Clinical Trial Protocol

Clinical Trial Protocol Number	**MS200006-0039**
Title	**A single-arm, interventional, multi-center, pilot study to evaluate the efficacy of oral Bisoprolol on heart rate reduction in Chinese Chronic Heart Failure patients with NYHA class II – IV (Biso-CHF Study)**
Phase	**IV**
IND Number	**Not applicable**
EudraCT Number	**Not applicable**
Coordinating Investigator	PPD PPD
Sponsor	**Merck Serono Co.,Ltd** **25F, Nuo Center Office, No.A2, Jiangtai Road, Chaoyang District, Beijing 100016, P.R.China**
Clinical Trial Protocol Version	*01 March 2016/Version 0.2*
Replaces Version	NA

[redacted]

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

PPD

Signature

PPD

Date of Signature

PPD

PPD

Merck Serono Co., Ltd

25F, Nuo Center Office, No.A2, Jiangtai Road, Chaoyang District, Beijing 100016, P.R.China

Tel: PPD

Fax: PPD

E-mail: PPD

[redacted]

[redacted]

Coordinating Investigator

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

_____ _____

Signature Date of Signature

Tel:

Fax:

E-mail:

Coordinating Investigator Signature

Trial Title	**A single-arm, interventional, multi-center, pilot study to evaluate the efficacy of oral Bisoprolol on heart rate reduction in Chinese Chronic Heart Failure patients with NYHA class II – IV (Biso-CHF Study)**
Clinical Trial Protocol Version/Date	01 March 2015 Version 0.2.
Center Number	10
Principal Investigator	PPD

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

_____ _____

Signature Date of Signature

PPD

PP
D
PPD

Tel: PPD

Fax:

E-mail:

Protocol Table of Contents

Table of In-Text Tables

Not applicable

Table of In-Text Figures

Not applicable

List of Abbreviations

ACS	Acute coronary syndrome
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
Bpm	beat per minute
CRF	Case Report Form
CHF	Chronic Heart Failure
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbA1c	hemoglobin A1c
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention To Treat
IVRS	Interactive Voice Response System
IVST	interventricular septal thickness
LVEF	Left ventricular ejection fraction
LVEDD	left ventricle end-diastolic dimension
LVESD	left ventricular end-systolic dimension
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NDHP-CCBs	Non-dihydropyridine calcium channel blockers Pharmacodynamics
NTPro-BNP	N-terminal Pro-B-type Natriuretic Peptide
NYHA	New York Heart Association

PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure

1 Synopsis

Clinical Trial Protocol Number	**MS200006-0039**
Title	**A single-arm, interventional, multi-center, pilot study to evaluate the efficacy of oral Bisoprolol on heart rate reduction in Chinese Chronic Heart Failure patients with NYHA class II – IV (Biso-CHF Study)**
Trial Phase	IV
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	Not applicable
Coordinating Investigator	PPD
Sponsor	Merck Serono Co.,Ltd 25F, Nuo Center Office, No.A2, Jiangtai Road, Chaoyang District, Beijing 100016, P.R.China
Sponsor Legal Representative in the European Union	Not applicable
Trial centers/countries	10 (Center)/1 (country)
Planned trial period (first subject in-last subject out)	Dec, 2016 – Oct, 2018
Trial Registry	www.clinicaltrials.gov (in process)

Objectives:

Primary objectives

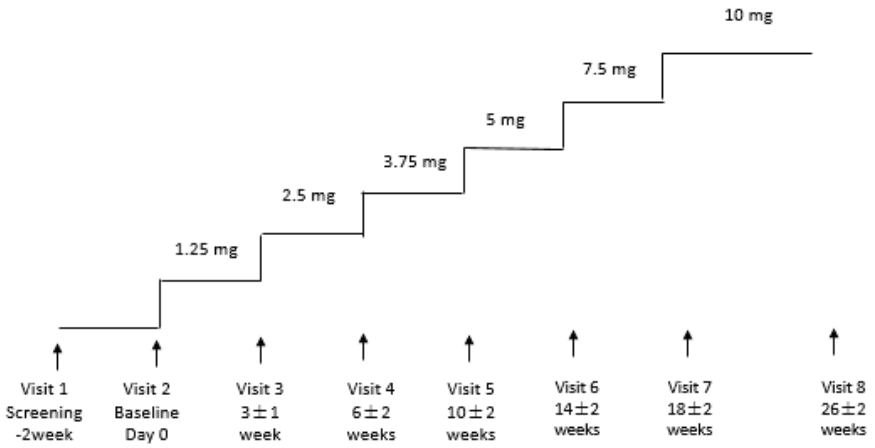
To explore the heart rate control under different doses of Bisoprolol in Chinese Heart Failure patients with NYHA class II- IV

Secondary Objectives

To explore other efficacy parameters and safety profile of Bisoprolol treatment in Chinese Heart Failure patients

Methodology: A single-arm, interventional, multi-center pilot study to evaluate the efficacy of different dose of oral Bisoprolol on heart rate reduction in Chinese Chronic Heart Failure (CHF) patients with New York Heart Association (NYHA) class II – IV. 236 eligible CHF patients will be enrolled and given oral Bisoprolol up-titration treatment from 1.25mg to 2.5mg,

3.75mg, 5mg, 7.5mg and 10mg during 26 weeks treatment period. For all the patients, 6-mins walk test and Questionnaires will be tested at both screening period and end of treatment. Other laboratory parameters will be collected at Screening, 6 weeks, 14 weeks and 26 weeks of treatment. There will be 8 visits from the beginning to the end of the study.



Planned number of subjects: 236

Primary endpoints: Resting heart rate under 2.5mg (6±2weeks), 5mg (14±2weeks) and 10mg (26±2weeks) of Bisoprolol vs at baseline

Secondary endpoints:

- Resting heart rate at 1.25mg (3±1weeks), 3.75mg (10±2weeks), and 7.5mg (18±2weeks) vs at baseline
- Heart function detected by ultrasound cardiogram (UCG): including LVEF, left ventricular end-systolic dimension (LVESD) and left ventricle end-diastolic dimension (LVEDD), interventricular septal thickness (IVST) and E/A ration at baseline, 5mg (14±2weeks) and 10mg (26±2weeks).
- Systolic and diastolic blood pressure, symptoms and NYHA classification at all visits.
- Proportion of patient number whose Resting heart rate ＜ 70 and ＞55 bpm at all visits
- Quality of life [based on the MOS item short from health survey (SF-36) and Minnesota Living with Heart Failure (MLHFQ)] at baseline and end of treatment.
- 6-minute walk test and N-terminal Pro-B-type Natriuretic Peptide (NT Pro-BNP) at baseline and end of treatment.

• Average 24 hour heart rate, average daytime heart rate, average night time heart rate, proportion of arrhythmia, proportion of 24hour heart rate >70bpm, proportion of 24hour heart rate <55bpm at Baseline, 2.5mg (6±2weeks), 5mg(14±2weeks) and end of treatment (Based on 24 hour Holter); • Patient Compliance at the end of study; • All cause mortality, cardiac death, re-admission rate due to heart failure at the end of study • All AEs and SAEs
Pharmacokinetics: Not Applicable
Other assessments: Not Applicable

Diagnosis and key inclusion and exclusion criteria:

Inclusion criteria

- 18-80 y, male or female
- Chronic Heart failure patients with medical history of cardiac disease or other related cardiovascular disease
- Left ventricular ejection fraction (LVEF)≤ 40%
- NYHA class of II - IV

  NYHA II：Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitation.

  NYHA III：Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes undue breathlessness, fatigue or palpitation.

  NYHA IV：Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort increased.
- Signed Informed Consent Form (ICF)

Exclusion criteria

- Acute coronary syndrome (ACS) within 3 months
- Under beta-blocker treatment for the last 2 weeks
- Under other medicine treatment which may affect heart rate, like Non-dihydropyridine calcium channel blockers (NDHP-CCBs) or ivabradine for the last 2 weeks; Under Digoxin treatment (>0.125mg)
- Uncontrolled Diabetes [hemoglobin A1c, (HbA1c) >7.5%]
- Severe or uncontrolled hypertension [resting Systolic Blood Pressure (SBP) >180 mmHg, or resting Diastolic Blood Pressure (DBP) >110mmHg at screening period]
- Severe hypotension (resting SBP<90mmHg，or resting DBP<50mmHg)
- Resting heart rate <60 beat per minute (bpm)
- Any contradiction to Bisoprolol according to label, including:
  - acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
  - cardiogenic shock
  - AV block of second or third degree (without a pacemaker)
  - sick sinus syndrome
  - sinoatrial block
  - slowed heart rate, causing symptoms (symptomatic bradycardia),
  - decreased blood pressure, causing symptoms (symptomatic hypotension),
  - severe bronchial asthma or severe chronic obstructive pulmonary disease
  - sever forms of peripheral arterial occlusive disease and Raynaud's syndrome

- untreated phaeochromocytoma
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

- Severe Arrhythmia including atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter or ventricular tachycardia
- Significant valvular heart disease, congenital heart disease, pulmonary heart disease or perinatal heart disease
- Acute pulmonary edema
- Severe hepatic dysfunction, defined as:

  - Serum Alanine Aminotransferase (ALT) > triple the upper limit of the normal range; and/or

  - Serum Aspartate Aminotransferase (AST) > triple the upper limit of the normal value range and/or
- Severe renal dysfunction, defined as:

  - Serum creatinine > twice the upper limit of the normal range

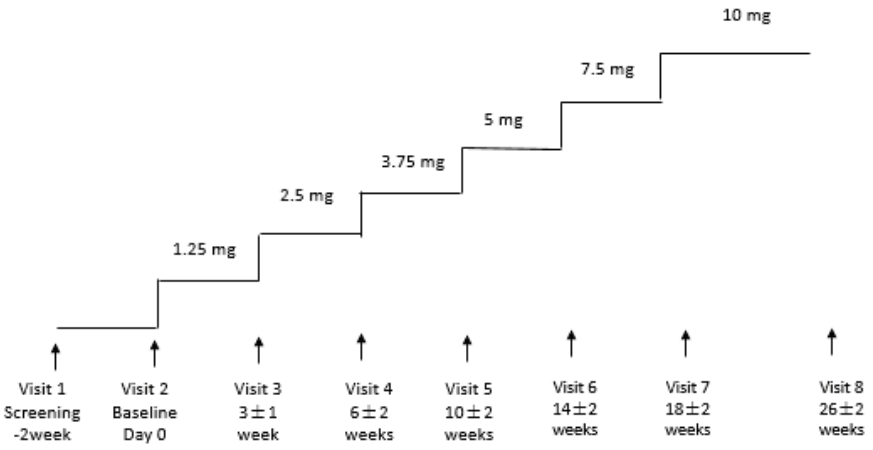
  - Chronic Kidney Disease (CKD) [glomerular filtration rate (GFR)<45 ml/min]
- hyperthyroidism or hypothyroidism
- Severe infectious disease, eg. Human Immunodeficiency Virus (HIV) positive or active tuberculosis
- Severe autoimmune disease, e.g. lupus erythematosus, multiple sclerosis
- Severe respiratory, digestive, hematological disease (including Anemia of Hb < 100g/L) or tumor
- Known to be hypersensitivity to Bisoprolol, or any of the excipient
- Substance or alcohol abuse
- Received heart transplantation or pacemaker implantation; revascularization treatment within 3 months; or plan to receive above treatment in 6months
- Currently undertaking other treatment that may affect the safety and/or efficacy evaluation, e.g. beta receptors agonists, etc.
- No legal ability or legal ability is limited
- Patients unlikely to cooperate in the study or with inability or unwillingness to give informed consent

- Child-bearing period women without effective contraceptive measures, pregnancy and lactation
- Participation in another clinical trial within the past 90 days
- Other significant disease that in the Investigator's opinion would exclude the subject from the trial

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

Bisoprolol (Concor® Tablets 5.0mg/ Concor® Tablets 2.5mg) / Oral /once daily , 26 weeks

Patients receive oral Bisoprolol, starting from 1.25mg (3±1weeks), up-titration to 2.5mg (6±2weeks), 3.75mg (10±2weeks), 5mg (14±2weeks), 7.5mg (18±2weeks) with an interval of 2-4 weeks, then up-titration to 10mg after 8 weeks (26±2weeks).



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

Standardized therapy recommended by *China Heart Failure Guideline 2014*

Planned trial and treatment duration per subject: 26 weeks

Statistical methods:

- It is supposed that the mean change from baseline of heart rate is -3.8bpm at week 6 and -7.4bpm at week 14. The Standard Deviation is assumed to be 10bpm across time.
- Based on assumption above about treatment effect and up-titration status at different visit, assuming 236 subjects under 15% dropout rate, distance from mean to limit of the 95% confidence interval of the change from baseline of mean heart rate is 1.54 at week 6 and 2.12 at week 14. Due the limit evidence at week 26, there is no robust extrapolation.

For primary Analysis

- Linear regression will be applied with change from baseline of HR as dependent variable and baseline HR and age as covariates at week 6, 14 and 26, respectively.

For Secondary Analysis

- Same approach will be used for secondary continuous endpoints

Descriptive statistics will be generated for all primary and secondary endpoints.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:
Merck Serono Co., Ltd.

Address: 25F, Nuo Center Office, No.A2, Jiangtai Road, Chaoyang District, Beijing 100016,

P.R.China

Tel.: +86（10）59072473 Fax: +86（10）59072699

The trial will be conducted at 10 sites in China.

The Coordinating Investigator PPD, CAMS and PUMC, represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix.

The trial will appear in the following clinical trial registries:

Specify:

- www.clinicaltrials.gov
- Any special committees or boards, such as a Safety or Data Monitoring Committee, Endpoint Adjudication Committee, or Steering Committee (Tasks and memberships may be included here or cross referenced to relevant sections below. Full details may be provided in separate charter or appendix). Consult the appropriate contract or Alliance Manual to ensure that the correct terminology is used for applicable trials.
  - If a Safety Monitoring Committee is used, appropriate Merck Group SOPs or Working Instructions must be consulted to ensure compliance. It is recommended that Global Drug Safety review the scientific content.
- Responsibilities for drug supply and distribution, for example, the use of regional distribution centers

  To be determined (TBD)
- Drug Safety responsibilities

  PPD Merck Serono, PPD
- Role of the Sponsor
- Any further important trial administrative information.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background information

3.1 Background

3.1.1 Chronic Heart Failure

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1]. CHF is the end stage and main death cause of most cardiovascular disease. Recent European data (ESC-HF pilot study) demonstrate that 12-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients were 17% and 7%, respectively, and the 12-month hospitalization rates were 44% and 32%, respectively [2]. The Cardiovascular Health Study, a US longitudinal cohort of community-dwelling older adults, reported 1-, 5-, and 10-year mortality rates of 19%, 56%, and 83%, respectively, after the onset of HF [3].

The prevalence of CHF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people＞70 years of age [4-6]. In China, CHF was reported to 0.9 %, 0.7% and 1.0% for the general population, the males and females, respectively. Also, prevalence of CHF increased substantially with aging, which is 0.4%, 1.0%, 1.3 % and 1.3 % in 35 -44, 45 -54, 55-64, 65 -74 years of age groups, respectively [7] .

The large societal burden of CHF presents a substantial financial challenge to the health care system, with estimated annual direct costs of $2.8 billion in Canada [8]. In the United States, estimated yearly expenditures of $30.7 billion are expected to rise to $69 billion/y by 2030 [9], with proportional increases forecast in China over this time frame as well.

3.1.2 Elevated Heart Rate and CHF

Increased resting HR has been shown to be a negative prognostic indicator in failure [10].The BEAUTIFUL study found that patients with coronary artery disease (CAD), left ventricular systolic dysfunction, and a heart rate (HR) >70 bpm had increased cardiovascular mortality, increased HF hospitalization, myocardial infarction, and need for coronary revascularization[11].

β-blockers work in chronic HF by antagonizing the effects of the sympathetic nervous system. This results in decreased heart rate, increased diastolic filling times, and decreased peripheral vascular resistance. They have been used in the treatment of CHF for decades but their benefits were only confirmed through randomized controlled trials in the late 1990s and early 2000s. The most important trials were the CIBIS II (bisoprolol) [12], COPERNICUS (carvedilol) [13], and MERIT-HF (metoprolol CR/XL) [14] trials. When looked at in combination, more than 9000

patients were studied. Results showed a relative risk reduction (RRR) in mortality versus placebo of approximately 34 % and a RRR in heart failure hospitalization of 28–36% [15].

A recent meta-analysis of 23 trials looking at the use of β-blockers in the treatment of heart failure found that the magnitude of heart rate reduction is significantly associated with survival benefit, independent of the actual dosage used. Every HR reduction of 5 bpm resulted in an 18 % reduction in mortality [16]. Beta blockers could reduce heart rate and this is consistently reflected in current guidelines for CHF. It was recommended to control the heart rate to 55-60 bpm for these patients in most clinical guidelines, *including 2014 Chinese Heart Failure Guideline* [17].

3.1.3 Bisoprolol titration in CHF

Bisoprolol is a beta-1 selective blocker with the highest selectivity for this receptor, in doses less than 10 mg it has very little or no effect on beta-2 receptors. Bisoprolol was first tested in CHF in the CIBIS I trial which enrolled 641 patients and showed improvement in functional class, less hospitalizations for heart failure and a trend to improved survival. The much larger randomized CIBIS II assigned 2647 patients with class III or IV HF and an LVEF <40% to Bisoprolol or placebo; the patients also received standard therapy with diuretics and ACE inhibitors. After an average follow-up of 1.4 years, the trial was prematurely stopped when the benefits were observed in the active treatment group: significant reduction in total all-cause mortality (11.8 versus 17.3 percent] that was independent of the severity or cause of HF. This benefit was primarily due to a reduction in SCD (3.6 versus 6.3%, $P< 0.001$], with a non-significant trend toward fewer deaths from HF; significant 15% reduction in hospital admissions for any cause and a 30% reduction in admissions for HF ($P < 0.0001$). CIBIS II showed that both baseline heart rate and its change over time are prognostic markers, with lower baseline heart rate and greater reductions being better [12]. Not only did Bisoprolol increase survival and reduce hospital admissions in CIBIS II, it also cut the cost of care in so doing [18].

A recent study reported an attempt to Bisoprolol up-titrate toward guideline-recommended dosages offers additional benefit in terms of restoration of LV systolic function and remodeling for HF patients with systolic dysfunction [19].

Although clinical trials have consistently shown overall high beta-blocker tolerability, many patients even in the trial setting were unable to achieve target beta-blocker doses. For example, the mean dose of carvedilol in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial [13] was 37 mg compared with the target dose of 50 mg/d and, in the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) [14], metoprolol succinate dose on average was 159 mg as compared with the target dose of 200 mg. Only about two thirds of the patients in both these trials reached target doses. These results not only suggest that heart rate may be a major determinant of the ability to titrate beta-blocker dose and their tolerability, but that it may also serve as a therapeutic target for beta-blocker therapy.

It has been shown that beneficial effects of beta-blockers are related to the magnitude of heart rate reduction [20], which favors the selective beta1-adrenoceptor-blocker bisoprolol [21].In CIBIS-ELD trial [22], indicates the heart rate after up-titration, predicted all-cause mortality risk in elderly

patients with chronic heart failure. Achieved resting heart rate between 55 and 64 bpm bisoprolol up-titration was associated with lower long-term mortality risk and the lowest frequency of adverse events. For every 10 bpm. increase in heart rate, a corresponding 19% increase was seen in all-cause mortality after adjusting for age, sex, beta-blocker pre-treatment, ventricular function, heart rate, and NYHA class at baseline. This finding is consistent with results from a large prospective observational survey, where 26% of the patients were uptitrated to the target dose [23].

However, up-titration is frequently associated with challenging, dose-related side effects such as hypotension, bradycardia, dizziness, and sometimes worsening of concomitant COPD, predominantly with non-selective beta-blockers [24-26]. As a consequence, recommended target doses can rarely be reached. A recent analysis demonstrates that among other dose-related effects, heart rate reduction was the major factor limiting beta-blocker up-titration to recommended doses [27].

To sum up, data from various clinical studies have demonstrated elevated resting heart rate is associated with increased morbidity and mortality in patients with chronic systolic heart failure (CHF). It has also been shown that titration of doses of BBs improves outcomes of morbidity and mortality in CHF patients with reduced ejection fraction. However, there is only few studies to investigate the heart rate reduction during Bisoprolol up-titration in Chinese CHF. It remains unclear about the magnitude of heart rate reduction during Bisoprolol up-titration in Chinese CHF and this study serves as the first one to explore. This study will mainly investigate the heart control efficacy of oral Bisoprolol during the up-titration, as well as other efficacy, safety and compliance in treatment of Chinese CHF patients.

3.2 Risk-benefit assessment

a. The pre-clinical, clinical-pharmacological and clinical results together form a rational basis for the planned clinical trial.

b. The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the Investigational Medicinal Product (IMP) as specified in this clinical trial protocol. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable.

c. Based on the pre-clinical and clinical data available to date, the conduct of the trial is regarded as justifiable at the planned dose ranges.

d. Besides the study drug Bisoprolol, all subjects need to undergo ECG, UCG and Holter test both at baseline and end of treatment. These tests are common used in clinical practice and have been proven to be safe and well tolerant. For subjects suffer from CHF with all current standard therapies, the free test of cardiac function may allow both health care givers and subjects themselves know better with current condition and guide their treatment;

4 Trial Objectives

4.1 Primary Objectives

To explore the heart rate control (the change of heart rate) under different doses of Bisoprolol in Chinese Heart Failure patients with NYHA class II- IV.

4.2 Secondary Objectives

To explore other efficacy parameters and safety profile of Bisoprolol treatment in Chinese Heart Failure patients. Secondary endpoints include：

- Resting heart rate at 1.25mg (3±1weeks), 3.75mg (10±2weeks), and 7.5mg (18±2weeks) vs at baseline
- Heart function detected by UCG: including LVEF, left ventricular end-systolic dimension (LVESD) and left ventricle end-diastolic dimension (LVEDD), interventricular septal thickness (IVST) and E/a ration at baseline, 5mg (14±2weeks) and 10mg (26±2weeks).
- Systolic and diastolic blood pressure, symptoms and NYHA classification at all visits.
- Proportion of patient number whose Resting heart rate ＜ 70 and ＞55 bpm at all visits
- Quality of life [based on the MOS item short from health survey (SF-36) and Minnesota Living with Heart Failure (MLHFQ)] at baseline and end of treatment.
- 6-minute walk test and N-terminal Pro-B-type Natriuretic Peptide (NT Pro-BNP) at baseline and end of treatment.
- Average 24 hour heart rate, average daytime heart rate, average night time heart rate, proportion of arrhythmia, proportion of 24hour heart rate >70bpm, proportion of 24hour heart rate <55bpm at Baseline, 2.5mg (6±2weeks), 5mg(14±2weeks) and end of treatment (Based on 24 hour Holter);
- Patient compliance at the end of study;
- All cause mortality, cardiac death, re-admission rate due to heart failure at the end of study
- All AEs and SAEs

4.3 Other Objectives

Not applicable.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a single-arm, non-randomized, open label, interventional, multi-center, phase IV pilot study

5.1.1 Major aspects of the trial

There will be a 2-week screening period when baseline lab tests, electrocardiogram (ECG), ultrasound cardiogram (UCG), Holter and Questionnaires will be conducted in this period. Patients who met all the inclusion criteria but none of the exclusion criteria will be enrolled. Totally 236 patients will be enrolled in the study. The anticipated period of the whole study is approximately 21 months including a 14-month recruitment period and a 26-week treatment period.

All enrolled patients will start to take oral Bisoprolol 1.25mg, once daily. All other cardiovascular medicines must be stabilized at least one month before screening period and could be continued. There will be 8 visits in total. Oral Bisoprolol needs to be started from 1.25mg (3±1weeks), up-titrated to 2.5mg (6±2weeks), 3.75mg (10±2weeks), 5mg (14±2weeks), 7.5mg (18±2weeks) with an interval of 3-4 weeks, then up-titrated to 10 mg after 8 weeks (26±2weeks). Symptoms, ECG and safety endpoints will be assessed at all visits. Lab tests will be assessed at 2.5mg (6±2weeks), 5mg (14±2weeks) and 10mg (26±2weeks). Please refer to Figure 1 for a detailed study diagram.

The Up-titration should be judged by the investigator and patients must well tolerate the previous dose. Intolerance may be defined as:

(1) Resting heart rate ＜55bpm;

(2) Blood pressure ＜ 90/50 millimetre(s) of mercury(mmHg);

(3) Adverse Event (AE) lead to intolerance as judged by the investigator;

The primary endpoint is:

Resting heart rate under 2.5mg (6±2weeks), 5mg (14±2weeks) and 10mg (26±2weeks) of Bisoprolol vs at baseline

The secondary endpoints include:

- Resting heart rate at 1.25mg (3±1weeks), 3.75mg (10±2weeks), and 7.5mg (18±2weeks) vs at baseline
- Heart function detected by UCG: including LVEF, left ventricular end-systolic dimension (LVESD) and left ventricle end-diastolic dimension (LVEDD), interventricular septal thickness (IVST) and E/a ration at baseline, 5mg (14±2weeks) and 10mg (26±2weeks).
- Systolic and diastolic blood pressure, symptoms and NYHA classification at all visits.

- Proportion of patient number whose Resting heart rate ＜ 70 and ＞55 bpm at all visits
- Quality of life [based on the MOS item short from health survey (SF-36) and Minnesota Living with Heart Failure (MLHFQ)] at baseline and end of treatment.
- 6-minute walk test and N-terminal Pro-B-type Natriuretic Peptide (NT Pro-BNP) at baseline and end of treatment.
- Average 24 hour heart rate, average daytime heart rate, average night time heart rate, proportion of arrhythmia, proportion of 24hour heart rate >70bpm, proportion of 24hour heart rate <55bpm at Baseline, 2.5mg (6±2weeks), 5mg(14±2weeks) and end of treatment (Based on 24 hour Holter);
- Patient Compliance at the end of study;
- All cause mortality, cardiac death, re-admission rate due to heart failure at the end of study
- All AEs and SAEs.

Medical history, physical examination, lab tests, ECG and UCG should be conducted in a 2-week screening period (Visit 1). If patients have conducted lab tests, ECG or Echocardiogram in this period, but not specifically for this trial, the result could also be used for the screening. Totally 236 patients who meet all the inclusion criteria but none of the exclusion criteria will be enrolled in the study.

5.1.2 Schematic diagram of the study plan

See Appendix III.

5.2 Discussion of Trial Design

This is a single-arm, non-randomized, open label, interventional, multi-center, phase IV study. Beta blockers are one of the cornerstones of heart failure pharmacotherapy since they were proven to reduce morbidity and mortality and consequently recommended by clinical guidelines. Therefore it will violate the basic ethical benefits when a placebo control group was set in this trial. Because the main purpose of this trial is to explore the heart rate control under different doses of Bisoprolol, but not head-to-head comparison of heart rate control level, no other active control drug group was set. Due to good efficacy of Bisoprolol and aim of this trial, open label and non-randomized design was adopted. Resting heart rate is chosen for the assessment of primary endpoints because it is an easy and applicable standard to guide clinical practice recommended by all guidelines for CHF treatment. Bisoprolol is proven to improve prognosis for chronic heart failure patients with good efficacy on heart rate control. However, there are few clinical evidences to show Bisoprolol's effect on resting heart rate control data during up-titration in CHF patients in China before. In order to investigate Bisoprolol's effect on heart rate control during dose up-

titration, and to collect more information and parameters for further studies, this interventional, pilot study is designed.

5.2.1 Inclusion of Special Populations

Not applicable

5.3 Selection of Trial Population

Only patients meeting all inclusion criteria and none of the exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessment that is not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

- 18-80 y, male or female
- Chronic Heart failure patients with medical history of cardiac disease or other related cardiovascular disease
- Left ventricular ejection fraction (LVEF)≤ 40%
- NYHA class of II - IV

  NYHA II：Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitation.

  NYHA III：Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes undue breathlessness, fatigue or palpitation.

  NYHA IV：Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort increased.
- Signed Informed Consent Form (ICF)

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

- Acute coronary syndrome (ACS) within 3 months
- Under beta-blocker treatment for the last 2 weeks
- Under other medicine treatment which may affect heart rate, like Non-dihydropyridine calcium channel blockers (NDHP-CCBs) or ivabradine for the last 2 weeks; Under Digoxin treatment (>0.125mg)
- Uncontrolled Diabetes [hemoglobin A1c, (HbA1c) >7.5%]

- Severe or uncontrolled hypertension [resting Systolic Blood Pressure (SBP) >180 mmHg, or resting Diastolic Blood Pressure (DBP) >110mmHg at screening period]
- Severe hypotension (resting SBP<90mmHg，or resting DBP<50mmHg)
- Resting heart rate <60 beat per minute (bpm)

- Any contradiction to Bisoprolol according to label, including:
  - acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
  - cardiogenic shock
  - AV block of second or third degree (without a pacemaker)
  - sick sinus syndrome
  - sinoatrial block
  - slowed heart rate, causing symptoms (symptomatic bradycardia),
  - decreased blood pressure, causing symptoms (symptomatic hypotension),
  - severe bronchial asthma or severe chronic obstructive pulmonary disease
  - sever forms of peripheral arterial occlusive disease and Raynaud's syndrome
  - untreated phaeochromocytoma
  - metabolic acidosis
  - hypersensitivity to bisoprolol or to any of the excipients
- Severe Arrhythmia including atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter or ventricular tachycardia
- Significant valvular heart disease, congenital heart disease, pulmonary heart disease or perinatal heart disease
- Acute pulmonary edema
- Severe hepatic dysfunction, defined as:
  - Serum Alanine Aminotransferase (ALT) > triple the upper limit of the normal range; and/or
  - Serum Aspartate Aminotransferase (AST) > triple the upper limit of the normal value range and/or
- Severe renal dysfunction, defined as:
  - Serum creatinine > twice the upper limit of the normal range
  - Chronic Kidney Disease (CKD) [glomerular filtration rate (GFR)<45 ml/min]
- hyperthyroidism or hypothyroidism
- Severe infectious disease, eg Human Immunodeficiency Virus (HIV) positive or active tuberculosis
- Severe autoimmune disease, e.g. lupus erythematosus, multiple sclerosis
- Severe respiratory, digestive, hematological disease (including Anemia of Hb ＜100g/L) or tumor

- Known to be hypersensitivity to Bisoprolol, or any of the excipient
- Substance or alcohol abuse
- Received heart transplantation or pacemaker implantation; revascularization treatment within 3 months; or plan to receive above treatment in 6months
- Currently undertaking other treatment that may affect the safety and/or efficacy evaluation, e.g. beta receptors agonists, etc.
- No legal ability or legal ability is limited
- Patients unlikely to cooperate in the study or with inability or unwillingness to give informed consent
- Child-bearing period women without effective contraceptive measures, pregnancy and lactation
- Participation in another clinical trial within the past 90 days
- Other significant condition that in the Investigator's opinion would exclude the subject from the trial

5.4 Criteria for Initiation of Trial Treatment

All subjects can initiate trial treatment as long as the enrollment is confirmed.

5.5 Criteria for Subject Withdrawal

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in any of the following event:

- Withdrawal of the subject's consent.
- Participation in any other interventional trial during the duration of this trial
- Withdrawal of the Investigational Medicinal Product

If a subject has failed to attend scheduled trial visits, the reasons must be collected and recorded in CRF by investigator as completely and accurately as possible.

In any case, the appropriate Case Report Form (CRF) section must be completed.

5.5.1 Withdrawal from Trial Therapy

A subject must be withdrawn from trial therapy if any of the following occurs:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional drug, or dose adjustment of other drugs that investigator believes would affect the elevation of the safety and/or efficacy, including but not

limited to ACEI, ARB, Statins, β-blockers, CCB, ivabradine, and trimetazidine, also other long-term Chinese traditional medicines for the treatment of CHF.

- Occurrence of adverse events, if discontinuation of trial drug is desired or considered necessary by the Investigator and/or the subject.
- Occurrence of pregnancy.
- Use of a non-permitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP.
- Non-compliance.
- Subject withdrew consent
- Subject lost to follow up
- Participation in another clinical trial
- Any events that unacceptably endanger the safety of the subject.

5.6 Premature Termination of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g. due to:
  - Evidence of inefficacy of the IMP,
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.

  (Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g. toxicology.)
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.
- Withdrawal of the IMP from the market for safety reasons.

Ethics Committee and Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons,

for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP,
- Visits specified by the protocol are still taking place,
- Procedures or interventions according to the protocol are still being undertaken in any subject,
- The post-treatment follow up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

Bisoprolol (Concor® Tablets, 2.5mg), film-coated tablets are white and heart-shaped with a break-line on both sides; Bisoprolol (Concor® Tablets, 5mg), film-coated tablets are yellowish-white and heart-shaped with a break-line on both sides; manufactured by Merck Serono Co. Ltd.

6.2 Dosage and Administration

During the whole study duration, enrolled subjects would take Concor® orally, Once daily. The whole tablet is to be swallowed with water, not chewed.

Patients receive oral Bisoprolol, starting from 1.25mg (3±1weeks), up-titration to 2.5mg (6±2weeks), 3.75mg (10±2weeks), 5mg (14±2weeks), 7.5mg (18±2weeks) with an interval of 2-4 weeks, then up-titration to 10mg after 8 weeks (26±2weeks).

6.3 Assignment to Treatment Groups

Not Applicable.

6.4 Non-investigational Medicinal Products to be Used

No other drugs are mandatory in this trial.

The standard treatment for CHF should include ACEI/ARB, β-blockers, aldosterone antagonists and diuretic if condition permits.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the CRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the CRF.

6.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the Investigator's discretion. Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

Patients should take all the current standard therapy for CHF. It should include ACEI/ARB, β-blockers, aldosterone antagonists and diuretics if permits. Other medicines for CHF treatment are also permitted, such as trimetazidine, and other Chinese traditional medicines, such as Tong Xin Luo capsule.

The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the CRF.

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

6.5.2 Prohibited Medicines

NDHP-CCBs, ivabradine, beta receptors agonists and Digoxin (>0.125mg) treatment which may influence the heart control level of Bisoprolol.

Any other additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the CRF, noting the name, dose, duration and indication of each drug.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, e.g., because of AEs, the subject should withdraw from the study, the data should only be used for safety.

The product label should be consulted with regards to combinations not recommended and combinations to be used with caution.

6.5.3 Other Interventions

If the subjects undergone PCI, CABG, pacemaker implantation or heart transplantation during the study, they should withdraw from the trial. If patients need to perform other surgeries that need hospitalization, they should withdraw from the trial.

6.5.4 Special Precautions

(1) For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use (It has been reported that, if the PTP sheet is accidentally swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in perforation, and possible severe complications such as mediastinitis);

(2) Instruct the patient to avoid moisture and to keep the medicine in a cool place;

(3) Keep out of children;

(4) Expired drug should not be used.

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Packaging: 2.5/5mg tablets, boxes of 10 tablets in PTP.

Labeling: “use only for clinical study MS200006-0039” will be labelled on the box by an idpendent Company.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP Guidelines.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

Bisoprolol should be stored in room temperature and avoid moisture.

6.8 Investigational Medicinal Product Accountability

The Storage Manager at the trial site who was assigned by the Head of the trial site is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

After the conclusion of the trial contract with the trial site, the Sponsor (or designee) may deliver the IMP to the Storage Manager at the trial site.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation provided by Sponsor and returning it to the Sponsor. A copy will be archived for the Investigator Site File.
- IMP dispensing will be carefully recorded by the Storage Manager on the appropriate drug accountability forms provided by sponsor so that accurate records will be available for verification by the Sponsor Monitor at each monitoring visit.
- IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the site.
  - IMP accountability forms (provided by the Sponsor and completed at the site).
  - The use of each dose by each subject.
  - The disposition (including return, if applicable) of any unused IMP.
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.

The Storage Manager should maintain records that adequately document the following:

- The subjects received the doses specified by the clinical trial protocol/amendment(s); and
- All IMP provided by the Sponsor were fully reconciled.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be re-dispensed to a different subject.

The Sponsor Monitor will periodically collect the IMP accountability forms and will check all the IMPs to be returned or discarded before arrangements for returns (both unused and used containers) are made at the trial site or their destruction by the trial site is authorized.

6.9 Assessment of Investigational Medicinal Product Compliance

Subjects should be instructed to bring with them to each visit both opened and unopened IMP packages, in order to allow the assessment of compliance with trial treatment. IMP administration must be recorded in the CRF, as applicable.

Medication possession ratio (MPR) is used to assess the medicine compliance. MPR is defined as the actual drug number taken by the patients divided by the drug number should be taken by the patients according to the protocol. MPR between 80%-100% is defined as good compliance. Medication rate of <80% or >100% is defined as insufficient compliance.

6.10 Blinding

Not Applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the CRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

For monitoring purposes, any case of overdose – whether or not associated with an adverse event (serious or non-serious) – must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

In a clinical trial conducted in European CAD patients, the dose of Bisoprolol was 20mg daily, and patients showed good tolerance of the medicine and less coronary events at 1 year follow-up[28].While the maximum recommended dose is 10 mg once daily in China.

6.13 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs.

The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for patients with [the medical condition].

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Day 0 is defined as the first day of enrollment and oral Bisoprolol administration in subject.

The trial procedures and assessment contents are as follow:

1. Screening Visit/Visit 1: Day-14 to Day 0: this visit entails the following:

Before any procedures that are related to the trial is undertaken, informed consent of the patient should be obtained. Thereafter, basic information of the patient will be obtained and patients are screened for eligibility based on the inclusion and exclusion criteria.

a) Record birth date, gender, height, weight, BMI, waist circumference, current medical condition and past medical history, including concomitant therapies

b) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate)

c) NYHA classification and clinical symptoms

d) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

e) Echocardiography: LVEF， LVESD, LVEDD, IVST and E/A ratio

f) Routine blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets), liver function (ALT, AST), renal function (Bun, Cr), fasting blood glucose and blood lipids (TC, TG, LDL-C and HDL-C), electrolyte (K, Na) , NT Pro-BNP(data within -28 days of liver function, renal function, fasting blood glucose and blood lipids are accepted)

g) Routine urine test(PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin)，urine pregnancy test

h) Questionnaires: SF-36 and MLHFQ

i) 6-minute walk test

j) Holter: heart rate (24 hour, day time, night time); sinus rhythm/arrhythmia, specify; proportion of 24 hour heart rate ＞70bpm, proportion of 24hour heart rate ＜55 bpm; proportion of arrhythmia

k) Record adverse events, concomitant drugs/procedure;

l) Signed the informed consent form

2. Visit 2 (Baseline) Day 0: this visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Record adverse events, concomitant drugs/procedure and use of study drug;

3. Visit 3 (1.25mg measurement) 3±1week: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Record adverse events, concomitant drugs/procedure and use of study drug;

4. Visit 4 (2.5mg measurement) 6±2week: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Routine blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets)

e) Routine urine test(PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin)

f) Holter: heart rate (24 hour, day time, night time); sinus rhythm/arrhythmia, specify; proportion of 24 hour heart rate ＞70bpm, proportion of 24hour heart rate ＜55 bpm; proportion of arrhythmia

g) Record adverse events, concomitant drugs/procedure and use of study drug;

5. Visit 5 (3.75mg measurement) 10±2weeks: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Record adverse events, concomitant drugs/procedure and use of study drug;

6. Visit 6 (5mg measurement) 14±2weeks: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Routine blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets)

e) Routine urine test (PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin)

f) Echocardiography: LVEF， LVESD, LVEDD, IVST and E/A ratio

g) Holter: heart rate (24 hour, day time, night time); sinus rhythm/arrhythmia, specify; proportion of 24 hour heart rate ＞70bpm, proportion of 24hour heart rate ＜55 bpm; proportion of arrhythmia

h) Record adverse events, concomitant drugs/procedure and use of study drug;

7. Visit 7 (7.5mg measurement) 18±2weeks: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight

b) NYHA classification and clinical symptoms;

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Record adverse events, concomitant drugs/procedure and use of study drug;

8. Visit 8 (10mg measurement) 26±2weeks: This visit entails the following:

a) Perform physical examinations, including vital signs (systolic and diastolic blood pressure, resting heart rate); Weight, BMI, waist circumference

b) NYHA classification and clinical symptoms

c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;

d) Echocardiography: LVEF, LVESD, LVEDD, IVST and E/A ratio

e) Routine blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets), liver function (ALT, AST), renal function (Bun, Cr), fasting blood glucose and blood lipids (TC, TG, LDL-C and HDL-C), electrolyte (K, Na) , NT Pro-BNP

f) Routine urine test (PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin)

g) Questionnaires: SF-36 and MLHFQ

h) 6-minute walk test

i) Holter: heart rate (24 hour, day time, night time); sinus rhythm/arrhythmia, specify; proportion of 24 hour heart rate ＞70bpm, proportion of 24hour heart rate ＜55 bpm; proportion of arrhythmia

j) Record adverse events, concomitant drugs/procedure and use of study drug;

k) Patient Compliance

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subjects legal representative has provided written informed consent according to the procedure described in Section 9.2.

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, sex (gender), race, ethnicity.

Major demographic information is as follows:

1. Birth date

2. Gender

3. Race

7.2.1 Medical history

The following information will be collected for the medical history of the subjects:

Chronic Heart Failure

1. Basic information: Initial cardiovascular disease (start date, stop date/ongoing); start date of heart failure; frequency of heart failure acceleration in recent 6 month (how many times/ 6months) and how many times result to hospitalization when applicable; previous treatment procedures (PCI or CABG), time of the procedure; history of MI or not, if yes, the time need to be recorded;

2. Current medicine treatment at screening period of the study: name, dose, initiation date (month/year)

7.2.1.1 Other medical history

1. History of hypertension/ heart failure/ diabetes; the severity of these diseases; the current medicine therapy at the screening period of the study;

2. Other medical histories and concomitant medicines.

7.2.2 Vital signs and physical examination

Vital signs and physical examination should at least include the following items:

1. General status:

Heart rate (resting heart rate) measurement: sit rest for 5 minutes, no smoking, no excitatory food and beverage such as tea and coffee for 30 minutes, measurements are taken at sitting position for a continuous record of 3 minutes. Heartbeats in each minute are calculated and averaged to obtain the resting heart rate.

Blood pressure measurement: sit rest for 5 minutes, no smoking, no excitatory food and beverage such as tea and coffee for 30 minutes, measurements are taken at sitting position, with the elbow at the same level with the heart. Diastolic blood pressure is recorded at the fifth Korotkoff sound, repeated after 2 minutes and averaged. If the difference in diastolic blood pressure readings is > 5mmHg, measurement is repeated again after 2 minutes, and the 3 readings are averaged.

2. Physical examination of the respiratory system

3. Physical examination of the cardiovascular system

4. Physical examination of other systems

5. Body mass index: body weight (Kg)/Height ^{2}(m^2)

6. Measurement of waist circumstance: At screening visit, under fasting, standing, calm breathing conditions, feet apart 25-30cm, waist circumstance is measured at horizontal position at the midpoint of iliac spine and the 12th rib, with measuring tape close to but not press the skin, accurate to 0.1cm.

7.2.3 Lab test items

Lab examination should include at least the following items: hematological examination, and echocardiography need to be done at the screening visit and last visit; ECG need to be done at every visit.

1. Hematology tests (all these lab test need to be done by fast in the morning):

a) Full blood count: red blood cell count, neutrophils, hemoglobin, white blood cell count and platelet count

b) Liver function (ALT, AST)

c) Kidney function (BUN, Cr)

d) Fasting blood glucose

e) Blood lipid levels (TC, TG, HDL-C, LDL-C)

f) NT Pro-BNP

g) Electrolyte (K, Na)

2. Routine urine test(PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin), urine pregnancy test

2. ECG: heart rate; sinus rhythm/arrhythmia, depict what kind of arrhythmia; cardiac hypertrophy (yes/no); abnormal ST-T change (yes/no);

3. Echocardiography: to measure LVEF， LVESD,LVEDD, IVST and E/A ratio

4. 6-min walk test: is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes.

5. SF-36 and MLHFQ： the detailed description of questionnaire test will be described in Appendix II and II.

6. Holter: Average 24 hour heart rate, average daytime heart rate, average night time heart rate, proportion of arrhythmia, proportion of 24hour heart rate >70bpm, proportion of 24hour heart rate <55bpm.

7.3 Efficacy Assessments

7.3.1 Resting heart rate

Resting heart rate obtained from the method described above.

7.3.2 Echocardiography

LVEF，LVESD, LVEDD, IVST and E/A ratio.

7.3.3 SF-36 questionnaire

The SF-36 assesses 8 health status domains (ie, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from 0 to 100 (See appendix II).

7.3.4 The Minnesota Living with Heart Failure Questionnaire (MLHF)

The questionnaire has 21 items. Questions assess the impact of frequent physical symptoms of heart failure - shortness of breath, fatigue, swollen ankles and difficulty sleeping. Other items ask about the effects of heart failure on physical and social functions including walking and climbing stairs, household work, need to rest, working to earn a living, going places away from home, doing

things with family or friends, recreational activities, sports or hobbies, sexual activities, eating foods he patient likes and mental and emotional functions of concentration and memory, worry, loss of self control, and being a burden to others. Since treatments might have direct effects on a patient's life in addition to their effects on symptoms and functional limitations of heart failure, questions about side effects of medications, hospital stays and costs of care were included to help measure the overall impact of treatments for heart failure on patients' quality of life.
Scoring: Simple summation of responses. Total score (min = 0, max = 105), physical dimension (min= 0, max = 40) emotional dimension (min = 0, max = 25); the higher the summed score, the worse is the impact of heart failure on a patient's quality of life (See Appendix I).

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2).

The reporting period for AEs is described in Section **Error! Reference source not found.**.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of 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.

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

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 4.0 (publication date: 28 May 2009), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described above.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to IMP using the following definitions.

Unrelated: Not reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, 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 a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

- **Adverse Reaction(ADR)**

In accordance with GCP, adverse drug reaction is an adverse event considered related to drug treatment.

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.

NOTE: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; not an event that hypothetically might have caused death if it was more severe.

- 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.

Note: 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 above. 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, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a SAE as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her 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.

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 in the appropriate section of the CRF. Among these AEs, all SAEs or non-serious ADRs must be additionally documented and reported using an Adverse Event Safety Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times, when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. If an AE constitutes a DLT this has to be documented accordingly

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

7.4.1.3 Definition of the Adverse Event Reporting Period

The adverse event reporting period for safety surveillance begins when the subject is included in the trial (date of first signature of informed consent) and continues until the 30-Day Post-Treatment Safety Follow-up.

Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

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

In the event of any new SAE or new non-serious ADR occurring during the reporting period, the Investigator must immediately (within a maximum 24 HOURS after becoming aware of the event) report to Merck Serono Global Drug Safety Department by telephone, by fax or by emails.
Names, addresses, telephone and fax numbers for AE reporting as follows:
Merck Serono Global Drug Safety Department

Address: Merck KGaA, Frankfurter Straße 250, D-64293 Darmstadt, Germany;

Email: GlobalDrugSafety@merckgroup.com

Fax: 49(0) 6151 72 6914;

Telephone: PPD

When an SAE or its follow-up information is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

All written reports should be transmitted with the Adverse Event Safety Report Form (Clinical Trials), which must be completed by the Investigator following specific completion instructions.

The AE section of the CRF must be completed, and a copy of the information must be transmitted along with the Adverse Event Safety Report Form (Clinical Trials). Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator/reporter must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure that the Sponsor promptly assesses the event and, where applicable, meets the strict regulatory timelines with expedited safety reporting.

Requests for follow-up will usually be made via the responsible Monitor. Although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly for further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees and Investigators

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

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with the ICH GCP guidelines, the Sponsor will inform Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's approval/favorable opinion to continue the trial." In particular and in line with respective applicable 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 the safety reports

in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead EC/IRB and will maintain records of these notifications. When direct reporting 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.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section **Error! Reference source not found.**) and are assessed for final outcome at the 30-Day Follow-up Safety Visit. All SAEs ongoing at the 30-Day Follow-up Safety Visit (note any other type or category of AE to be followed up) must be monitored and followed up by the Investigator until stabilization or 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 also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Pregnancies are not considered per se to be adverse events. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the CRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor 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 7.4.1.4.

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 of these outcomes using the Pregnancy Report Form, and if an abnormal outcome occurs, the SAE Report Form 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 7.4.1.4, while normal outcomes must be reported within 45 days from 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 must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

All clinical laboratory assessments have been detailed listed in Section 7.1 and Section 7.2.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

All vital signs, physical examinations, and other assessments have been detailed listed in Section 7.1 and Section 7.2.

7.5 Pharmacokinetics

Not applicable.

7.6 Biomarkers

Not applicable.

7.7 Other Assessments

Not Applicable.

8 Statistics

8.1 Sample Size

A single-arm, interventional, multi-center pilot study to evaluate the efficacy of different dose of oral Bisoprolol on heart rate reduction in Chinese Chronic Heart Failure (CHF) patients with New York Heart Association (NYHA) class II – IV.

Suppose the difference of Mean change from baseline follows normal distribution, and the following assumptions are made to determine the sample size:

- It is supposed that the mean change from baseline of heart rate is -3.8bpm at week 6 and -7.4bpm at week 14. The Standard Deviation is assumed to be 10bpm across time.
- Based on assumption above about treatment effect and up-titration status at different visit, assuming 236 subjects under 15% dropout rate, distance from mean to limit of the 95% confidence interval of the change from baseline of mean heart rate is 1.54 at week 6 and 2.12 at week 14. Due the limit evidence at week 26, there is no robust extrapolation.

8.2 Randomization

Not Applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

Resting heart rate under 2.5mg (6±2weeks), 5mg (14±2weeks) and 10mg (26±2weeks) of Bisoprolol vs at baseline.

8.3.2 Secondary Endpoints

- Resting heart rate at 1.25mg (3±1weeks), 3.75mg (10±2weeks), and 7.5mg (18±2weeks) vs at baseline
- Heart function detected by UCG: including LVEF, left ventricular end-systolic dimension (LVESD) and left ventricle end-diastolic dimension (LVEDD), interventricular septal thickness (IVST) and E/a ration at baseline, 5mg (14±2weeks) and 10mg (26±2weeks).
- Systolic and diastolic blood pressure, symptoms and NYHA classification at all visits.
- Proportion of patient number whose Resting heart rate ＜ 70 and ＞55 bpm at all visits
- Quality of life [based on the MOS item short from health survey (SF-36) and Minnesota Living with Heart Failure (MLHFQ)] at baseline and end of treatment.
- 6-minute walk test and N-terminal Pro-B-type Natriuretic Peptide (NT Pro-BNP) at baseline and end of treatment.
- Average 24 hour heart rate, average daytime heart rate, average night time heart rate, proportion of arrhythmia, proportion of 24hour heart rate >70bpm, proportion of 24hour heart rate <55bpm at Baseline, 2.5mg (6±2weeks), 5mg(14±2weeks) and end of treatment (Based on 24 hour Holter);
- Patient Compliance at the end of study;
- All cause mortality, cardiac death, re-admission rate due to heart failure at the end of study

8.3.4 Safety Endpoints

Assessment of safety endpoints will include:

- All AEs and SAEs

- All deaths.
- All AEs and SAEs occurred during treatment period.
- Vital signs (heart rate, and blood pressure).
- Clinical laboratory assessments from hematology and biochemistry samples.
- Drug exposure.

8.3.5 Further Endpoints of Interest

No further endpoints of interest.

8.4 Analysis Sets

- ***Screen Population***

The screening population will include all subjects who provide written informed consent and who undergo screening assessments, regardless of treatment status in the trial.

- ***Full Analysis Set (FAS)***
  - Enrolled
  - Presence of measurement at baseline and time point of interest
- ***Per Protocol (PP)***

  The per protocol set of subjects is defined as a subset of the FAS analysis set who are compliant with the clinical trial protocol, and is characterized by criteria such as:
  - The completion of a certain minimal exposure to the trial drug.
  - The absence of any major clinical trial protocol violations.

  Major protocol violation will be defined in the Statistical Analysis Plan (SAP).

  The PP population will be identified before database lock and will be used to test the primary endpoint as sensitivity analysis..
- ***Safety***

  The safety population will include all subjects who received at least one dose of trial treatment.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Statistical analysis will be performed using CRF data obtained until database lock. The FAS population will be used primarily to present baseline characteristics and analyze efficacy data. Selected efficacy analyses will be repeated for the PP population.

If confidence intervals are to be calculated, 2-sided with significance level 0.05 is used, unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, i.e., number of subject (N), mean, median, standard deviation (S.D.), 25th and 75th percentile (Q1-Q3), minimum and maximum. Counts of missing observation will be included in the denominator and presented as a separate category.

For all variables, the baseline value will be defined as the last measurement taken prior to the first administration of treatment drug.

The dropouts and missing data will not be imputed.

8.5.2 Analysis of Primary Endpoints

Liner regression will be applied with change from baseline of HR as dependent variable and baseline HR and age as covariates at week 6, 14 and 26, respectively.

Furthermore, the mean value, standard deviation and 95% confidence interval (CI) will be calculated for the difference between HR at baseline and after week 6, 14 and 26 weeks treatment.

This analysis will be done both in FAS population and PP population.

8.5.3 Analysis of Secondary Endpoints

Same approach will be used for secondary continuous endpoints. For secondary endpoints such as SBP, DBP, NT-Pro BNP, left ventricular ejection fraction (EF%), left ventricular end-systolic dimension (LVESD), left ventricular wall thickness, E/A ratio,6min walk test, questionnaires score, paired t test will be used to compare the difference of these parameters between baseline and after 26 week treatment directly, furthermore, 95% confidence interval will also be calculated.

The SF-36 assesses 8 health status domains (ie, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from 0 to 100 [29-31].

The questionnaire of Minnesota Living with Heart Failure Questionnaire (MLHF) has 21 items. Questions assess the impact of frequent physical symptoms of heart failure - shortness of breath, fatigue, swollen ankles and difficulty sleeping. Other items ask about the effects of heart failure on physical and social functions including walking and climbing stairs, household work, need to rest, working to earn a living, going places away from home, doing things with family or friends, recreational activities, sports or hobbies, sexual activities, eating foods the patient likes and mental and emotional functions of concentration and memory, worry, loss of self control, and being a burden to others. Since treatments might have direct effects on a patient's life in addition to their effects on symptoms and functional limitations of heart failure, questions about side effects of medications, hospital stays and costs of care were included to help measure the overall impact of treatments for heart failure on patients' quality of life.
Scoring: Simple summation of responses. Total score (min = 0, max = 105), physical dimension (min= 0, max = 40) emotional dimension (min = 0, max = 25); the higher the summed score, the worse is the impact of heart failure on a patient's quality of life [32-34].

8.5.4 Analysis of Safety and Other Endpoints

All safety analyses will be performed on the safety population. AEs will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of treatment-emergent adverse events will be tabulated. In addition, the incidence of treatment-emergent AEs considered related to study medication (i.e., those AEs judged by the investigator to be either certainly, probably or possibly related to study medication and those with missing casual relationship) as well as the incidence of treatment-emergent AEs with severe or very severe intensity will also be reported.

All SAEs and those AEs leading to permanent discontinuation of study medication will be reported. Summary statistics will be provided for body weight, vital signs, ECG parameters and safety-related laboratory analyses. Summaries will consist of the number of patients assessed, sample mean value observed together with its associated standard error, sample mean change versus baseline together with its associated standard error and 95% confidence interval.

8.6 Interim and Additional Planned Analyses

No formal interim analysis is planned.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which 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 subject information sheet must be prepared in the local language in accordance with ICH GCP and 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 will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject and the Investigator. This process should be recorded in medical history as documentation.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived 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 Informed Consent Form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the EC/IRB for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but patient confidentiality will be strictly maintained.

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.

For subject registration, the investigator will fill out the subject registration form completely and send it to the subject registration center by fax.

When it is confirmed that the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject registration center registers the subject and informs the Investigator and the Sponsor of the registration number by fax. If the subject is ineligible for the trial and is therefore not given a registration number, a subject number is allocated and documented.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

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. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, Merck Serono provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating in 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, this clinical trial protocol will be submitted together with its associated documents (Informed Consent Form) to the responsible EC/IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at Sponsor.

The EC/IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable

opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

As a China local post-market study, the health authorities do not release the clinical trial approval letter, the clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form).

10 Trial Management

10.1 Case Report Form Handling

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The Investigator or designee will be responsible for entering trial data in the electronic CRF (eCRF) provided by the Sponsor. 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. Makrocare will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF 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 file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the available demographic and medical information for the subject, and 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 MS200006-0039 , and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to Echocardiography scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

For data that may be recorded directly in the CRF such as a questionnaire or diary, there will be no record in the original subject file and therefore the data entered in the CRF will be considered source data. The clinical trial protocol or the Manual of Operations should clearly and completely specify all subject data in the CRF to be considered source data.

Electronic subject files 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

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

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 Good Clinical Practice (ICH Topic E6, 1996), and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to EC and to the relevant IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant EC/IRB. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in 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 will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

11 Publication

The first publication will include the results of the analysis of the primary endpoint and will include data from all trial sites. 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 review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

12 References Cited in the Text

1. Ponikowski P, Voors AA, Anker SD, et al. Eur J Heart Fail. 2016 Aug;18(8):891-975.
2. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013 Jul;15(7):808-17.
3. K. Murad, D.C. Goff Jr., T.M. Morgan, et al. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the Cardiovascular Health Study JACC Heart Fail, 3 (2015), pp. 542–5.
4. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93: 1137–1146.
5. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
6. Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J England; 2004;25:1614–1619.
7. GU Df, HUANG Gy, HE J, et al. Investigation of prevalence and distributing feature of chronic heart failure in Chinese adult population Chin J Cardiol, January 2003 , Vol.31 No 1.
8. Heart & Stroke foundation. 2016 REPORT ON THE HEALTH OF CANADIANS
9. P.A. Heidenreich, N.M. Albert, L.A. Allen, et al. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association Circ Heart Fail, 6 (2013), pp. 606–619.
10. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet (London, England). 2010;376(9744):875–85.
11. Ferrari R, Ford I, Fox K, Steg PG, Tendera M. The BEAUTIFUL study: randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction—baseline characteristics of the study population. Cardiology. 2008;110(4):271–82.
12. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet (London, England). 1999;353(9146):9–13.
13. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194–9.
14. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet (London, England). 1999;353(9169):2001–7.
15. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803–69.
16. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-

blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med. 2009;150(11):784–94.
17. Zhonghua Xin Xue Guan Bing Za Zhi. Chinese guidelines for the diagnosis and treatment of heart failure 2014. Chin J Cardiol,014 Feb;42(2):98-122.
18. Reduced costs with bisoprolol treatment for heart failure: an economic analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II). Eur Heart J. 2001 Jun;22(12):1021-31.
19. Han SW1, Choi SW1, Ryu KH Beneficial Effect on Surrogate Markers of Heart Failure with Bisoprolol Up-Titration to Recommended Targets in Korean Patients with Heart Failure and Left Ventricular Systolic Dysfunction. Cardiovasc Ther. 2016 Jun;34(3):172-9.
20. F.A. McAlister, N. Wiebe, J.A. Ezekowitz, A.A. Leung, P.W. Armstrong Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure Ann Intern Med, 150 (2009), pp. 784–794.
21. H.D. Düngen, S. Apostolović, S. Inkrot, et al. Titration to target dose of bisoprolol versus carvedilol in elderly patients with heart failure: the CIBIS-ELD trial Eur J Heart Fail, 13 (6) (2011), pp. 670–680.
22. H.D. Düngen, S. Apostolović, S. Inkrot, et al. Bisoprolol vs. carvedilol in elderly patients with heart failure: rationale and design of the CIBIS-ELD trial Clin Res Cardiol, 97 (2008), pp. 578–586.
23. M. Lainscak, C. Moullet, N. Schön, et al. Treatment of chronic heart failure with carvedilol in daily practice: the SATELLITE survey experience Int J Cardiol, 122 (2007), pp. 149–155.
24. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003;24:464–474.
25. Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. Arch Intern Med 2004;164:1389–1394
26. Zugck C, Franke J, Gelbrich G, Frankenstein L, et al. Implementation of pharmacotherapy guidelines in heart failure: experience from the German Competence Network Heart Failure. Clin Res Cardiol 2012;101:263–272.
27. Gelbrich G, Edelmann F, Inkrot S, et al. Cibis-Eld investigators Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. Int J Cardiol 2012;155:160–166.
28. Von Arnim T. Prognostic significance of transient ischemic episodes: response to treatment shows improved prognosis. Results of the Total Ischemic Burden Bisoprolol Study (TIBBs) follow-up. J Am Coll Cardiol. 1996 Jul;28(1)_20-4
29. McHorney CA, Ware JE, Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31:247–263.
30. Ware JE, Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–483.
31. McHorney, C. A., Ware, J. E., Lu, J. F. R., & Sherbourne, C. D. (1994). The MOS 36-item short form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*, 40–66.
32. Fayers PM et al. Incomplete quality of life data in randomized trails: missing items. Statistics

in Medicine 1998;17:679-696.
33. Schaffer JL and Graham JW. Missing data: our view of the state of the art. Psychological Methods 2002;7:147-177.
34. Raghunathan TE, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. Survey Methodology 2001;27:85-95

Appendix I

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

http://www.mlhfq.org/

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Instructions for Data Collection and Scoring：

1. Patients should respond to the questionnaire prior to other assessments and interactions that may bias their responses. You might tell the patient that you would like to get his or her opinion before doing your medical assessment.

2. Ample, uninterrupted time should be provided for the patient to complete the questionnaire. We recommend that the patient answer the questions without being influenced by others such as their spouse or family members. Studies show that patient proxies often have different perspectives.

3. We recommend that you use the first question to give the respondent more detailed instructions as follows.

a. Read the introductory paragraph at the top of the questionnaire.

b. Read the first question with the respondent – “Did your heart failure prevent you living as you wanted during the last month (4 weeks) by causing swelling in your ankles or legs?” Then tell the respondent -

If you did not have any ankle or leg swelling during the past month (4 weeks) you should circle the zero (0) after this question.

If you did have swelling that was caused by a sprained ankle or some other cause that you are sure was not related to heart failure, you should circle the zero (0) after this question.

If you had swelling that might be related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do or feeling the way you would like to feel. In other words, how much did the swelling affect your life? Circle either the 0, 1, 2, 3, 4 or 5 to indicate how much the swelling affected your life during the past month – zero (0) means not at all, one (1) means very little and five (5) very much.

Ask the patient read and respond to all 21 questions. The entire questionnaire may be read directly to the patient if one is careful not to influence responses by verbal or physical cues.

Check to make sure the patient has responded to each question. If a question does not apply to the patient they should circle the zero (0). Make sure there is only one answer clearly marked for each question.

Score the questionnaire by summating the responses to all 21 questions. In addition, a physical dimension score (items 2, 3, 4, 5, 6, 7, 12, 13 on the version sent with these instructions) and emotional dimension score (items 17, 18, 19, 20, 21) have been identified by factor analysis and may be scored by simple summation to further characterize the effect of heart failure on a patient's life.

Partially complete questionnaires do occur despite best efforts to minimize missing data. However, missing data can greatly bias the data and complicate analysis. To reiterate, you need to make sure the respondents understand to mark zero for any items that do not apply to them, rather than leave a blank. Whenever possible review the questionnaire before the respondent leaves to make sure there are no unanswered questions or questions with more than one answer.

Several methods to impute missing data are discussed in the literature, Multiple imputation using completed questions and perhaps other study variables to predict missing responses should be considered. If a missing response is not imputed, the item will be eliminated from that person's score (the sum of responses). Since intermittently missing data can greatly affect within-person changes in scores, you might want to use the same subset of questions to represent a person at all times by omitting questions that have missing data at any point in time. We do not have any recommendations about when missing data become too extensive to render the information being collected useless.

Did your heart failure prevent you from living as you wanted during the last month by		NO	Very Little				Very Much
1.	causing swelling in your ankles or legs, etc.?	0	1	2	3	4	5
2.	making you sit or lie down to rest during the day?	0	1	2	3	4	5
3.	making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4.	making your working around the house or yard difficult?	0	1	2	3	4	5
5.	making your going places away from home difficult?	0	1	2	3	4	5
6.	making your sleeping well at night difficult?	0	1	2	3	4	5
7.	making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8.	making your working to earn a living difficult?	0	1	2	3	4	5
9.	making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10.	making your sexual activities difficult?	0	1	2	3	4	5

11.	making you eat less of the foods you like?	0	1	2	3	4	5
12.	making you short of breath?	0	1	2	3	4	5
13.	making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14.	making you stay in a hospital?	0	1	2	3	4	5
15.	costing you money for medical care?	0	1	2	3	4	5
16.	giving you side effects from treatments?	0	1	2	3	4	5
17.	making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18.	making you feel a loss of self-control in your life?	0	1	2	3	4	5
19.	making you worry?	0	1	2	3	4	5
20.	making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21.	making you feel depressed?	0	1	2	3	4	5

Appendix II

SF-36 QUESTIONNAIRE

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

(1)Excellent (2)Very (3)Good (4)Good Fair (5)Poor

Compared to one year ago, how would you rate your health in general now?

(1)Much better now than one year ago

(2)Somewhat better now than one year ago

(3)About the same

(4)Somewhat worse now than one year ago

(5)Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

(1)Yes, Limited a lot (2)Yes, Limited a Little (3)No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Lifting or carrying groceries

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Climbing several flights of stairs

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Climbing one flight of stairs

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Bending, kneeling, or stooping

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Walking more than a mile

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Walking several blocks

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Walking one block

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

Bathing or dressing yourself

(1)Yes, Limited a Lot (2)Yes, Limited a Little (3)No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

(1)Yes (2)No

Accomplished less than you would like

(1)Yes (2)No

Were limited in the kind of work or other activities

(1)Yes (2)No

Had difficulty performing the work or other activities (for example, it took extra effort)

(1)Yes (2)No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

(1)Yes (2)No

Accomplished less than you would like

(1)Yes (2)No

Didn't do work or other activities as carefully as usual

(1)Yes (2)No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(1)Not at all (2)Slightly (3)Moderately (4)Severe (5)Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

(1)None (2)Very Mild (3)Mild Moderate (4)Severe (5)Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(1)Not at all (2)A little bit (3)Moderately (4)Quite a bit (5)Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Have you been a very nervous person?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Have you felt calm and peaceful?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Did you have a lot of energy?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Have you felt downhearted and blue?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Did you feel worn out?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Have you been a happy person?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

Did you feel tired?

(1)All of the time

(2)Most of the time

(3)A good Bit of the Time

(4)Some of the time

(5)A little bit of the time

(6)None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(1)All of the time

(2)Most of the time

(3)Some of the time

(4)A little bit of the time

(5)None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

(1)Definitely true (2)Mostly true (3)Don't know (4)Mostly false (5)Definitely false

I am as healthy as anybody I know

(1)Definitely true (2)Mostly true (3)Don't know (4)Mostly false (5)Definitely false

I expect my health to get worse

(1)Definitely true (2)Mostly true (3)Don't know (4)Mostly false (5)Definitely false

My health is excellent

(1)Definitely true (2)Mostly true (3)Don't know (4)Mostly false (5)Definitely false

The SF-36 assesses 8 health status domains (ie, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from 0 to 100.

Appendix III **Schedule of Assessments**

	Visit 1 **Screening visit** (-2week to Day 0)	**Visit 2** (Day 0)	**Visit 3** (3±1 weeks)	**Visit 4** (6±2 weeks)	**Visit 5** (10±**2** weeks)	**Visit 6** (14±**2** weeks)	**Visit 7** (18±**2** weeks)	**Visit 8** (26±**2** weeks)
Signing the ICF	×							
Demographic data	×							
Inclusion and exclusion criteria	×							
Medical history	×							
Vital signs & Physical examination	×	×	×	×	×	×	×	×
NYHA classification and symptoms	×	×	×	×	×	×	×	×
ECG	×	×	×	×	×	×	×	×
Routine blood test and routine urine test	×			×		×		×

Hepatic and renal functions, Blood glucose and lipids, K&Na, NT Pro-BNP	×							×
Urine pregnancy test	×							
Echocardiography	×					×		×
6-min walk test	×							×
SF-36 & MLHFQ	×							×
Holter	×			×		×		×
Cardiovascular events	×	×	×	×	×	×	×	×
Concor® therapy		×	×	×	×	×	×	×
Adverse event record	×	×	×	×	×	×	×	×
Concomitant medicine/procedure	×	×	×	×	×	×	×	×
Patient Compliance								×