













Clinical Trial Protocol

Clinical Trial Protocol Number	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
Phase	I
IND Number	Not applicable
EudraCT Number	Not applicable
Principal Investigator	PPD     
Sponsor	Merck KGaA (Darmstadt, Germany) Frankfurter Strasse 250 64293 Darmstadt Germany Protocol Lead: PPD    Merck Serono Co., Ltd. PPD    

Medical Responsible:

PPD

Merck Serono Co., Ltd.

PPD

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- Confidential -

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	adverse event
AUC _{0-t}	area under the (plasma) concentration-time curve from time 0 to time t
AUC _{0-∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC _{extra}	extrapolated part of AUC _{0-∞} calculated by C_{last}/λ_z , expressed in percent
BE	bioequivalence
BMI	body mass index
bpm	beats per minute
C _{max}	the maximum plasma concentration observed
CI	confidence interval
CL/f	total clearance following extravascular administration
CRU	Clinical Research Unit
CYP	cytochrome P450
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic Case Report Form
EGIS	EGIS Pharmaceuticals Public Limited Company
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
PK	pharmacokinetic(s)
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SOP	standard operating procedure
t_{\max}	time of maximum plasma concentration observed
TP	treponema pallidum
$t_{1/2}$	half-life
V_{ss}/f	apparent volume of distribution at steady-state after extravascular administration
WOCBP	woman of childbearing potential
λ_z	terminal elimination rate constant

1 Synopsis

Clinical Trial Protocol Number	EMR200006-001
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Trial Phase	I
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	Not applicable
Principal Investigator	PPD
Sponsor	Merck KGaA (Darmstadt, Germany)
Sponsor Legal Representative in the European Union	Merck KGaA (Darmstadt, Germany)
Trial center/country	PPD
Planned trial period (first subject in-last subject out)	July 20 th 2017-Sep 24 th 2017
Trial Registry	Chinadrugtrials.org.cn 2016L04630
Objectives: Primary Objective: <ul style="list-style-type: none"> To demonstrate bioequivalence (BE) between the bisoprolol-amlodipine fixed-dose-combination tablet (investigational product) and bisoprolol and amlodipine tablets administered concomitantly (comparators) given as a single oral dose in fasting and fed state. Secondary Objectives: <ul style="list-style-type: none"> 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. 	

Methodology:

This trial is designed as a phase I, open-label, randomized, 2-period, 2-sequence, crossover trial where subjects will be randomized to receive, in each period, either

- One fixed-dose-combination tablet of 5 mg/5 mg bisoprolol-amlodipine (Concor AM[®]), or
- 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 cohort (fasting or fed) in both treatment periods.

The trial has a duration of approximately 5 weeks for the fasting or fed cohort 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- Day 8)
- Washout (duration of 14 days; Day 1- Day 14)
- Admission to the CRU on Day 14
- Period 2 (duration of 8 days; Day 15- Day 22)
- Washout (duration of 14 days; Day 15- Day 28)
- End of Trial (visit occurring after the second 14-day washout on Day 29) or premature withdrawal from the trial.

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 cohort). Sixteen subjects each will be enrolled into the fasting cohort and fed cohort, respectively, and statistically powered to provide adequate sample size for BE testing.

Primary endpoint:

Primary endpoints will be the PK parameters area under the (plasma) concentration-time curves 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}), half-life ($t_{1/2}$), area under the plasma concentration 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_{ss}/f) for bisoprolol and amlodipine, as well as safety and tolerability.

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.

Other assessments:

The safety assessments comprise adverse events, laboratory tests, vital signs, electrocardiogram (ECG) and concomitant medications.

Diagnosis and key inclusion and exclusion criteria:

Subjects meeting all of the following criteria will be considered for enrollment in the trial:

- Availability for the entire trial period and willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the volunteer
- Chinese male and female volunteer
- Volunteer aged ≥ 18 years, but ≤ 55 years
- Volunteer with a body mass index greater than or equal to 18 and below 28 kg/m²
- Systolic blood pressure (in supine position) within 100 to 139 mmHg (inclusive) and diastolic blood pressure (in supine position) within 65 to 90 mmHg (inclusive) at Screening, during Admission to the Clinical Research Unit (CRU) (12 hour predose) and before each dosing
- Clinical laboratory values (within 1 month before screening) within the laboratory's stated normal range; if not within this range, they must lack clinical significance (laboratory tests are listed in Section 7.1)
- Healthy according to assessment of the medical history, ECG, vital signs, physical examination, laboratory results, negative drug screening, and negative serology tests (except results after vaccination)
- Non-smoker or ex-smoker, not using any nicotine product; an ex-smoker being defined as someone who completely stopped smoking for at least 12 months before Day 1 of the trial
- Each subject has to be capable of understanding the trial procedures and sign the ICF prior to their participation in the trial
- Subjects must consent to adhere to the recommended contraceptive methods as detailed in Section 6.7.5 and Appendix I.

Subjects presenting with any of the following will not be included in the trial:

- Significant history of hypersensitivity to bisoprolol, amlodipine, other dihydropyridines, or any related products (including excipients of the formulations)
- Significant history of severe hypersensitivity reactions (eg, angioedema) to any drugs
- Pulse rate (in supine position) less than 60 beats per minute (bpm) or more than 100 bpm at screening
- Presence of significant arrhythmia: QTc interval prolongation (QTc greater than 430 msec), severe sinus node dysfunction, or second or third atrioventricular block
- History of low blood pressure ($< 100/65$ mmHg) or vegetative dystonia
- History or presence of peripheral arterial occlusion or Raynaud's syndrome
- Presence of diabetes mellitus

- History or presence of asthma
- Presence of significant gastrointestinal, liver, kidney disease, surgery, or any other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs or known to potentiate or predispose to undesired effects
- Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, and human immunodeficiency virus [HIV] antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin, St. John's wort or other herbal medicine known with effect on CYP enzymes) within 28 days before Day 1 of this trial
- Presence or history of significant cardiovascular, pulmonary, hematologic, neurologic, endocrine, immunologic, or dermatological disease
- Presence or history of significant angina pectoris, acute myocardial infarction or ST segment and T wave changes other than non-clinically significant minor changes
- Presence or history of ventricular arrhythmia (such as ventricular tachycardia or ventricular fibrillation) or of congestive heart failure
- Acute conditions which might alter the renal function (eg, dehydration, severe infection)
- Surgery in the previous 28 days before Day 1 of this trial
- Any history of tuberculosis and/or prophylaxis for tuberculosis within 10 years of Day 1 of the trial
- Positive results to HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or treponema pallidum (TP) antibody tests
- Donation of 50 mL or more of blood within 28 days before Day 1 of the trial; donation of 500 mL or more of blood within 56 days before Day 1 of the trial
- History of suicidal tendency, history of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases
- Poor motivation, intellectual problems likely to limit the validity of consent to participate in the trial or limit the ability to comply with the protocol requirements or inability to cooperate adequately, inability to understand and to observe the instructions of the physician
- Maintenance therapy with any drug, or significant history of drug dependency or alcohol abuse ($> 3 \times 14$ g alcohol per day, intake of excessive alcohol, acute or chronic use)
- Positive urine screening of drugs of abuse (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine), or positive breath test of alcohol
- Positive pregnancy test (only for females of child-bearing potential) or females breast feeding a child

- Consumption of large quantities of methylxanthine-containing beverages (more than 600 mg caffeine/day: 1 cup (250 mL) of coffee contains approximately 100 mg of caffeine, 1 cup of black or green tea contains approximately 30 mg and 1 glass of cola contains approximately 20 mg caffeine)
- Volunteers who took an investigational product (in another clinical trial) by prescription within 2 weeks or an over-the-counter medication taken within 1 week before drug administration.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule:

5 mg/5 mg bisoprolol-amlodipine combination tablet (Concor AM[®]) administered either as a single dose on Day 1 or a single dose on Day 15 of the trial.

Reference therapy: dose/mode of administration/dosing schedule:

5 mg bisoprolol tablet (Concor[®]) and 5 mg amlodipine tablet (Norvasc[®]) administered concomitantly either as a single dose on Day 1 or a single dose on Day 15 of the trial.

Planned trial and treatment duration per subject:

The planned treatment consists of initial screening assessments (within 7 days prior to the first trial drug administration) followed by 2 trial periods consisting of 8 days of blood sampling in a crossover trial design. Each trial period includes a single dose of trial drug administration and the doses are separated by a 14-day Washout period. An End of Trial visit (Day 29) will be conducted 14 days after administration in Period 2. The overall trial duration for each subject is approximately 5 weeks (or approximately 35 days) including the Screening and End of Trial visit.

Statistical methods:

Based on the results of the previously conducted BE trial, a within-subject coefficient of variation (CV) for AUC_{0-t} and C_{max} has been calculated. The sample size in fasting cohort calculation is mainly driven by AUC_{0-t} of amlodipine due to the largest ratio (111.22%) of geometric least square mean and intra-subject CV (10.4%). With 12 evaluable subjects at least 80% power can be achieved for all 4 parameter's 90% confidence intervals 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. Assume there is no difference between fasting and fed states [10, 11], a total of 32 subjects are planned to be enrolled.

Table 1 Schedule of Assessments

Assessments ^a	Screening		Period 1										Period 2									End of Trial	Premature Withdrawal
Day	-7 ~ -2	-1 Admission	1 ^b	2	3	4	5	6	7	8 Discharge	9-13	14 Admission	15 ^b	16	17	18	19	20	21	22 Discharge	23-28	29	
Informed consent form signed	X																						
Demographic information	X																						
Inclusion/exclusion criteria	X																						
History of alcohol and nicotine consumption	X																						
Medical history	X																						
Prior medications	X ^c																						
Laboratory tests	X									X		X								X		X	
Serum Pregnancy test (only for females of child-bearing potential)	X									X										X		X	
HIV antibody, HBsAg, HCV antibody, and TP antibody tests	X																						
Urine screening of drugs of abuse and breath test of alcohol	X	X										X											
Urine nicotine	X																						
Randomization			X																				
Drug administration			X										X										
Blood sampling for Pharmacokinetics ^d			X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X		X	

Bisoprolol & Amlodipine Bioequivalence Trial of Concor AM® vs Bisoprolol and Amlodipine in Chinese Subjects

EMR200006-001

Assessments ^a	Screening		Period 1										Period 2								End of Trial	Premature Withdrawal
Day	-7 ~ -2	-1 Admission	1 ^b	2	3	4	5	6	7	8 Discharge	9-13	14 Admission	15 ^b	16	17	18	19	20	21	22 Discharge	23-28	29
Physical examination	X	X								X		X								X		X
Vital signs (blood pressure, pulse rate, temperature and respiration) ^e	X	X	X	X	X	X		X		X		X	X	X	X	X		X		X		X
Electrocardiogram ^f	X	X	X							X		X	X	X						X		X
Chest X-ray	X									X										X		X
AEs and concomitant therapies ^g																						

Continuous

AE = adverse event; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TP = treponema pallidum

^a Subject will participate in the clinical trial on an in-house basis during Day -1 to Day 8 and also during Days 14 to 22. Subjects are excused from the clinic during certain days after each period: from trial Day 9 to Day 13 and from trial Day 23 to Day 28.

^b After the single dose administration, Washout begins.

^c Prior medication within 1 month before the date of first signature of informed consent will be collected.

^d For every subject, during each treatment period, pharmacokinetic blood samples will be collected at the following times: at predose (Baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. One sample will be collected at End of Trial (Day 29) or Premature Withdrawal.

^e Vital signs will be taken at Screening, at admission (Day -1 and Day 14), prior to dosing and also at 4, 8, and 12 hours postdose at Day 1 and Day 15; and before blood sampling at Day 2, 3, 4, 6, and 8 in Period 1, then Day 16, 17, 18, 20, and 22 in Period 2, and at Premature Withdrawal (if applicable).

^f Electrocardiograms will be taken at Screening, at admission (Day -1 and Day 14), prior to dosing and also at 4 hours postdose at Day 1 and Day 15; at 48 hours postdose at Day 3 and Day 17; then at discharge of each period (Day 8 and Day 22), and at Premature Withdrawal (if applicable).

^g AEs and concomitant therapies will be collected continuously from the date of first signature of informed consent.

2 Sponsor, Investigators and Trial Administrative Structure

2.1 Trial Structure

The Sponsor's legal representative is Merck KGaA (Darmstadt, Germany) at the address Frankfurter Strasse 250, 64293 Darmstadt, Germany.

Merck will supply the bisoprolol-amlodipine 5 mg/5 mg medication. Bisoprolol-amlodipine 5 mg/5 mg will be produced under Good Manufacturing Practice conditions by PPD [REDACTED] and will be finally released by a qualified person of Merck.

2.2 Trial Center/Country

The trial will be conducted in one single center in China.

3 Background Information

3.1 Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. It is indicated for the treatment of hypertension and for prophylaxis of chronic stable angina pectoris.

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined, but it reduces total ischemic burden by the following 2 actions: it dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this reduced load on the heart consequently reduces myocardial energy consumption and oxygen requirements. It also probably involves dilation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

The recommended initial dose is 5 mg once daily and can be increased after 1 to 2 weeks to a maximum dose of 10 mg once daily.

After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration reached between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%. The absorption of amlodipine is not altered by the presence of food. Amlodipine is metabolized through the cytochrome P450 (CYP) system, mainly via CYP 3A4 isoenzyme.

Amlodipine is extensively (about 90%) converted to inactive metabolites (via hepatic metabolism) with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life ($t_{1/2}$) of about 35 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Following administration of recommended doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by any significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 mg and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24 hour dose interval with minimal peak to trough differences in blood pressure reduction. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. In normotensive patients with angina, amlodipine has not

been associated with any clinically significant reductions in blood pressure or changes in heart rate.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST-segment depression, and decreases the frequency of angina attack.

Following the administration of amlodipine, the most frequent adverse events (AEs) were edema and headache. Palpitations, dizziness, flushing, nausea, abdominal pain, fatigue, rash, muscle cramps, paresthesia, dyspepsia, somnolence, diarrhea, flatulence, dyspnea, abnormal vision, pain, and asthenia were also reported.

3.2 Bisoprolol

Bisoprolol is a potent, highly synthetic β_1 -selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing activity or intrinsic sympathomimetic activity in its therapeutic dosage range. This preferential effect is not absolute, however, and at higher doses bisoprolol may also inhibit β_2 -adrenoceptors, located chiefly in the bronchial and vascular musculature. Bisoprolol is a racemic mixture and the S (-) enantiomer is responsible for most of the β -blocking activity. It may be used alone or in combination with other antihypertensive agents. It is indicated for the management of hypertension and angina pectoris.

As with other β_1 -blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin levels. Factors which may be involved include: antagonism of β -adrenoceptors to decreased cardiac output, inhibition of renin release by the kidneys, and diminution of tonic sympathetic outflow from the vasomotor centers in the brain. In normal volunteers, bisoprolol therapy resulted in a reduction of exercise and isoproterenol-induced tachycardia. The maximal effect occurred within 1 to 4 hours postdose. Effects persisted for 24 hours at doses equal to or greater than 5 mg.

Bisoprolol is well absorbed following oral administration. The absolute bioavailability after a 10 mg dose is greater than 80%. Absorption is not affected by the presence of food. The first pass metabolism of bisoprolol is less than 20%. Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2 to 4 hours of dosing with 5 to 20 mg, and mean peak values range from 16 ng/mL after a 5 mg dose to 70 ng/mL after a 20 mg dose. Once daily dosing with bisoprolol results in less than a 2-fold inter-subject variation in peak plasma levels. The plasma elimination $t_{1/2}$ is 10 to 12 hours and is slightly longer in elderly patients in part because of decreased renal function in that population. Steady-state is attained within 5 days with once-daily dosing. In both young and elderly populations, plasma accumulation is low; the accumulation factor ranges from 1.1 to 1.3, and is what would be expected from the first order kinetics and once-daily dosing. Plasma concentrations are proportional to administered dose in the range of 5 to 20 mg. Pharmacokinetic (PK) characteristics of the 2 enantiomers are similar.

Bisoprolol is eliminated equally by renal and non-renal pathways with about 50% of the dose appearing unchanged in the urine and the remainder appearing in the form of inactive metabolites. Less than 2% of the dose is excreted in the feces.

Following administration of bisoprolol, the most frequently reported adverse reactions were feeling of coldness, numbness in the extremities, tiredness, dizziness, headache, nausea, diarrhea, and constipation.

3.3 Trial Rationale

Concor AM[®] is a fixed-dose-combination tablet and this formulation has been already marketed in multiple countries. The tablet contains bisoprolol and amlodipine. This combination allows to increase the antihypertensive and anti-anginal efficacy by complementary mechanism of actions of the 2 active compounds: vasoselective effect of the calcium channel blocker amlodipine (decrease of peripheral resistance) and cardioselective beta-blocker bisoprolol (decrease of cardiac output).

A bioequivalence (BE) trial is proposed to support registration of Concor AM[®] in China.

Bisoprolol tablet (Concor[®]) and amlodipine tablet (Norvasc[®]) have both been marketed in China for a long time and the clinical practice of treating hypertension and angina with co-administration of bisoprolol and amlodipine is already recommended by the China Food and Drug Administration guideline [1]. Moreover, the combination product of bisoprolol-amlodipine can fulfill a previously unmet healthcare need in the treatment of hypertension and angina in China.

4 Trial Objectives

4.1 Primary Objectives

The primary objective of this trial is:

- To demonstrate BE between the bisoprolol-amlodipine fixed-dose-combination tablet (investigational product) and bisoprolol and amlodipine tablets administered concomitantly (comparators) given as a single oral dose in fasting and fed state.

4.2 Secondary Objectives

The secondary objectives of this trial are:

- To compare the PK profiles of bisoprolol and amlodipine between the investigational product and the 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.

5 Investigational Plan

5.1 Overall Trial Design and Plan

The trial is designed to assess BE between a single oral dose of bisoprolol-amlodipine fixed-dose-combination tablet (investigational product) and bisoprolol and amlodipine (the comparators), each given concomitantly as a single dose in fasting or fed state.

This is a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial where subjects will be randomized to receive, 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 5 mg bisoprolol (Concor[®]) co-administrated with 5 mg amlodipine 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 cohort (fasting or fed) in both treatment periods.

The trial has a duration of approximately 5 weeks for the fasting or fed cohort 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- Day 8)
- Washout (duration of 14 days; Day 1- Day 14)
- Admission to the CRU on Day 14
- Period 2 (duration of 8 days; Day 15- Day 22)
- Washout (duration of 14 days; Day 15- Day 28)
- End of Trial (visit occurring after the second 14-day washout on Day 29) or premature withdrawal from the trial.

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 cohort). Sixteen subjects each will be enrolled into the fasting cohort and fed cohort, respectively, and are 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.

Trial design and flow chart are shown in [Figure 1](#) and [Figure 2](#). Detailed schedule of trial procedures/assessments will be provided in [Table 1](#).

Figure 1

Schematic of Trial Design

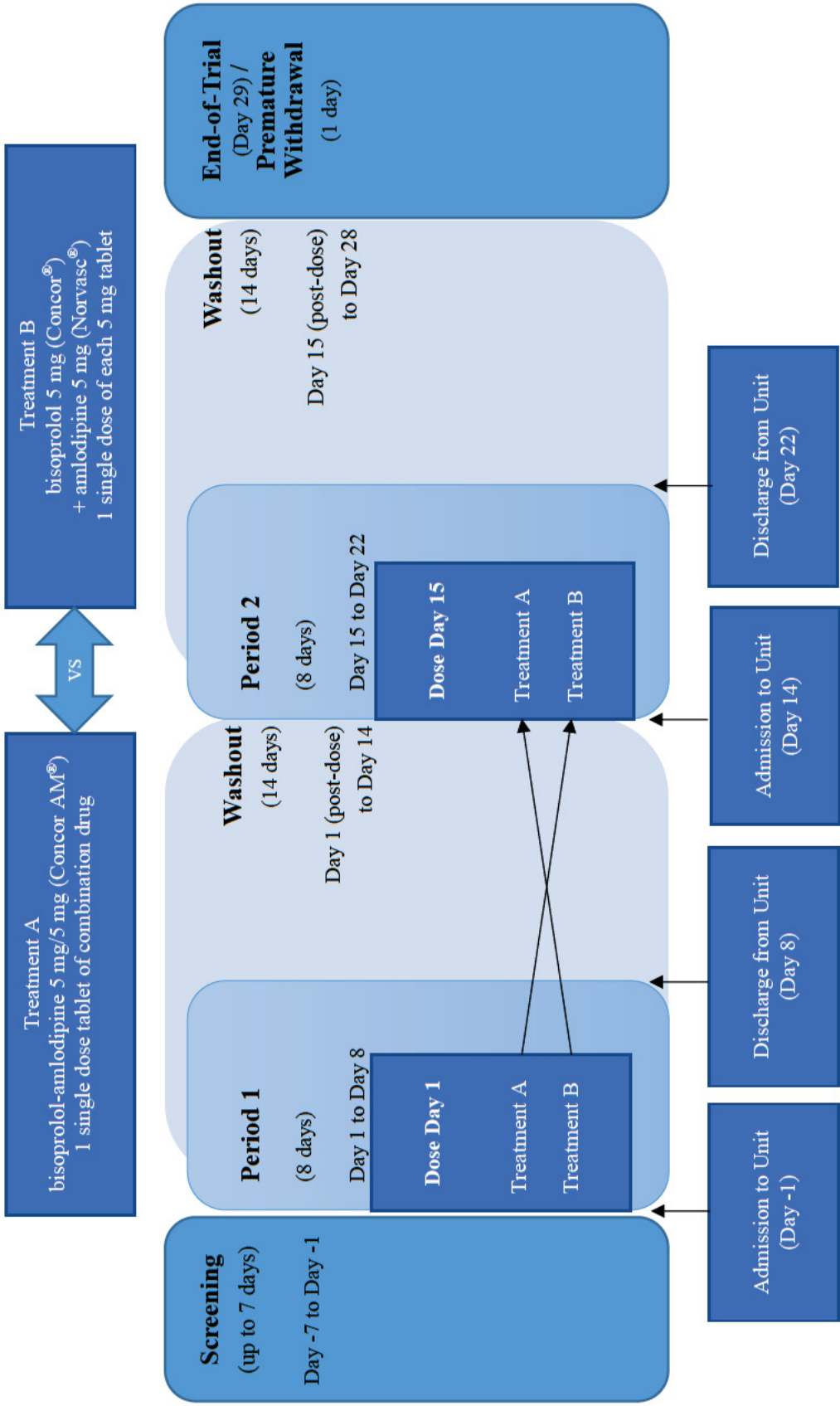
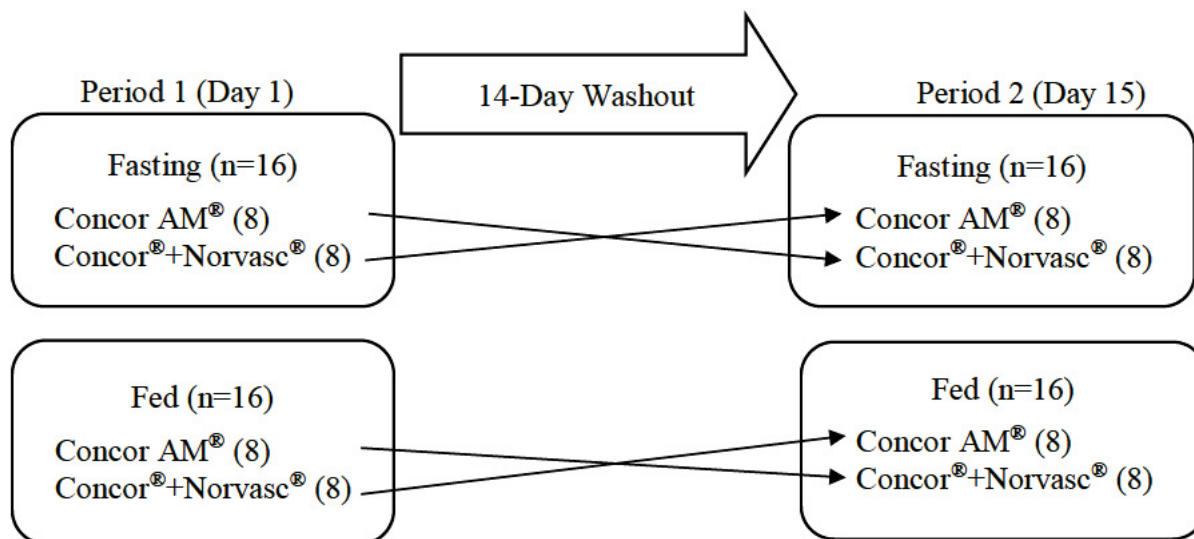


Figure 2 Trial Design Diagram with Subject Numbers



Note: Statistically powered for both fasting and fed cohorts.

The Fasting and Fed Cohorts can be scheduled in parallel or “staggered” to finish one cohort completely before the other cohort starts.

5.2 Discussion of Trial Design

5.2.1 Scientific Rationale for Trial Design

The fixed combination of the investigational product bisoprolol and amlodipine has distinct advantages due to their separate and synergistic pharmacological mechanisms of action for management of hypertension and angina. Amlodipine is a long-acting dihydropyridine calcium channel blocker that dilates the coronary arteries and reduces peripheral vascular resistance by direct vascular smooth muscle relaxation. Bisoprolol is a highly selective β_1 -blocking agent that decreases cardiac output and heart rate by depression of plasma renin levels. Additionally, as a β blocking agent, bisoprolol can reduce the calcium channel blocker’s adverse reaction of reflex increasing heart rate [2]. Therefore, the action of the combination of calcium channel blocker and β blocking agent can synergistically reduce blood pressure and control angina pectoris [3]. Furthermore, a series of guidelines for management of hypertension have been recommended for the combination treatment of a β -blocking agent along with a dihydropyridine calcium channel blocker and published by the Emergency Cardiovascular Care, the American College of Cardiology, and the American Heart Association [4, 5].

This fixed-dose-combination can provide patients with greater benefit for treatment of hypertension or angina with 2 considerations. First, a single tablet would provide an administration convenience that may increase patient compliance. A second consideration is the following. A survey in 11,861 Chinese patients revealed that 38.5% of antihypertensive patients take a fixed-dose-combination for treatment, and this is similar to the 40.8% who reported taking the

single agent treatment. But the current Chinese market does not include β blockers [6] as an active component in fixed-dose-combinations. Therefore, the fixed-dose-combination bisoprolol-amlodipine can fulfill a unique healthcare need in the Chinese fixed-dose-combination market for hypertension and angina treatment.

5.2.2 Justification for Dose

The 5 mg/5 mg dose of Concor AM[®] is the intended clinical dose levels and within the dose proportionality range for both bisoprolol and amlodipine. CCI

. In the current trial, a 5 mg/5 mg dose combination tablet will be evaluated using a similar design to the previous higher dose strength trial, it not only meets the medical need for registering a lower dose strength tablet in China, but also adds additional data to the overall fixed-dose-combination usage.

5.2.3 Rationale for Endpoints

The primary objective of the trial is to demonstrate the BE between the bisoprolol-amlodipine fixed-dose-combination tablet and the comparators (co-administrated bisoprolol and amlodipine) after single oral administration in healthy Chinese subjects. With this primary objective, the endpoints maximum plasma concentration observed (C_{max}) and area under the (plasma) concentration-time curve from time 0 to time t (AUC_{0-t}) are established as standard primary endpoints according to the Chinese guideline for BE studies [8]. The guideline states that BE criteria is determined by the confidence intervals (CIs) of the geometric means for AUC_{0-t} and C_{max} from both bisoprolol and amlodipine, which should be within in the acceptance range of 80.00% to 125.00% for all 4 primary endpoints.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment in the trial:

1. Availability for the entire trial period and willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the volunteer
2. Chinese male and female volunteer
3. Volunteer aged ≥ 18 years, but ≤ 55 years
4. Volunteer with a body mass index (BMI) greater than or equal to 18 and below 28 kg/m²
5. Systolic blood pressure (in supine position) within 100 to 139 mmHg (inclusive) and diastolic blood pressure (in supine position) within 65 to 90 mmHg (inclusive) at Screening, during Admission to the Clinical Research Unit (CRU) (12 hour predose) and before each dosing

6. Clinical laboratory values (within 1 month before screening) within the laboratory's stated normal range; if not within this range, they must lack clinical significance (laboratory tests are listed in Section 7.1)
7. Healthy according to assessment of the medical history, electrocardiogram (ECG), vital signs, physical examination, laboratory results, negative drug screening, and negative serology tests (except results after vaccination)
8. Non-smoker or ex-smoker, not using any nicotine product; an ex-smoker being defined as someone who completely stopped smoking for at least 12 months before Day 1 of the trial
9. Each subject has to be capable of understanding the trial procedures and sign the ICF prior to their participation in the trial
10. Subjects must consent to adhere to the recommended contraceptive methods as detailed in Section 6.7.5 and Appendix I.

5.3.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

1. Significant history of hypersensitivity to bisoprolol, amlodipine, other dihydropyridines, or any related products (including excipients of the formulations)
2. Significant history of severe hypersensitivity reactions (eg, angioedema) to any drugs
3. Pulse rate (in supine position) less than 60 beats per minute (bpm) or more than 100 bpm at screening
4. Presence of significant arrhythmia: QTc interval prolongation (QTc greater than 430 msec), severe sinus node dysfunction, or second or third atrioventricular block
5. History of low blood pressure (< 100/65 mmHg) or vegetative dystonia
6. History or presence of peripheral arterial occlusion or Raynaud's syndrome
7. Presence of diabetes mellitus
8. History or presence of asthma
9. Presence of significant gastrointestinal, liver, kidney disease, surgery, or any other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs or known to potentiate or predispose to undesired effects
10. Use of any enzyme-modifying drugs, including strong inhibitors of CYP enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, and human immunodeficiency virus [HIV] antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin, St. John's wort or other herbal medicine known with effect on CYP enzymes) within 28 days before Day 1 of this trial
11. Presence or history of significant cardiovascular, pulmonary, hematologic, neurologic, endocrine, immunologic, or dermatological disease
12. Presence or history of significant angina pectoris, acute myocardial infarction or ST segment and T wave changes other than non-clinically significant minor changes

13. Presence or history of ventricular arrhythmia (such as ventricular tachycardia or ventricular fibrillation) or of congestive heart failure
14. Acute conditions which might alter the renal function (eg, dehydration, severe infection)
15. Surgery in the previous 28 days before Day 1 of this trial
16. Any history of tuberculosis and/or prophylaxis for tuberculosis within 10 years of Day 1 of the trial
17. Positive results to HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or treponema pallidum (TP) antibody tests
18. Donation of 50 mL or more of blood within 28 days before Day 1 of the trial; donation of 500 mL or more of blood within 56 days before Day 1 of the trial
19. History of suicidal tendency, history of, or disposition to seizures, state of confusion, clinically relevant psychiatric diseases
20. Poor motivation, intellectual problems likely to limit the validity of consent to participate in the trial or limit the ability to comply with the protocol requirements or inability to cooperate adequately, inability to understand and to observe the instructions of the physician
21. Maintenance therapy with any drug, or significant history of drug dependency or alcohol abuse ($> 3 \times 14$ g alcohol per day, intake of excessive alcohol, acute or chronic use)
22. Positive urine screening of drugs of abuse (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine), or positive breath test of alcohol
23. Positive pregnancy test (only for females of child-bearing potential), or females breast feeding a child
24. Consumption of large quantities of methylxanthine-containing beverages (more than 600 mg caffeine/day: 1 cup (250 mL) of coffee contains approximately 100 mg of caffeine, 1 cup of black or green tea contains approximately 30 mg and 1 glass of cola contains approximately 20 mg caffeine)
25. Volunteers who took an investigational product (in another clinical trial) by prescription within 2 weeks or an over-the-counter medication taken within 1 week before drug administration.

5.4 Criteria for Initiation of Trial Treatment

Not applicable.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in the event of withdrawal of the subject's consent.

Subjects who withdraw from the trial will also be withdrawn from the investigational medicinal product (IMP). Dropout will not be replaced for this trial as long as the minimum evaluable sample size is met.

5.5.2 Withdrawal from the Trial

Furthermore, participation in this clinical trial can be discontinued by the Investigator for one of the following reasons:

1. On Day 1 before trial drug administration of Period 1 and additionally on Day 15 before trial drug administration of Period 2, if the supine blood pressure before drug administration is below 100/65 mmHg or above 139/90 mmHg, the subject has to be withdrawn from the trial
2. Adverse events, as assessed by the Investigator to affect the outcome of the trial endpoints
3. Significant protocol violation such as restrictions regarding alcohol and drug use, and nonadherence to the fasting or fed state
4. Difficulties with blood collection
5. Emesis experienced within 16 hours following drug administration because of incomplete absorption (this period of time corresponds also to 2 times the median time of maximum plasma concentration observed [t_{max}] of amlodipine). Subjects experiencing vomiting later than 16 hours postdose will not be withdrawn unless otherwise decided by the Investigator in light of subject's safety or trial integrity
6. Subject is uncooperative during the trial
7. Use of any medication
8. Withdrawal by Investigator's judgement.

Concomitant medication of any drug is prohibited. Any possible drug interaction caused by a concomitant medication with the IMP during the trial must be completely avoided in this trial.

Details of reasons for premature withdrawal of subjects will be recorded and documented in the final report.

In case of premature withdrawal from the trial, the investigations scheduled for premature withdrawal visit should be performed, if possible, with focus on the most relevant assessments (Section 7.1, "Schedule of Assessments" and Table 1). In any case, the appropriate electronic Case Report Form (eCRF) section must be completed.

Dropouts within each sequence will be replaced if the total number of evaluable subjects within the sequence falls below 12 (Section 8.2.1).

5.5.3 Withdrawal from the Investigational Medicinal Product

Subjects who withdraw from the trial will also be withdrawn from the IMP using the same criteria (Section 5.5.1).

5.6 Premature Termination of the Trial

This trial is to be conducted in healthy volunteers using products in which the safety profile of the 2 products is very well known. A 30-year marketing history with a large population exposure has established that the safety of these products is proven in the population with the target disease. As the safety of these products has been demonstrated in diseased patients, the conduct of this trial in healthy volunteers poses very little risk of premature withdrawal of the trial due to safety issues. However, in every case of (premature) withdrawal, the assessments scheduled for premature withdrawal visit must be conducted (Section 6.15).

5.7 Definition of End of Trial

The End of Trial is defined as the last contact of the last subject (usually the End of Trial visit [Day 29], which is scheduled for 14 days after the administration day in Period 2 [Day 15]).

6 Investigational Medicinal Products and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Products

Investigational product:

One tablet of bisoprolol-amlodipine 5 mg/5 mg (as a combination formulation of the 2 active ingredients)

Manufacturer: An appropriate packaging site under the control of Merck; final release will be conducted by a qualified person of Merck

Tablet description: Bisoprolol-amlodipine fixed-dose-combination tablet: equivalent to 5 mg of bisoprolol fumarate and 5 mg of amlodipine per tablet

Comparator-1:

Tablet description: Bisoprolol fumarate (Concor[®]), light yellow, heart-shaped biconvex film coated tablets, scored on both side

Manufacturer: Bisoprolol; Merck (Darmstadt, Germany) at Frankfurter Strasse 250 64293 Darmstadt Germany

Comparator-2:

Tablet description: Amlodipine besylate (Norvasc[®]), equivalent to 5 mg of amlodipine per tablet; supplied as white, octagonal tablet, scored, debossed on 1 side with "NRV 5" and with "Pfizer" on the opposite side

Manufacturer: Amlodipine; CCI

All trial products will be sourced from respective manufacturer as listed below. A set of in-vitro experiment including dissolution profile and content uniformity are being planned to confirm the dissolution profile of the comparator are within specifications. These in-vitro testing results will be available before the clinical trial conduct.

Drug Treatment	Investigational Product	Comparator-1	Comparator-2
Formulation:	Concor AM [®] Bisoprolol-Amlodipine 5mg/5mg	Concor [®] Bisoprolol 5 mg tablet	Norvasc [®] Amlodipine 5 mg tablet
Manufacturer:	CCI [REDACTED]	Merck KGaA., Germany	CCI [REDACTED]
Storage Condition	Store in original package; Do not store above 30°C; Protected from light.	Store in original package; Do not store above 25°C; Do not freeze; Protected from light.	Store in original package; Do not store above 25°C; Do not freeze; Protected from light.

6.2 Dosage and Administration

Potential trial subjects will be examined at a screening examination to determine their eligibility for participation. These tests are to be conducted within 7 days before the first trial administration (Day 1, Period 1).

On the evening before the dosing day in each period, subjects will be admitted to the CRU to fast prior to Day 1 dosing (administered the next morning). During the fast, subjects will refrain from all food and drinks except water from the evening after dinner of Day -1. Water will be provided until 2 hours predose; the drug will be given with 240 mL (8 ounces) of water at room temperature; water will then be allowed *ad libitum* beginning 1 hour after the administration of the drug.

- The subjects in the fasting cohort will have fasted for at least 10 hours by the time of predose blood sample collected after 07:00 on the first day of each period.
- For the fed cohort, subjects will consume a standard breakfast started from 30 minutes before dosing and finished by 10 minutes before dosing. The single dose of trial drug administration will occur 10 minutes after breakfast completion around 07:00 in the morning of the first day of each period. The content of the breakfast will match the high-fat, high-calorie recommendation based on the regulatory guideline.

All subjects will be required to refrain from drinking water during the first 1 hour after drug administration and to refrain from eating during the first 4 hours. Standard diet for lunch and dinner will be served for both fasting and fed cohorts. Beverages should be controlled: fluid intake will be controlled for each in-house period for all subjects. The subjects should drink at least 2 L of water during the first 24 hours after drug administration.

On Day 1 before first trial drug administration, ECG and vital signs will be assessed. If the subject does not meet all eligibility requirements, the subject cannot be randomized to the trial.

6.3 Assignment to Treatment Sequences

Each eligible subject will receive his allocated treatment according to a computer-generated randomization schedule.

Sequence A-B:

- Day 1 (Period 1), Treatment A: the administration of a single dose of 5 mg/5 mg bisoprolol-amlodipine (fixed-dose-combination tablet; investigational product);
- Day 15 (Period 2), Treatment B: the administration of a single dose of 5 mg bisoprolol (1 tablet) and a single dose of 5 mg amlodipine (1 tablet) given concomitantly (comparators).

Sequence B-A:

- Day 1 (Period 1), Treatment B: the administration of a single dose of 5 mg bisoprolol (1 tablet) and a single dose of 5 mg amlodipine (1 tablet) given concomitantly (comparators);
- Day 15 (Period 2), Treatment A: the administration of a single dose of 5 mg/5 mg bisoprolol-amlodipine (fixed-dose-combination tablet; investigational product).

The 2 doses will be separated by a Washout period of 14 days ([Table 2](#)).

Table 2 Assignment to Administration Sequences

	Day 1 of Period 1	Day 1 of Period 2
Sequence A-B	Bisoprolol-Amlodipine (5 mg/5 mg × 1) (Investigational product)	Bisoprolol (5 mg × 1) + Amlodipine (5 mg × 1) (Comparator)
Sequence B-A	Bisoprolol (5 mg × 1) + Amlodipine (5 mg × 1) (Comparator)	Bisoprolol-Amlodipine (5 mg /5 mg × 1) (Investigational product)

This 2 × 2 crossover design for comparison of 2 treatments complies with the Chinese guideline for BE trials [8]. The guideline recommends 2 sequences in order to minimize the effect of individual and periodic differences. The guideline suggests that the duration of Washout period should be at least 7 times $t_{1/2}$. Therefore, 14 days have been assigned as the Washout period duration to assure that the main collection times in Period 2 can occur on a weekday.

6.4 Non Investigational Medicinal Products to be Used

No other drugs are required by the protocol.

6.5 Concomitant Medications and Therapies

Concurrent administration of any medication is prohibited during the trial.

Subjects enrolled in this trial should be in good general health and therefore should not be taking any other medication. No concomitant medication (including nonprescription medication or multi-vitamin preparations or herbal medications, including traditional Chinese medicines) will be permitted during the trial (that is, within the period of time from the screening examination to the End of Trial examination).

Upon use of any concomitant medication the subject shall then discontinue his/her participation in the trial treatment.

The concomitant medication shall be documented in the eCRF stating the international nonproprietary name and trade name of the medication, its dose, duration, galenic form, route of administration, date and time of all administrations and indication. The data recorded up to the time at which the subject in question will be withdrawn shall be taken for the evaluation of the trial substance's safety and tolerability.

Any additional concomitant therapy that becomes necessary during the trial must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

6.5.1 Permitted Medicines

No concomitant medication is allowed during the trial.

Any additional concomitant therapy that becomes necessary during the trial must be recorded in the corresponding section of the eCRF.

6.5.2 Prohibited Medicines

Prohibitive medications also include cold preparations, aspirin, antacid preparations, vitamins, and natural products used for therapeutic benefits.

The following medications are specifically mentioned in the exclusion criteria for the trial:

- Maintenance therapy with any drug or significant history of drug dependency

- Use of any enzyme-modifying drugs, including strong inhibitors of CYP enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, and HIV antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin, St. John's wort or other herbal medicine known with effect on CYP enzymes) within 28 days before Day 1 of this trial.

6.6 Food Restriction and Standardization Diet

Fluids

Subjects are not allowed to excessively consume beverages containing xanthine (> 5 cups of coffee a day or equivalent) and need to stop caffeine consumption from 48 hours prior to drug administration until collection of the last PK sample in each period. Subjects also need to stop intake of grapefruit, cranberry or juices of these 2 fruits, from 14 days prior to drug administration until collection of the last PK sample in each period. During the hospitalization periods (evening of Day -1 to Day 8 of each period), water is allowed as desired, except for 2 hours before and until 1 hour after drug administrations on Day 1 or Day 15 respectively.

Food

Subjects included in the fed cohort must agree to consume the trial high-fat breakfast. In the fed cohort, the breakfast should be similar in fat and caloric composition of the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) Chinese breakfast according to the standard of the trial center. During the hospitalization periods, subjects will receive breakfast, lunch, and dinner at regular times (as applicable).

Prior to each drug administration (ie, Day 1 or Day 15), subjects in both cohorts need to fast overnight for at least 10 hours.

Fasting cohort: In the morning of Day 1 or Day 15, after drug intake, the subjects should observe a fasting period of 4 hours until a standard lunch will be served. The dinner will be served approximately 12 hours after dosing.

Fed cohort: In the morning of Day 1 or Day 15, subjects in fed cohort need to start the intake of the high-fat breakfast 30 minutes prior to drug administration and complete by 10 minutes before dosing. The drug will be administered 10 minutes after the end of the meal with 240 mL of water. After administration, subjects should observe a fasting period of 4 hours until a standard lunch will be served. The dinner will be served approximately 12 hours after dosing.

6.7 Special Precautions

6.7.1 Alcohol Prohibition

The subjects have to abstain from alcohol from 2½ days (~60 hours) prior to dosing and through the End of Trial visit.

In case of any suspicion of alcohol consumption, a test for alcohol may be performed to confirm the Investigator's judgment.

6.7.2 Smoking Prohibition

Smoking is included as an exclusion criterion barring eligibility into the trial and smoking is also prohibited during the trial.

6.7.3 Clinical Research Unit Inpatient Procedures

Overnight Fast

In the evening before the dosing day, subjects will be admitted to the CRU at ~12 hours prior to Day 1 or Day 15 dosing respectively. Subjects will refrain from all food and drinks except water from the evening following dinner of Day -1 or Day 14 respectively, and they will have fasted for at least 10 hours at the time of Baseline sampling (fasting cohort) or breakfast (fed cohort) the next morning. Water will be provided until 2 hours predose; water will be allowed beginning 1 hour after the administration of the drug. Beverages should be controlled: fluid intake will be controlled for each in-house period for all subjects. The subjects should drink at least 2 L of water during the first 24 hours after drug administration.

Trial Drug Administration

The single dose of trial drug administration will occur after 07:00 on the first day of each period. Subjects will take the medication in a seated position. A total volume of 240 mL water will be consumed with the medication. Following the administration of the drug, hands and mouth will be checked in order to confirm the consumption of the medication. All subjects will be required to refrain from drinking water during the first 1 hour after drug administration and refrain from eating during the first 4 hours. Standard diet for lunch and dinner will be served. The fluid intake will be controlled during the in-house stay.

Posture and Physical Activities

Subjects will remain in bed in an upright or semi-reclined position for at least the first 4 hours following drug administration. During this interval and under supervision, subjects are permitted to leave their bed for brief periods, eg, to use the washroom facilities. After this 4-hour period, subjects may get up, but only under supervision. Furthermore, subjects will be advised to exercise caution with their activities throughout the rest of each period of the trial. Subjects will not engage in strenuous activity at any time during the trial periods.

6.7.4 Safety Considerations

On the last assessment day of each period, the Investigator will decide whether or not the subjects need to return for additional visits to the clinic. At any visit, subjects will be advised to remain at the clinical site if significant AEs are present.

6.7.5 Contraception

Male participants:

A male participant must agree to use and to have their female partners to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in [Appendix I](#) of this protocol during the treatment period and for at least 14 days after the last dose of trial treatment and refrain from donating sperm during this period.

Female participants:

A female participant is eligible to participate if she is not pregnant (see [Appendix I](#)), not breastfeeding, and at least one of the following conditions applies:

- a. Not a woman of childbearing potential (WOCBP) as defined in [Appendix I](#)

OR

- b. A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in [Appendix I](#) of this protocol during the treatment period and for at least 14 days after the last dose of trial treatment.

6.8 Packaging and Labeling of the Investigational Medicinal Product

The packaging, labeling and documentation of IMP will be done according to Annex 13 and GMP requirements, so that it shall be possible to retrace the composition and pharmaceutical quality.

6.9 Preparation, Handling and Storage of the Investigational Medicinal Product

Instructions for the preparation, handling, and storage of the IMPs will be provided. Additional details on the preparation and administration of the IMPs will be provided in the IMP Manual.

All IMP treatment boxes supplied to the trial center must be stored carefully, safely, and separately from other drugs.

Trial medication must not be used for any purpose other than the trial. The administration of trial medication to subjects who have not been enrolled into the trial is not covered by the subject's trial insurance.

The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the trial medication:

Upon receipt of trial treatment boxes at the trial center, the following must be performed by the trial staff:

- Inventory at the center
- Administration to each subject
- Destruction of unused medication.

It must be ensured that the trial drug is not used at the trial site:

- After the expiry date or
- After the retest date unless the trial drug is reanalyzed and its release date extended.

These procedures are to be closely monitored by the trial monitor and trial manager.

Instruction of destruction of IMP will be provided in the IMP Manual. The unused and remained trial medication and the expired testing sample has to be destroyed under Sponsor's greenlight and follow the instruction in IMP Manual.

6.10 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for IMP, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator File.
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor Monitor at each monitoring visit.
- IMP accountability records will include:
- Confirmation of IMP delivery to the trial site.
 - The inventory at the site of IMP provided by the Sponsor and prepared at the site.
 - The use of each dose by each subject.
 - The return to the Sponsor or alternative disposition of unused IMP.
 - Dates, quantities, batch numbers, expiry dates and formulation, as well as the subjects' trial numbers.
- The Investigator should maintain records that adequately document:
 - That the subjects were provided the doses specified by the clinical trial protocol/amendment(s), and
 - That all IMP provided by the Sponsor was fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. Investigational medicinal product that has been dispensed to a subject must not be redispensed to a different subject.

The Sponsor Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site. Following the administration of the drug, hands and mouth will be checked in order to confirm the consumption of the medication.

6.11 Assessment of Investigational Medicinal Product Compliance

The trial treatments will be administered either by the Investigator or under his or her direct supervision in a CRU.

Investigational medicinal product administration and any reason for non-compliance should be recorded in the eCRF.

6.12 Blinding

This trial is an open-label trial design. Blinding is not applicable.

6.13 Emergency Unblinding

Not applicable.

6.14 Treatment of Overdose

This is a trial where the IMPs will be administered by the Investigator/Clinical Trial Coordinator. Therefore, the risk of overdose will be negligible. In case of unexpected events, the supervising physician is responsible for diagnosis and treatment of unexpected adverse reactions according to accepted standard medical care and full documentation. The following actions should be considered.

Amlodipine

If any unforeseen overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Bisoprolol

In general, if overdose occurs, supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol fumarate is not dialyzable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia:	Administer intravenous atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.
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Hypotension:	Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.
Heart Block:	For second or third degree heart block, patients should be carefully monitored and treated with isoproterenol infusion or transvenous cardiac pacemaker insertion, as appropriate.
Congestive Heart Failure:	Initiate conventional therapy (ie, digitalis, diuretics, inotropic agents, vasodilating agents).
Bronchospasm:	Administer bronchodilator therapy such as isoproterenol and/or aminophylline.
Hypoglycemia:	Administer intravenous glucose.

6.15 Medical Care of Subjects after End of Trial

After a subject has completed the second Washout of the trial (14 days after last dose) or has withdrawn prematurely, an End of Trial visit (Day 29, if subject completed the trial) or premature withdrawal visit will be conducted and safety assessments will be performed.

Upon the careful screening for healthy subjects such as detailed in the eligibility criteria for this trial, no serious AEs are expected during this trial. However, in case of any ongoing AE at the End of Trial visit or Premature Withdrawal visit, these AEs must be monitored until they have either returned to normal or are no longer considered as clinically relevant by the Investigator or can be explained. If necessary, other medical disciplines should be consulted.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

The schedule of assessments will include:

- Screening (determining eligibility to the trial, including assessments during admission to CRU; Day -7 to Day -1)
- Admission to the CRU before Period 1 (Day -1)
- Period 1 (Day 1 to Day 8)
- Washout Period 1
- Admission to the CRU before Period 2 (Day 14)
- Period 2 (Day 15 to Day 22)
- Washout Period 2
- End of Trial (Day 29)/Premature Withdrawal ([Table 1](#)).

Subject will participate in the clinical trial on an in-house basis during Day -1 to Day 8 and also during Days 14 to Day 22.

The description of these trial intervals are as follow.

7.1.1 Screening (Day -7 to Day -1)

The following assessments will be conducted during Screening (between Day -7 and Day -1) to determine eligibility of the subject for randomization to the trial.

Informed Consent (ICF)

Prior to performing any trial assessments, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section [9.2](#). The ICF will be signed by the subject prior to the subject's inclusion into the trial.

Inclusion/exclusion Criteria

Potential trial subjects will be examined at screening to determine their eligibility for clinical trial participation. The inclusion and exclusion criteria will be reviewed to determine eligibility for the trial while collecting the necessary information. All screening assessments are to be conducted within 7 days before the start of the trial.

Demographic Information

Demographic information will consist of data collected for age, sex, race (Chinese, non-Chinese), height and weight. The BMI (kg/m²) will be calculated.

Other Baseline Information

Other baseline information will include inquiry for the history of alcohol and nicotine consumption plus the baseline assessments described in more detail below: physical examination, vital signs, ECG recordings, medical history, and laboratory tests.

Medical history will include screening for past illnesses associated with allergic disorders; eyes, ears, nose, and throat; and past illnesses describing the cardiac, vascular, pulmonary, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, psychiatric, dermatological, hematological systems of the body, and previous treatments.

Prior medications within 1 month before the date of first signature of informed consent will be collected.

Concomitant medications, treatments, and AEs will be collected from the date of first signature of informed consent.

Physical Examination

A detailed physical examination will be performed. This examination includes assessments of the general appearance, skin and mucosa, superficial lymph nodes, head and neck, chest, abdomen, musculoskeletal, and neurological systems.

Vital Signs

Blood pressure (systolic and diastolic pressures), pulse rate, body temperature, and respiration (frequency per minute) will be measured and recorded. Blood pressure and pulse rate will be recorded in a supine position after the subject has rested comfortably for at least 5 minutes.

Electrocardiogram Recording

A 12-lead ECG (including QTc evaluation) will be performed.

Results of the ECG recordings will be included in the subject's eCRF. Printouts for each ECG will include date, time, initials of the technician/nurse, and initials of the Investigator who reviewed the printout. At least 5 to 7 beats will be monitored at a speed of 25 mm/sec for each lead and a single lead (V2) run (see Section 7.3.4 for specific ECG determinations and procedures).

Chest X-ray

A chest X-ray examination will be performed.

Laboratory Tests

Hematology assessments

Parameter	Dimension/Unit
Erythrocytes	$\times 10^{12}/L$
Hemoglobin	g/L
Hematocrit	%
Mean corpuscular volume	fL
Mean corpuscular hemoglobin	pg
Mean corpuscular hemoglobin concentration	g/L
Red blood cell distribution width	%
Platelets	$\times 10^9/L$
Mean platelet volume	fL
Thrombocytocrit	%
Platelet distribution width	%
White blood cells	$\times 10^9/L$

Hematology assessments for differential white blood cell counts

Parameter	Dimension/Unit
Neutrophils	$10^9/L$ and %
Monocytes	$10^9/L$ and %
Lymphocytes	$10^9/L$ and %

Biochemistry assessments

Parameter	Dimension/Unit
Alanine aminotransferase	IU/L
Aspartate aminotransferase	IU/L
Total bilirubin	μmol/L
Direct bilirubin	μmol/L
Indirect bilirubin	μmol/L
Protein total	g/L
Albumin	g/L
Globulin	g/L
A/G	(Not applicable)
Alkaline phosphatase	IU/L
Glutaryl transpeptidase	IU/L
Urea nitrogen	mmol/L
Creatinine	μmol/L
Cholesterol	mmol/L
Triglycerides	mmol/L
Glucose	mmol/L
Creatine kinase	IU/L
Lactate dehydrogenase	IU/L
Calcium	mmol/L
Phosphorus	mmol/L
α-Amylase	U/L
Sodium	mmol/L
Potassium	mmol/L
Chloride	mmol/L

Note: If creatine kinase is above the upper limit of normal and evaluated as clinically relevant, a retest should be done and the creatine phosphokinase MB isoenzyme should be determined.

Urinalysis

Appearance, blood, glucose, ketones, nitrite, pH, protein, and leukocytes will be assessed. Microscopic examination will only be performed if dipstick test is positive for leukocytes, blood, nitrites, or proteins.

Serum pregnancy test

Pregnancy testing for females of childbearing potential only (Human Chorionic Gonadotropin in serum)

Other laboratory tests

Serology

HIV antibody
HBsAg
HCV antibody
TP antibody

Urine screening of drugs of abuse

The following urine tests for drug abuse will be conducted: levels for other drugs of abuse (eg, cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine).

Breath test of alcohol

Levels of alcohol in breath will be tested.

Urine nicotine

Levels of nicotine in urine will be tested.

7.1.2 Admission to Clinical Research Unit (Day -1)

In the evening before the dosing day, subjects will be admitted in an in-house status to the CRU at least 12 hours prior to Day 1 dosing for an overnight fast. Subjects will refrain from all food and drinks except water from the evening after dinner of Day -1. They will have fasted for at least 10 hours by the time of drug administration (fasting cohort) or standard breakfast (fed cohort) next morning (see Section 6.7.3).

Trial eligibility assessments will be performed including: physical examination, vital signs, ECG and concomitant medications, treatments and diseases as well as testing for drug abuse.

If the subject is determined to be ineligible for the trial due to any of the above assessments, the subject will be considered a screening failure and will not continue to randomization to the trial.

Adverse events will be collected and recorded on the eCRF.

7.1.3 Period 1 (Day 1 to Day 8)

Day 1, Trial Drug Administration

On Day 1, the following assessments will be conducted and/or collected and recorded on the eCRF.

Trial Eligibility Assessments

Subjects will be assessed for vital signs (blood pressure, pulse rate, temperature and respiration). Blood pressure assessments determine eligibility to be randomized to the trial. The blood pressure (measured in supine position after at least 5 minutes rest) must not be below 100 mmHg and/or 65 mmHg or above 139 mmHg and/or 90 mmHg.

A 12-lead ECG (including QTc evaluation) will be performed.

Any concomitant medications, diseases and treatments should be documented. Concurrent administration of any medication will be prohibited during the trial (Section 6.5).

If the subject is determined to be ineligible for any of the above assessments, the subject will not be randomized to the trial.

Any AEs and serious adverse events (SAEs) should also be recorded.

Randomization

Eligible subjects will then be randomly assigned to one of 2 sequences (Table 2).

Baseline Sampling

Eligible subjects will have their baseline blood sample collected before IMP administration in Period 1.

Trial Drug Administration

As per randomization, each subject will receive a single dose of bisoprolol-amlodipine 5 mg/5 mg (given as 1 tablet of 5 mg/5 mg) or a single dose of 5 mg bisoprolol and 5 mg amlodipine (given as 1 tablet of 5 mg bisoprolol and 1 tablet of 5 mg amlodipine, co-administrated) accordingly.

The single dose of trial drug administration will occur after 07:00 in the morning of the first day of each period. A total volume of 240 mL water will be consumed with the medication. All subjects will be required to refrain from drinking water during the first 1 hour after drug administration and refrain from eating during the first 4 hours. Standard diet for lunch and dinner will be served. Beverages should be controlled: fluid intake will be controlled for each in-house period for all subjects. The subjects should drink at least 2 L of water during the first 24 hours after drug administration.

Blood Sampling (Postdose)

Blood samples for the determination of bisoprolol and amlodipine will be taken at the specified times ([Table 3](#)).

Pharmacokinetic Sampling procedure

For bisoprolol and amlodipine, whole blood samples will be collected in coded, precooled ethylenediamine tetraacetic acid dipotassium salt coated vacutainers by indwelling cannula (short-term peripheral catheter) for the first day and by direct venipuncture for the rest of the time. Blood samples will be kept in an ice water bath pending processing.

For every subject, during each treatment period, a total of 20 samples, approximately 4 mL each whole blood, will be collected at the following times: at predose (Baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. One sample will be collected at End of Trial (Day 29)/Premature Withdrawal. The PK collection time is based on known single-dose PK profiles of both drugs and should be frequent and long enough to characterize the peak and extent of exposure. Plasma samples will be prepared, divided into 2 aliquots and stored at -20 °C.

Subjects who complete both treatment periods will have a total of 41 samples (4 mL whole blood each sample) collected. Total blood volume collection for PK sampling is approximately 164 mL over 5 weeks.

A validated bioanalytical method, using HPLC with MS/MS detection, will be applied to analyze plasma concentration of bisoprolol and amlodipine. The assay and all related procedure will be developed and cross-validated with previously established methods to ensure quality standard and technical specifications are met. Based on previous method, the following criteria are expected:

Analytes: bisoprolol and amlodipine in human plasma

Assay range: bisoprolol 0.500 – 75.000 ng/mL; amlodipine 50.0 – 15000.0 pg/mL

Details of the assay may differ from above and will be provided in the Analytical plan separately.

The complete schedule for each trial period is presented in [Table 3](#). The clock time of all blood draws will be recorded and reported for each subject in the eCRF. The actual sampling times, if available, will always be used for calculation.

Table 3 Sampling 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

Safety Monitoring

Vital signs (blood pressure, pulse rate, temperature and respiration) will be repeated prior to dosing and at 4, 8, and 12 hours postdose.

A 12-lead ECG (including QTc evaluation) will be performed 4 hours postdose.

Any concomitant diseases and treatments should be documented. Any AEs and SAEs should also be recorded.

Concurrent administration of any medication will be prohibited during the trial (Section 6.5.1).

Day 2 to Day 8, Period 1

Pharmacokinetic Blood Sampling (Postdose, continued)

During the 7 days following Day 1, blood samples will be taken according to the trial schedule (Table 3). On Day 2, sampling will be conducted at 24 and 36 hours; from Day 4 to Day 8, sampling will be conducted every 24 hours. Subjects will be allowed to leave the CRU on Day 8 after the morning blood sampling collection (168-hour sample).

Safety Monitoring

Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial. Any AEs and SAEs should also be recorded.

Vital signs (blood pressure, pulse rate, temperature and respiration) will be assessed before blood sampling from Day 2 to Day 8.

A 12-lead ECG (including QTc evaluation) will be performed 48 hours postdose at Day 3.

At the day of discharge, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Serum pregnancy test will be performed for females of childbearing potential only. Physical examination, ECG, and chest X-ray will be performed.

On the morning of Day 8 in the CRU after the blood sampling collection (168-hour sample), the Investigator will decide whether or not the subject needs to stay for any additional time in the clinic. If there are no safety concerns based on the assessment by the Investigator, the subject will be allowed to leave the CRU.

7.1.4 Washout Period 1

The 2 administrations of trial drug are separated by a washout of 14 days. Washout begins postdose on Day 1 and continues for 14 days.

7.1.5 Admission to Clinical Research Unit (Day 14)

In the evening before the dosing day, subjects will be admitted to the CRU at least 12 hours prior to Day 15 dosing for an overnight fast. Subjects will refrain from all food and drinks except water from the evening after dinner of Day 14. They will have fasted for at least 10 hours at the time of drug administration (fasting cohort) or standard breakfast (fed cohort) next morning (see Section 6.6).

Trial eligibility assessments will include: physical examination, vital signs (blood pressure, pulse rate, temperature and respiration), ECG, and concomitant medications (Table 1). Testing for drug

abuse will be performed. In addition, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed.

If the subject is determined to be ineligible for any of the above assessments, the subject will be dismissed from the CRU and will not continue with the trial.

Any AEs will be collected and recorded on the eCRF.

7.1.6 Period 2 (Day 15 to Day 22)

Day 15, Trial Drug Administration

Procedures outlined on Day 1 in Period 1 will be repeated on Day 15 for continuing trial eligibility into Period 2 (except for randomization).

Baseline Sampling

Eligible subjects will have their baseline blood sample collected before trial drug administration in Period 2.

Trial Drug Administration

Each subject will receive the trial medication according to the randomization plan (investigational product and comparators).

The single dose of trial drug administration will occur after 07:00 in the morning of Day 15. A total volume of 240 mL water will be consumed with the medication. All subjects will be required to refrain from drinking water during the first 1 hour after drug administration and refrain from eating during the first 4 hours. Standard diet for lunch and dinner will be served. Beverages should be controlled: fluid intake will be controlled for each in-house period for all subjects. The subjects should drink at least 2 L of water during the first 24 hours after drug administration.

Pharmacokinetic Blood Sampling (Postdose)

Blood samples for the determination of bisoprolol and amlodipine will be taken at the specified times: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 15 hours ([Table 3](#)).

Safety Monitoring

Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial ([Section 6.5.1](#)).

Any AEs and SAEs are also to be recorded.

Vital signs (blood pressure, pulse rate, temperature and respiration) will be taken prior to dosing and also at 4, 8, and 12 hours postdose.

A 12-lead ECG (including QTc evaluation) will be performed 4 hours postdose.

Day 16 to Day 22

Pharmacokinetic Blood Sampling (Postdose, continued)

Blood samples for the determination of bisoprolol and amlodipine will be taken at the specified times ([Table 3](#)).

On Day 16, sampling will be conducted at 24 and 36 hours; from Day 18 to Day 22, sampling will be conducted every 24 hours. The subject is allowed to leave the CRU on Day 22 after the morning blood sampling (168 hour sample).

Safety Monitoring

Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial (Section [6.5.1](#)).

Any AEs and SAEs should also be recorded.

Vital signs (blood pressure, pulse rate, temperature and respiration) will be assessed before blood sampling from Day 16 to Day 22.

A 12-lead ECG (including QTc evaluation) will be performed 48 hours postdose at Day 17.

At the day of discharge, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Serum pregnancy test will be performed for females of childbearing potential only. Physical examination, ECG, and chest X-ray will be performed.

On the morning of Day 22 in the clinic after the morning blood sampling collection (168-hour sample), the Investigator will decide whether or not the subject needs to stay for any additional time in the clinic. If there are no safety concerns based on the assessment by the Investigator, the subject will be allowed to leave the clinic.

7.1.7 Washout Period 2

Washout in Period 2 begins postdose on Day 15 and continues for 14 days through Day 28.

7.1.8 End of Trial (Day 29)/Premature Withdrawal

End of Trial

At End of Trial (Day 29), AEs will be assessed. The case conclusion has to be filled in.

If AEs or pathological findings, ie, clinically relevant deviations from baseline findings are obtained during the final examination, these findings must be monitored until they have either returned to normal or are no longer considered as clinically relevant or can be explained. If necessary, other medical disciplines should be consulted.

Pharmacokinetic Blood Sampling

Blood samples for the determination of bisoprolol and amlodipine will be taken ([Table 3](#)).

Premature Withdrawal

The assessments at Premature Withdrawal visit include: physical examination, vital signs (blood pressure, pulse rate, temperature, and respiratory), ECG, laboratory tests (hematology, biochemistry, and urinalysis), Chest X-ray, and AEs ([Table 1](#)). The case conclusion has to be filled in. Serum pregnancy test will be performed for females of childbearing potential only.

If AEs or pathological findings, ie, clinically relevant deviations from baseline findings are obtained during the final examination, these findings must be monitored until they have either returned to normal or are no longer considered as clinically relevant or can be explained. If necessary, other medical disciplines should be consulted.

Pharmacokinetic Blood Sampling

Blood samples for the determination of bisoprolol and amlodipine will be taken ([Table 3](#)).

7.1.9 Estimated Blood Sample Volumes per Subject

The blood sample volumes of each subject are estimated in [Table 4](#).

Table 4 Estimated Blood Sample Volumes per Subject

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening	Serum virology	4
	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	<i>Approximate Total</i>	<i>14</i>
Period 1	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	4*20
	<i>Approximate Total</i>	<i>90</i>
Period 2	Hematology	2*2
	Biochemistry	4*2
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	4*20
	<i>Approximate Total</i>	<i>96</i>
End of Trial	Pharmacokinetics	4
	<i>Approximate Total</i>	<i>4</i>
Premature Withdrawal	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	4
	<i>Approximate Total</i>	<i>14</i>
Approximate Total of Each Subject (without premature withdrawal)		<i>204</i>

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, sex, race, and height and weight. The BMI (kg/m²) will be calculated.

7.3 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analyzing of baseline medical conditions, physical examination findings, vital signs (blood pressure, pulse rate, temperature and respiration), ECG, laboratory tests, and AEs.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject (Section 7.3.1.2, "Methods of Recording and Assessing Adverse Events").

The reporting period for collecting AEs is described in Section 7.3.1.3.

7.3.1 Adverse Events

7.3.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered an AE, and the death is considered the outcome of the AE.

Investigators must assess the severity/intensity of AEs according to the Qualitative Toxicity Scale as one of the following:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out usual activities.

Investigators must also systematically assess the causal relationship of AEs to the bisoprolol-amlodipine fixed-dose-combination tablet and the comparators (bisoprolol and amlodipine) using the following definitions. Decisive factors for the assessment of causal

relationship of an AE to the treatments include, but may not be limited to, temporal relationship between the AE and the treatments, known side effects of treatments, medical history, concomitant medication, course of the underlying disease, or trial procedures:

Not related: Not suspected to be reasonably related to the bisoprolol-amlodipine fixed-dose-combination tablet or the comparators. Adverse event could not medically (pharmacologically/clinically) be attributed to the bisoprolol-amlodipine combination tablet or the comparators under trial in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to bisoprolol-amlodipine fixed-dose-combination tablet and the comparators. Adverse event could medically (pharmacologically/clinically) be attributed to the bisoprolol-amlodipine fixed-dose-combination tablet and the comparators under trial in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (eg, anemia and increased alanine aminotransferase must be reported as the AE rather than the abnormal value itself.

Adverse Drug Reaction

In accordance with Good Clinical Practice (GCP), an adverse drug reaction (ADR) is defined in this study as any AE considered to be related to drug treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening.

NOTE: The term “life-threatening” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, that is as follows:

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize

the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, in the development of drug dependency, or in drug abuse.

Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to simplify trial treatment or trial procedures (eg, an overnight stay to facilitate related hydration therapy applications) are not considered an SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.3.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his condition. During the reporting period of the trial any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

All AEs must be documented in the appropriate section of the eCRF. Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis. Among these AEs, all serious AEs must be additionally documented and reported using an SAE Report Form (Clinical Trial) as described in Section 7.3.1.4.

The following aspects must be recorded for each AE in the eCRF:

- 1) Description of the AE in medical terms, not as reported by the subject
- 2) Date/time of onset (only in relation to administration of IMP: before, during, or after)
- 3) Severity grade (Section 7.3.1.1), assessed by the Investigator according to the Qualitative Toxicity Scale
- 4) Causal relationship to the IMP applied per protocol, assessed by the Investigator
- 5) Action taken with regard to trial treatments
- 6) Concomitant medication
- 7) Outcome
- 8) Seriousness (appropriate criteria documented).

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.3.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment period. The complete trial duration for collecting AEs is defined as beginning with the date of the signing of the consent form (up to 7 days before Day 1 of trial Period 1), continuing during the

investigational trial drug administration, and collection continued until 14 days after the day of the last investigational trial drug administration (that is, End of Trial visit, Day 29). In case of early termination, AEs until Premature Withdrawal visit will be collected.

7.3.1.4 Procedure for Reporting Serious Adverse Events and Non-serious Adverse Drug Reactions

In the event of any SAE occurring in Treatment A or B group during the reporting period, and in the event of any non-serious ADRs related with Treatment B, the Investigator must inform Sponsor or its designee in writing, within a maximum of 24 HOURS after becoming aware of the event. All written reports should be transmitted using the AE Report Form, which must be completed by the Investigator following specific completion instructions.

To do so, the Investigator/reporter must complete a Sponsor SAE report following specific instructions (SAE report Completion Instruction) and using preferably the electronic template, and send it directly to the Sponsor's designee by electronic mail or facsimile. Name, address, telephone, and fax numbers for SAE reporting will be included in the trial specific AE Report Form as shown below:

E-mail: PPD [REDACTED]

Facsimile: PPD [REDACTED]

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. All written reports should be transmitted using the SAE Report Form (Clinical Trials), which must be completed by the Investigator following specific completion instructions.

Reporting procedures and timelines are reported in the same manner as for follow-up information for any new information for a subject as was collected on a previously reported SAE.

Specific guidance can be found in SAE Report Form Instructions provided by the Sponsor.

The Investigator or reporter must respond to any request for follow-up information (eg, additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Monitor, although in exceptional circumstances the Sponsor's Drug Safety department or its designee may contact the Investigator directly to obtain clarification or to discuss a particularly critical event.

7.3.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

In the event of any SAE occurring during the reporting period, the Investigator must immediately (ie, within 24 hours of becoming aware of the event) report to regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular SAEs with outcome of death) involving his/her subjects to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the trial.

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (“suspected unexpected serious adverse reactions” or SUSARs). The Investigator should place copies of these Safety reports in the Investigator Site File. National regulations will be taken into account with regard to safety report notifications to Investigators.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

7.3.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of the clinical trial and is considered to be related to Concor AM[®], Concor[®] or Norvasc[®] must be monitored and followed up until the outcome is known, unless the subject is documented as “lost to follow-up.” Reasonable attempts to obtain this information must be made and documented. It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.3.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (eg, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.3.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.3.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.3.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.3.3 Clinical Laboratory Assessments

Safety and tolerability will be assessed by monitoring laboratory measurements.

It is essential that Merck Serono 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 Serono.

7.3.4 Electrocardiogram

A 12-lead ECG (including QTc evaluation) will be performed.

After the subject has rested for at least 5 minutes in the supine position, a 12-lead ECG will be conducted by placing peripheral leads I, II, III, aVR, aVL, aVF followed by the precordial leads V1-V6 and all 12 leads recorded. At least 2 to 3 beats will be monitored at a speed of 25 mm/sec for each lead and a single lead (V2) run. Printouts for each ECG will include date, time, initials of the technician/nurse who performed the test and initials of the personnel who reviewed the printout (ie, a medical physician). Results of the ECG recordings will be included in the subject's eCRF.

The following parameters will be assessed:

- RR-Interval [ms]
- PR-Interval [ms]
- QRS-Duration [ms]
- QT-Interval [ms]
- QTc (Bazett) [ms]
- QTcF (Fridericia) [ms]
- Heart Rate [bpm]
- Rhythm (sinusal - other)

QT / QTc interval will be automatically computed using the Bazett correction formula ($QTcB = QT / \sqrt{RR}$) and the Fridericia correction formula ($QTcF = QT / \sqrt[3]{RR}$) by the ECG device according to the recently approved International Council for Harmonisation (ICH) guidance E1. In case of QTc values outside of the normal range, ECGs will be manually re-evaluated by a physician.

7.3.5 Vital Signs, Physical Examinations, and Other Assessments

Safety and tolerability will be assessed by monitoring of vital signs (blood pressure, pulse rate, temperature and respiration) and physical examinations.

Despite the fact that bisoprolol and amlodipine are usually safe and well tolerated, one cannot fully exclude the possibility of an incidence of bradycardia or hypotension.

7.3.6 Pharmacokinetics

7.3.6.1 Sample Processing, Labeling and Storage

At each sampling time point (Section 7.1, Schedule of Assessments), the following process will be followed for the collection of plasma samples for quantification of bisoprolol and amlodipine.

- Approximately 4 mL venous blood will be taken from the subject into a precooled vacutainer.
- Completely and gently invert the vacutainer 8 to 10 times and then centrifuge at 1,500 to 2,000 g for 15 min at 4 C. This must be conducted within 30 min after blood draw. The samples will be kept in an ice bath at all times before centrifugation.
- The resulting plasma will be split equally into 2×1.8 mL transfer vials using a calibrated pipette. The vials will be labeled Vial A and Vial B, respectively. Vial A should contain a minimum of 1 mL; Vial B will be reserved as the back-up sample.
- These tubes will be labeled containing the following information.
 - Test subject ID
 - Plasma
 - Visit Name
 - Sampling date
 - Vial A or Vial B
- The samples will be frozen upright at -20 C or below until shipment. The Vial A and Vial B samples from the same subject should always be stored in separate boxes.
- The samples will be stored at the site for not more than 1 month. Storage of the samples should be monitored closely by the site and the site should complete the Freezer Temperature Logs on a weekly basis.

7.3.6.2 Sample Shipment

All frozen plasma samples will be shipped in dry ice to PPD [REDACTED]. Vial A and Vial B samples from the same subject / time point will never be shipped together. Dry ice shipments can only be made from Mondays to Wednesdays and is not to be made on the day before Local Public Holidays or on Local Public Holidays.

Before shipments are conducted, the site should perform a review to ensure all samples are present and are labeled correctly. Shipment will be made to the following address:

PPD [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

7.4 Information to be Collected on Clinical Screening Failures

Subjects who sign the ICF but do not start trial treatment for any reason will be considered Clinical Screening Failures. The following eCRF pages must be completed for all Clinical Screening Failures:

- Clinical screening Disposition page (including reason for the subject not starting study treatment)
- Informed consent
- Demography
- Adverse events (only if an SAE occurs)
- Inclusion/exclusion criteria.

8 Pharmacokinetic and Statistical Analyses

8.1 Pharmacokinetic Analysis

The following PK parameters will be calculated from plasma concentrations of bisoprolol and amlodipine by applying non-compartmental analysis methods according respective Standard Operating Procedures (SOPs).

C_{\max}	the maximum plasma concentration observed
t_{\max}	time of maximum plasma concentration observed
AUC_{0-t}	area under the (plasma) concentration-time curve from time 0 to the last sampling time at which the concentration is at or above the lower limit of quantification, calculated using mixed log-linear trapezoidal rule
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{extra}	extrapolated part of $AUC_{0-\infty}$ calculated by $C_{\text{last}}/\lambda_z$, expressed in percent
λ_z	terminal elimination rate constant
$t_{1/2}$	half-life
CL/f	total clearance following extravascular administration
V_{ss}/f	apparent volume of distribution at steady-state after extravascular administration

The PK parameter evaluation will be performed using the validated PK software tool Phoenix/WinNonlin.

8.2 Statistical Analysis

8.2.1 Sample Size

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 mg/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

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 [10, 11], and the observed variability has been comparable between fasting and fed dosing states. By applying statistical powering also to the fed cohort, assuming the intra-subject variability is similar in fed state with standard meal consumption [10, 11]. 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

Randomization

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 cohort and 16 in fed cohort) 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 as presented in [Table 5](#).

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.

Table 5 Randomization Allocation

	Day 1 of Period 1	Day 1 of Period 2
Fasting cohort (n= 16)	Treatment A (n= 8)	Treatment B (n= 8)
	Treatment B (n= 8)	Treatment A (n= 8)
Fed cohort (n= 16)	Treatment A (n= 8)	Treatment B (n= 8)
	Treatment B (n= 8)	Treatment A (n= 8)

The first 4 discontinued subjects of each cohort 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.

8.2.2 Endpoints

8.2.2.1 Primary Endpoints

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

- AUC_{0-t} of bisoprolol
- C_{max} of bisoprolol
- AUC_{0-t} of amlodipine
- C_{max} of amlodipine

8.2.2.2 Secondary Endpoints

The secondary endpoints are the following PK parameters determined from plasma concentrations of both analytes, bisoprolol and amlodipine:

- t_{max}
- $t_{1/2}$
- $AUC_{0-\infty}$
- AUC_{extra}
- λ_z
- CL/f
- V_{ss}/f

All PK parameters (primary endpoints and secondary endpoints) will be calculated from plasma concentrations of bisoprolol and amlodipine by applying non-compartmental analysis methods according to respective SOPs.

8.2.2.3 Safety Endpoints

Safety and tolerability will be assessed by monitoring of:

- Assessment of general safety and tolerability
- Adverse Events
- Vital signs (blood pressure, pulse rate, temperature and respiration)
- Biochemistry, hematology, and urinalysis
- Computerized 12-lead ECG recordings (including QTc evaluation)
- Physical examination

8.2.3 Analysis Sets

Per-protocol population

The per-protocol population includes all randomized subjects who have been treated according to protocol and fulfill the following criteria:

- All inclusion/exclusion criteria satisfied, unless some criteria were waived by the Investigator/Sponsor
- Absence of relevant protocol violations with respect to factors likely to affect the comparability of PK results
- Adequate investigational product compliance
- Primary PK variables AUC_{0-t} and C_{max} of bisoprolol or amlodipine in plasma should be available for both trial treatments

If subjects received concomitant medication for the treatment of AEs within 48 hours after dosing, their inclusion in the per-protocol population should be approved by the Sponsor.

Safety population

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

Pharmacokinetic population

The PK Population may include all subjects who completed the trial with adequate trial medication compliance, without any relevant protocol violations 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 in both cohorts. If subjects would receive concomitant medication for the treatment of an AE, their inclusion in the PK Population will be decided on a case-by-case basis. All PK analyses will be based on this population analysis set.

8.2.4 Description of Statistical Analyses

8.2.4.1 General Considerations

Details of the statistical analysis will be presented in a statistical analysis plan prior to database lock.

The statistical analysis will not be started until all data have been corrected and checked for plausibility, and until all necessary coding and assessments have been completed.

All data recorded during the trial will be presented in individual data listings performed on the safety population. All data will be evaluated as observed values; no imputation method for missing values will be used. Methods for concentration data below the lower limit of quantification will be described in the statistical analysis plan. The consideration of covariates in the mixed effect model is not planned.

All statistical analyses will be performed by Merck (Darmstadt, Germany).

8.2.4.2 Analysis of Primary Endpoints

The null and alternative hypotheses are the following, to be applied to both treatments:

$$H_0 : \text{for } AUC_{0-t} \quad \mu_T / \mu_C \leq 0.8 \text{ or } \mu_T / \mu_C \geq 1.25 \\ \text{for } C_{\max} \quad \mu_T / \mu_C \leq 0.8 \text{ or } \mu_T / \mu_C \geq 1.25, \text{ for at least 1 primary endpoint}$$

$$H_1 : \text{for } AUC_{0-t} \quad 0.8 < \mu_T / \mu_C < 1.25 \\ \text{for } C_{\max} \quad 0.8 < \mu_T / \mu_C < 1.25, \text{ for all 4 primary endpoints}$$

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

The analysis of primary endpoints will be based on PK Population (Section 8.2.3)

The primary variable, C_{\max} and AUC_{0-t} in fasting or fed cohort will be log-transformed and mixed effect model will be applied. The model will include effects for sequence, treatment and period. Subject within sequence will be included as random effect.

Based on the residual (within-subject) variation, 90% CIs for the ratio of geometric means will be calculated. The BE can be established if all the 4 sets of the 90% CIs on the ratios between investigational product and comparators of the geometric means fall within 80.00% to 125.00%.

8.2.4.3 Analysis of Secondary Endpoints

For t_{\max} , the Hodges-Lehmann estimates [9] for the pairwise treatment differences and the corresponding 90% CIs according to the Tukey method will be calculated.

The mixed model as described above will also be applied to $AUC_{0-\infty}$. A 90% CI will be calculated for the ratios of geometric means of the investigational product and comparators (eg, Treatment A/Treatment B).

Summaries using descriptive analyses for the remaining PK parameters and the safety variables will be performed as described in Section 8.2.4.4 and Section 8.2.4.5.

8.2.4.4 Analysis of Safety Endpoints

All data recorded during the trial will be presented in individual data listings performed on the safety population.

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, standard deviation (SD), standard error of the mean (SEM), 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.

After coding of AEs according to the Medical Dictionary for Regulatory Activity classification (current version) 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.

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
- Intensity
- Causality relationship to investigational product
- Outcome

- Action taken to investigational product
- Other action
- Seriousness

Incidence of treatment-emergent adverse events will be summarized using frequency of events and number of subjects experiencing these events per treatment, preferred term, and system/organ class.

In addition, all treatment-emergent adverse events will be tabulated by intensity and relationship to drug per treatment and cohort. An AE will be considered “treatment-emergent” if it occurred after the first investigational product administration or if it occurred before the first investigational product administration and worsened after.

Results of physical examination will only be listed by treatment, subject, period, time point, and body system.

Handling of discontinued subjects and missing data

If 4 subjects within one sequence have already discontinued and 12 subjects remain in that sequence, any further discontinued subjects will be replaced in this sequence.

8.2.4.5 Analysis of Further Endpoints

Analyses described in this subsection will be performed in general for the PK population.

Demographic parameters (age, height, and weight) will be summarized by means of tabulated descriptive statistics (the number of observations [N], arithmetic mean, median, SD, SEM, minimum and maximum) by treatment, cohort, and overall.

Plasma concentrations below lower limit of quantitation will be analyzed as zero for descriptive statistics. Plasma concentration data will be summarized by treatment, analyte and scheduled time point showing the number of observations (N), arithmetic mean, SD, SEM, CV(%), minimum, median and maximum.

Mean plasma concentrations per treatment and analyte will be plotted (linear scale with SD, and semi-logarithmic scale) using scheduled time points for bisoprolol.

Mean plasma concentrations per treatment and analyte will be plotted (linear scale with SD, and semi-logarithmic scale) using scheduled time points for amlodipine.

Results of subjects not in the per-protocol population will be annotated and listed together with the data of the other subjects, but will not be used for descriptive statistics and mean curves.

Individual plasma concentrations (linear and semi-logarithmic scales) will be plotted by treatment (showing all subjects simultaneously) and by subject (showing all treatments simultaneously).

8.2.5 Interim and Additional Planned Analyses

Not applicable.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

9.3 Subject Identification and Privacy

Immediately after informed consent has been obtained, a unique subject number will be assigned to each subject at inclusion into the trial. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected during the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose and to answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

Merck Serono/EMD Serono will provide the appropriate information to contact a physician. This includes the provision of a 24 hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each subject participating to the trial. Insurance conditions will meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with the ICF to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File by the Sponsor.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (eg, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the country involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the designated Contracted Research Organization. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The data management department of the designated Contracted Research Organization will be responsible for data processing, in accordance with the defined data management procedures under the supervision of the Sponsor. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. Portable document format files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Sex
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification
- Date of subject's inclusion into the trial (ie, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's End of Trial visit, or
- Date of premature withdrawal and reason for premature withdrawal of the subject from the trial or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

Electronic subject files (if applicable) will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The site Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the IMP(s), and the subjects' original medical records/files.

Independent Quality Assurance activities will be performed on the clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and

to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the Site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor/designee in consultation with the Principal Investigator and other relevant committees or cohorts.

10.6.2 Publication

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by Investigators or their representatives will require presubmission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection.

11 References Cited in the Text

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12 Appendices

Appendix I Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of participant's medical records, medical examination, or medical history interview.

2. Premenarchal (not applicable)

3. Postmenopausal female

- Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Contraceptive Guidance

Taken from the CTFG guidelines, which are the guidelines referenced by the EMA. Deviations from use of "highly effective" are possible under certain situations as detailed in the CTFG guidelines.

Highly Effective Contraceptive Methods That Are User Dependent	
Failure rate of < 1% per year when used consistently and correctly.	
<ul style="list-style-type: none"> Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> oral (not allowed for women taking part in the study but allowed for female partners of male volunteers) intravaginal transdermal 	
<ul style="list-style-type: none"> Progestogen-only hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> oral injectable 	
Highly Effective Methods That Are User Independent	
<ul style="list-style-type: none"> Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^b Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) bilateral tubal occlusion 	
<ul style="list-style-type: none"> Vasectomized partner <p>(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</p>	
<ul style="list-style-type: none"> Sexual abstinence <p>(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.)</p>	
<p>NOTES:</p> <p>a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.</p> <p>b) Hormonal contraception may be susceptible to interaction with the trial drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 14 days after the last dose of trial treatment</p>	

Appendix II: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial 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 or Fed
State

IND Number: Not applicable

EudraCT Number: Not applicable

Clinical Trial Protocol Date / 03 May 2017 / Version 3.0
Version:

Protocol Lead:

I approve the design of the clinical trial:

PPD

PPD

Signature

Date of Signature

Name, academic degree:

PPD

Function / Title:

Institution:

Merck Serono Co., Ltd.

Address:

PPD

Telephone number:

PPD

Fax number:

PPD

E-mail address:

PPD

Signature Page – Principal Investigator

Trial 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 or Fed
State

IND Number: Not applicable

EudraCT Number: Not applicable

Clinical Trial Protocol Date / 03 May 2017 / Version 3.0
Version:

I, the undersigned, am responsible for the conduct of the trial and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation GCP (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title: Principle Investigator

Institution:

Address:

PPD

Telephone number:

PPD

Fax number:

PPD

E-mail address:

PPD

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree	PPD
Function / Title:	Biostatistician
Institution	Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd.
Address	Merck Serono Co., Ltd. PPD PPD PPD PPD
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Name, academic degree	PPD
Function / Title:	PPD
Institution	Merck Serono Co., Ltd.
Address	PPD PPD PPD
Telephone number	PPD
Fax number	
E-mail address	PPD

Appendix III: Protocol Amendments and List of Changes

Table of Previous Protocol Amendments

Protocol amendment included in this clinical trial protocol:

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1.0	Y	16 February 2017	China	Y

Amendment 2.0

Rationale

The purposes of this protocol amendment (Amendment 2.0, 03 May 2017) are to:

- Change the blood volume for PK sample based on the recommendation from Ethics Committee and justified technical requirement.
- Remove ‘orange’ and ‘orange juice’ from food restriction based on the internal scientific feedback, which is deemed as not relevant with study medication.
- Update the storage conditions for IMPs according to the label of study medications.
- Addition of non-serious ADRs related with Treatment B according to the requirement from China Health Authority.

This amendment is not considered substantial as these changes are related with operational details, which will not influence the study design.

Major Scientific Changes

The major scientific changes of this protocol amendment (Amendment No.2.0) are:

- Changed the blood volume for PK sample from 5 mL to 4 mL whole blood;
- Removed the wording of ‘orange’ and ‘orange juice’ from food restriction;
- Updated the details of storage conditions for IMPs;
- Added the procedure for reporting non-serious ADRs related with Treatment B.










Administrative and Editorial Changes

Correction of administrative, minor editorial changes and inconsistencies throughout the document that have been identified since the finalization of the clinical trial protocol.

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 2.0, 16 February 2017 (Amendment No. 1.0)

Change	Section	Page	Previous Wording	New Wording																
Updated the protocol number	Cover page Synopsis headers	1 10 All pages	EMR200006-0001	EMR200006-0001																
Specified the duration of prior medication, concomitant therapies, and AEs	Table 1 Schedule of Assessments Section 7.1.1 Screening (Day -7 to Day -1)	16-17 43	Prior medication within 1 month before screening will be collected.	See below Table Prior medication within 1 month before screening signature of informed consent will be collected. Concomitant medications, treatments, and AEs will be collected from the date of first signature of informed consent.																
Corrected the typo of treatment in Figure 1	Figure 1 Schematic of Trial Design	25		See below Figure																
Simplified the wording based upon the description in Section 6.6	Section 5.3.1 Inclusion Criteria (Number 5)	27	Systolic blood pressure (in supine position) within 100 to 139 mmHg (inclusive) and diastolic blood pressure (in supine position) within 65 to 90 mmHg (inclusive) at Screening, during Admission to the Clinical Research Unit (CRU) (12 hour predose fast) and before each dosing	Systolic blood pressure (in supine position) within 100 to 139 mmHg (inclusive) and diastolic blood pressure (in supine position) within 65 to 90 mmHg (inclusive) at Screening, during Admission to the Clinical Research Unit (CRU) (12 hour predose- fast) and before each dosing																
The information was added to keep consistent with the description in Section 6.7.5	Section 5.3.2 Exclusion Criteria (Number 23)	29	Positive pregnancy test (only for females of child-bearing potential)	Positive pregnancy test (only for females of child-bearing potential), or females breast feeding a child																
Updated the storage condition for the investigational medicinal products	Section 6.1 Description of the Investigational Medicinal Products	33	<table><tr><td><u>Drug Treatment</u></td><td><u>Investigational Product</u></td><td><u>Comparator-1</u></td><td><u>Comparator-2</u></td></tr><tr><td><u>Formulation:</u></td><td>Concor AM Bisoprolol-A mlodipine 5mg/5mg</td><td>Concor Bisoprolol 5 mg tablet</td><td>Norvasc Amlodipine mg tablet</td></tr></table>	<u>Drug Treatment</u>	<u>Investigational Product</u>	<u>Comparator-1</u>	<u>Comparator-2</u>	<u>Formulation:</u>	Concor AM Bisoprolol-A mlodipine 5mg/5mg	Concor Bisoprolol 5 mg tablet	Norvasc Amlodipine mg tablet	<table><tr><td><u>Drug Treatment</u></td><td><u>Investigational Product</u></td><td><u>Comparator-1</u></td><td><u>Comparator-2</u></td></tr><tr><td><u>Formulation:</u></td><td>Concor AM[®]</td><td>Concor[®] Bisoprolol 5 mg tablet</td><td>Norvasc[®] Amlodipine 5 mg tablet</td></tr></table>	<u>Drug Treatment</u>	<u>Investigational Product</u>	<u>Comparator-1</u>	<u>Comparator-2</u>	<u>Formulation:</u>	Concor AM [®]	Concor [®] Bisoprolol 5 mg tablet	Norvasc [®] Amlodipine 5 mg tablet
<u>Drug Treatment</u>	<u>Investigational Product</u>	<u>Comparator-1</u>	<u>Comparator-2</u>																	
<u>Formulation:</u>	Concor AM Bisoprolol-A mlodipine 5mg/5mg	Concor Bisoprolol 5 mg tablet	Norvasc Amlodipine mg tablet																	
<u>Drug Treatment</u>	<u>Investigational Product</u>	<u>Comparator-1</u>	<u>Comparator-2</u>																	
<u>Formulation:</u>	Concor AM [®]	Concor [®] Bisoprolol 5 mg tablet	Norvasc [®] Amlodipine 5 mg tablet																	

Change	Section	Page	Previous Wording	New Wording
			<div> <div> <u>Manufacturer:</u>  </div> <div>  </div> <div> Merck KGaA., Germany </div> </div> <div> <div> <u>Storage Condition</u> Do not store above 30°C </div> <div>  </div> <div> Do not store above 30°C </div> </div> <div> <div>  </div> <div> Store in original package; Protected from light </div> </div>	<div> Bisoprolol-Am lodypine 5mg/5mg </div> <div>  </div> <div> Merck KGaA., Germany </div>
Updated the restriction of fluid intake	Section 6.6 Food Restriction and Standardization Diet	36	<div> <u>Manufacturer:</u>  </div> <div> <u>Storage Condition</u> Do not store above 30°C </div> <div> Store in original package; Protected from light </div>	<div> <u>Manufacturer:</u>  </div> <div> <u>Storage Condition</u> Do not store above 30°C; Protected from light. </div> <div> Store in original package; Do not store above 25°C; Do not freeze; Protected from light. </div>
Clarification that IMP Manual will be provided instead of Manual of Operation	Section 6.8 Packaging and Labelling of the Investigational Medicinal Product	38	<div> <u>Manufacturer:</u>  </div> <div> <u>Storage Condition</u> Do not store above 30°C </div> <div> Store in original package; Protected from light </div>	<div> <u>Manufacturer:</u>  </div> <div> <u>Storage Condition</u> Do not store above 30°C; Protected from light. </div> <div> Store in original package; Do not store above 25°C; Do not freeze; Protected from light. </div>

Change	Section	Page	Previous Wording	New Wording																																								
	Section 6.9 Preparation, Handling and Storage of the Investigational Medicinal Product	 Instruction of destruction of IMP will be provided in the MOP. The unused and remained trial medication and the expired testing sample has to be destroyed under Sponsor’s greenlight and follow the instruction in MOP. Instruction of destruction of IMP will be provided in the MOP IMP Manual . The unused and remained trial medication and the expired testing sample has to be destroyed under Sponsor’s greenlight and follow the instruction in MOP IMP Manual .																																								
Updated the units of laboratory tests	Section 7.1.1 Screening (Day -7 to Day -1)	44-45	<table><tr><th colspan="2">Laboratory Tests</th></tr><tr><th colspan="2"><u>Hematology assessments</u></th></tr><tr><th>Parameter</th><th>Dimension/Unit</th></tr><tr><td>Erythrocytes</td><td>×10¹²/L</td></tr><tr><td>Hemoglobin</td><td>g/L</td></tr><tr><td>Hematocrit</td><td>L/L</td></tr></table> <table><tr><th colspan="2"><u>Biochemistry assessments</u></th></tr><tr><th>Parameter</th><th>Dimension/Unit</th></tr><tr><td>Phosphorus</td><td>mmol/L</td></tr><tr><td>α-Amylase</td><td>IU/L</td></tr></table>	Laboratory Tests		<u>Hematology assessments</u>		Parameter	Dimension/Unit	Erythrocytes	×10 ¹² /L	Hemoglobin	g/L	Hematocrit	L/L	<u>Biochemistry assessments</u>		Parameter	Dimension/Unit	Phosphorus	mmol/L	α-Amylase	IU/L	<table><tr><th colspan="2">Laboratory Tests</th></tr><tr><th colspan="2"><u>Hematology assessments</u></th></tr><tr><th>Parameter</th><th>Dimension/Unit</th></tr><tr><td>Erythrocytes</td><td>×10¹²/L</td></tr><tr><td>Hemoglobin</td><td>g/L</td></tr><tr><td>Hematocrit</td><td>L/L%</td></tr></table> <table><tr><th colspan="2"><u>Biochemistry assessments</u></th></tr><tr><th>Parameter</th><th>Dimension/Unit</th></tr><tr><td>Phosphorus</td><td>mmol/L</td></tr><tr><td>α-Amylase</td><td>IU/L</td></tr></table>	Laboratory Tests		<u>Hematology assessments</u>		Parameter	Dimension/Unit	Erythrocytes	×10 ¹² /L	Hemoglobin	g/L	Hematocrit	L/L %	<u>Biochemistry assessments</u>		Parameter	Dimension/Unit	Phosphorus	mmol/L	α-Amylase	IU/L
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<u>Biochemistry assessments</u>																																												
Parameter	Dimension/Unit																																											
Phosphorus	mmol/L																																											
α-Amylase	IU/L																																											
Updated the blood volume of PK sampling	Section 7.1.3 Period 1 (Day 1 to Day 8) Section 7.1.9 (Table 4; see below table)	48 54	<p>For every subject, during each treatment period, a total of 20 samples, approximately 5 mL each whole blood, will be collected at the following times: at predose (Baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. One sample will be collected at End of Trial (Day 29)/Premature Withdrawal. The PK collection time is based on known single-dose PK profiles of both drugs and should be frequent and long enough to characterize the peak and extent of exposure. Plasma samples will be prepared, divided into 2 aliquots and stored at -20 °C.</p> <p>Subjects who complete both treatment periods will have a total of 41 samples (5 mL whole blood each sample) collected. Total blood volume collection is approximately 205 mL over 5 weeks.</p>	<p>For every subject, during each treatment period, a total of 20 samples, approximately 45 mL each whole blood, will be collected at the following times: at predose (Baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. One sample will be collected at End of Trial (Day 29)/Premature Withdrawal. The PK collection time is based on known single-dose PK profiles of both drugs and should be frequent and long enough to characterize the peak and extent of exposure. Plasma samples will be prepared, divided into 2 aliquots and stored at -20 °C.</p> <p>Subjects who complete both treatment periods will have a total of 41 samples (45 mL whole blood each sample) collected. Total blood volume collection for PK sampling is approximately 164205 mL over 5 weeks.</p>																																								
Added the definition of ADR	Section 7.3.1.1 Adverse Event Definition	55	-	Adverse Drug Reaction																																								

Bisoprolol & Amlodipine **Bioequivalence Trial of Concor AM[®] vs Bisoprolol and Amlodipine in Chinese Subjects**

EMR200006-001

Change	Section	Page	Previous Wording	New Wording
Added the procedure for reporting non-serious ADRs related with treatment B according to the requirement from China health authority; Updated the wording of the process of reporting SAEs based upon the changes in real operation	Section 7.3.1.4 Procedure for Reporting Serious Adverse Events and Non-serious Adverse Drug Reaction	58	<p>In the event of any SAE occurring during the reporting period, the Investigator must immediately (ie, within a maximum 24 HOURS after becoming aware of the event) inform Global Drug Safety by telephone, by fax or by e-mail.</p> <p>To do so, the Investigator/reporter must complete a Sponsor SAE report following specific instructions (SAE report Completion Instruction) and using preferably the electronic template, and send it directly to the Sponsor's Global Drug Safety department by electronic mail or facsimile, using the dedicated e-mail address and facsimile numbers specified below.</p> <p>E-mail: PPD Facsimile: PPD</p>	<p>In accordance with Good Clinical Practice (GCP), an adverse drug reaction (ADR) is defined in this study as any AE considered to be related to drug treatment.</p> <p>In the event of any SAE occurring in Treatment A or B group during the reporting period, and in the event of any non-serious ADRs related with Treatment B, the Investigator must immediately inform Sponsor or its designee in writing, within a maximum of 24 HOURS after becoming aware of the event, to the Global Drug Safety. All written reports should be transmitted using the AE Report Form, which must be completed by telephone, by fax or by e-mail to the Investigator following specific completion instructions.</p> <p>To do so, the Investigator/reporter must complete a Sponsor SAE report following specific instructions (SAE report Completion Instruction) and using preferably the electronic template, and send it directly to the Sponsor's Global Drug Safety department designee by electronic mail or facsimile, using the dedicated e-mail. Name, address, telephone, and facsimilefax numbers specified below for SAE reporting will be included in the trial specific AE Report Form as shown below.</p> <p>E-mail: PPD kuntuo.pv@kuntuo.com Facsimile: PPD</p>
Updated the blood volume of PK sampling; and updated the wording for sample processing and labeling based upon the changes in real operation	Section 7.3.6.1 Sample Processing, Labeling and Storage	61	<p>At each sampling time point (Section 7.1, Schedule of Assessments), the following process will be followed for the collection of plasma samples for quantification of bisoprolol and amlodipine.</p> <ul style="list-style-type: none"> Approximately 5 mL venous blood will be taken from the subject into a precooled vacutainer. Completely and gently invert the vacutainer 8 to 10 times and then centrifuge at 1,500 g for 15 min at 4°C. This must be conducted within 30 min after blood draw. The samples will be kept in an ice bath at all times before centrifugation. The separated plasma will be transferred into a spin tube and centrifuged again at 2,000 g for a further 15 min to ensure that no debris is present in the plasma. 	<p>At each sampling time point (Section 7.1, Schedule of Assessments), the following process will be followed for the collection of plasma samples for quantification of bisoprolol and amlodipine.</p> <ul style="list-style-type: none"> Approximately 54 mL venous blood will be taken from the subject into a precooled vacutainer. Completely and gently invert the vacutainer 8 to 10 times and then centrifuge at 1,500 to 2,000 g for 15 min at 4°C. This must be conducted within 30 min after blood draw. The samples will be kept in an ice bath at all times before centrifugation. The separated plasma will be transferred into a spin tube and centrifuged again at 2,000 g for a further 15 min to ensure that no debris is present in the plasma.

Change	Section	Page	Previous Wording	New Wording
			<ul style="list-style-type: none"> The resulting plasma will be split into 2 × 2 mL transfer vials using a calibrated pipette. The vials will be labeled Vial A and Vial B, respectively. Vial A should contain a minimum of 1 mL; Vial B will be reserved as the back-up sample. These tubes will be labeled containing the following information. <ul style="list-style-type: none"> Test subject ID Drug administered Plasma Test period/time point Visit Name Sampling date Vial A or Vial B 	<ul style="list-style-type: none"> The resulting plasma will be split equally into 2 × 21.8 mL transfer vials using a calibrated pipette. The vials will be labeled Vial A and Vial B, respectively. Vial A should contain a minimum of 1 mL; Vial B will be reserved as the back-up sample. These tubes will be labeled containing the following information. <ul style="list-style-type: none"> Test subject ID Drug administered Plasma Test period/time point Visit Name Sampling date Vial A or Vial B
Clarified the randomization process	Section 8.2.1	65	<p>A total of 32 eligible healthy male and female Chinese subjects 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 Period 1 to one of the 2 cohorts (fasting or fed). Then each state will be randomized in a 1:1 ratio to one of 2 treatment sequences: Sequence A-B or Sequence B-A as presented in Table 5.</p>	<p>A total of 32 eligible healthy male and female Chinese subjects (16 in fasting cohort and 16 in fed cohort) 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 Period 1 to one of the 2 cohorts (fasting or fed). Then each state will be randomized in a 1:1 ratio to one of 2 treatment sequences: Sequence A-B or Sequence B-A as presented in Table 5.</p>
Specified the condition for using oral contraceptives based upon the information in Section 6.5	Appendix I Contraceptive Guidance and Woman of Childbearing Potential	80	<p>Highly Effective Contraceptive Methods That Are User Dependent</p> <p>Failure rate of < 1% per year when used consistently and correctly.</p> <ul style="list-style-type: none"> Combined (estrogen- and progestogen- containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> oral intravaginal transdermal 	<p>Highly Effective Contraceptive Methods That Are User Dependent</p> <p>Failure rate of < 1% per year when used consistently and correctly.</p> <ul style="list-style-type: none"> Combined (estrogen- and progestogen- containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> oral (not allowed for women taking part in the study but allowed for female partners of male volunteers) intravaginal transdermal
Administrative change on clinical team lead	Appendix II	84	<p>Name, academic degree PPD</p> <p>Function / Title: PPD Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd.</p> <p>Institution</p>	<p>Name, academic degree PPD</p> <p>Function / Title: PPD PPD PPD PPD</p>

Bioequivalence Trial of Concor AM[®] vs Bisoprolol and Amlodipine in Chinese Subjects

[illegible]

Update on Table 1 Schedule of Assessments

Assessments ^a	Screening		Period 1								Period 2									End of Trial	Premature Withdrawal	
Day	-7 ~ -2	-1 Admission	1 ^b	2	3	4	5	6	7	8 Discharge	9-13	14 Admission	15 ^b	16	17	18	19	20	21	22 Discharge	23-28	29
Informed consent form signed	X																					
Demographic information	X																					
Inclusion/exclusion criteria	X																					
History of alcohol and nicotine consumption	X																					
Medical history	X																					
Prior medications	X ^c																					
Laboratory tests	X									X		X								X		X
Serum Pregnancy test (only for females of child-bearing potential)	X									X										X		X
HIV antibody, HBsAg, HCV antibody, and TP antibody tests	X																					
Urine screening of drugs of abuse and breath test of alcohol	X	X										X										
Urine nicotine	X																					
Randomization			X																			
Drug administration			X										X									
Blood sampling for Pharmacokinetics ^d			X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X		X

Bisoprolol & Amlodipine Bioequivalence Trial of Concor AM[®] vs Bisoprolol and Amlodipine in Chinese Subjects

EMR200006-001

Assessments ^a	Screening		Period 1								Period 2								End of Trial	Premature Withdrawal		
Day	-7 ~ -2	-1 Admission	1 ^b	2	3	4	5	6	7	8 Discharge	9-13	14 Admission	15 ^b	16	17	18	19	20	21	22 Discharge	23-28	29
Physical examination	X	X								X		X								X		X
Vital signs (blood pressure, pulse rate, temperature and respiration) ^e	X	X	X	X	X		X			X		X	X	X	X	X		X		X		X
Electrocardiogram ^f	X	X	X							X		X	X	X						X		X
Chest X-ray	X									X										X		X
AEs and concomitant therapies ^g																						

Continuous

AE = adverse event; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TP = treponema pallidum

^a Subject will participate in the clinical trial on an in-house basis during Day -1 to Day 8 and also during Days 14 to 22. Subjects are excused from the clinic during certain days after each period: from trial Day 9 to Day 13 and from trial Day 23 to Day 28.

^b After the single dose administration, Washout begins.

^c Prior medication within 1 month before the date of first signature of informed consent will be collected.

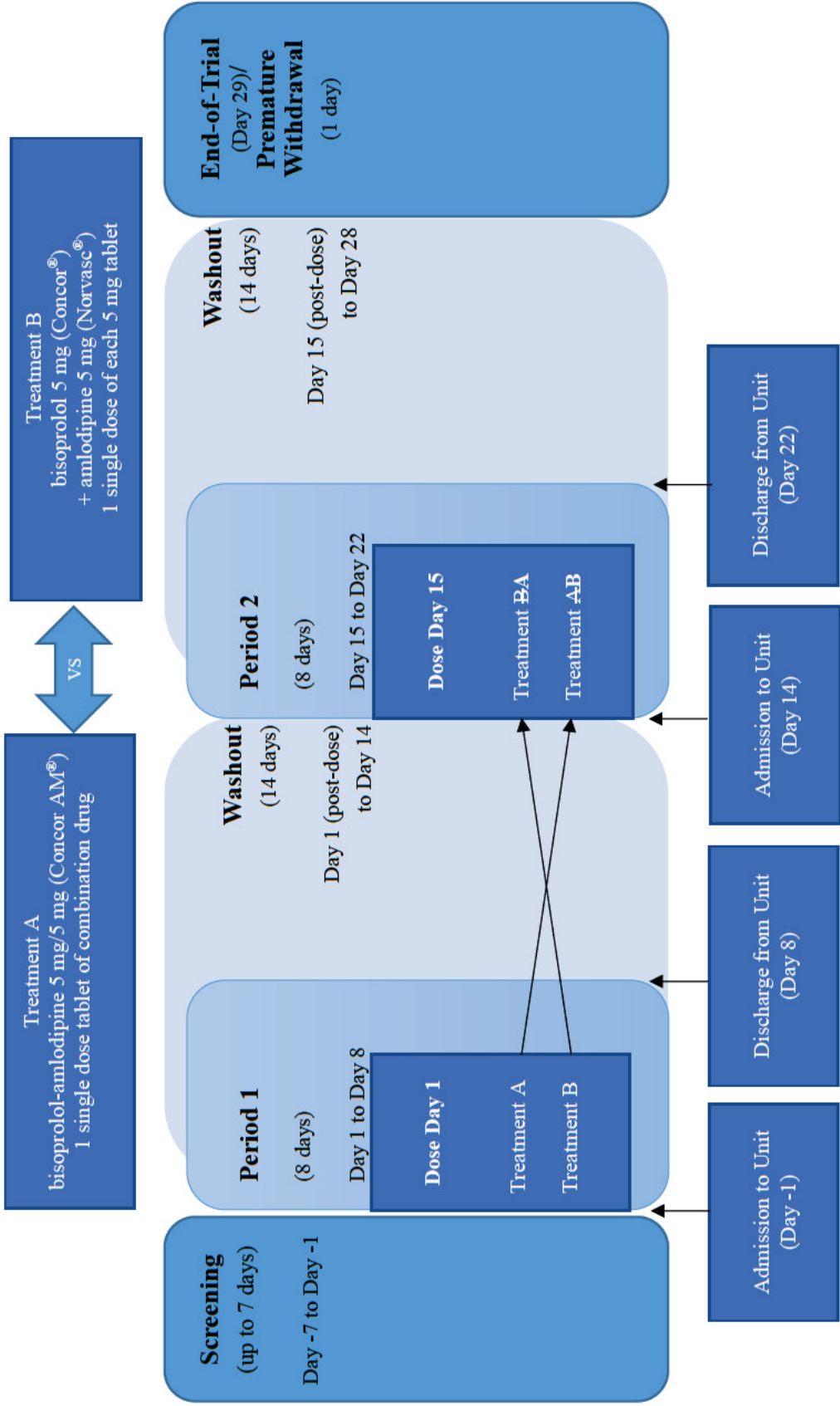
^d For every subject, during each treatment period, pharmacokinetic blood samples will be collected at the following times: at predose (Baseline) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. One sample will be collected at End of Trial (Day 29) or Premature Withdrawal.

^e Vital signs will be taken at Screening, at admission (Day -1 and Day 14), prior to dosing and also at 4, 8, and 12 hours postdose at Day 1 and Day 15; and before blood sampling at Day 2, 3, 4, 6, and 8 in Period 1, then Day 16, 17, 18, 20, and 22 in Period 2, and at Premature Withdrawal (if applicable).

^f Electrocardiograms will be taken at Screening, at admission (Day -1 and Day 14), prior to dosing and also at 4 hours postdose at Day 1 and Day 15; at 48 hours postdose at Day 3 and Day 17; then at discharge of each period (Day 8 and Day 22), and at Premature Withdrawal (if applicable).

^g AEs and concomitant therapies will be collected continuously from the date of first signature of informed consent.

Update on Figure 1 Schematic of Trial Design



Section 7.1.9 (Estimated Blood Sample Volumes per Subject) with Table 4

The blood sample volumes of each subject are estimated in [Table 4](#).

Table 4 Estimated Blood Sample Volumes per Subject

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening	Serum virology	4
	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	<i>Approximate Total</i>	<i>14</i>
Period 1	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	45*20
	<i>Approximate Total</i>	110 90
Period 2	Hematology	2*2
	Biochemistry	4*2
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	45*20
	<i>Approximate Total</i>	116 96
End of Trial	Pharmacokinetics	45
	<i>Approximate Total</i>	45
Premature Withdrawal	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	45
	<i>Approximate Total</i>	15 14
Approximate Total of Each Subject (without premature withdrawal)		245 204