Statistical Analysis Plan

Study title: Drug Cocktail Interaction Study to Investigate the Effect of St. John's Wort dry Extract Ze 117 on Several Cytochrome P450 Enzymes and on Transporter P-Glycoprotein in Healthy Volunteers.

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1 INTRODUCTION

The objective of this statistical analysis plan (SAP) is to specify the statistical analysis in more detail than stated in the protocol for the trial. The statistical analysis plan does not change the analysis described in the protocol, but it should be precise enough to serve as a guideline for statistical programming and creation of tables.

This SAP was developed with reference to the valid protocol (final version 2.0, dated 15-Jan-2018 and Non-Substantial Amendment, dated 13-Feb-2018).

2 RESPONSIBILITIES

The following persons will perform the statistical analysis (including SAS®-programming), the biometrical interpretation, the biometrical reporting and the internal quality control:

Responsible biometrician / project biometrician:

Name: Mikael Hansson, MSc

Title: Biostatistician

Project SAS®-programmer / data analyst:

Name: Annette Koltermann

Title: Senior Data Analyst / SAS Programmer

Pharmacokineticist:

Name: James Dickinson

Title: Vice President Clinical Services

3 STUDY OBJECTIVES

Primary objective

- To evaluate a possible interaction (induction or inhibition) of St. John's wort dry extract Ze 117 on several cytochrome P450 enzymes and the transporter P-gp by comparing the primary pharmacokinetic parameters of the cocktail substrates.

Secondary objective

- To evaluate a possible interaction (induction or inhibition) of St. John's wort dry extract Ze 117 on several cytochrome P450 enzymes and the transporter P-gp by comparing the secondary pharmacokinetic parameters of the cocktail substrates and their relevant metabolites.
- To evaluate the safety of Ze 117 alone and in combination with the probe drugs.

4 DESIGN OF THE STUDY

This is an open-label, non-randomized, single-sequence Phase I study.

Subjects will receive 500 mg Ze 117 in the morning of Days 8 to Day 17. A cocktail consisting of 7 probe drugs will be given three times as a single dose each (Day 1, Day 8, Day 17):

The compilation of the probe drugs is selected according to the validated cocktail (Geneva cocktail [1]) and contains the following probes:

- Caffeine (CYP1A2)
- Bupropion (CYP2B6)
- Flurbiprofen (CYP2C9)
- Omeprazole (CYP2C19)
- Dextromethorphan (CYP2D6)
- Midazolam (CYP3A4)
- Fexofenadine (P-gp)

5 SAMPLE SIZE AND POWER ESTIMATION

10 ± 1 male and 10 ± 1 female participants are planned to be included in this study.

The intra-subject coefficients of variation (CVs) for the AUCs of the administered cocktail probe drugs vary between 8% and 30% as reported in Bosilkovska et al 2016 [1].

A sample size of 16 subjects will allow a rejection of each null hypothesis "interaction present induction/inhibition" with $\alpha = 0.05$ (one-sided) and a power of at least 99% for a tolerance zone of 0.50 – 2.0 [3] assuming as a conservative approach that the intra-individual CVs exceed 30% and the true ratio of μtest/μreference = 1.0.

A sample size of 16 subjects will allow a rejection of each null hypothesis "interaction present induction/inhibition" with $\alpha = 0.05$ (one-sided) and a power of at least 90% for a tolerance zone of 0.70 – 1.43 [4] assuming that the intra-individual CVs exceed 30% and the true ratio of μtest/μreference = 1.0. Additional 4 subjects will be included to account for drop-outs as a safety margin, resulting in a total sample size of N=20.

Sample size calculations were performed using SAS 9.4 for equivalence of a one-sample mean in a multiplicative model.

6 ANALYSIS SETS

Safety set

Safety analysis will be performed on the Safety Set:

all included subjects who have received one dose of study drug.

Pharmacokinetic set

The evaluation of PK data will be based on the PK Set, a subset of the Safety Set, which is characterized by the following criteria:

- the proper completion of the study at least up the end of PK sampling

- the availability of PK samples to allow the determination of the primary PK parameters (a subject could be excluded after data base lock based on the primary PK parameters not being reliably derivable)
- the absence of any important protocol deviation which would impede the reliability of pharmacokinetic assessments. (Reasons to exclude the results from a subject in a particular period are events such as non-conformance during drug administration, vomiting and diarrhoea or any other reason which could render the plasma concentration-profile unreliable. The use of concomitant medication could be also a reason for excluding a subject.)

Protocol deviations will be discussed between the sponsor and CRO and allocation of subjects to study populations will be fixed prior to database lock and prior to availability of bioanalytical data.

7 PRESENTATION OF DATA

Tables and listings will be produced in accordance with the principles outlined by the International Council of Harmonisation (ICH) E3 guideline.

If not stated otherwise, descriptive statistics for qualitative data include number of cases and percentages. The percentages will be calculated taking into account the number of subjects in the population under consideration. Descriptive statistics for quantitative data include: number of cases, minimum, median, maximum, mean, standard deviation, coefficient of variation (CV; if appropriate). For plasma concentrations and PK parameters geometric mean and geometric CV also will be derived.

Summary statistics based on PK concentrations and PK parameters (including min and max) will be rounded to 3 significant figures.

The listed values of PK concentrations and PK parameters will be rounded to 3 significant figures.

The ratio of geometric means and confidence interval for the ratio of geometric means will be rounded to 2 decimal places and will be presented as a percentage.

Listings will be prepared including data that were not used for descriptive analysis for whatever reason, but annotated accordingly. Missing results will be indicated at the appropriate places allowing a distinction between reasons why the respective result is missing. Data will be used to the largest possible extent, without any extrapolation or imputation of missing results. Tables of descriptive statistics will additionally show the number of missing values.

In general, the scheduled measurement (rather than the control, if any) will be used in the statistical calculations for presentation in the tables of descriptive statistics (unless the scheduled measurement was considered unreliable, e.g. due to technical reasons, and needed to be replaced by an unscheduled repeat measurement). All data are presented in the data listings.

Baseline is defined as the last scheduled measurement before treatment.

Data listings will include all subjects, i.e. evaluable and not evaluable. Subjects will be identified by the unique subject number. Whenever applicable, the listing also will show the treatment to which the respective subject had been assigned at the specific time.

8 SOFTWARE

Software to perform descriptive and inferential analyses will be SAS® version 9.4.

The non-compartmental PK parameters will be calculated from the individual blood concentration-time data of the probe drugs and their metabolites on Days 1, 8 and 17 using Phoenix WinNonlin 7.0 or later.

9 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

Demographic variables and baseline physical characteristics (age, sex, race, weight, height, BMI, smoking status) will be summarized for the safety and the PK population, if different. The descriptive statistics will include number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number of observations and their percentages for categorical parameters.

Inclusion and exclusion criteria ensure that participants are healthy and fit for the trial without any relevant concomitant or previous illness or treatment that might have an influence on study results. These data as well as medical history will also be listed.

10 PHARMACOKINETIC PARAMETERS

The following pharmacokinetic parameters will be calculated for each subject and each treatment by non-compartmental analysis for levels of each probe drug and their metabolites in plasma. Primary and secondary parameters are defined as follows:

10.1 Primary Pharmacokinetic Parameters

AUC_{0-t} (h*ng/mL) = area under the plasma concentration-time curve up to the last sampling time with a concentration above the lower limit of quantification at Days 1 and 17 for each of the probe drugs.

10.2 Secondary Pharmacokinetic Parameters

AUC_{0-t} (h*ng/mL) = at Day 8

For Days 1, 8 and 17:

AUC_{0-inf} (h*ng/mL) = area under the concentration time curve from time 0 extrapolated to infinity calculated by adding C_z/λ_z to AUC_{0-t}

C_{max} (ng/mL) = measured maximal concentration

t_{max} (h) = time of observed maximal concentration

λ_z (/h) = terminal rate constant, by log linear regression

$t_{½}$ (h) = terminal half-life, calculated as (ln 2)/ λ_z

for each of the probe drugs and their metabolites.

The pre-dose sample always will be considered as if it had been taken simultaneously with the drug administration. If there should have been any deviations in post-dose sampling, the actual sampling

times relative to drug administration will be used unless stated otherwise. Missing data will not be replaced or imputed in any way. Concentrations below the lower limit of quantification (LLOQ) will be treated as zero.

AUC_{0-t} will be regarded as unreliable and will not be reported if more than two consecutive results are missing or if the concentrations were quantifiable for fewer than 5 time points. C_{max} and t_{max} will be regarded as unreliable if the maximum was observed preceding or following a sample with missing data. In case of multiple peaks, C_{max} and t_{max} refer to the highest measured concentration even if there should be earlier peaks. In case of two or more samples with the same concentration (as supplied by the analyst), t_{max} refers to the earlier of these.

The data points to be used for calculation of λ_z will be determined by visual inspection of concentration-time curves in log-linear scaling. The calculation will be considered sufficiently reliable in case of a coefficient of determination $r^2>0.85$ and unreliable in case of $r^2<0.8$. Cases in-between will be considered case-by-case. The starting time (T_k) for calculation of λ_z and the number of data points in the regression (N_z) as well as the coefficient of determination r^2 will also be tabulated.

The value of AUC_{0-inf} will be considered unreliable but will be reported if the terminal area beyond the last quantified sample is greater than 20% of the total AUC_{0-inf}.

Tabulation of Individual Data

The results of subject samples measured will be listed separately for each treatment and tables will be prepared showing descriptive statistics for concentrations at each sampling time. Samples with an unquantifiably low concentration will be identified. Results of subjects excluded from the Pharmacokinetic Set will be listed together with the data of the other subjects, will be annotated accordingly but will not be used for descriptive statistics and calculation of pharmacokinetic parameters. Similar listings and tables will be prepared for pharmacokinetic parameters.

For each subject in the Pharmacokinetic Set and each substance concentration-time curves will be plotted on a linear as well as on a log-linear scale, showing all treatments simultaneously. Similar plots will be generated for the mean concentration-time curves (incl. figures showing the mean course without standard deviation on a linear as well as on a log-linear scale and a figure showing the mean course with standard deviation on a linear scale).

The individual plasma concentrations of the probe drugs and their metabolites will be listed and tabulated by treatment and time point for all subjects with at least one PK assessment.

11 STATISTICAL METHODOLOGY FOR PHARMACOKINETIC ENDPOINTS

Descriptive statistics for all PK parameters will be calculated by analyte (probe drugs and metabolites). These tables will include number of observations, mean, standard deviation, median, minimum and maximum and additionally the geometric mean and geometric CV (not for t_{max}).

11.1 Statistical Hypothesis to be Tested

In order to preserve the overall alpha level of 5% for this study a hierarchical testing strategy will be used [2].

The null hypothesis will follow Schuirmann's two one-side tests procedure (α=0.05), i.e. assuming that there is an effect and the geometric mean ratio lies outside the limits.

The three different limits for the geometric mean ratio for AUC_{0-t} are:

(1) Mild effect limits (0.50 to 2.00) [3]

(2) Extended bioequivalence limits (0.70 to 1.43) also referred to as tolerance zone of 0.70–1.43 for phenotyping metrics in [4]

(3) Bioequivalence limits (0.8 to 1.25) [5]

A 90% CI for the ratio of the geometric means for AUC_{0-t} which lies entirely within the limits provides evidence of at most mild effect/extended bioequivalence/bioequivalence of Ze 117 regarding inhibiting/inducing the respective probe drugs.

The testing will be performed for each probe drug for the mild effect limits followed by the extended bioequivalence limits and finally the bioequivalence limits.

The order will correspond to a hierarchical testing strategyand therefore no adjustments for multiplicity will be performed.

The same hypotheses as for the primary parameter will be tested for the secondary pharmacokinetic parameters AUC_{0-t} (Day 8), AUC_{0-inf} and C_{max} (Day 1, 8 and 17) for probe drugs and metabolites.

11.2 Analysis of Primary Pharmacokinetic Parameters

The PK analysis will be performed based upon the Pharmacokinetic Set.

In order to assess the effect of multiple doses of Ze 117 on the primary parameter AUC_{0-t} of the probe drugs on Day 17 one way ANOVA models with terms for subject and treatment on the log transformed (base e) parameters will be performed (probe drug alone [Day 1] or probe drug co-administered with Ze 117 [Day 17]).

The estimated treatment differences between Day 17 and Day 1 will be transformed back to original scale and presented as a ratio between treatments including the corresponding 90% confidence interval.

11.3 Analysis of Secondary Pharmacokinetic Parameters

The same model as described in chapter 11.2 will be applied for the secondary parameters AUC_{0-t} on Day 8 and AUC_{0-inf} and C_{max}, t_{max}, λ_z , $t_{1/2}$ on Days 8 and 17 compared to Day 1 for each of the probe drugs and their metabolites.

12 SAFETY ENDPOINTS

12.1 Analysis Sets Analysed for Safety

All safety data of subjects who received at least one of the investigational products will be included in the safety analysis. All data will be used to their largest possible extent without any attempt to impute or extrapolate missing data.

12.2 Extent of Exposure

Not applicable as the deviation from the planned dosing is expected to be minimal in this trial.

12.3 Adverse Events

Frequency tables will be compiled showing the number of subjects per treatment affected by one or more of the following treatment emergent adverse events (TEAEs) including percentages and the number of events:

- TEAEs
- serious TEAEs
- severe TEAEs
- TEAEs leading to discontinuation
- Ze 117 related TEAEs (relationship certain, probable/likely or missing)
- probe drug/metabolite related TEAEs (relationship certain, probable/likely or missing)
- Ze 117 related serious TEAEs
- probe drug/metabolite related serious TEAEs
- Ze 117 related severe TEAEs
- probe drug/metabolite related severe TEAEs

Additionally, TEAEs will be tabulated by system organ class and preferred term.

Adverse event listings will be divided into pre-treatment AEs and TEAEs. AEs and TEAEs will be coded with the current version of Medical Dictionary for Regulatory Activities (MedDRA).

These listings will contain, at minimum:

- subject number
- treatment at start of AE,
- System organ class, preferred term, and AE as reported (in German and English)
- corresponding drug administration date and time
- Start date and time of AE
- Stop date and time of AE
- time since corresponding drug administration date and time
- duration of AE
- seriousness
- severity
- action taken
- relationship to Ze 117
- relationship to probe drug
- outcome
- led to study termination

12.4 Prior and Concomitant Medications

Any prior and concomitant medication will be encoded with WHO-DD, latest version. Prior and concomitant medications will be listed by subject (all subjects).

Variables: generic or trade name (as reported in CRF), WHO drug name, dose/intake, frequency, route, indication, start/end date and time.

12.5 Clinical Laboratory Examinations

Laboratory data will be listed separately for clinical chemistry, hematology, coagulation and urinalysis. Possibly clinically significant lab values will be listed separately.

Laboratory data will be listed by subject. Variables: subject, parameter, unit, results at each of the assessment times, comments (if any). Values outside of normal ranges will be highlighted or annotated. Another listing will show only abnormal laboratory values considered possibly clinically relevant. Shift tables from baseline to Day 8 and Day 18 will be produced for the categories normal, abnormal not clinically relevant and abnormal possibly clinically relevant.

12.6 Vital Signs

Vital Signs will be listed by subject, study time and treatment. Variables: subject, study time, date, clock time, systolic BP, diastolic BP, pulse, body temperature.

Tables: Descriptive statistics of vital signs by visit will be presented by treatment.

12.7 12-lead ECGs

ECG results (normal / abnormal with comment) will be listed sorted by subject, study time and treatment.

Clinically significant ECG assessments will be listed separately.

12.8 Physical Examination

Physical examination (performed yes/no) will be listed by subject. Any abnormality will be recorded either in the medical history or as an adverse event.

12.9 Drug Administration and Blood Sampling

A listing of date and time of each drug administration and each blood sampling including time deviations will be provided sorted by subject.

13 STATISTICAL METHODOLOGY FOR SAFETY ENDPOINTS

The safety data will be evaluated descriptively only.

14 CHANGES FROM THE PROTOCOL

The statistical analysis plan conforms to the study protocol and its amendment(s).

15 INTERIM ANALYSES

Interim analyses are not anticipated.

16 GENERAL FORMAT OF TABLES, FIGURES AND SUBJECT DATA

There are no sponsor-specific guidelines or SOPs that have to be observed for the analysis or report generation.

The standard report is an integrated study report according to Nuvisan SOPs and ICH-guidelines. The sponsor does not require any specific formats (e.g. footer, header, margins, fonts) to be observed. The TLFs provided for the report will be formatted with font courier new with at least 7 points.

Treatment labels to be used in listings and tables will be:

T1: Ze 117 + Geneva cocktail (Day 17)
T2: Ze 117 + Geneva cocktail (Day 8)
R: Geneva coktail (Day 1)

The following lists (Section 17) provide an overview of a possible TOC numbered according to ICH recommendations:

17 Appendix

17.1 List of End-of-Text-Tables

Numbering system according to the ICH recommendations

14.1 Demographics and Other Baseline Characteristics (Safety and PK set, if different)
14.1.1 Mean Age, Height, Weight and BMI at Screening
14.1.2 Distribution Statistics of Gender, Ethnic Origin and Smoking Status

14.2 Pharmacokinetic Data (Pharmacokinetic set)
14.2.1 Summary Data on Plasma Concentrations
14.2.3 Summary Data on Pharmacokinetic Parameters
14.2.4 Summary of Statistical Results Comparing Pharmacokinetic Parameters between Treatments

14.3 Safety Data (Safety set)
14.3.1 Displays of Adverse Events
14.3.1.1 Overview of Treatment Emergent Adverse Events
14.3.1.2 Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.1.3 Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
14.3.2 Listings of Death, Other Serious and Significant Adverse Events
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
14.3.4 Listings of Possibly Clinically Relevant Abnormal Laboratory Values
14.3.4.1 Listings of Possibly Clinically Relevant Abnormal Clinical Chemistry Laboratory Values
14.3.4.2 Listings of Possibly Clinically Relevant Abnormal Hematology Laboratory Values
14.3.4.3 Listings of Possibly Clinically Relevant Abnormal Coagulation Laboratory Values
14.3.4.4 Listings of Possibly Clinically Relevant Abnormal Urinalysis Laboratory Values
14.3.5 Clinical Laboratory Evaluations
14.3.5.1 Clinical Chemistry Shifts from Baseline to Time Point
14.3.5.2 Hematology Shifts from Baseline to Time Point
14.3.5.3 Coagulation Shifts from Baseline to Time Point
14.3.5.4 Urinalysis Shifts from Baseline to Time Point
14.3.6 Other Safety Evaluations
14.3.6.1 Clinically Significant ECG Results

17.2 List of End-of-Text-Figures

Numbering system according to the ICH recommendations

14.2.2 Mean Plasma Concentration-Time Profiles (Pharmacokinetic set)

17.3 List of Appendices to the CTR

Numbering system according to the ICH E3 recommendations

16.1.9.2 Statistical Analysis Output (Pharmacokinetic set)

16.2 Subject Data Listings

16.2.1 Discontinued Subjects (if any)
16.2.2 Major Protocol Deviations/Reasons for Exclusion from Analysis Sets (if any)
16.2.3 Analysis Sets (All Subjects)
16.2.4 Demographic Data and Baseline Characteristics (Safety set)
16.2.4.1 Demographic Data
16.2.4.2 Female Contraception/Childbearing Potential
16.2.4.3 Study Dates
16.2.4.4 Not Fulfilled Inclusion/Exclusion Criteria, Eligibility and Check of Restrictions
16.2.4.5 Medical History
16.2.4.6 Nicotine Consumption
16.2.4.7 Alcohol Consumption
16.2.5 Compliance and/or Drug Concentration Data (Pharmacokinetic set)
16.2.5.1 Drug Concentration Data – Plasma (Lists and Figures)
16.2.5.2 Pharmacokinetic Analysis
16.2.6 Individual Data (Safety set)
16.2.6.1 Vital Signs
16.2.6.2 12-Lead ECG
16.2.6.3 Physical Examination
16.2.6.4 Prior and Concomitant Medications
16.2.6.5 Drug Administration, Pharmacokinetic Blood Sampling Times and Time Deviations
16.2.6.6 Study Completion Status
16.2.7 Adverse Event Listings (Safety set)
16.2.7.1 Pre-Treatment Adverse Events
16.2.7.2 Treatment Emergent Adverse Event Listing by Subject
16.2.7.3 Treatment Emergent Adverse Event Listing by Treatment
16.2.8 Individual Laboratory Measurements by Subject (Safety set)
16.2.8.1 Dates and Times of Laboratory Sampling
16.2.8.2 Clinical Chemistry Laboratory Results
16.2.8.3 Hematology Laboratory Results
16.2.8.4 Coagualtion Laboratory Results
16.2.8.5 Urinalysis Laboratory Results
16.2.8.6 Other Tests

18 References

1. Bosilkovska M, Samer CF, Déglon J, Thomas A, Walder B, Desmeules J A, Daali Y. Evaluation of Mutual Drug–Drug Interaction within Geneva Cocktail for Cytochrome P450 Phenotyping using Innovative Dried Blood Sampling Method. Basic & Clinical Pharmacology & Toxicology. 2016;DOI: 10.1111/bcpt.12586

2. Committee for Human Medicinal Products (CHMP), CPMP/EWP/908/99, POINTS TO CONSIDER ON MULTIPLICITY ISSUES IN CLINICAL TRIALS

3. Committee for Human Medicinal Products (CHMP), CPMP/EWP/560/95/Rev. 1 Corr. 2, 21 June 2012, Guideline on the investigation of drug interactions

4. Doroshyenko O., Rokitta D., Xadoyan G. Klement S., Schläfke S, Dienel A. Gramatté T., Lück H, Fuhr U. Drug Cocktail Interaction Study on the Effect of the Orally Administered Lavender Oil Preparation Silexan on Cytochrome P450 Enzymes in Healthy Volunteers, Drug Metab Dispos 41:987–993, May 2013

5. Committee for Human Medicinal Products (CHMP), CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE, January 2010