Statistical Analysis Plan

TITLE PAGE

A Phase I, Randomised, Open Label, Single Center, Single Oral Dose, Three Treatment, Three Period, Three Sequence, Change-over Bioequivalence Study of Paracetamol Orodispersible Tablet 500 mg (Haleon) to assess Bioequivalence with Alvedon 500 mg Film-Coated Tablet (Haleon, Sweden) and Panadol 500 mg Film-Coated Tablet (Haleon, Australia) in Healthy Adult Subjects Under Fasting Conditions

Working title: Paracetamol bioequivalence trial with oral single dose administration

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Statistical Analysis Plan - clinical trial phase: I

Confidential

SocraMetrics

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2 ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
ANOVA	Analysis of Variances
BLOQ	Below Lower Limit of Quantitation
CRF	Case Report Form
CRO	Contract Research Organisation
CSV	Comma Separated Value
CV / CV%	Coefficient of Variation
FAS	Full Analysis Set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantitation
Ln/lg	Natural logarithm/decadic logarithm
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NCA	Non-compartmental analysis
PPS	Per Protocol Set
PT	Preferred Term
PTAE (PT as domain)	Pre-Treatment Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event

Above mentioned abbreviations may but need not necessarily occur in this document. For definitions of pharmacokinetic parameters please refer to chapter 8.3.1.

3 RESPONSIBILITIES AND CONTACT ADDRESSES

With regard to responsibilities and contact addresses reference is made to the clinical trial protocol.

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5 DOCUMENT TRACKING

5.1 VERSION HISTORY

Version	Reason
Version 01 Final	Initial version

5.2 CHANGES IN THE EVALUATION

5.2.1 Analysis of t_{max}

During preparation of the statistical analysis plan (SAP), it was recognized, that the evaluation of the pharmacokinetic parameter t_{max} was not completely in line with applicable European guidelines. According to the "Paracetamol oral use immediate release formulations product-specific bioequivalence guidance" published by EMA (EMA/CHMP/356877/2017 Rev.1*), comparable median (≤ 20% difference, 80.00–125.00%) and range should be established for t_{max}.

Thus, evaluation of t_{max} was identified to be clarified and complemented. This adds to the evaluation of one of the primary target variables, but the data to be considered (taken from plasma concentrations) was already part of the evaluation and by this change only an additional procedure for treatment comparison is implemented. This addition is considered as having no impact on the safety of the subjects, the rights of the subjects or on the reliability and integrity of the data generated in the clinical trial.

The additional evaluation of t_{max} in line with the European guideline is now implemented by means of this statistical analysis plan prior to initiation of the main clinical part of the trial/randomisation.

According to the clinical trial protocol, for instance chapters 15.3.7.2.2 and 15.3.7.2.3, a Wilcoxon Signed Rank test will be used to analyse t_{max} (of Test versus Reference 1 and Reference 2 separately) nonparametrically in order to assess the median of differences between treatments. It was defined that, if no statistically significant difference is observed (and also classical bioequivalence for AUC and C_{max} is shown), bioequivalence for the compared treatments was to be concluded.

This evaluation is kept, but is considered as descriptive, that is, not necessarily to be fulfilled in order to conclude on bioequivalence of compared products.

Rather, in accordance with the product-specific guidance "EMA/CHMP/356877/2017 Rev.1*" for paracetamol oral use immediate release formulations, the ratio of the medians of compared treatments is calculated. That is, formally the criterion based on the Wilcoxon Signed Rank test is replaced by the direct comparison of the medians for compared treatments as now described in chapter 8.3.3.

5.2.2 Additional analysis set for evaluation for safety and clinical parameters

According to the study protocol the evaluation of Adverse Events and vital signs incl. body temperature should be evaluated with regard to treatment. Thus, the planed population (analysis set) "randomized population" (RP)) is not meaningful as this population did not receive any treatment. Thus, additionally to the randomized population these statistical evaluations will be presented also for the safety population (for definition see chapter 6.3).

Furthermore, the evaluation of the demographics and anthropometrics will also be provided for the randomised population and additionally in the PKAS set as described in chapter 8.4.3 and 8.5.3.

6 STUDY INFORMATION

6.1 DOCUMENTS AND OTHER BACKGROUND DETAILS

The Statistical Analysis Plan is based on the following documents:

- Clinical Trial Protocol, Final revised, dated 07.05.2024
- Data Management Plan, current version at time of performing data analysis
- eCRF, Final version, dated 11.03.2025

The Statistical Analysis Plan has been finalised before initiation of randomisation and, thus, prior to database lock under agreement with SocraTec R&D GmbH and the sponsor.

6.2 STUDY DESIGN AND OBJECTIVES

Study design has been defined in the clinical trial protocol as follows:

This single center, open-label, randomised (order of treatments), balanced, single dose trial will be performed in a 3-period, 3-sequence-change-over design. Fifty-four (54) healthy subjects of both sexes (27 male, 27 female) are intended to be randomised in order to obtain 42 evaluable subjects.

The IMPs will be administered in fasted state as single oral doses of 500 mg paracetamol. 1 tablet of Test and 1 film-coated tablet of Reference 1 and 1 film-coated tablet of Reference 2 will be administered. Blood sampling will be performed over 24 h post dose in order to characterise pharmacokinetic parameters.

The clinical trial will be performed as a change-over investigation with intra-individual comparison, thus reducing variability of the pharmacokinetic parameters, which is expected to be higher between subjects than within an individual subject.

The washout between administrations will be at least 72 hours, in order to ensure that the entire active ingredient from the preceding treatment period will be cleared from the body before administration of the subsequent treatment.

Study objectives have been defined in the clinical trial protocol as follows:

The primary aims of this clinical trial are:

- *Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus Haleon´s paracetamol 500 mg film-coated tablets marketed in Sweden under the name of Alvedon tablets (Reference 1) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations.*

and/or:

- *Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus the marketed Haleon´s paracetamol 500 mg film-coated tablets marketed in Australia under the name of Panadol tablets (Reference 2) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations.*

The secondary aims of this clinical trial are:

- *Assess the pharmacokinetic profile of paracetamol after fasted single dose administration of Test, Reference 1 and Reference 2.*

- *Descriptive characterisation of safety and tolerability of Test and Reference products considering adverse events observed during the trial.*

Treatments have been defined in the clinical trial protocol as follows:

Within this clinical trial, there will be 3 different treatments. The treatments are defined as follows:

- *A: oral single dose administration of 1 orodispersible tablet of Test under fasting conditions*
- *B: oral single dose administration of 1 film-coated tablet of Reference 1 under fasting conditions*
- *C: oral single dose administration of 1 film-coated tablet of Reference 2 under fasting conditions*

6.3 ANALYSIS SETS

Analysis sets have been defined in the clinical trial protocol as follows:

***Screened Population**: The Screened Population is defined as all subjects who were screened. Listings which include screen failure subjects or eligible subjects who were not randomised will be used for the Screened Population.*

***Randomised Population**: The Randomised Population is defined as eligible subjects who are randomised to participate in the study.*

***Safety population (SP)**: The Safety Population is defined as all randomised subjects who receive at least one dose of study medication.*

***PK Population (PKP)**: The PK Population is defined as all randomised subjects who have at least one measurable PK parameter. This population will be used for PK listings.*

***PK Analysis Set (PKAS)**: The PKAS is defined as all subjects in the PK population who complete at least two periods with one test formulation and who have no major protocol deviations concerning pharmacokinetics. This analysis set will be used in PK summaries and the primary and secondary analysis.*

A subject may remain in a specific analysis set but may be excluded from a specific evaluation/treatment comparison.

In this context, the term "major" is considered synonymous to the term "important" regarding relevance of protocol deviations.

In general, subjects could be excluded from statistical analysis based on clinical reasons according to chapter 12.3.3 [of the Clinical Trial Protocol]. Moreover, analytical reasons (relevant analytical failure) may be considered for exclusion from statistical analysis.

Only data of subjects who are part of at least one of the defined analysis sets will be included in the database, i.e., their data will be listed and evaluated. In the database only a minimal data set is available for the screening failures. In the database only a minimal data set is available for the screening failures.

Relevant deviations and their classification are identified during data review meeting. As applicable, the resulting subject-wise composition of analysis sets as well as handling of specific data are documented.

7 GENERAL CONSIDERATIONS

7.1 DATA REVIEW PRIOR TO BIOANALYTICAL DETERMINATION

Prior to bioanalysis, a review of relevant study data, that were defined in Standard Operating Procedures of SocraTec R&D, is going to be performed by representatives of the sponsor, SocraTec R&D and SocraMetrics and be discussed with the sponsor, in order to decide whether subjects should be excluded from evaluation of pharmacokinetics in line with the current Guideline on the Investigation of Bioequivalence.

7.2 DATA REVIEW PRIOR TO DATABASE HARD LOCK

Furthermore, prior to starting the evaluation of the data, a review of study data will be performed by representatives of the sponsor, SocraTec R&D, and SocraMetrics, and discussed during a Data Review Meeting. During Data Review Meeting all protocol deviations are reviewed in order to confirm the classification as "major" and "minor" and the assignment of the analysis sets. General applicability of the planned statistical procedure on the study data set is discussed and identified necessary changes are documented.

7.3 UNBLINDING

Not applicable.

7.4 GENERAL COURSE OF DATA MANAGEMENT PROCEDURES

A general overview of the data management process interacting with the SAP in chronological order is given below:

- "Data Review Meeting (DRM)" as presented in chapter 7.2
- "Final operational database": After generation of final data listings, the operational database will be hard locked (database closure).
- "Statistical evaluation": Generation of descriptive statistics, frequency tables, listings and figures of clinical parameters in accordance with the Statistical analysis Plan and the clinical trial protocol by data management and statistical department.

Thus, the SAP must be finalized and, if possible, ratified, prior to database closure and the subsequent initiation of evaluation.

7.5 MISSING DATA

Missing data will generally not be transformed and remain untouched. If applicable, specific requirements for certain parameters are provided in the affiliated chapters.

For evaluation, flags of missing data will generally be kept or replaced by equivalent remarks of missing data. Calculations and statistics will generally be given, including the underlying number of valid individual values, i.e., missing values will not be included. Exceptions are statistics, for which the descriptive evaluation of the observation "missing" is relevant information per se, where these will be included in the affiliated mock tables (see chapter 9).

7.6 DECIMAL PLACES AND SIGNIFICANT DIGITS OF DATA

Decimal places for data derived during procedures defined in this SAP are defined, that are applied if no specific conventions are given for a specific parameter. Raw data will generally not be changed with regard to decimal places and presentation in listings or in the database is not affected. Decimal places during calculations will be accepted as provided by the software. For reporting of parameters, it is specified, if technically feasible:

- Counts will be presented without decimal places.
- Percentages (including point estimates) will generally be presented with 2 decimal places (or as ratio with 4 decimal places).
- Derived parameters will be given with the same number of decimal places as the parameter used for calculation with the lowest number of decimal places.
- Times and calculated times presented as hours will be presented with 2 decimal places.
- For descriptive statistics of individual values:
  - parameters directly taken from the values (i.e., minimum, maximum, sum) will be presented with the same number of decimal places.
  - parameters calculated from the values (i.e., mean, standard deviation, median) will be presented with one additional decimal place.
- Pharmacokinetic evaluation: all PK-parameters and statistics will be presented with 3 significant digits except counts and point estimates (see above).

Rounding is done by means of the half away from zero rounding procedure.

7.7 DATA REQUIRING ADAPTATION IN LISTING

When shortcomings in used data files (listings) with no substantial impact on the evaluation are identified during evaluation, data can be adapted as necessary as long as such adaptations are self-evident. As such adaptations are intended to achieve processability and are of formal nature, the adapted data will not become part of the database.

An example of not accepted adaptation is a wrong concentration or time value, i.e., actual data in the data sets used. In those cases, correction of data by the data provider should be initiated.

Examples of acceptable adaptations are:

- replacement of a column label that cannot be used with the intended software
- deletion of unnecessary delimiters in a data set
- automated adaptation of values of key parameters (such as subject ID) in order to allow correct processing, e.g., addition of the prefix "subject_" to the subject N°.
- separation of multiple information within one cell (e.g., “period I, study day 01” to “period I” and “study day 01”)

Such adaptations must either be done by reproducible automated steps as part of the statistical analysis or by manual implementation into copies of the respective dataset prior to statistical analysis. In case that established quality control measures do not cover these adaptations, the person conducting the affected evaluation will define additional checks.

7.8 USED SOFTWARE

Listed programs will be used in the stated version or higher resulting in specific output formats.

7.9 QUALITY CONTROL OF STATISTICAL PROCEDURES

As defined in the Clinical Trial Protocol:

> *All processes as well as quality control will be performed according to the SOPs of SocraMetrics GmbH. Quality control measures include checks of data, checks of calculations as well as formal checks of tables, listings and figures. All steps of quality control will be documented by signature of the reviewer and date of review. Within the review of the results general applicability of the planned statistical procedure on the trial data set will be checked. If findings of the review suggest changes to the procedures given by the clinical trial protocol, those changes will be appropriately addressed.*

8 STATISTICAL ANALYSIS

With regard to the variables to be obtained in the clinical trial reference is made to the affiliated Data Management Plan. Statistical evaluation will be based on values taken from the final database. For listings of data not defined in this SAP as to be generated as part of the evaluation reference is made to the Data Management Plan.

In general, variables will be used to generate tables presenting descriptive statistics depending on the structure of the data. General regulations are provided for those cases, where specific requirements for data presentation are not defined in detail in the following.

Unless otherwise defined for variables intended to be described by statistical means:

- descriptive statistics will at least comprise N, arithmetic mean, SD, minimum, first quartile Q1, median, third quartile Q3, maximum; for pharmacokinetic data also geometric mean and geometric CV%, of a parameter (for continuous values)
- frequency analysis will at least comprise N and N% (for categorical variables).

For detailed specification of figures, tables and listings (FTL) derived from evaluation for each individual parameter see chapter 9.

In case further statistical evaluation not yet specified in the SAP will be required, these will be agreed upon between SocraMetrics GmbH, SocraTec R&D GmbH, and the sponsor and appropriately documented in a new version or an addendum of the SAP.

8.1 INTERIM ANALYSES

No interim analysis is planned.

8.2 HOMOGENEITY AT BASELINE

Not applicable.

8.3 EVALUATION – OTHER - PHARMACOKINETIC DATA

8.3.1 Study parameters - pharmacokinetic data

All kinetic parameters will be determined model-independently for each treatment using Phoenix WinNonlin, software program. Pharmacokinetic characteristics will be determined directly from the measured concentrations.

As defined in the Clinical Trial Protocol:

> *Considering plasma concentration and the appendant scheduled and real sampling times the following pharmacokinetic parameters will be determined by means of non-compartmental analysis for*
>
> - *paracetamol*

Determination will be repeated considering scheduled times for information, descriptive statistics and treatment comparisons will be provided; however, the primary analysis will be based on actual times allowing for more appropriate calculation.

$AUC_{0\text{-}tlast}$	*area under the concentration vs. time curve from dosing time to the last measurement time point with a concentration value above the lower limit of quantitation, calculated by means of the linear up/log down method (linear trapezoidal rule for increases in concentration/logarithmic trapezoidal rule for decreases in concentrations*
$AUC_{0\text{-}inf}$	$AUC_{0\text{-}tlast} + AUC_{expol}$
$AUC_{expol\%}$	$AUC_{expol} \times 100 / AUC_{0\text{-}inf}$, where $AUC_{expol} = C_{last}/L_z$
C_{max}	*maximum observed concentration, directly taken from measured concentration values*
C_{last}	*observed concentration at the last time point with a concentration value above the lower limit of quantitation, directly taken from measured concentration values*
t_{max}	*time to reach maximum concentration, obtained directly from measured values*
t_{last}	*last time point with a concentration value above the lower limit of quantitation, directly taken from measured concentration values*
$t_{1/2}$	*apparent terminal elimination half-life,* $t_{1/2} = ln(2) / L_z$
L_z	*apparent terminal elimination rate constant determined by log-linear regression*
t_{lag}	*time from IMP application to last sampling time point before first concentration value above the lower limit of quantitation, directly taken from measured concentration values*

In addition, the following parameters will be provided:

Lzlower	first sampling time included in determination of L_z
Lzupper	last sampling time included in determination of L_z
N_{Lz}	number of time points included in L_Z estimation

Due to technical requirements of the Phoenix software program considered for the pharmacokinetic and statistic evaluations, the following symbols may be used during the evaluation synonymously: ∞ *= inf,* $\lambda = L_z$, τ *= T/Tau,* $t_{1/2}$ *= HL_Lambda_z, "," = "_".*

Parameters will also be calculated for subjects excluded from the valid analysis set and be reported separately, as far as feasible.

8.3.2 Data conventions for pharmacokinetic data

8.3.2.1 Baseline correction

Not applicable.

8.3.2.2 Handling of missing data

In general, any transformation to a numeric format that may be necessary for correct processing will result in (additional) missing values from text values. This will not apply to values marked as BLOQ when handled as described in chapter 8.3.2.3.

As defined in the Clinical Trial Protocol:

> *Missing data will generally not be transformed and remain untouched. Calculations and statistics will be given including the underlying number of individual values (N), i.e., missing values will not be included.*
>
> *During evaluation of plasma concentration data, the software will automatically interpolate between the concentration value before and the value after a "missing" value, if possible. Missing data will not be considered for calculation of mean concentrations. In case of missing time data, the observation time point will not be considered in all evaluations that would require the time data.*
>
> *In cases of missing value for a pharmacokinetic metric, this value will be reported as missing. For pairwise comparisons also the value being compared to will be considered missing, i.e., it will be excluded from the comparison.*

However, this value will remain in descriptive statistics, if the subject is considered eligible.

8.3.2.3 Handling of values given as "below the limit of quantitation"

Handling of values given as "below the limit of quantitation" has been defined in the clinical trial protocol as follows:

> *Values below the limit of quantitation (e.g. labelled as "BLOQ", "<LLOQ"; hereinafter referred to as BLOQ value) will be handled as follows:*
>
> - *For evaluation and general graphical presentation of analytical data:*
>   - *BLOQ marks will be transformed to "zero".*
>
> *Values below the LLOQ are to be omitted from the calculation of K_{el} and $t_{½}$*

8.3.2.4 Handling of specific time points

For samples taken prior to a single dose administration, the actual and scheduled sample times will be set to "0" for evaluation.

Deviations between actual and scheduled times are documented in accordance with the clinical Trial Protocol and discussed as protocol deviations.

8.3.2.5 Study particularities

Not applicable.

8.3.3 Statistical evaluation - pharmacokinetic data

The statistical evaluation of pharmacokinetics has been defined in the clinical trial protocol as follows:

The statistical analysis will be performed as a valid case analysis including all subjects of the PKAS (or PKP for listings) (for definitions of study populations see chapter [6.3]*). No subgroup analysis is planned.*

Determination will be repeated considering scheduled times for information. Descriptive statistics and treatment comparisons will be provided; however, the primary analysis will be based on actual times allowing for more appropriate calculation.

Data from subjects could be excluded from statistical analysis based on clinical reasons according to chapter 12.3.1 [of the clinical trial protocol]. *Moreover, analytical reasons (relevant analytical failure) may be considered for exclusion from statistical analysis.*

If no or only very low concentrations are observed after administration of one of the Reference products or after the administration of Test, the following procedure is used: if the $AUC_{0\text{-}tlast}$ is less than 5% of the geometric mean of all other values observed for Reference or Test product, the affected period should be excluded from all BE assessments. Thus, the subject would be excluded from BE assessment in an affected Test vs. Reference comparison.

If verified pre-dose concentrations [from one blood sample taken prior to administration] *occur, the following procedure is used: If the pre-dose concentration is less than or equal to 5 % of the C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. If the pre-dose value is greater than 5% of C_{max}, the affected period should be excluded from all BE assessments. Thus, the subject would be excluded from BE assessment in an affected Test vs. Reference comparison.*

Concentration data and pharmacokinetic parameters from dropped out or excluded subjects will be presented in the individual listings, if available, but will not be included in the summary statistics. Bioequivalence assessment will be based on the results calculated without the data of the excluded subjects, i.e., the PKAS.

Exclusion of subjects or individual data documented prior to the evaluation will be considered.

8.3.3.1 Descriptive statistics and graphical presentations

The statistical evaluation of pharmacokinetics has been defined in the clinical trial protocol as follows:

Individual, overlays of individual and mean concentration vs. time curves will be provided, both linearly and log-linearly considering treatment and analyte as appropriate.

Individual concentration vs. time profiles will be based on real sampling times; mean curves will be based on scheduled times.

As well as:

Mean concentrations will be listed in tabular form including descriptive statistics (at least N, (if applicable N_{obs}, N_{miss}), arithmetic mean, SD, minimum, median, maximum) based on scheduled times for the PKAS.

Individual values of PK parameters will be tabulated for the PKP and PKAS. For the PKAS, descriptive statistics (number of subjects (N), arithmetic means, SD, CV%, geometric means, geometric CV, medians, minimum, maximum, Q1, and Q3) will be presented for all pharmacokinetic parameters, separately for each treatment.

In general, data points of mean curves will only be presented, if at least two thirds (⅔) of the values related to the number of values according to the set for evaluation are available.

8.3.3.2 Inferential statistics and additional evaluations

The statistical evaluation of pharmacokinetic parameters has been defined in the clinical trial protocol as follows:

Treatment comparisons will be performed as a valid case analysis including all subjects of the PKAS in the pairwise comparisons as appropriate (for definitions of study populations see chapter [6.3]*).*

In this study, two different reference products will be compared with the test product. Hence, two separate comparisons will be run, and no multiplicity adjustment will be performed.

The statistical analysis will be carried out on the basis of a multiplicative model for values of $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max}-values.

An Analysis of Variance (ANOVA) model will be fitted to the ln-transformed PK variables (AUC and C_{max}), as the dependent variable, and treatment, period, sequence and subject nested within sequence as fixed effects in order to provide the parametric analysis in accordance with current guideline [2].

For each pairwise comparison, only the data from the 2 corresponding treatments will be included in the model.

Least-squares estimate of treatment effects will be calculated and a 90% CI for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric least square means between the test and reference and its CI.

Analyses of variances will be performed as pairwise comparison of $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}-values after ln-transformation for:

- *Test vs. Reference 1*
- *Test vs. Reference 2*

Intra-subject variability will be estimated, and period, subject and sequence effects will be determined.

Affiliated statistical analyses will be performed with an error probability of 0.05 (type-I error probability).

A Wilcoxon Signed Rank test will be used to analyze t_{max} nonparametrically. Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on PKAS for:

- *Test vs. Reference 1*
- *Test vs. Reference 2*

This comparison is conducted to provide a further treatment comparison at a descriptive level. As described in chapter 5.2.1, as part of the treatment comparison to conclude on bioequivalence, for these comparisons the ratio of the median t_{max} values of the products will be calculated.

In accordance with current guideline [2] parameters subject to ANOVA will be tested parametrically. The model used is as follows for non-replicated crossover designs:

Fixed effects model is:

Dependent Parameter = Intercept + Sequence + Treatment + Period + Subject(Sequence)

8.3.3.3 Applied SAS code

Evaluation will be conducted in SAS; an equivalent code for fitting the above ANOVA model for treatment comparison would be similar to (assuming that Reference is coded as "Reference" which is alphabetically earlier than "Test"). Raw outputs will be provided in addition.

Note: In cases considering European guidelines PROC GLM, i.e., solely fixed effects, is often used; however, PROC MIXED would be considered acceptable as long as all subjects provide a complete valid data set (data for both compared treatments). That is, subjects to be excluded are reliably excluded, as the choice of subjects as fixed or random effect then has no impact on the result.

SAS code for fitting the above non-parametric comparison will be similar to:

8.3.3.4 Test for equivalence by the confidence interval inclusion approach

Test for equivalence has been defined in the clinical trial protocol as follows:

$AUC_{0\text{-}tlast}$, C_{max} and t_{max} -values are chosen as primary target variables.

The BE between a new CCI *500 mg ODT (Test) and the marketed Panadol/Alvedon 500 mg film-coated Tablet (Reference) in fasted state will be declared:*

- *If the 90% confidence intervals (CIs) for the ratio (%) of the geometric means of the primary PK parameters, $AUC_{0\text{-}t}$ and C_{max} of the paracetamol profiles are completely within the 80.00% to 125.00% range.*
- [Criterion based on statistically significant difference replaced by:] If the ratio (%) of median t_{max} is within the 80.00 to 125.00% range.

For AUC and C_{max} the assessment of equivalence will, thus, be based upon a two-sided 90 % confidence interval for the ratio of the (adjusted) geometric means for the primary endpoints using a pre-set acceptance range. This method is equivalent to the two one-sided t-tests procedure (TOST), each at the 5 % significance level. That is, if the classical (100-2•α) % confidence interval for difference or ratio is within the equivalence limits (including), then both the H_0 given below for the 2 tests are also rejected at the α level by the two one-sided t-tests procedure.

In general, the following hypotheses are covered for ln-transformed data:

H_0: $(T - R) \leq -\delta$ or $(T - R) \geq \delta$ versus

H_1: $-\delta < (T - R) < \delta$ (acceptance of bioequivalence),

where T and R are the means of logarithmically (natural) transformed PK parameter for the test and reference, respectively and δ is the PK equivalence limit that defines the acceptance range on the logarithmic scale.

Bioequivalence assessment should be based on the results calculated without the data of the excluded subjects (see chapter 15.3.7.2 [of the Clinical Trial protocol]).

8.3.3.5 Complementary information

As defined in the clinical trial protocol:

> *A possible deviation from normal Gaussian distribution of investigated parameters is addressed considered by performing logarithmic transformation prior to entering analyses, i.e. transformation to the natural logarithm (ln) is performed for approximation. Concentration dependent pharmacokinetic parameters (e.g. $AUC_{0\text{-}tlast}$, C_{max}) will be ln-transformed while purely time dependent parameters (e.g. t_{max}) will remain untouched and, insofar as they are evaluated, enter analyses without transformation. Obtained results, e.g. point estimates and 90 % confidence intervals for the difference of ln-transformed values, will then be retransformed into the linear scale.*
>
> *CV_{ANOVA} (%) will be calculated for every parameter evaluated from the residual variance indicated in the corresponding ANOVA output. In general, CV_{ANOVA} (%) is derived as $CV_{ANOVA}=100•(e^{MSE}-1)^{0.5}$, where MSE is the (residual) mean square error from ANOVA.*

The ANOVA output from evaluation includes classical two-sided confidence intervals for confidence levels »100 – 2•α« for a preset confidence level, if required.

For ln-transformed data classical confidence intervals are determined using the students-t distribution, where

- lower/upper limit = product difference -/+ t(1-α, df) • standard error of the difference.

These values are then transformed to be on the arithmetic scale and translated to percentages.

8.4 EVALUATION - SAFETY - ADVERSE EVENTS

8.4.1 Study parameters - Adverse Events

For definition of Pre-Treatment Adverse Event (PTAE), Adverse Event (AE), a Serious Pre-Treatment Adverse Event (Serious PTAE), a Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (Serious ADR), an Adverse Drug Reaction (ADR), and an Unexpected Adverse Drug Reaction or a Suspected Unexpected Serious Adverse Reaction (SUSAR) reference is made to the Clinical Trial Protocol chapter 4.2.11 and 13.3.6.

This evaluation is of exploratory nature and limited to a descriptive characterisation of safety and tolerability.

8.4.2 Data conventions - Adverse Events

For statistical evaluation of safety data, the final database will be used, i.e., no changes will be made to the data.

8.4.2.1 Handling of missing data

See chapter 7.4.

8.4.3 Statistical evaluation – Adverse Events

As defined in the clinical trial protocol:

> *Statistical evaluation will be performed for the randomised population* [and safety population] *(for definition see chapter* [6.3]*).*

8.4.3.1 Descriptive statistics and graphical presentations

As defined in the clinical trial protocol:

> *PTAE and AEs will be evaluated considering action taken, frequency, seriousness, and intensity. Furthermore, AEs will be evaluated considering relationship to the IMP, outcome as well as treatment and period. Both will be described by absolute and relative frequency.*

8.4.3.2 Inferential statistics and additional evaluations

Not applicable.

8.5 EVALUATION – OTHER - CLINICAL DATA

8.5.1 Study parameters - clinical data

The following parameters will be evaluated descriptively:

- demographic data (age, sex, childbearing potential)
- anthropometric data (body weight, height, BMI)
- medical history - findings, concomitant diseases and surgeries or procedures
- prior and concomitant medication
- vital signs (blood pressure, pulse rate, body temperature)
- clinical laboratory data

8.5.2 Data conventions - clinical data

For statistical evaluation of the clinical data, the final database will be used, i.e., no changes will be made to the data.

8.5.2.1 Handling of missing data

See also chapter 7.4. Missing data will generally not be transformed and remain untouched. For evaluation, remarks of missing data will generally be kept. However, any transformation from text values to a numeric format that may be necessary for correct processing will result in missing values for any texts that cannot be converted without a doubt.

8.5.2.2 Handling of clinical laboratory data

In case clinical laboratory parameters have been re-measured, the descriptive statistics and frequencies will include the last valid re-measured value.

Regarding calculations of a descriptive statistic for clinical laboratory values, this is only possible for parameters with numerical values and not for parameters in which the result is presented with special characters or as text. In those cases, a frequency analysis is planned under the convention the parameter also has a textual normal value. Otherwise, the values will be counted as "missing" in descriptive statistics.

In descriptive statistics of clinical laboratory parameters, parameters with numerical values below a lower limit of quantification will be evaluated as "0". If these parameters have values that cannot unambiguously be converted to numbers, these values will be treated as missing.

Values reported as ">ULOQ" (or similarly) will be replaced by the upper limit of quantification, if unambiguously convertible.

8.5.2.3 ATC level

Evaluation of medication will be based on level 5 of the ATC code. In case, coding at this level is not available, code of the next lower level (broader, level 4 or 3) available will be used instead for the affected medication. In case no ATC code is available, the term “no code available” will be used.

8.5.3 Statistical evaluation - clinical data

8.5.3.1 Descriptive statistics and graphical presentations

8.5.3.1.1 Demographic and anthropometric data, medical history - findings, concomitant diseases and surgeries, prior and concomitant medication

As defined in the clinical trial protocol:

Statistical evaluation will be performed for the SP and PKP [and randomised population as well as PKAS] *(for definition see chapter* [6.3]*), with exception of childbearing potential, for which statistical evaluation will be performed only for the randomised population.*

Continuous data will be evaluated descriptively (number of subjects (N), arithmetic mean, SD, median, minimum, maximum) and will be provided overall and by sequence.

A frequency analysis will be conducted for sex and childbearing potential, as well as for the results of prior and concomitant medication.

8.5.3.1.2 Vital signs (blood pressure, pulse rate and body temperature)

As defined in the clinical trial protocol:

Statistical evaluation will be performed for the randomised population [and safety population] *(for definition see chapter* [6.3]*).*

Evaluation will be conducted for vital signs and body temperature.

Descriptive statistics (number of subjects (N), arithmetic mean, SD, minimum, median, maximum) will be created.

Vital signs and body temperature will be analysed with regard to time point of assessment and treatment.

8.5.3.1.3 Clinical laboratory parameters

As defined in the clinical trial protocol:

Statistical evaluation will be performed for the randomised population [and safety population] *(for definition see chapter* [6.3]*).*

Descriptive statistics (number of subjects (N), arithmetic mean, SD, minimum, median, maximum) will be calculated for clinical laboratory parameters determined, where possible.

Frequencies of values inside and out of normal range (with further classification of above or below normal range) will be provided, where possible.

8.5.3.2 Inferential statistics and additional evaluations

Not applicable.

9 DATA OUTPUT

9.1 DATA OUTPUTS FOR GENERATION OF THE CLINICAL TRIAL REPORT

A detailed presentation of tables to be created is presented in the following. Whilst formal deviations are acceptable in general, determinations concerning the content have to be followed as far as applicable (and reasonable for the pre-defined analysis set). Formal deviations may in particular include order of treatments.

Several levels of a sorting parameter are preferably not given in detail but are indicated as "*…item"*. In case few specific entries have to be presented, these are given in *italics*. Repetitive entries are not repeated in full but indicated by "…". A "TOTAL" will indicate that all observations listed separately per item for a sorting variable will be pooled for an additional evaluation affecting all sorting parameters. Where a specific analysis variable is to be given in the table, this is indicated by [analysis variable].

If analogous figures, tables or listings have to be provided, a reference to the preceding object may be provided rather than a full repetition of the figure, table or listing. In case it becomes necessary to split tables during generation of outputs, e.g., these are requested for more than one population and would become too large, if this is included as a grouping variable, the planned table number is appended by an index in ascending alphabetical order for each sub-table.

In case no data for a presentation is available, the provided document will include the table title and the information "no data available".

As example, a frequency table (by visits (grouping 1) and sex (analysis variable) per treatment (grouping 2)) results in (arbitrary numbers used):

		Treatment			
		…treatment		Total	
Visit	[Analysis variable]	N	%	N	%
…visit	*…analysis variable*				
	Missing				
TOTAL	TOTAL				

→

		Treatment					
		Arm 1		Arm 2		Total	
Visit	Sex	N	%	N	%	N	%
Visit 1	Female	2	16.67	3	16.67	5	16.67
	Male	4	33.33	6	33.33	10	33.33
	Missing	6	50.00	9	50.00	15	50.00
	TOTAL	12	100.00	18	100.00	30	100.00
Visit 2	Female	6	50.00	9	50.00	15	50.00
	Male	4	33.33	6	33.33	10	33.33
	Missing	2	16.67	3	16.67	5	16.67
	TOTAL	12	100.00	18	100.00	30	100.00
TOTAL	Female	8	33.33	12	33.33	20	33.33
	Male	8	33.33	12	33.33	20	33.33
	Missing	8	33.33	12	33.33	20	33.33
	TOTAL	24	100.00	36	100.00	60	100.00

This would be a transposed output; in the non-transposed output, grouping variable 2 and the analysis variable would be interchanged, resulting in "Missing" and "TOTAL" (as N_{tot}) being found as columns and "Total" as row, e.g.:

		Sex						
		Female		Male		Missing		
Visit	Treatment	N	%	N	%	N	%	N_{tot}
Visit 1	Arm 1	2	16.67	4	33.33	6	50.00	12
	Arm 2	3	16.67	6	33.33	9	50.00	18
	Total	5	16.67	10	33.33	15	50.00	30
Visit 2	...							

As example, a descriptive statistic table (by visits (grouping variable 1) for weight and height (analysis variables) per treatment (grouping variable 2) results in (arbitrary numbers used):

			Treatment
Visit	Analysis variable	Parameter	*...treatment*
...visit	*...analysis variable*	N	
		Mean	
TOTAL			

→

			Treatment		
Visit	Analysis variable	Parameter	Arm 1	Arm 2	Total
Visit 1	Height	N	1	2	3
		Mean	100	200	167
	Weight	N	1	2	3
		Mean	50	100	83
Visit 2	Height	N	3	4	7
		Mean	200	300	257
	Weight	N	3	4	7
		Mean	60	120	94
TOTAL	Height	N	4	6	10
		Mean	175	267	230
	Weight	N	4	6	10
		Mean	58	113	91

This would be a transposed output; in the non-transposed output, grouping variable 2 and the analysis variable would be interchanged, resulting in treatment "Total" as a row, e.g.:

Visit	Treatment	Parameter	Height	Weight
Visit 1	Arm 1	N	1	1
		Mean	100	50
	Arm 2	N	2	2
		Mean	200	100
	Total	N	3	3
		Mean	167	83
Visit 2	...			

The format of the tables should be:

- portrait format, margins: 2.5 cm left side, 2.5 cm right side, 3.0 cm from the top, 3.0 cm from the bottom
- font "Arial" with a font size of 9 pt. A font size of 8 pt is allowed for single tables.

9.1.1 Demographics and other baseline characteristics

Table 15.1- 1: Number of subjects assigned to each analysis set - frequency - referring to total number of observations N_{tot}

Analysis set: Screened population

	Total	
Analysis set	N	%
…analysis set		
Total		

Table 15.1- 2: Reason for screening failure – frequency - referring to total number of observations N_{tot}

Analysis set: Screened population

	Primary reason					
	…reason*		Missing		Total	
Visit	N	%	N	%	N	%
…visit	*N*	*(% of N_{tot})*	*N*	*(% of N_{tot})*	N	(% of N_{tot})
Total						

*considering single reasons or combination of reasons in individual subjects

Table 15.1- 3: Demographic data – anthropometrics at screening examination – descriptive statistics

Analysis set: RP, SP, PKP, PKAS

Time point	Parameter	Age [years]	Height [m]	Weight [kg]	BMI [kg/m^2]
…time point	N				
	Arithmetic Mean				
	SD				
	Minimum				
	Median				
	Maximum				

Table 15.1- 4: Demographic data - sex at screening examination - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP, PKP, PKAS

	Sex				
	…sex		Missing		
Time point	N	[%]	N	[%]	N_{tot}
…time point	*N*	*(% of N_{tot})*	*N*	*(% of N_{tot})*	*N_{tot}*

Table 15.1- 5: Demographic data - childbearing potential at screening examination – frequency analysis (females only) – (% referring to N_{tot})

Analysis set: RP

	Childbearing potential				
	…childbearing potential		Missing		
Time point	N	[%]	N	[%]	N_{tot}
…time point	*N*	*(% of N_{tot})*	*N*	*(% of N_{tot})*	*N_{tot}*

Table 15.1- 6: Previous medication - active ingredients by [redacted] ATC code level 5 or broader - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP

	Total	
Active ingredients by WHO ATC code level 5 or broader	N	[%]
…API	*N*	*(% of N_{tot})*

Table 15.1- 7: Concomitant medication - active ingredients by WHO ATC code level 5 or broader - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP

See Table 15.1- 6

Table 15.1- 8: Medical history – completed medical history according to MedDRA by SOC and PT - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP

		Total	
SOC	PT	N	%
…SOC	*…PT*	*N*	*(% of N_{tot})*
TOTAL			

Table 15.1- 9: Medical history - surgeries according to MedDRA by SOC and PT - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP

See Table 15.1- 8

Table 15.1- 10: Medical history - concomitant diseases according to MedDRA by SOC and PT - frequency analysis (% referring to N_{tot})

Analysis set: RP, SP

See Table 15.1- 8

Table 15.1- 11: Vital signs - vital signs at screening examination by treatment - descriptive statistics

Analysis set: RP, SP

Treatment	Time point		*...vital sign*
...treatment	*...time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.1- 12: Body temperature - body temperature at screening examination by treatment - descriptive statistics

Analysis set: RP, SP

Treatment	Time point		Body temperature [°C]
...treatment	*...time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.1- 13: Laboratory examination - laboratory parameters at screening examination by sex, matrix, and system - descriptive statistics

Analysis set: RP, SP

Sex: *sex*, Matrix: *matrix*, System: *system*									
Time point	Laboratory parameter	Unit	Normal value	N	Arithmetic Mean	SD	Minimum	Median	Maximum
...time point	*...parameter*								

Table 15.1- 14: Laboratory examination - laboratory parameters at screening examination with regard to normal value by sex, matrix, and system - frequency analysis

Analysis set: RP, SP

Sex: *sex*, Matrix: *matrix*, System: *system*		Unit	N	within normal value	out of normal value	below normal value	above normal value
Time point	Laboratory parameter						
...time point	*...parameter*						

9.1.2 Efficacy

Not applicable.

9.1.3 Safety data

9.1.3.1 Display of Adverse Events

Table 15.3- 1: PTAE - frequency (PT by SOC) - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP

			Events total: N_{tot} Subjects total: N_{set}	
SOC			Total	
	PT		No. findings	No. subjects
		Total	*N (% of N_{tot})*	*N (% of N_{set})*
...SOC			*N (% of N_{tot})*	*N (% of N_{set})*
	...PT		*N (% of N_{tot})*	*N (% of N_{set})*

Table 15.3- 2: PTAE - maximum intensity (PT by SOC) - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP

				Events total: N_{tot} Subjects total: N_{set}	
	SOC			Total	
Maximum intensity		PT		No. findings	No. subjects
...maximum intensity			Total	*N (% of N_{tot})*	*N (% of N_{set})*
	...SOC			*N (% of N_{tot})*	*N (% of N_{set})*
		...PT		*N (% of N_{tot})*	*N (% of N_{set})*

Table 15.3- 3: PTAE - action taken (PT by SOC) frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP

				Events total: N_{tot} Subjects total: N_{set}	
	SOC			Total	
Action taken		PT		No. findings	No. subjects
...action taken			Total	*N (% of N_{tot})*	*N (% of N_{set})*
	...SOC			*N (% of N_{tot})*	*N (% of N_{set})*
		...PT		*N (% of N_{tot})*	*N (% of N_{set})*

Table 15.3- 4: PTAE - seriousness (PT by SOC) - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP

			Events total: N_{tot} Subjects total: N_{set}	
	SOC		Total	
Seriousness	PT		No findings	No subjects
...seriousness		Total	*N (% of N_{tot})*	*N (% of N_{set})*
	...SOC		*N (% of N_{tot})*	*N (% of N_{set})*
	...PT		*N (% of N_{tot})*	*N (% of N_{set})*

Table 15.3- 5: AE - frequency (PT by SOC) by treatment - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP, SP

				Events total: N_{tot} Subjects total: N_{set}		
			Treatment			
SOC			*...treatment*		Total	
PT			No. findings	No. subjects	No. findings	No. subjects
		Total	*N_{tot} (100%)*	*N_{set} (100%)*	*N_{tot} (100%)*	*N_{set} (100%)*
...SOC			*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*
...PT			*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*

Table 15.3- 6: AE - ICH E3-table: display of AE (PT by SOC) by treatment with subject identifications - statistics (% referring to total number of findings N_{tot}/subjects N_{set})

Analysis set: RP, SP

Total/*...treatment*									N = *N_{tot}*
SOC	Mild		Moderate		Severe		Total		Total
PT	R	NR	R	NR	R	NR	R	NR	R+NR
...SOC	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*
...PT	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*	*N (% of N_{tot})*
Subject N° of subjects									

R: related - NR: not related - N: number total

Table 15.3- 7: AE - maximum intensity (PT by SOC) by treatment - frequency analysis % referring to total number of findings N_{tot}/subjects N_{set})

Analysis set: RP, SP

								Events total: N_{tot} Subjects total: N_{set}
				Treatment				
	SOC			*...treatment*		Total		
Maximum intensity		PT		No findings	No subjects	No findings	No subjects	
...maximum intensity			Total	*N (% of N_{tot})*	*N (% of N_{set})*	*N_{tot} (100%)*	*N_{set} (100%)*	
	...SOC			*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
		...PT		*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	

Table 15.3- 8: AE - action taken (PT by SOC) by treatment - frequency analysis % referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP, SP

							Events total: N_{tot} Subjects total: N_{set}
			Treatment				
	SOC		*...treatment*		Total		
Action taken		PT	No findings	No subjects	No findings	No subjects	
...action taken		Total	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
	...SOC		*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
		...PT	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	

Table 15.3- 9: AE - relationship to IMP (PT by SOC) by treatment - frequency analysis – (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP, SP

							Events total: N_{tot} Subjects total: N_{set}
			Treatment				
	SOC		*...treatment*		Total		
Relationship to IMP		PT	No findings	No subjects	No findings	No subjects	
...relationship		Total	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
	...SOC		*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
		...PT	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	

Table 15.3- 10: AE - outcome (PT by SOC) by treatment - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP, SP

								Events total: N_{tot} Subjects total: N_{set}
				Treatment				
	SOC			*...treatment*		Total		
Outcome		PT		No findings	No subjects	No findings	No subjects	
...outcome			Total	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
	...SOC			*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
		...PT		*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	

Table 15.3- 11: AE - seriousness (PT by SOC) by treatment - frequency analysis (% referring to total number of findings N_{tot}/all subjects in the analysis set N_{set})

Analysis set: RP, SP

							Events total: N_{tot} Subjects total: N_{set}
			Treatment				
	SOC		*...treatment*		Total		
Seriousness		PT	No findings	No subjects	No findings	No subjects	
...seriousness		Total	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
	...SOC		*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	
		...PT	*N (% of N_{tot})*	*N (% of N_{set})*	*N (% of N_{tot})*	*N (% of N_{set})*	

Table 15.3- 12: AE - analysis, period I by treatment - frequency analysis (% referring to total number of findings N_{tot}/findings under treatment $N_{treatment}$)

Analysis set: RP, SP

	Treatment			
Total subjects	*...treatment*		Total	
N *(number of subjects)*	abs. freq.	rel. freq.	abs. freq.	rel. freq.
AE	*$N_{treatment}$*	*(% of N_{tot})*	*N_{tot}*	*(100%)*
Maximum intensity				
...maximum intensity	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Causality of AE to IMP				
...causality	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Action taken				
...action taken	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Outcome				
...outcome	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Seriousness				
Not serious	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Serious	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
Connected evaluation				
...intensity	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*
...causality	*N*	*(% of $N_{treatment}$)*	*N*	*(% of N_{tot})*

Table 15.3- 13: AE - analysis, period II by treatment - frequency analysis (% referring to total number of findings N_{tot}/findings under treatment $N_{treatment}$)

Analysis set: RP, SP

See Table 15.3- 11

Table 15.3- 14: AE - analysis, period III by treatment - frequency analysis (% referring to total number of findings N_{tot}/findings under treatment $N_{treatment}$)

Analysis set: RP, SP

See Table 15.3- 11

Table 15.3- 15: AE - analysis, total by treatment - frequency analysis (% referring to total number of findings N_{tot}/findings under treatment $N_{treatment}$)

Analysis set: RP, SP

See Table 15.3- 11

9.1.3.2 Safety-listings of deaths, other serious and significant Adverse Events

As applicable.

9.1.3.3 Safety-narratives of deaths, other serious and certain other significant Adverse Events

As applicable.

9.1.3.4 Safety-abnormal laboratory value listing (each subject)

Not applicable.

9.1.3.5 Safety-other safety characteristics

Table 15.3- 16: Vital signs – vital signs within study – descriptive statistics

Analysis set: RP, SP

Treatment	Time point		*...vital sign*
...treatment	*...time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.3- 17: Body temperature – body temperature within study– descriptive statistics

Analysis set: RP, SP

Treatment	Time point		Body temperature [°C]
...treatment	*...time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.3- 18: Vital signs - vital signs at end of study examination - descriptive statistics

Analysis set: RP, SP

Treatment	Time point		*...vital sign*
...treatment	*...time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.3- 19: Body temperature – body temperature at end of study examination – descriptive statistics

Analysis set: RP, SP

Treatment	Time point		Body temperature [°C]
…treatment	*…time point*	N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
TOTAL	TOTAL		

Table 15.3- 20: Laboratory examination - laboratory parameters at end of study examination by sex, matrix, and system - descriptive statistics

Analysis set: RP, SP

Sex: *sex*, Matrix: *matrix*, System: *system*									
Time point	Laboratory parameter	Unit	Normal value	N	Arithmetic Mean	SD	Minimum	Median	Maximum
…time point	*…parameter*								

Table 15.3- 21: Laboratory examination - laboratory parameters at end of study examination with regard to normal value by sex, matrix, and system - frequency analysis

Analysis set: RP, SP

Sex: *sex*, Matrix: *matrix*, System: *system*		Unit	N	within normal value	out of normal value	below normal value	above normal value
Time point	Laboratory parameter						
…time point	*…parameter*						

9.1.4 Other data

Table 15.4- 1: PK - Mean plasma concentrations by analyte, treatment and time - descriptive statistics

Analysis set: PKAS

Analyte	Treatment	Time	N	N_{miss}	N_{obs}	Arithmetic mean	SD	Minimum	Median	Maximum	Geometric mean	CV% geometric mean
…analyte	*…treatment*	*…time*										

Table 15.4- 2: PK - Individual plasma pharmacokinetic parameters by analyte, treatment and subject – listing and descriptive statistics

Analysis set: PKP, PKAS, Excluded (from PKAS)

Analyte	Treatment	Subject	*…parameter*
…analyte	…treatment	…subject	
		N	
		Arithmetic Mean	
		SD	
		Minimum	
		Median	
		Maximum	
		Geometric Mean	
		CV% Geom. Mean	

Table 15.4- 3: PK - Comparison of effects by analyte and parameter for ANOVA - inferential statistics

Analysis set: PKAS (pairwise comparisons)

Analyte	Parameter	Observations	Effect	Test	Reference	LSM Test	LSM Reference	Conf Level	Point Estimate	Lower_Limit CI	Upper_Limit CI	CV
…analyte	*…parameter*											

Table 15.4- 4: PK - Comparison of effects by analyte and parameter for ratio of t_{max}- inferential statistics

Analysis set: PKAS (pairwise comparisons)

Analyte	Parameter	Observations	Effect	Test	Reference	Point_Estimate
…analyte	*…parameter*					

Table 15.4- 5: PK - Comparison of effects by analyte and parameter t_{max} by signed-rank test – inferential statistics

Analysis set: PKAS (pairwise comparisons)

Analyte	Parameter	Observations	Test	Reference	Test statistics	p-value
…analyte	*…parameter*					

Table 15.4- 6: PK - Comparison of effects by analyte and parameter t_{max} by Hodges-Lehmann

Analysis set: PKAS (pairwise comparisons)

Analyte	Parameter	Observations	Test	Reference	Conf_level	Point_Estimate	Lower_Limit_CI	Upper_Limit_CI
…analyte	*…parameter*							

9.2 FIGURES PROVIDED FOR GENERATION OF THE REPORT (INCL APPENDIX 16.2)

9.2.1 Pharmacokinetic figures

Description Title proposal	Presentation/ comparison	Type and population
Figure 1: Single curves of plasma concentration vs. time per analyte and subject, grouped by treatment, linear plot	P	XY-plot; PKAS and Excluded
Individual plasma concentration vs. time curves of paracetamol after oral single dose administration of 1 tablet of [redacted]ODT (Test), 1 tablet of Alvedon Film-Coated Tablet (Reference 1) and 1 tablet of Panadol Film-Coated Tablet (Reference 2) under fasting conditions (500 mg paracetamol per treatment) to XX subjects, linear plot		
Figure 2: -, log-linear plot	P	XY-plot; PKAS
-, log-linear plot		
Figure 3: - including L_z-estimation, log-linear plot	P	XY-plot; PKAS and Excluded
-, delineating data points for estimation of L_z, log-linear plot		
Figure 4: Individual overlays of plasma concentration vs. time curves per analyte and treatment, grouped by subject, linear plot	P	XY-plot / PKAS
Figure 5: -, log-linear plot	P	XY-plot / PKAS
Figure 6: Mean plasma concentration vs. time curves per analyte, grouped by treatment, linear plot	C	XY-plot / PKAS
Figure 7: -, log-linear plot	C	XY-plot / PKAS

P: presentation emphasizes variability or range of a measurement in a specific group by using optimal scaling of axis/widest spread possible.

C: comparison emphasizes the variability of a mean value or the difference between groups by using uniform scaling of axis/consistent frame of reference.

10 REFERENCES

[1] Pharsight: Phoenix WinNonlin User's Guide, 6.3

[2] CPMP/EWP/QWP/1401/98 Rev. 1 Corr.**: Guideline on the Investigation of Bioequivalence. Committee for Medicinal Products for Human Use (2010)