Randomized, Parallel-group, Double-blind, Comparative Bioequivalence Trial of MabionCD20 (Mabion SA) Compared to MabThera (rituximab by Hoffman-La Roche) in Patients with Diffuse Large B-cell Lymphoma

Statistical analysis plan

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STUDY STATISTICIAN	Jacek Koziarek
TRIAL CHIEF INVESTIGATOR	Katarzyna Bartosik
SAP AUTHOR	Mateusz Piechaczek and Marian Płaszczyca

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Contents

1 List of abbreviations

Abbreviation	Text
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the curve
BSA	Body surface area
C_{max}	Maximal concentration
C_{trough}	Plasma concentration just before final infusion (Week 22)
CI	Confidence interval
CV	Coefficient of variation
DLBCL	Diffuse large B-cell lymphoma
DRM	Data review meeting
DSMB	Data Safety and Monitoring Board
eCRF	Electronic case record form
ECG	Electrocardiogram
ICH	International conference on harmonization
ITT	Intention to Treat
LLT	Low level term
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
SAE	Serious adverse event
SAF	Safety population
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TFL	Tables, figures and listings
WHO	World Health Organization

2 General

This statistical analysis plan reflects study protocol MabionCD20- 002NHL version final 4.0, dated 29-September-2016. It follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9 and all details for the statistical analysis of this study will be provided in this document.

All aspects of the statistical analysis shall be covered by this document. It provides a technical and detailed description of handling the collected data and statistical methods deployed.

2.1 SOPs to be followed

The statistical analysis will be carried out according to Biostat SOPs. The report will be written according to the ICH Guidelines.

3 Overview of the protocol

3.1 Objectives of the study

3.1.1 Primary objective

To demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product: MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma, based on:

1. Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until the second administration at Week 4 (AUC 1-4);
2. Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured at steady state after the fifth administration (Week 13) until Week 26 (AUC 13-26).

3.1.2 Secondary objectives

To demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma based on:

- Comparative analysis of the secondary pharmacokinetic parameters:
  - Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26 (AUC 1-26);
  - Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion;
  - Maximum plasma drug concentration (Cmax) at steady state after the 5^{th} and 8^{th} infusions;
  - Elimination Rate Constant (K_{el}) at steady state after the 5^{th} and 8^{th} infusions;
  - Elimination Half-Life ($T_{½}$) at steady state after the 5^{th} and 8^{th} infusions;
  - Clearance at steady state after the 5^{th} and 8^{th} infusions;
- Comparative analysis of the pharmacodynamic parameter: area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell);

- The percentage of patients achieving the efficacy endpoints as following: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD).
- Comparative safety and immunogenicity of MabionCD20 and MabThera based on the following safety endpoints: adverse events, clinical laboratory assessment, presence of Human Antichimeric Antibodies (HACA).

The endpoint variables that are used in order to achieve these objectives are detailed in section 3.4.2.

3.2 Study design

This is a multicenter, randomized, parallel-group, double-blind phase IIIb comparative study of two monoclonal antibody medicinal products: MabionCD20 (Mabion SA) and MabThera (Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma eligible for treatment with rituximab according to MabThera Summary of Product Characteristic.

Trial population is diagnosed according to WHO classification of lymphomas and patient enrollment is based on the diagnosis of DLBCL at each study center.

Patients are randomly assigned, without stratification, to 1 of 2 treatment groups: MabionCD20 or MabThera with treatment allocation ratio of 5:2, both receive background chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP). The duration of the study is 12 months.

The treatment and observation phase lasts until week 26 with a follow-up phase until Week 46.

The sponsor, investigators and patients will be blinded to treatment allocation until week 26 of the last patient, at which time the sponsor will be unblinded for the purposes of data analysis.

3.3 Sample size

The study is a double-blind, multicenter, randomized, parallel-group study of 2 treatments, MabionCD20 (Test Product) compared to MabThera® (Reference Product).

Pharmacokinetic equivalence:

With an expected mean ratio of 90 - 110% and Coefficient of Variation of 50% as well as assumed 5:2 MabionCD20 to Mabthera treatment allocation at least 112 patients (80 patients in MabionCD20 group and 32 patients in MabThera group) are required to complete the study to achieve a power of 80% and to demonstrate equivalence within the 70%-143% interval. Assuming a 20% drop-out rate, total of 140 patients should be randomized (100 patients in MabionCD20 group and 40 patients in MabThera group).

Assuming a 20% screen failure rate a total of 175 patients needs to be screened.

3.4 Endpoints

3.4.1 Primary study endpoints

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until the second administration at Week 4 (AUC 1-4);

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured at steady state after the fifth administration (Week 13) until Week 26 (AUC 13-26).

3.4.2 Secondary endpoints

3.4.2.1 Pharmacokinetic endpoints:

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26 (AUC 1-26);
- Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion;
- Maximum plasma drug concentration (Cmax) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Rate Constant (Kel) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Half-Life (T ½) at steady state after the 5th and 8th infusions;
- Clearance at steady state after the 5^{th} and 8^{th} infusions.

3.4.2.2 Pharmacodynamic Endpoint:

- Area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell);

3.4.2.3 Efficacy endpoint

- Tumor responses will be evaluated at Week 11 and 26 according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas (Cheson B et al. 1999) into following categories:
  - Complete response (CR)
  - Partial response (PR)
  - Stable disease (SD)
  - Progressive disease (PR)

3.4.3 Safety variables

- Adverse events (AEs)
- Serious AEs
- Clinical laboratory results
- Vital signs
  - Diastolic Blood Pressure
  - Systolic Blood Pressure
  - Respiratory Rate
  - Pulse
  - Temperature
- ECG abnormalities
- Clinically significant changes in patient's physical examination

3.4.4 Immunogenicity Endpoints:

- Percentage of patients who developed detectable Human Anti-Chimeric Antibodies (HACA). Immunogenicity endpoints will be evaluated at Week 26.

3.5 Study flow charts

See protocol.

4 General aspects of the statistical analysis

4.1 Analyses planned and already performed

The study is a clinical multicenter, randomized, parallel-group, double-blind phase IIIb comparative study. The main analysis will be performed after last patient concludes visit 13 (26th week of observation), additionally a follow-up analysis will take place following conclusion of visit 14th (on 46th week of observation) by the last patient.

Both main as well as follow-up report will incorporate results of primary and secondary variables analyses including pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity.

4.2 Analysis populations

The statistical analysis will be based on the following study populations:

- Intent To Treat (ITT) population: This analysis population comprises all patients randomized into the study, receiving at least one dose of study medication and having at least one complete post baseline assessment of the area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until the second administration at Week 4 (AUC 1-4). If this is not the case, it will be decided on how to proceed with these patients in the DSMB). However, patients who terminate the study early due to an adverse event related to study medication will not be excluded from the ITT. Patients will be analyzed according to the treatment they were randomized to.
- Per protocol (PP) population: This analysis population will be a subset of the ITT population that includes only those patients without major detected protocol deviations and having PK assessment at Week 26. The per-protocol analysis population will be the main population used for the efficacy analyses.
- Safety population (SAF): This analysis population comprises all patients randomized into the study and receiving at least one portion of an infusion of study medication. Patients will be analyzed according to the treatment they were treated with. This population will be used for all safety analyses.

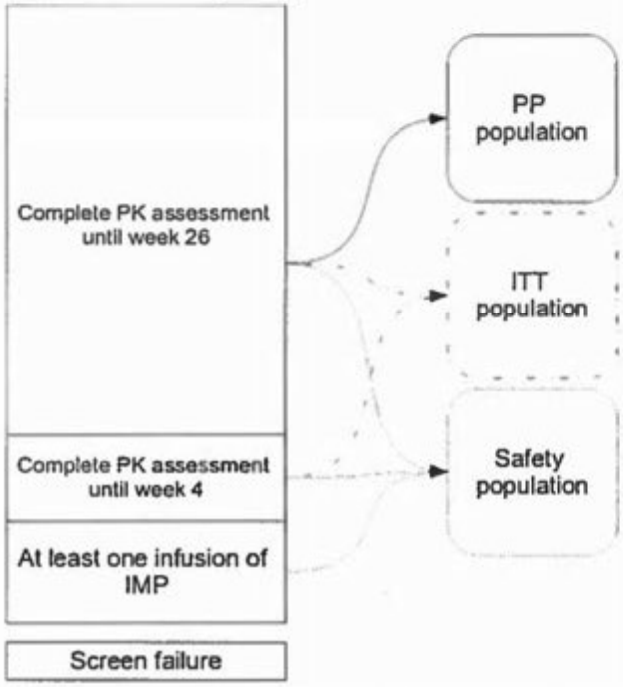

Figure 1: Diagram of analysis population.

4.3 Protocol deviations

For the allocation of patients to analysis populations, all protocol deviations will be reviewed according to the criteria specified below. A blind data review plan, which will be finalized prior to the blind data review meeting, might further specify the criteria. This plan will further specify all data and listings that are needed to review and assess the protocol deviations.

The determination of major and minor protocol deviations will be performed during the blind data review meeting documented in the blind data review meeting minutes, which will be

finalized prior to unblinding of the treatment group for the main analysis of data of the double-blind treatment period.

The following protocol violations are defined as major and will thus lead to the exclusion of a patient from the population:

Number	Protocol deviation	Reasons for exclusion from PP population	Reasons for exclusion from ITT population
1	Early termination of study and / or no valid assessment of AUC 13-26 at Week 26	X	
2	Early termination of study and / or no valid assessment of AUC 1-4 at Week 4	X	X
2	Prohibited medication administered that is expected to influence pharmacokinetical parameters at Week 26	X	X
3	Violation of in- or exclusion criteria that have an impact on PK variables at Week 26	X	
4a	Major deviations from visit schedule for visit week 26	X	
4b	Major deviation from blood sampling schedule for PK parameters	X	
5	Dose or administration of study medication deviates substantially from protocol schedule	X	X
6	Other deviation from protocol that influences substantially the values of PK set variables at Week 26.	X	

4.4 Changes from specifications in the protocol

Not applicable

5 Statistical analysis specifications

5.1 General

All tests of significance, unless otherwise specified, will be two-sided with a maximal type I error risk of 5%.

5.1.1 Definitions

5.1.1.1 Day 1 and relative study days

Day 1 is defined as the day of the first infusion of study medication (reference date). In general, any date provided in patient listings will be presented as study day (in addition to the date provided): If a date is later than the reference date then the study day is calculated as study day = date - reference date +1.

If a date is prior the reference date then the study day is a negative number calculated as day = date - reference date. No study day 0 will exist.

5.1.2 Specifications for summary tables

For **continuous variables**, summary statistics will generally consist of sample size N, number of missing values, arithmetic mean, standard deviation (SD), median, minimum,

and maximum. Summaries of PK and PD variables will contain the geometric mean and the coefficient of variation in addition.

Binary/categorical data will be summarized and displayed in frequency tables showing sample size, absolute and relative frequencies.

In general, data will be included in summary tables stratified by randomized treatment group.

5.1.3 Data listings

Appendix 2 contains the list of listings that will be produced for the CSR. Data will be listed as documented. Relevant generated and transformed variables will be listed next to the original data items. Any imputed value will be flagged.

In all listings the patient identifier and the randomized treatment group will be included. The patient identifier consists of the center and the patient number, additionally a flag specifying analysis set will be provided.

In general, patient listings will be sorted by patient identifier and visit (if applicable), unless otherwise stated.

Patient listings of data that is collected independently from visits (e.g. adverse events, medical histories or medication) will be sorted by patient identifier, day of onset or start day of administration, duration and MedDRA preferred term or WHO base substance name, respectively.

Missing values in the listings will be represented as NA (not available) for both text and numerical data. In case of partially missing dates (when day or day and month is unknown) missing data will be represented as series of 9s – for example 2017-05 will be presented as 2017-05-99. Any imputed data will be presented separately from raw data or flagged accordingly in order to be able to review all data as collected.

5.1.4 Handling of wthdrawals, missing values and outliers

These definitions apply to the first 26 weeks of the study.

For the main analyses performed using the PP population, data will be analyzed as observed during the study, no imputation rule will be applied.

For the ITT approach of the efficacy variables, patients withdrawn due to AE will be considered non-responders at the time of early termination visit, provided that AUC 1-4 can be calculated. No imputation for PK and PD parameters will be used. For other missing data, the last observation carried forward (LOCF) imputation method will be applied.

A worst-case scenario will be used in the estimation of partial dates for adverse events and concomitant medications. That is, for an incomplete start date the first day of the month or the first month of the year will be used. For an incomplete stop date the last day of the month or the last month of the year will be used. If an estimated start date of an adverse event is earlier than the date of day 1 or the start date is completely missing, day 1 will be used, unless documented data does not allow for this interpretation.

Whenever estimated dates will be calculated, the incomplete date will be listed and the study day will be calculated using the estimated date. These study days will be flagged as estimated in listings.

For other situations regarding missing data not mentioned in this document, missing data will generally not be replaced or imputed.

5.2 Disposition of patients

The number of patients screened, the number of patients randomized and the number of patients in each analysis population will be summarized. The reasons for exclusion from each analysis population will be summarized for all patients randomized. The reasons for non-eligibility for randomization, i.e. the violated inclusion or exclusion criteria will be listed for all non-randomized patients by visit.

Major protocol deviations (leading to the exclusion from the PP) and minor protocol deviations (not leading to the exclusion from the PP) will be summarized for the safety population. The determination of major and minor protocol deviations will be performed during the blind data review meeting documented in the blind data review meeting minutes, which will be finalized prior to unblinding of the treatment group for the main analysis of data of the double-blind treatment.

The number of patients who completed the study and the number of patients who terminated the study early will be summarized in frequency tables for the safety, the ITT and the PP populations.

The timing of early termination will be summarized for each study month for the safety, the ITT and the PP populations.

Consolidated Standards of Reporting Trials (CONSORT) diagram (Moher et al. 2001) will be used to present abovementioned data in a graphical form (see SAP appendix).

5.3 Demographics and baseline characteristics

Demographic data and other baseline characteristics will be summarized for Safety, ITT, and PP population by treatment group and overall. The following variables will be summarized:

- Age as continuous variable and in categories (< 65 years / ≥ 65 years)
- Sex (male / female)
- Race (unless all the patients belong to one)
- Weight and height
- Vital signs
- BSA
- Ann Arbor staging
- ECOG/WHO performance status
- IPI assessment
- Number of extranodal sites
- Patient staging
- β2 microglobulin

Additionally baseline clinical data (WBC, RBC, hematocrit, hemoglobin, platelet count, WBC, AST, ALT, total bilirubin, serum creatinine, alkaline phosphatase, blood urea nitrogen, IgG, IgA, IgM) will be summarized by gender and treatment.

All other screening or day 1 safety assessments will be listed only unless specified differently below.

5.4 Medical history

Current medical conditions are defined as those medical histories that are ongoing at the screening visit. Medical histories and current medical conditions will be coded using the MedDRA dictionary version 21.0. Medical histories and current medical conditions will be summarized by treatment group and overall for the safety population.

5.5 Concomitant medication, rescue medication and premedication

Any medication will be classified using the World Health Organization (WHO) Drug Dictionary Version: June 1, 2012.

The categories rescue and premedication will be analyzed as documented in the eCRF. All medication other than rescue medication or premedication will be categorized into prior medication, which stopped prior to the administration of the first dose of study medication, and concomitant medication, which was administered at or after the first dose of study medication.

All medications of each patients will be listed separately for the different categories of medication (prior, concomitant, rescue, premedication).

5.6 Study drug exposure

The duration of infusion for each infusion will be calculated using the exact start and stop time for start of infusion and stop of infusion.

The number of infusions will be summarized in frequency tables for the safety, ITT and PP populations The duration of infusion and the total dose of study medication administered will be summarized by visit and overall for the safety, ITT and PP populations.

5.7 Pharmacokinetic and pharmacodynamic endpoints

The primary efficacy endpoint is to demonstrate high level of biosimilarity between between MabionCD20 (MABION SA) and the reference product: MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma, based on:

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until the second administration at Week 4 (AUC 1-4);
- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured at steady state after the fifth administration (Week 13) until Week 26 (AUC 13-26).

Equivalence will be demonstrated within 70%-143% interval.

The hypotheses to be tested are:

H_{01}: $\mu_T-\mu_R \leq -\delta$

H_{11}: $\mu_T-\mu_R > -\delta$

and

H_{02}: $\mu_T-\mu_R \geq +\delta$

H_{12}: $\mu_T-\mu+<+\delta$

Where: μ_T and μ_R are mean AUC.

Hypotheses will be tested using two one-sided t-tests as described by Schuirmann (1987).

The exact description of methods for derivation of pharmacokinetic and pharmacodynamic endpoints is outside the scope of this SAP. The bioanalytical reports will provide all details.

5.7.1 Descriptive analysis of PK data

Descriptive summaries of plasma concentration and PK parameters will include N, the arithmetic mean value, SD, median, minimum and maximum if data is not log-transformed, and the geometric mean value and geometric %CV, median, minimum and maximum if the data is log-transformed. The geometric %CV will be calculated as $100*(\exp(\sigma^2)-1)^{1/2}$, with σ^2 = variance of log-transformed data.

The geometric mean of plasma concentrations in each treatment groups will be shown graphically from Day 1 until the C_{trough} (measured directly before final infusion in Week 22), as well as from Day 1 until Week 26 (Visit 13).

5.7.2 Analysis of PK endpoints

Data will be log-transformed prior to analysis.

For all PK endpoints specified in 3.4.1 and 3.4.2.1 the parametric point estimators for the mean ratio between treatment groups and, consistent with the two one-sided tests for bioequivalence [Schuirmann, 1987], the shortest 90% confidence intervals will be calculated and presented, respectively, using the LSMeans and the root of residual mean squares from the ANOVA of log-transformed data with subsequent exponential transformation [Chow S C, Liu J P, 2000].

The ANOVA model will contain treatment as factor. Additionally, due to unequal geographical distribution of centers and patients the following location groups will be used:

- Georgia (all sites),
- Site UKR03 (due to large number of patients this location will be treated separately),
- Western Ukraine (sites: NHL-UKR-13, NHL-UKR-14, NHL-UKR-15, NHL-UKR-16, NHL-UKR-17),
- Central Ukraine (sites NHL-UKR-02, NHL-UKR-06, NHL-UKR-07, NHL-UKR-09, NHL-UKR-12),
- Eastern Ukraine (sites: NHL-UKR-05, NHL-UKR-08, NHL-UKR-10).

5.7.3 Confirmative analysis of the primary PK endpoints

If both of two-sided 90% confidence intervals for AUC_{0-t} for AUC 1-4 AND AUC 13-26 respectively are completely contained within the interval 0.7 to 1.43 then the bioequivalence between the two treatments will be established. Sensitivity analyses will be performed based on the subset of the ITT population with PK data measured.

5.7.4 Subgroup analyses for PK endpoints

Subgroups for primary and secondary PK endpoints will be defined using HACA.

5.7.5 Analysis of PD endpoint

The two treatment groups will be compared with respect to the PD endpoints as listed in 3.4.2.2 in a descriptive manner. For $AUC_{0-t\ B\text{-}cell}$ between-group mean differences and 95% CI will be calculated using an ANOVA with treatment and center as factors. Data will be log-transformed if assumption of normality is not satisfied. In this case ratios of means will be used to compare the two treatment groups. All PD measurements and calculated parameters will be listed for all patients with data available.

The geometric means of PD variables in both treatment groups will be presented graphically showing the whole study period on the time axis.

5.8 Efficacy endpoints

All efficacy will be provided for the PP population, but efficacy analysis for the primary endpoint "*Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until the second administration at Week 4 (AUC 1-4)*" will be provided for ITT population.

5.8.1 Efficacy variable

Within each treatment group, percentage of patients achieving the complete response, partial response, presenting stable or progressive disease (as defined by International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas) will be presented.

5.8.2 Subgroup analyses for efficacy endpoints

No analysis in subgroups are planned.

5.9 Immunogenicity endpoints

5.9.1 Immunogenicity variable

Frequency of Human Antichimeric Antibodies (HACA) will be tabulated by treatment.

5.10 Safety

Safety data will be summarized for the safety population.

5.10.1 Adverse event analysis

Any undesirable signs, symptoms or medical conditions occurring or worsening of pre-existing conditions between signing informed consent and the first administration study medication are considered as pre-treatment AEs. Undesirable signs, symptoms or medical conditions or worsening of pre-existing conditions occurring after the first administration of study medication are considered as treatment emergent adverse events (TEAEs).

A TEAE will be analyzed as related to study medication (i.e. as adverse drug reaction, ADR) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite' or if the relationship to study treatment is missing.

An overview table presenting the incidence of the following AE categories will be presented. Percentage of patients in each category will be compared between treatments as a difference in proportions between treatments including a 95% CI based on the Agresti – Caffo method (2000)[1]:

- All AEs
- Pre-treatment AEs
- Serious AEs (SAEs) (including pre-treatment SAEs)
- Treatment emergent SAEs (TESAEs)
- Severe TEAEs
- Related TEAEs
- Related severe TEAEs
- TEAEs leading to reduction of dose
- TEAEs leading to interruption of dose
- TEAEs leading to permanent discontinuation (i.e. withdrawal) of study medication

[1] Agresti-Caffo 95% CI will be calculated only for adverse events registered until week 26.

- Related TEAEs leading to permanent discontinuation of study medication
- AEs leading to death (i.e. outcome of AE is fatal)
- TEAEs leading to death
- Related TEAEs leading to death

All treatment emergent AEs (TEAEs) and all serious TEAEs will be tabulated by MedDRA SOC and PT presenting the number and percentage of patients reporting the AE and the number of AEs reported. Additional tables will distinguish the events by whether the AE was related to study medication and by maximum severity.

All AEs documented in the eCRF will be listed by patient. Data listings will include patient ID, treatment group, verbatim term, preferred term, system organ class, start and stop date and relative day of the AE, severity, medications (yes/no), seriousness, action taken with study medication, relationship to study medication, and outcome will be provided. TEAEs will be flagged as such. In addition, separate listings for all SAE's, deaths and AEs leading to discontinuation (action taken with study treatment = drug withdrawn or AE is reason for early termination) will be presented.

5.10.2 Safety laboratory data

Baseline for safety laboratory data is defined as the last pre-treatment value measured for each parameter separately. Data from early termination visits will not be included in summary tables.

All laboratory safety data will be listed, including flags for values outside normal ranges.

Numeric laboratory data along with its change from baseline will be summarized by study visit. Shift tables using the categories 'lower than normal range', 'within normal range' and 'higher than normal range' will be provided for each parameter, comparing the baseline value to all post-baseline values.

Discrete laboratory data will be summarized by frequency at each level of measurement and visit.

Results from pregnancy testing will be listed only.

5.10.3 Vital signs

Baseline for vital signs data is defined as the last pre-treatment value measured for each parameter separately. Data from early termination visits will not be included in summary tables. Vital sign data along with its change from baseline will be summarized by study visit.

5.10.4 Physical examination, ECG and other safety data

The number of patients with at least one clinically relevant finding detected during the physical examination or the ECG will be summarized in frequency tables for each scheduled assessment or visit.

6 Software and statistical programming

R programming will be performed according to Biostat standards as defined in PS11/2016 SOP "Data analysis" and related work instructions. The statistical analysis will be performed using the R statistical software package (Version 3.3 or later). All pharmacokinetic and pharmacodynamics analyses will be performed in Phoenix WinNonlin 6.2 or later.

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8 Appendix to the SAP

The appendix contains table shells ('mock-up tables') for each type of tables and a table of contents for summary tables and listings that will be produced.