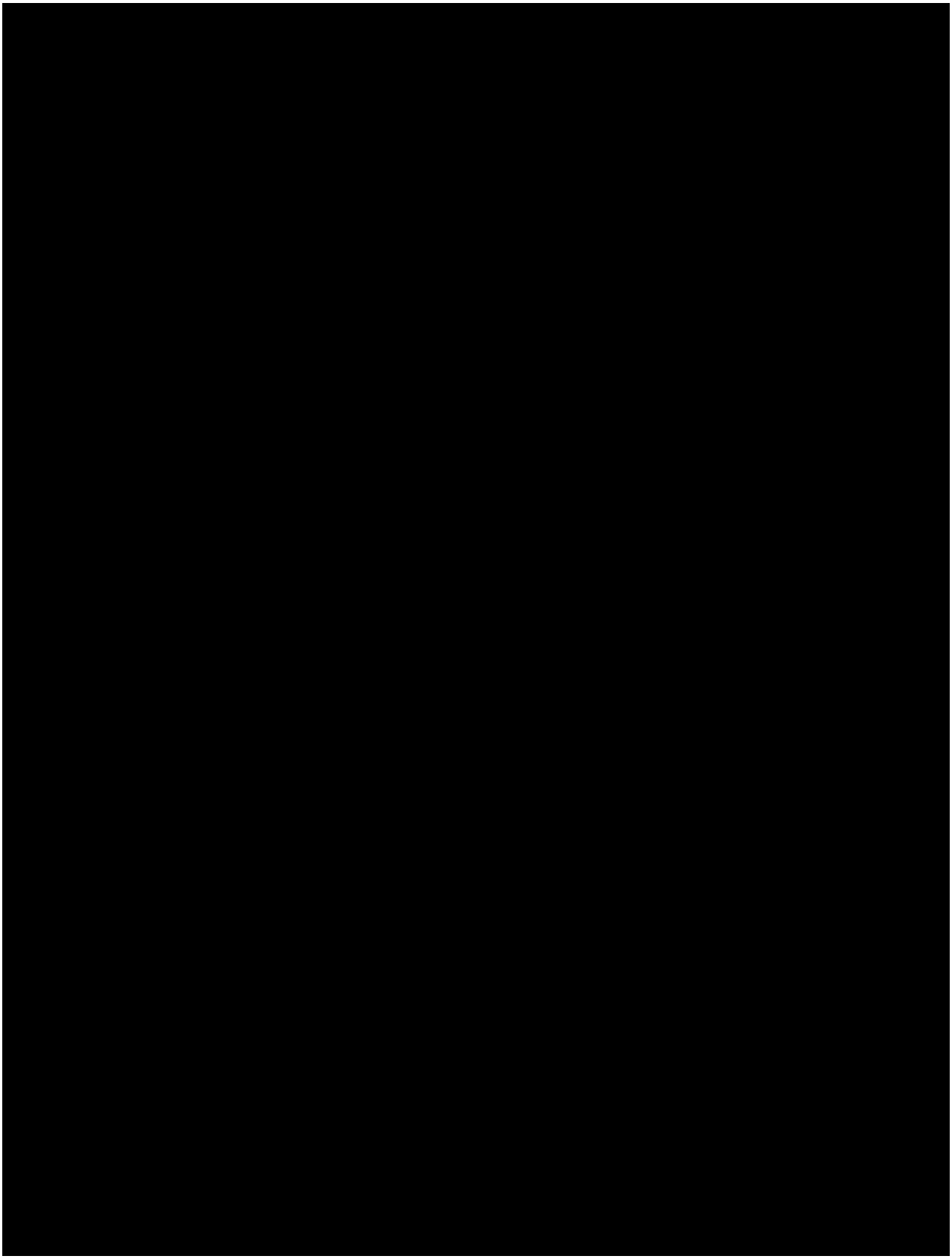
Primary analyses:
Section 7.3.2 of the CTP:
*The secondary efficacy endpoints (*refer to Section 5.2.2 and Section 5.4*) will be analysed descriptively based on the TS.*
Boxplots by time-point and treatment group will be provided (for absolute values and changes from baseline).

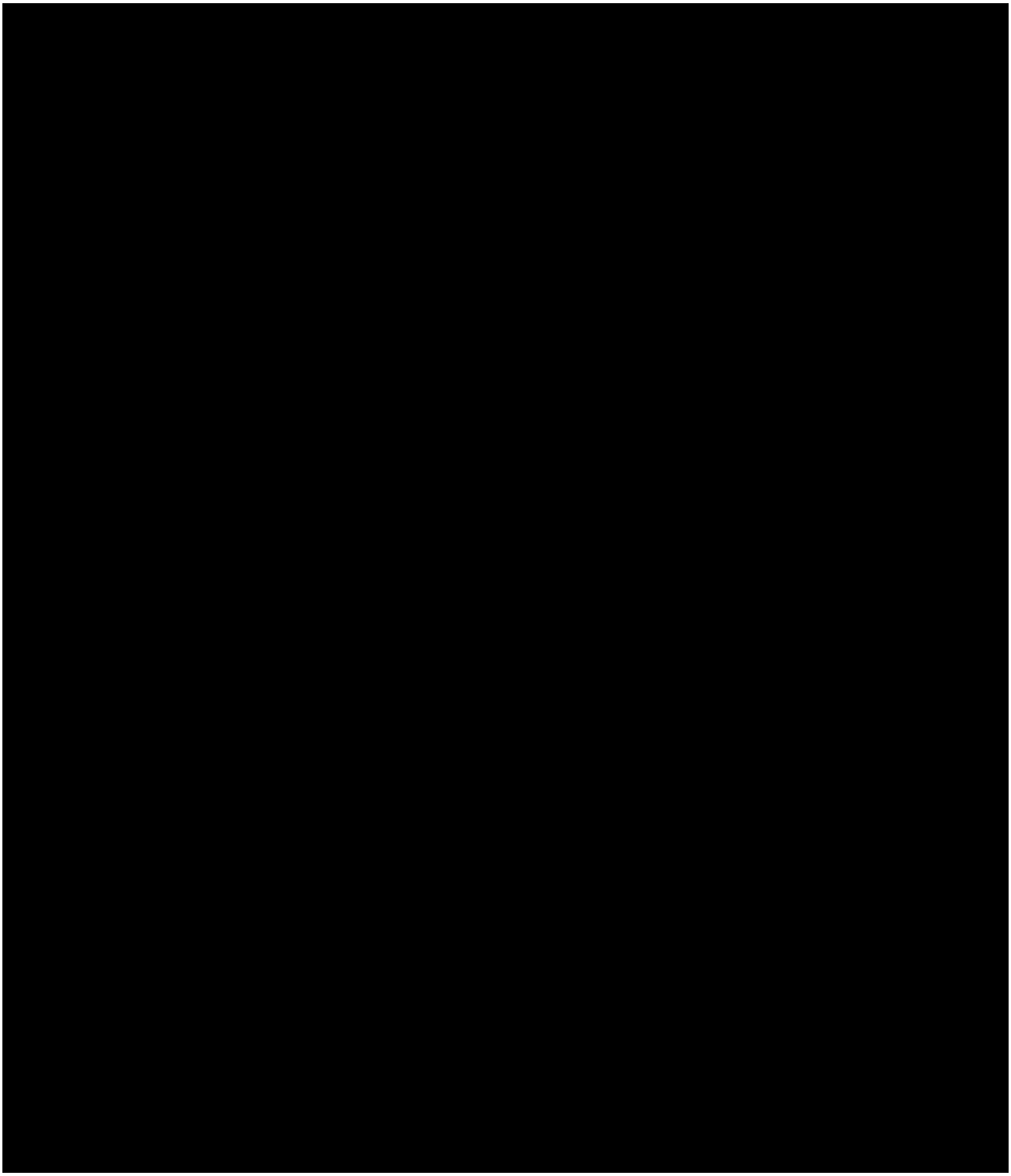
Airway resistance includes 'Total airways resistance', 'Total specific airways resistance', 'Effective airway resistance' and 'Effective specific airway resistance'.

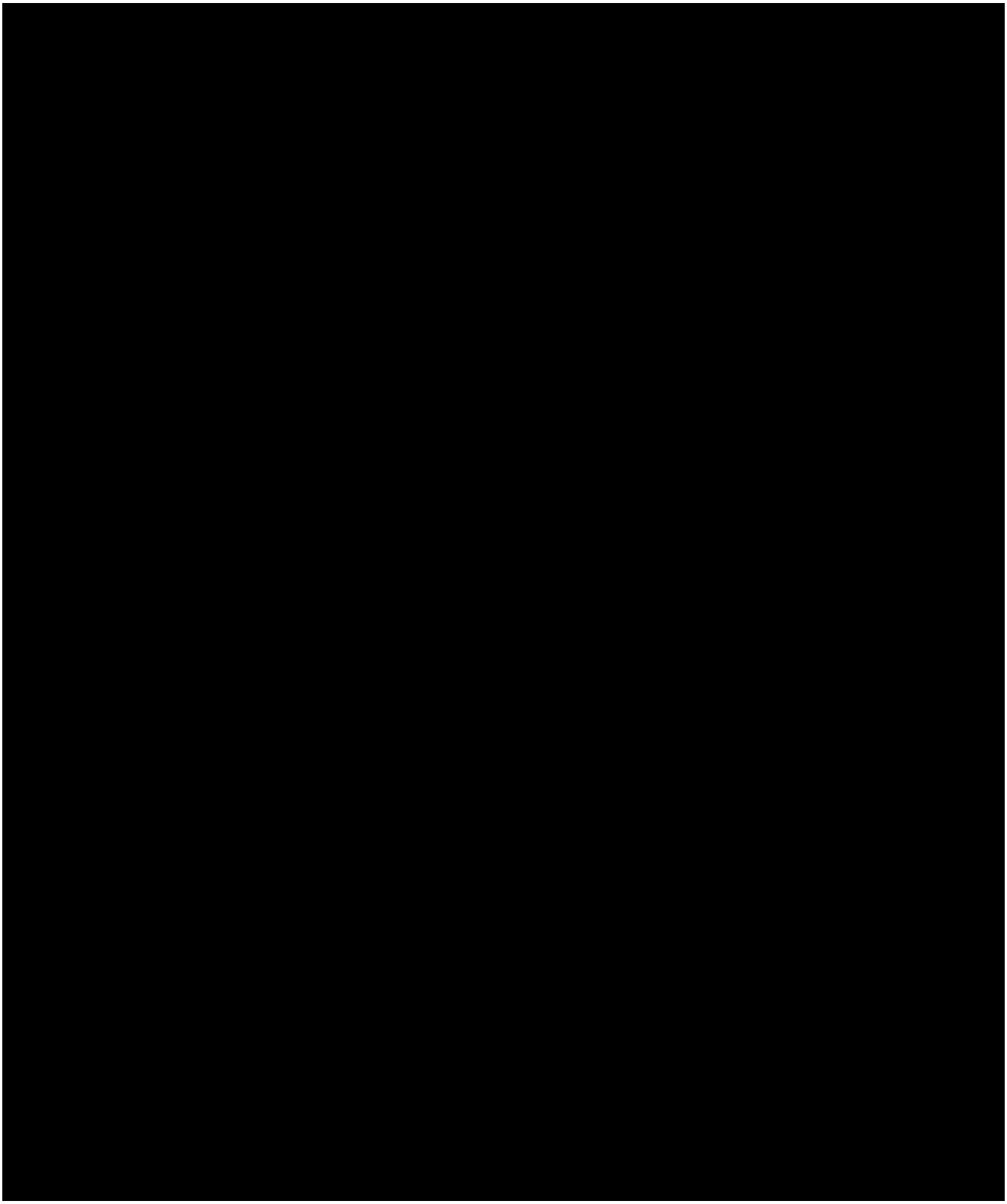
*The secondary PK endpoints (*refer to Section 5.2.2*) will be analysed descriptively based on the PKS. Analyses will be performed for the parent drug.*

Further exploratory analyses:









7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by dose group.

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] (8).

The standard AE analyses will be based on the number of patients 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 and Table 6.1: 2.

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

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

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *an elevation of AST (Aspartate 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*
  - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

  These lab findings constitute a hepatic injury alert and the patients 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 event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

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 patients with AEs will be summarized by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with serious AEs, for patients with drug-related AEs, for patients with drug related serious adverse events and for patients 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 frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

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

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

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (10). In addition to the standard descriptive tables, line graphs (mean values and standard deviation over time) of absolute values, changes from baseline and percent changes from baseline will be provided for the normalised laboratory parameters.

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 possible clinically significant will be flagged in the data listings.

Clinically relevant findings in laboratory data will be reported as adverse events 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 significant abnormal or not (at the RPM/DBLM at the latest).

Descriptive statistics of laboratory data including change from baseline will be calculated by visit based on the worst value of the patient at that visit.

7.8.3 Vital signs

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

7.8.4 ECG

Continuous ECG monitoring (SRD part only)

Clinically relevant abnormal findings will be reported as adverse events.

No separate listing or analysis of continuous ECG monitoring will be prepared.

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as adverse events.

No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

The descriptive evaluations of ECG data will be based on the TS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR only listings will be provided. Occurrences of notable findings will be flagged.

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all patients with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time of QTcF, QT, HR, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations will be evaluated using a random coefficient model. For patients in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included. For the handling of missing values, see Section 6.6.

The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo patients will be included in the analysis, setting their plasma concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression is provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF). These figures will be generated for each patient (presented in Statistical Appendix of the CTR), as well as for means per active treatment (presented in the End-of-Text part of the CTR).

The relationship between BI 894416 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 894416 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of the C_{max} (SRD part) / $C_{max,ss}$ (MRD part) for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et al. (12) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as

continuous covariates, treatment and time as fixed categorical effects, and a random intercept and slope for each patient. For more details refer to Section 9.3.

For visualization, a scatterplot of the BI 894416 plasma concentration against the following individual QTcF values will be provided: For each patient on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this patient and time point. This results in estimates for "individual ΔΔQTcF" values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as and the geometric mean of C_{max} (SRD part) / $C_{max,ss}$ (MRD part) for each dose will additionally be displayed in the plot.

To check model assumptions, the conditional residuals will be plotted and presented in the Statistical Appendix of the CTR. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored in order to better characterise the PK-ECG relationship (e.g. effect compartment models, non-linear models, etc.).

All of the above described graphical and statistical analyses will be also performed for HR in place of QTcF.

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1 using all time points. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

7.8.5 Others

Physical examination

Physical examination findings, including general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin 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.

Neurological examination

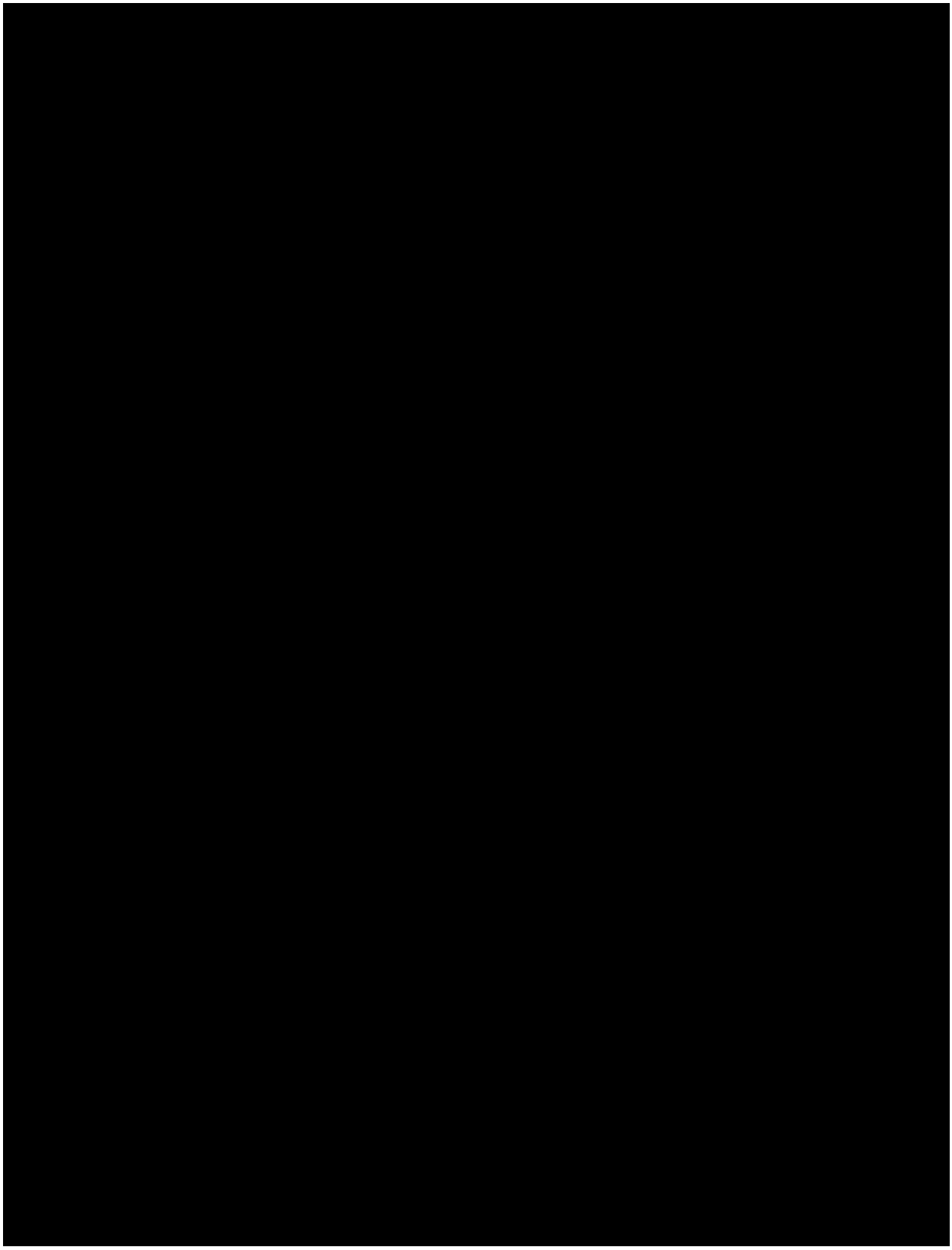
Neurological examination findings, including general level of arousal, orientation, eye movement, pupil size and pupil reactivity, reflexes, assessment of muscle strength, gait, romberg test, tremor, point-to-point movements and sensitivity will be reported as relevant

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 neurological examination findings will be prepared.

8. 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, IDEA for CON
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, version 1.6, KMED.
4.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", 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
10.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
11.	001-MCS-36-472_RD-03: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
12.	Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn 2017 [R18-0143]
13.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 2010 [R10-2920]
14.	U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 (access date: 9 April 2017); U.S.Department of Health and Human Services, National Institutes of Health, National Cancer Institute 2017 [R18-1357]



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**10-FEB-21**	[redacted]	None	This is the final TSAP