Statistical Analysis Plan

Clinical Trial Protocol Identification No.	EMR200006-001
Title:	A Randomized, Two-period Crossover Trial Examining Bioequivalence of Bisoprolol-Amlodipine 5 mg/5 mg Combination Tablets versus Bisoprolol 5 mg Tablets and Amlodipine 5 mg Tablets Given Concomitantly in Healthy Subjects in Fasting and Fed State
Trial Phase	Phase I
Investigational Medicinal Product(s)	Bisoprolol Amlodipine 5 mg/5 mg Combination Tablets
Clinical Trial Protocol Version	28 April 2017 / Version Final 1.0
Statistical Analysis Plan Author	PPD Biostatistician PPD Biostatistician PPD Pharmacokineticist
Statistical Analysis Plan Date and Version	18 Sep 2017/ Final Version 2.2
Statistical Analysis Plan Reviewers	Merck-Serono Reviewers: PPD, Trial Biostatistician, Merck Serono PPD Reviewers: PPD Senior Biostatistician, PPD PPD, Biostatistician, PPD PPD, Senior Research Pharmacokineticist, PPD PPD, Senior Research Pharmacokineticist, PPD

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Statistical Analysis Plan (18 Sep 2017, Final Version 2.2): EMR200006-001

A Randomized, Two-period Crossover Trial Examining Bioequivalence of Bisoprolol-Amlodipine 5 mg/5 mg Combination Tablets versus Bisoprolol 5 mg Tablets and Amlodipine 5 mg Tablets Given Concomitantly in Healthy Subjects in Fasting and Fed State

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3 List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse Event
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity
AUC_{0-t}	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$
BE	Bioequivalence
CI	Confidence Interval
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration.
C_{max}	Maximum observed plasma concentration
CRO	Contract Research Organization
CSR	Clinical Study Report
CTR	Clinical Trial Report
CTMS	Clinical Trial Management System
CTP	Clinical Trial Protocol
CV	Coefficient of Variation (%)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LLOQ	Lower Level of Quantification

Max	Maximum
Mean	Arithmetic mean
Min	Minimum
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
N	Number of non-missing observations
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment-Emergent Adverse Event
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	The time to reach the maximum observed concentration
$V_{z/f}$	Apparent volume of distribution during the terminal phase following extravascular administration
λ_z	Terminal elimination rate constant

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
Draft V0.1	02Jun2017	PPD	Not Applicable – First Version
Final V1.0	28Jun2017	PPD	Update per internal comments
Final V1.1	26Jul2017	PPD	Update per sponsor's comments
Final V1.2	08Aug2017	PPD	Update per sponsor's comments
Final V2.0	01Sep2017	PPD	Update per sponsor's comments
Final V2.1	13Sep2017	PPD	Update per sponsor's comments
Final V2.2	18Sep2017	PPD	Update per sponsor's comments

5 Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for protocol EMR200006-001. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

The SAP is based upon Section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

Trial Objectives	**Primary Objectives** • To demonstrate bioequivalence (BE) between the bisoprolol-amlodipine fixed-dose-combination tablet (investigational product) and bisoprolol and amlodipine tablets administered concomitantly (comparator) given as a single oral dose in fasting and fed state. **Secondary Objectives** • To compare the pharmacokinetic (PK) profiles of bisoprolol and amlodipine between the investigational product and comparators. • To examine the safety and tolerability of bisoprolol and amlodipine for the fixed dose combination tablet compared with

	the bisoprolol and amlodipine tablets administered concomitantly. • To explore the effect of food intake on the PK of the 2 active ingredients.
Trial Endpoints	**Primary Endpoint** • Primary endpoints will be the PK parameters area under the (plasma) concentration-time curve (AUC) from time 0 to time t (AUC_{0-t}) and maximum plasma concentration observed (C_{max}) of bisoprolol and amlodipine. **Secondary Endpoints** • Secondary endpoints include time of maximum plasma concentration observed (t_{max}), apparent terminal half-life ($t_{1/2}$), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), the extrapolated part of area under the plasma concentration curve ($AUC_{extra\%}$), terminal elimination rate constant (λ_z), total clearance following extravascular administration ($CL_{/f}$), and apparent volume of distribution ($V_{z/f}$) for bisoprolol and amlodipine. Safety and tolerability will be assessed by AEs, vital signs, biochemistry, hematology, urinalysis, 12-lead ECG, and physical examination. **Safety endpoints:** • The safety assessments comprise adverse events, laboratory tests, vital signs, electrocardiogram (ECG) and concomitant medications.
Trial design	This is a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial where subjects will be randomized to receive the treatment, in each period, either • Treatment A: One fixed-dose-combination tablet of 5 mg/5 mg bisoprolol-amlodipine (Concor AM), or • Treatment B: One tablet of bisoprolol 5 mg (Concor®) co-administrated with amlodipine 5 mg tablet (Norvasc®). • Drug administration will be done with or without food depending on cohort allocation to either fasting or fed state. The subjects will remain in the same group (fasting or fed) in both treatment periods.

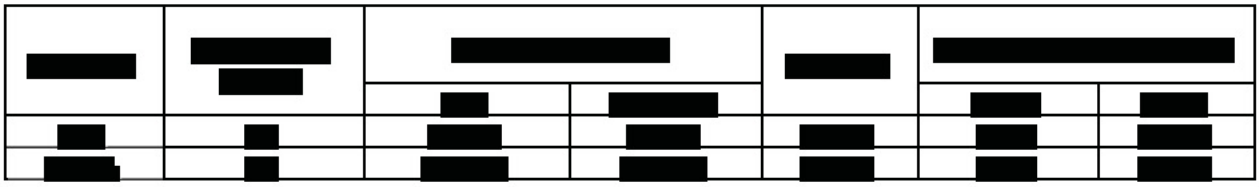
	In each group (fed and fasted), the subjects were randomized to one of 2 treatment sequences: A-B or B-A.
Planned number of subjects	A total of 32 healthy male and female Chinese subjects will be enrolled in the trial, with each gender representing no less than 1/3 of the total number (also evenly allocated to fasting vs. fed group). Sixteen subjects each will be enrolled into the fasting group and fed group, respectively, and statistically powered to provide adequate sample size for BE testing. Each subject will be administered both the investigational product and comparators in this 2 × 2 crossover BE trial to minimize the effect of the individual difference and periodic difference of the testing results.
Treatment and Trial Duration	The trial has a duration of approximately 5 weeks for the fasting or fed group respectively for each subject, including: • Screening (assessments to determine eligibility for entry into the trial; occurring from Day -7 to Day -1) • Admission to the Clinical Research Unit (CRU) on Day -1 • Period 1 (duration of 8 days; Day 1-8) • Washout (duration of 14 days; Day 1-14) • Admission to the CRU on Day 14 • Period 2 (duration of 8 days; Day 15-22) • Washout (duration of 14 days; Day 15-28) • End of Trial (visit occurring after the second 14-day washout on Day 29) or premature withdrawal from the trial.
Pharmacokinetics	The plasma concentrations of bisoprolol and amlodipine will be determined by a validated analytical method using HPLC with MS/MS detection. Pharmacokinetic parameters (primary and secondary endpoints) will be calculated according to non-compartmental analysis methods. The mixed trapezoidal rule will be used to calculate the area under the plasma concentration curve.
Randomization and Blinding	As this is an open-label trial, no method of blinding was used. Subjects were randomly assigned to one of the 2 treatment sequences (A-B, B-A) per group. Randomization occurred immediately before dosing on Treatment Period 1/Day 1.

7 Sample Size/Randomization

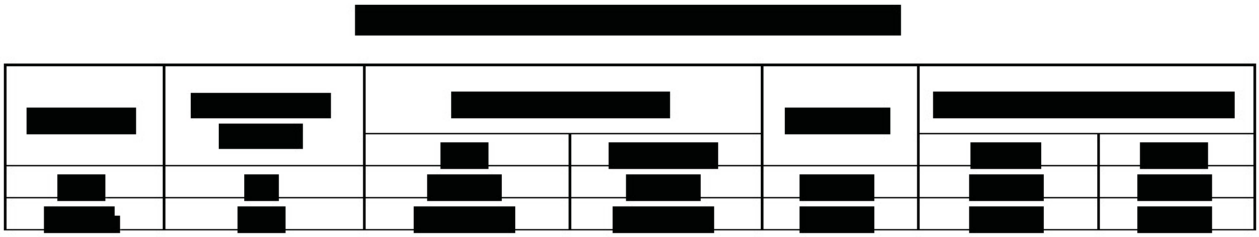
The BE is declared if all comparisons in primary hypothesis achieve the criteria – the 90% CIs for the ratios between the investigational product and comparators of geometric means of both AUC_{0-t} and C_{max} for bisoprolol and amlodipine in plasma are within 80.00% to 125.00%.

Based on the results of a BE trial conducted in 2008 by PPD [redacted] where a higher dose strength 10 m/10 mg fixed-dose-combination tablet was tested against respective single agent of bisoprolol and amlodipine, the expected effects in fasting state is presented below.

CCI [redacted]



[redacted]



[redacted]

With 12 evaluable subjects at least 80% power can be achieved for all 4 parameter's 90% CIs of the treatment ratio to fall within 80.00% to 125.00%. Taking account of the possible dropout, 4 additional subjects will be enrolled. In the case of full completion by all 16 subjects, a power of > 90% may be achieved.

Sample Size and Power Calculation Results

Sample Size	Power (%) for Bisoprolol		Power (%) for Amlodipine		Joint Power (%)
	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	
10	100.00	99.59	96.27	74.30	71.24
12	100.00	99.92	98.56	82.13	80.88
14	100.00	99.98	99.46	87.71	87.22
16	100.00	100.00	99.80	91.63	91.45

AUC_{0-t} = area under the (plasma) concentration-time curve from time 0 to time t; C_{max} = the maximum plasma concentration observed

Historical data showed no food effect on PK for either drugs, bisoprolol and amlodipine respectively [1, 2], and the observed variability has been comparable between fasting and fed dosing states. By applying statistical powering also to the fed group, assuming the intra-subject variability is similar in fed state with standard meal consumption [1, 2]. Based on the sample size calculation above, a 16-subject trial (12 subjects with adequate power and 4 subjects to cover potential dropout) provides at least 80% power to meet the BE criteria for both parameters and both products.

Sensitivity analysis has been performed to explore impact of potentially different variability on the sample size and power calculation. The outcome, as selectively displayed in the tables below, suggests that consistently high power (80%+) can be obtained with the proposed sample size.

Sensitivity Analysis 1:

Assume 5% variation for all ratios (95% ~ 105%) and 10% all intra-subject CV.

Sample Size	Power (%) for Bisoprolol		Power (%) for Amlodipine		Joint Power (%)
	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	
10	96.83	96.83	96.83	96.83	87.89
12	98.83	98.83	98.83	98.83	95.42
14	99.58	99.58	99.58	99.58	98.34
16	99.85	99.85	99.85	99.85	99.42

AUC_{0-t} = area under the (plasma) concentration-time curve from time 0 to time t; CV = coefficient of variation; C_{max} = the maximum plasma concentration observed

Sensitivity Analysis 2:

Assume 5% variation for all ratios (95% ~ 105%) except of Amlodipine AUC_{0-t} (90% ~ 110%), and 10% all intra-subject CVs.

Sample Size	Power (%) for Bisoprolol		Power (%) for Amlodipine		Joint Power (%)
	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	
10	96.83	96.83	96.83	77.74	70.56
12	98.83	98.83	98.83	85.17	82.23
14	99.58	99.58	99.58	90.25	89.13
16	99.85	99.85	99.85	93.66	93.26

AUC_{0-t} = area under the (plasma) concentration-time curve from time 0 to time t; C_{max} = the maximum plasma concentration observed

Each eligible subject will be allocated to a treatment sequence according to a computer-generated randomization schedule. Subjects will be identified only by their assigned subject number. The subjects will receive consecutive subject numbers in the order of their enrollment into the trial.

A total of 32 eligible healthy male and female Chinese subjects (16 in fasting group and 16 in fed group) who meet the eligibility criteria will be randomized (with each gender representing no less

than 1/3 of the total number) on Day 1 in a 1:1 ratio to one of 2 treatment sequences: Sequence A-B or Sequence B-A.

In Sequence A-B, subjects will receive bisoprolol-amlodipine 5 mg/5 mg combination tablets (Treatment A) in Period 1 and bisoprolol 5 mg tablets and amlodipine 5 mg tablets given concomitantly (Treatment B) in Period 2. In Sequence B-A, subjects will receive bisoprolol 5 mg tablets and amlodipine 5 mg tablets given concomitantly (Treatment B) in Period 1 and bisoprolol amlodipine 5 mg/5 mg combination tablets (Treatment A) in Period 2.

The first 4 discontinued subjects of each group will not be replaced. Subjects will only be replaced if the number of subjects within a sequence falls below 12. The subject who is replacing a discontinued subject will then be allocated to the treatment sequence of the subject who discontinued.

8 Overview of Planned Analyses

The methods described in this document will be applied to the preparation of tables, figures and listings (TLFs). Statistical analyses will be performed using cleaned electronic clinical report form (eCRF) data collected.

This SAP will cover the final analysis only. The final analysis will be performed only after the last subject has completed the study with all study data in-house and all data queries resolved. The SAP will be finalized prior to database lock.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The Screening Analysis Set has been added to include all subjects who signed informed consent in the study. The per-protocol population has been removed.

The PK parameter, apparent volume of distribution at steady-state after extravascular administration (V_{ss}/f) was originally proposed in the CTP (Clinical Trial Protocol). However, this PK parameter cannot be calculated based on the dosing regimen (i.e., single dose) and route of administration (i.e., oral). As such, the apparent volume of distribution during the terminal phase following extravascular administration (V_z/f) will be calculated instead to provide an estimate of the extent of drug distribution following a single oral dose.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

Protocol deviations describe how closely the study has been conducted according to the protocol as expected per GCP. Some of these deviations may be significant contributors to analysis bias.

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Examples of clinically important protocol deviations or important events for PK include, but may not be limited to, the following:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from GCP.
- Adverse events, vomiting, diarrhea, etc.
- Vomiting following oral dosing (these instances will be discussed on a case-by case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors
- Incomplete meal consumption prior to dosing
- Concomitant medication violations

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest. Important protocol deviations include

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

A data review will be held to discuss and update the definition of important protocol deviations so as to determine the evaluability of the subjects prior to database lock.

10.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set

The Screening Analysis Set includes all subjects who have signed the main informed consent (i.e., screening failures plus subjects enrolled).

Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of trial drug. In general, clinical data will be analyzed for the Safety Analysis Set.

Pharmacokinetic Analysis (PK) Set

The PK Analysis Set includes all subjects who completed the trial with adequate trial medication compliance, without any relevant protocol violations or events with respect to factors likely to affect the comparability of PK results, and with sufficient evaluable data to determine primary endpoints (AUC_{0-t} and C_{max}) for both treatments and analytes. If subjects receive concomitant medication that potentially affects PK for the treatment of an AE, their inclusion in the PK Analysis Set will be decided on a case-by-case basis. Emesis occurring within two times of the median t_{max} for a given analyte and the treatment will be considered a relevant event likely to affect the comparability of PK results. Similarly, a predose concentration for a given analyte and treatment

period which exceeds 5% of C_{max} will be considered a relevant event affecting PK results. All PK analyses will be based on the PK Analysis Set.

11 General Specifications for Statistical Analyses

Unless otherwise indicated all analyses will be presented separately for the two treatment groups under different food condition (fed and fasted).

Listings

All listings will be reported separately by food condition and sorted by treatment, or treatment sequence (A-B or B-A), and/or scheduled timepoint, as appropriate. Data which are only measured before administration of trial drug and/or at end of study will be sorted by subject and scheduled timepoint (if appropriate).

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory regardless of how many significant figures or decimal places the data carry. Pharmacokinetic parameters and actual elapsed sample collection times will be rounded for reporting purposes in by-subject listings. Actual elapsed sample collection times will be rounded to two decimal places with units of hours. For PK parameters, the standard rounding procedure will be as follows:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times [e.g., time to reach maximum observed plasma concentration (t_{max})] will be reported to two decimal places with units of hours.
- Values of AUC will be rounded to 3 significant figures.
- Percentages not derived directly from source data [e.g., percentage of area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) obtained by extrapolation ($AUC_{extra\%}$)] will be reported to 3 significant figures.
- Other parameters [e.g., apparent terminal half-life ($t_{1/2}$), terminal elimination rate constant (λ_Z), apparent total body clearance of drug from plasma following extravascular administration ($CL_{/f}$), apparent volume of distribution during the terminal phase following extravascular administration ($V_{z/f}$)] will be reported with 3 significant figures.

Tables and Descriptive Statistics

All data will be summarized by food condition, treatment, or treatment sequence, and/or scheduled time point, as appropriate. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Bisoprolol and amlodipine concentrations in plasma, and their PK parameters, will be presented in tables and descriptively summarized by food condition, treatment, and/or nominal time point, as appropriate.

Presentation of PK Concentration Data

Pharmacokinetic concentration data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

Derived parameters will be reported using precision similar to the precision of the data from which they were derived.

Descriptive statistics of plasma concentration will additionally show quartiles, and values below the lower limit of quantification (LLOQ) will be taken as zero.

Presentation of PK Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: number of non-missing observations (N), Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM).

Pharmacokinetic parameter C_{max} will be reported with the same precision as the source data and t_{max} will be reported to two decimal places. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the Study Data Tabulation Model (SDTM) PP/XD domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
SD:	4 significant digits

CV%, GeoCV%: 1 decimal place

To ensure a reliable estimate of the extent of exposure in pivotal trials (e.g., bioequivalence), AUC_{extra}% should be less than or equal to 20.0%. If AUC_{extra}% is greater than 20.0%, all parameters derived using λ_z (i.e., λ_z, $t_{1/2}$, $AUC_{0-\infty}$ AUC_{extra}%, V_z/f, and CL/f) will not be included in the calculation of descriptive statistics or statistical analyses.

Software

Pharmacokinetic parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 6.4 or higher (PPD). Pharmacokinetic figures will be developed using SigmaPlot® 12.5 or higher (PPD), Phoenix® WinNonlin® 6.4 or higher, or SAS® Windows Version 9.4 or higher (PPD).

All other statistical analyses will be performed using SAS® version 9.4 or higher.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using the following descriptive statistics unless otherwise specified, i.e.,

- number of subjects (N), number of subjects with non-missing values
- mean, SD
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum and maximum

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

Definition of baseline:

Baseline for assessments is defined as the last non-missing measurement taken prior to or on the day of the first trial drug administration.

For vital signs and electrocardiogram (ECG), an assessment performed on dosing date with time point marked as “predose” will be considered as baseline. If there is no time point, the last non-missing assessment prior to dosing will be taken as baseline.

In the case where the last non-missing measurement and the dosing date/time coincide, that measurement will be considered baseline, but AEs and medications commencing on the reference start date will be considered post baseline. Such as AE happened on dosing date (even AE before dosing, and there is no time to make judgement) it will be treated as a TEAE.

Definition of duration:

Duration will be calculated by the difference of start and stop date + 1 if not otherwise specified. For example, survival time (days) = date of death - the date of first administration + 1.

Conversion factors:

Unless specified, conversion of days to months /years will be defined as:

1 month = 30.4375 days

1 year = 365.25 days

Common calculations:

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

Handling of missing data:

Unless otherwise specified, missing data will not be replaced. Handling of missing data for PK parameter calculations are discussed under Section 16.3.3.

In all subject data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g., when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

For the derivation of new date variables the following rules will apply:

Partial birth dates will be handled this way: day will be imputed as 15 if it is missing, and month imputed as June if missing. If both of day and month are missing, they will be imputed as July 1st. If year is missing then the date will not be imputed.

Any adverse event (AE) with incomplete start and or end dates/times will be handled as described below for the classification as treatment-emergent, assignment to treatment periods and calculation of duration.

- Adverse events with unknown start times but known start dates, will be imputed with a time of 00:00 hours, unless the start date corresponds to any given dosing date, in which

case time of dosing will be used instead. However, if this results in a start time after end time of the AE, then the start time will be imputed to 00:00 hours instead.

- Any adverse event with completely unknown start dates will be imputed with date and time of the first administration of a study drug, unless the end date is known and prior to first administration. In the latter case, the start date will be imputed as the date of screening and a time of 00:00 hours.

- Adverse events with completely unknown end times, will be imputed with an end time of 23:59 hours.

- Adverse events with completely unknown end dates will be imputed with the date of study completion (or in case of withdrawal, date of discontinuation).

Partially known end dates will be treated as follows:

- If only the day is missing, the last day of the month will be imputed or the date of study completion/discontinuation if earlier.

- If day and month are both missing, then the end date of 31 December will be imputed or the date of study completion/discontinuation if earlier.

Assignment to the different treatment periods will be performed after the imputations have been performed. An AE will be assigned to a specific treatment period if it occurs after the IMP administration scheduled for that period and before the IMP administration in the next period (or study completion for the last period).

Trial day / treatment day:

Trial day / Treatment day are defined relative to the date of randomization / the date of first administration of trial drug (start of treatment). Trial Day 1 defines the day of randomization, the day before is defined as Trial Day –1 (no Trial Day 0 is defined). Treatment day will be calculated accordingly:

Trial day or treatment day =

- date of event – the date of first administration, if date of event < the date of first administration
- or date of event – the date of first administration + 1 , if date of event ≥ the date of first administration

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Trial Day or Treatment Day, and any corresponding durations will be presented as missing. Rules of handling missing dates relevant to efficacy will specified in the subsequent sections.

12 Trial Subjects

This section includes specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

All subjects who provide informed consent will be accounted for in this study. Subject disposition and withdrawals will be presented for the screening analysis set.

The following summaries will be produced by treatment sequence and overall, for each group:

- Total number of subjects screened (i.e., subjects who gave informed consent)
- Number of randomized subjects
- Number of subjects treated in each period
- Number of subjects that completed each treatment period
- Number of subjects who completed the trial
- Number of subjects who discontinued the study treatment after the first administration, grouped by the main reason
- Number of subjects who discontinued the study, grouped by the main reason
- Number of subjects included in Safety Analysis Set
- Number of subjects included in PK Analysis Set

Corresponding individual listings will be prepared (sorted by group, treatment sequence and subject).

Discontinued subjects will be listed with their reason of withdrawal.

Additionally, a listing of the screening failures will be produced with the reason of non-inclusion in the treatment phase.

Listings with visit dates will also be carried out by group, treatment sequence and subject.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

Important protocol deviations will be based upon the Clinical Trial Management System (CTMS) data and determined for all subjects by medical review processes. All the important protocol deviations will be included in SDTM datasets, if identified by means of medical review. The Analysis Data Model (ADaM) datasets will be derived from SDTM and include all important protocol deviations.

A data review will be held to discuss and update the definition of important protocol deviations so as to determine the evaluability of the subjects prior to database lock.

The following outputs will be provided by treatment sequence and overall, for each group:

- Summary of important protocol deviations relating to inclusion/exclusion criteria
- Summary of other important protocol deviations

All protocol deviations will be listed. A listing presenting protocol deviations relating to inclusion/exclusion criteria and a listing presenting other deviations will be carried out by group, treatment sequence and subject.

13 Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented using summary statistics for continuous variables and frequency tables for categorical variables.

13.1 Demographics

Demographic characteristics will be summarized overall and by treatment sequence for each group using the following information from the Screening/Baseline Visit CRF pages.

Demographic characteristics:

- Sex: Male, Female
- Race: Chinese, Non-Chinese
- Age (years): summary statistics
- Weight (kg): summary statistics
- Height (cm): summary statistics
- BMI (kg/m^2): summary statistics

Specifications for computation.

Age [years]:

- (date of given informed consent - date of birth + 1) / 365.25
- In case of missing date that according to section 11: day will be imputed as 15 if it is missing, and month imputed as June if missing. If both of day and month are missing, they will be imputed as July 1st. If year is missing then the date will not be imputed.

13.2 Medical History

The medical history will be summarized from the “Medical History” eCRF page, using MedDRA, version 20.0, preferred term as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables overall and by treatment sequence for each group: ordered by primary SOC and PT in alphabetical order.

13.3 Other Baseline Characteristics

The following baseline characteristics will be summarized overall and by treatment sequence for each group:

- Nicotine and Alcohol Consumption
- Urine screening of drugs of abuse
- Breath test of alcohol

Baseline characteristics with respect to vital signs, physical examinations, ECG recordings, and laboratory tests will describe in Section 17
Results of chest x-ray and serum pregnancy test (for women of childbearing potential) will be listed only.

14 Previous or Concomitant Medications/Procedures

All previous or concomitant medications will be coded by the most current WHODrug (enhanced) 01Mar2017.

Missing or partial dates for medications will not be imputed. In the case where it is not possible to define a medication as prior or concomitant, the event will be classified by the worst case; i.e. prior and concomitant.

Previous medications are medications taken prior to screening visit, other than trial medications and pre-medications for trial drug, which started and ended before first administration of trial drug. Prior medications within 1 month before screening will be collected.

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on-trial (include medications which started before the first trial drug treatment and were ongoing after first trial drug treatment, or started on or after the first day of trial drug treatment).

Previous and concomitant medications/procedures will be summarized overall for both groups as well as overall and by treatment sequence for each group, and by PT and ATC 2nd level, respectively. The listing of previous and concomitant medications/procedures will be generated.

15 Treatment Compliance and Exposure

Study drug administration will be listed by group, treatment sequence and subject with treatment, date and time of administration.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

The primary endpoints are the following PK parameters calculated from bisoprolol and amlodipine plasma concentrations:

- AUC0-t of bisoprolol
- Cmax of bisoprolol
- AUC0-t of amlodipine
- Cmax of amlodipine

The null and alternative hypotheses are as follows:

H_0 : *for* AUC_{0-t} $\mu_T / \mu_C \le 0.8$ *or* $\mu_T / \mu_C \ge 1.25$
for C_{max} $\mu_T / \mu_C \le 0.8$ *or* $\mu_T / \mu_C \ge 1.25$, for at least 1 primary endpoint

H_1 : *for* AUC_{0-t} $0.8 < \mu_T / \mu_C < 1.25$
for C_{max} $0.8 < \mu_T / \mu_C < 1.25$, for all 4 primary endpoints and for both fasting and fed groups

where μ_T and μ_C are the geometric means of the primary endpoints following investigational product (Treatment A) and comparators (Treatment B), respectively.

The analysis of primary endpoints will be based on the PK Population (Section 10.2)

The primary endpoints, C_{max} and AUC_{0-t} in fasting or fed group, will be log-transformed and a mixed-effects model will be applied. The model will include fixed effects for sequence, treatment, and period and a random effect of subject nested within sequence. Treatment differences on the log scale will be estimated for the parameters together with their 90% CIs. The least squares means together with their 95% CIs by treatment will also be estimated. Point estimates and CIs will be back-transformed to the original scale for presentation, i.e., ratios of geometric means and corresponding 90% CIs for Treatment A/Treatment B, geometric means and corresponding 95% CIs by treatment, respectively. Intra-subject CV estimated from the model will also be presented. The BE will be established if all 4 sets of the 90% CIs for the ratios of geometric means between the investigational product and the comparators fall within 80.00% to 125.00%.

The following example code could be used:

```
proc mixed data=pkparam;
 by food analyte param;
 class sequence period trt subjid;
 model lnest = sequence period trt /ddfm=kr;
 random subjid(sequence);
 estimate 'A vs B' trt 1 -1 /alpha=0.1 cl;
 lsmeans trt /alpha=0.05 cl;
```

```
run;
```

All primary PK endpoints will be descriptively summarized as described in Section **Error! Reference source not found.**. Graphs of individual values and geometric mean will be presented for primary PK parameters versus treatment and food condition. Boxplots will also be created for primary PK parameters versus group and treatment.

16.2 Secondary Endpoint Analyses

All secondary PK endpoints will be descriptively summarized as described in Section 11. The secondary PK endpoints are the following parameters in plasma for bisoprolol and amlodipine:

- t_{max}, $t_{1/2}$, λ_Z, $AUC_{0-\infty}$, $AUC_{extra\%}$, $CL_{/f}$, $V_{z/f}$.

For t_{max}, the Hodges-Lehmann estimates for the treatment differences and corresponding 90% CIs according to the Tukey method will be calculated.

The mixed-effects model for treatment comparison as described for the primary endpoints will also be applied to $AUC_{0-\infty}$. The ratios of geometric means and corresponding 90% CIs for Treatment A/Treatment B will be estimated.

All secondary endpoints (t_{max}, $t_{1/2}$, λ_Z, $AUC_{0-\infty}$, $AUC_{extra\%}$, $CL_{/f}$, and $V_{z/f}$) will be summarized descriptively by group and treatment on the PK analysis set.

16.3 Other Endpoint Analyses

16.3.1 Analysis on PK / Population PK Endpoints

Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

Pharmacokinetic concentrations which are erroneous due to a protocol deviation (as defined in the protocol), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analysis. In this case the rationale for exclusion must be provided in the Clinical Trial Report (CTR). Any other PK concentrations that appear implausible to the Pharmacokineticist/PKPD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CTR.

Plasma concentration data will be summarized descriptively for bisoprolol and amlodipine as described in Section 11. Values below the lower limit of quantification (LLOQ) will be taken as zero for descriptive statistics of PK concentrations. Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and displayed generally as “N.R.”.

Samples that are collected outside the specified time windows will be included in the PK analysis but excluded from the concentration summary. The PK sampling collection schedule is presented in Table 1 below.

Table 1 Pharmacokinetic Sample Collection Schedule

Trial Day	Period Day	Time of Blood Sample (hour)	Window Allowance (minute)
1	1 - Predose in Period 1	Baseline blood draw (10 minutes prior to drug administration)	±2
1	1 – Single dose administration and Washout begins	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15	±2
2	2	24, 36	±5
3	3	48	±5
4	4	72	±30
5	5	96	±30
6	6	120	±30
7	7	144	±30
8	8	168	±30
9 - 14			
15	1-Predose in Period 2	Baseline blood draw (10 minutes prior to drug administration)	±2
15	1- Single dose administration and Washout begins	0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15	±2
16	2	24, 36	±5
17	3	48	±5
18	4	72	±30
19	5	96	±30
20	6	120	±30
21	7	144	±30
22	8	168	±30
23 - 28			
End of Trial (Day 29)/Premature Withdrawal		1-sample	±30

Arithmetic mean plasma bisoprolol and amlodipine concentration versus scheduled (nominal) time plots will be provided for each treatment and food condition using a linear and semi-logarithmic scale. Mean plots will include SD error bars (±SD) when plotted on a linear scale. The mean plasma concentration-time profiles will be plotted for subjects included in the respective PK Analysis Set.

Individual plasma bisoprolol and amlodipine concentration versus actual time plots will be provided for each treatment by food condition using a linear and semi-logarithmic scale. Plots of individual profiles of plasma bisoprolol and amlodipine concentration versus actual time for all subjects within each treatment, presented on a single plot (i.e., spaghetti plots), will be provided by Fed/Fasting group, separately, using a linear and semi-logarithmic scale. All statistical analyses and descriptive summaries of PK data will be performed on the PK Analysis Set. Pharmacokinetic concentrations will be listed for all subjects by treatment and group; concentrations excluded from the PK analysis will be flagged within the listing

A listing of PK blood sample collection times by individual, as well as derived sampling time and time deviations, will be provided.

16.3.2 Estimation of Individual Pharmacokinetic Parameters by Noncompartmental Analysis

For the PK analysis, predose sample concentrations that are missing will be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at predose will be identified in the CTR, and if the anomalous predose concentration value is greater than 5.00% of the C_{max} in the profile, the profile will be excluded from summaries and inferential statistics as appropriate; handling of the data will be documented in the CTR. Pharmacokinetic parameters for the affected profile shall be calculated as part of the WinNonlin® run and will be listed.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods. Pharmacokinetic parameters will be evaluated and listed for all volunteers who provide sufficient concentration-time data. At least 3 valid, postdose concentration points will be required in the PK profile to obtain any PK parameter estimate.

Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data other than for a missing predose concentration as stated above.

For each subject in the PK Analysis Set the following PK parameters will be calculated for bisoprolol and amlodipine, where appropriate:

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the LLOQ. Calculated using the mixed log linear trapezoidal rule (linear up, log down). Units: ng*h/mL.

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$. Units: ng*h/mL.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100. The predicted $AUC_{0-\infty}$ should be used. Units: %.
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration. CL/f = Dose $_{p.o.}$ /$AUC_{0-\infty}$. The predicted $AUC_{0-\infty}$ should be used. The dose amounts to be used for this calculation are 5 mg for bisoprolol and 5 mg for amlodipine. Units: L/h.
C_{max}	Maximum observed concentration, taken directly from the observed concentration-time profile. Units: ng/mL.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values). Units: h.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$. Units: h.
$V_{z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration $V_{z/f}$ = Dose/($AUC_{0-\infty}*\lambda_z$) following single dose. Units: L.
λ_z	Terminal elimination rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve. Units: h^{-1}.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression ($\lambda_{z\ lower}$, $\lambda_{z\ upper}$) to determine λ_z.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness-of-fit statistic (Rsq) for calculation of λ_z.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The Rsq should be ≥0.800 and the observation period over which the regression line is estimated should be at least two-fold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g., $AUC_{0-\infty}$, $AUC_{extra\%}$, $CL_{/f}$, $t_{1/2}$, and $V_{z/f}$.) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

For both analytes, if more than 20% of $AUC_{0-\infty}$ is extrapolated ($AUC_{extra\%}$ >20.0%), then $AUC_{0-\infty}$ and λ_Z estimates and parameters derived from them (e.g., $CL_{/f}$) will be calculated and included in the listing, but flagged as unreliable and set to missing in summaries and in inferential statistical analysis.

The dose amount for investigational medicinal product (IMP) administered is that of the active, free drug substance only, and is synonymous with the measured analyte. No adjustment for the dose amount value of IMP will be applied when ‘dose’ is used in calculating PK parameters with formulas needing a dose value.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

16.3.3 Analysis PD Endpoints and Biomarker

Not applicable.

16.3.4 PK/PD Modelling and Simulation

Not applicable.

16.3.5 Analysis of Molecular Marker

Not applicable.

17 Safety Evaluation

Population: Safety Analysis Set
The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

All safety analyses will be peformed on the Safety Analysis Set. All safety data will be listed in individual subject listings by group, treatment sequence and subject.

All data recorded during the trial will be presented in individual data listings performed on the safety population. Moreover, all safety variables will be analyzed using descriptive statistics.

For the evaluation of safety parameters, the continuous variables will be summarized descriptively per treatment, period, time point, and overall by N, arithmetic mean, median, SD, and minimum and maximum values. Categorical variables will be presented in frequency tables with the counts of observations and corresponding percentages.

Blood pressures, pulse rate measurements and ECG recordings will be individually listed by treatment, subject number, period, and time point, and the abnormal values flagged according to reference laboratory ranges. All hematology and biochemistry parameters will be listed and summarized using descriptive statistics by treatment, period, and time point on observed values. Urinalysis will be summarized in frequency tables.

Safety and tolerability will be assessed by monitoring of assessment of general safety and tolerability, adverse events, vital signs, ECG, biochemistry, hematology, urinalysis, and physical examination. Results of physical examination will only be listed by treatment, subject, period, time point, and body system.

17.1 Adverse Events

After coding of AEs according to the Medical Dictionary for Regulatory Activity classification (version 20.0) and assignment to a system organ class and preferred term, all AEs recorded during the course of the trial will be listed by treatment and subject number.

An AE will be considered as 'treatment emergent' if it occurred after the first drug administration of each period or if it was present prior to drug administration but exacerbated after the drug administration. All other adverse events will be considered ‘pre-treatment’.

In the case where it is not possible to define an AE as being treatment emergent or not, the AE will be classified as treatment emergent as the most conservative approach.

The AE listings will include the following items:

- System organ class
- Preferred term
- Investigator’s description

- Whether the event is treatment-emergent
- Trial treatment at onset of event
- Date and time of onset and resolution
- Duration of the event
- Date and time of last administration before AE
- Days under treatment (for TEAEs) or Days in Study (for pre-treatment AEs)
- Severity/Intensity
- Causality relationship to investigational product
- Outcome
- Action taken to investigational product
- Other action
- Seriousness

17.1.1 All Adverse Events

A summary table describing all the TEAEs occurring during the trial will be produced overall and by group as well as by treatment for each group using frequency of events and number and percentage of subjects experiencing these events overall and by SOC and PT.

Group/SOC terms will be sorted by decreasing total frequency. Preferred terms within each group/SOC term will likewise be sorted by decreasing total frequency.

In addition, all TEAEs will be tabulated by intensity and relationship to drug in the same manner.

Multiple occurrences of the same TEAE in one subject during the same treatment in the trial will be counted as multiple events in the frequency counts for adverse events. If a subject experiences more than one occurrence of the same TEAE during the same treatment in the trial, the subject will only be counted once for that treatment using the worst severity and the strongest relationship.

In case a subject had events with missing and non-missing severities, the maximum of the non-missing severities will be displayed. In case all the TEAEs of a subject are all with missing severities then Moderate will be used unless there is any evidence that it should be Severe.

17.1.2 Adverse Events Leading to Treatment Discontinuation

All adverse events leading to trial or treatment discontinuation will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim.

17.1.3 Deaths

AEs leading to deaths will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim, if applicable.

17.1.4 Serious Adverse Events

All serious adverse events (SAEs) will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim.

17.2 Clinical Laboratory Evaluation

The following parameters will be measured during the trial as safety evaluation:

Hematology:	Biochemistry:	Serology:	Urinalysis:
Erythrocytes	Alanine Aminotransferase	HBsAg	Appearance
Hemoglobin	Aspartate Aminotransferase	HCV antibody	Blood
Hematocrit	Total Bilirubin	HIV antibody	Nitrite
Mean corpuscular volume	Direct Bilirubin	TP antibody	Ketone
Mean corpuscular hemoglobin concentration	Indirect Bilirubin		Protein
Red blood cell distribution width	Protein total		Glucose
Platelets	Albumin		pH
Mean platelet volume	Globulin		Leukocytes
Thrombocytocrit	A/G		Microscopic examination

Platelet distribution width	Alkaline Phosphatase		
White blood cells	Glutamyl Transpeptidase		
Neutrophils	Urea Nitrogen		
Monocytes	Creatinine		
Lymphocytes	Cholesterol		
	Triglycerides		
	Glucose		
	Creatine Kinase		
	Creatine Phosphokinase MB Isoenzyme		
	Lactate Dehydrogenase		
	Calcium		
	Phosphorus		
	α-Amylase		
	Sodium		
	Potassium		
	Chloride		

All biochemistry, hematology, and serology parameters will be summarized using descriptive statistics overall and by treatment sequence for each group at baseline and at screening to end of study visit as raw data and change from baseline. Biochemistry, hematology, and serology will

also be described by group, treatment and time point on observed values as raw data and change from baseline, ie, change between period 1 Baseline on Screening and period 1 visit on Day 8 to evaluate the change during period 1, and change between period 2 Baseline on Day 14 and period 2 Visit on Day 22 for change during period 2. In additional, frequency tables based on a classification of values as low, normal, or high with respect to the reference ranges will be summarized.

Urinalysis based on a classification of values as Normal/-, +-, +, ++, +++, ++++ will be summarized in frequency tables y treatment sequence and time point for each group. All abnormal laboratory values will be listed.

In addition, shift tables for laboratory tests (for hematology and biochemistry) based on a classification of values as low, normal, or high with respect to the reference ranges will be summarized and presented by group, treatment and time point, except for End of study visit which will be presented by treatment sequence for each group.

Baseline is Period 1 Day 1 pre-dose (or Screening if missing at Day 1 pre-dose) for Period 1 and end of study visit and Period 2 Day 1 pre-dose for Period 2.

It is essential that Merck be provided with a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to Merck. Subjects without post baseline laboratory samples will be excluded from analyses with respect to values after the baseline.

17.3 Vital Signs

The following parameters will be measured during the trial as safety evaluation:

Blood Pressure	Pulse rate	Temperature	Respiration Rate

Markedly abnormality of vital signs will be identified in accordance with the criteria as follows:

Vital Sign Parameter	**Unit**	**Low**	**High**
Systolic blood pressure	mmHg	< 85 mmHg	> 139 mmHg
Diastolic blood pressure	mmHg	< 50 mmHg	> 90 mmHg
Pulse rate	Beats/min	< 50 Beats/min	> 100 Beats/min
Temperature	^{0}C	< 36 ^{0}C	> 37.3 ^{0}C

Systolic and diastolic blood pressures (mmHg), pulse rate (beats/min) measurements in supine position as well as body temperature (°C) and respiration (breaths/min) will be presented by descriptive statistics overall and by treatment sequence for each group at screening and end of study visit, and by group, treatment and time point for the values obtained during the treatment periods as raw data and change from baseline.

Baseline is Period 1 Day 1 pre-dose (or Day-1 if missing at Day 1 pre-dose) for Period 1 and End of study visit and Period 2 Day 1 pre-dose for Period 2. All data will be listed by group, treatment sequence, subject, treatment, visit, and time point.

All marked abnormal for vital signs values will be listed. Vital signs variables will be summarized in frequency tables based on a classification by treatment.

All data will be listed by group, treatment sequence, subject, treatment, visit, and time point.

17.4 Other Safety or Tolerability Evaluations

ECG

The following parameters will be measured during the trial as safety evaluation:

RR-Interval	PR-Interval	QRS-Duration	QT-Interval	QTc (Bazett)	QTcF (Fridericia)	Heart Rate	Rhythm

12-lead ECG parameters (Heart rate (beats/min), PR (ms), QRS (ms), QT (ms), RR (ms), QTcB (ms) and QTcF (ms)) will be presented by descriptive statistics overall and by treatment sequence for each group at screening and end of study visit, and by group, treatment and time point for the values obtained during the treatment periods as raw data and change from baseline. 12-lead ECG parameters and result of ECG will be listed in individual subject listing by group, treatment sequence, subject, visit, treatment and time point. All marked abnormal for ECG values also will be listed.

Baseline is Period 1 Day-1 (or Screening if missing at Day-1) for Period 1 and End of study visit and Period 2 Day-1 for Period 2.

Physical Examinations, and Chest X-ray

Full physical examination and chest X-ray examination will be performed, abnormal values will be presented in listing only.

18 References

1. Leopold G., Pabst J., Ungethüm W., et al. Basic Pharmacokinetic of Bisoprolol, a New Highly Beta1-selective Adrenoceptor Antagonist. Journal of Clinical Pharmacology 1986; 26: 616-21.

2. Chung M., Calcagni A., Glue P., et al. Effect of Food on the Bioavailability of Amlodipine Besylate/Atorvastatin Calcium Combination Tablet. Journal of Clinical Pharmacology 2006; 46: 1212-6.