

# Clinical Trial Protocol

<b>Clinical Trial Protocol Number</b>	EMR200505_506
<b>Title</b>	An interventional, pilot study to evaluate the efficacy of oral nicorandil on improving microvascular function in female non-obstructive CAD patients (SPET study)
<b>Trial Phase</b>	IV
<b>Principal Investigator</b>	PPD [REDACTED]
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<b>Clinical Trial Protocol Version</b>	15 Apr 2018/ Protocol Amendment <III>



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## Signature Page

**Protocol Lead responsible for designing the clinical trial:**

I approve the design of the clinical trial.

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Date of Signature

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## Principal 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.

PPD

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**Principal Investigator Signature**

**Trial Title**

An interventional, pilot study to evaluate the efficacy of oral nicorandil on improving microvascular function in female non-obstructive CAD patients (SPET study)

**Clinical Trial Protocol Version/Date**

15 Apr 2018/ Protocol Amendment <III>

**Center Number**

PPD

**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.

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## List of Abbreviations

AE	Adverse Event
CFR	Coronary Flow Reserve
CRF	Case Report Form
CMD	Coronary Microvascular Dysfunction
CRO	Contract Research Organization
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EU	European Union
EEA	European Economic Area
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
IVRS	Interactive Voice Response System
MBF	Myocardial Blood Flow
MOP	Manual of Operations
MFR	Myocardial Blood Flow Reserve
PD	Pharmacodynamics
PET	Positron Emission Tomography
PGx	Pharmacogenetics/Pharmacogenomics

PK	Pharmacokinetics
SAE	Serious Adverse Event
SAQ	Seattle Angina Questionnaire
SRB	Safety Review Board
UCG	Ultrasound Cardiogram

<b>Trial title</b>	An interventional, pilot study to evaluate the efficacy of oral nicorandil on improving microvascular function in female non-obstructive CAD patients (SPET study)
<b>Trial number</b>	EMR200505-506
<b>Sponsor</b>	Merck Serono Co., Ltd
<b>Phase</b>	IV
<b>Trial center(s)/country(ies)</b>	1(hospital)/1(country)
<b>Planned trial period (first enrollment-last subject out)</b>	Sep, 2016 - Oct, 2019
<b>Trial objectives</b>	<p>Primary objective:</p> <p>To evaluate the improvement of microvascular function by positron emission tomography (PET) after twelve-week treatment of oral nicorandil in female no obstructive CAD patients;</p> <p>Secondary objectives:</p> <p>1) To evaluate the improve of myocardial blood flow (MBF) by rest and stress PET after twelve-week treatment of oral nicorandil</p> <p>2)To evaluate the improve of heart function by echocardiography after twelve-week treatment of oral nicorandil</p> <p>3) To evaluate the improve of angina attacks after twelve-week treatment of oral nicorandil</p>
<b>s</b>	This is a single-center, interventional, pilot clinical trial. 11-20 patients will be enrolled in the treatment group who will take oral nicorandil 5mg, t.i.d for 12 weeks,. For all the patients, rest cardiac PET and stress cardiac PET will be tested at both screening period and end of study. Other laboratory parameters and clinical symptoms will be collected at baseline, 4 weeks, 8 weeks and 12 weeks of treatment. There will be 5 visits from the beginning to the end of the study

<b>Planned number of subjects</b>	11-20
<b>Schedule of visits and assessments</b>	<p>Screening visit: ECG, lab tests, MFR by rest and stress PET, UCG;</p> <p>Visit 1(week 0): ECG, SAQ;</p> <p>Visit 2 (week 4): ECG;</p> <p>Visit 3 (week 8): ECG;</p> <p>Visit 4 (week 12): ECG, lab tests, MFR by rest and stress PET, UCG</p>

<p><b>Diagnosis and main inclusion and exclusion criteria</b></p>	<p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. Female</li> <li>2. Patients aged 18-70 years</li> <li>3. Patients with typical stable angina but without coronary obstruction (defined as coronary occlusion&lt;50%) by invasive coronary angiography or coronary computed tomography angiography (CTA) in recent three months<sup>5</sup>. All other long acting cardiovascular disease medicines, including but not limited to aspirin/clopidogrel, CCB, ACEI/ARB, <math>\beta</math>-blockers, statins, ivabradine, trimetazidine, et al, should be stable taken for at least two weeks before screening period</li> <li>6. For patients who met these four criteria above, MFR will be tested by stress PET. Patients whose MFR &lt;3.0 could be included in the study</li> </ol> <p><b>Exclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. Severe or uncontrolled hypertension (resting SBP <math>\geq</math> 160mmHg, or resting DBP<math>\geq</math>100mmHg at screening period)</li> <li>2. Patients with shock (including cardiogenic shock), or hypovolemia</li> <li>3. Severe hypotension (resting SBP&lt;90mmHg , or resting DBP&lt;60mmHg)</li> <li>4. Significant valvular heart disease, congenital heart disease or cardiomyopathy</li> <li>5. Congestive heart failure(NYHA III-IV), echocardiographic ejection fraction&lt;45%</li> </ol>
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	<p>6. Acute pulmonary edema;</p> <p>7. Hepatic or renal dysfunction, defined as:</p> <ul style="list-style-type: none"> <li>- Serum Alanine Aminotransferase (ALT) &gt; triple of the normal value upper limit;</li> <li>- Serum Aspartate Aminotransferase (AST) &gt; triple of the normal value upper limit</li> <li>- Serum creatinine &gt; twice of the normal value upper limit</li> </ul> <p>8. Glaucoma</p> <p>9. Active peptic ulcer or active skin ulcer</p> <p>10. Taking glyburide, PDE-5 inhibitors, soluble guanylate cyclase stimulator(s)</p> <p>11. Known to be hypersensitivity to nicorandil, nitrates, niacin, or any of the excipient</p> <p>12. With contraindication to complete stress PET test</p> <p>13. No legal ability and legal ability is limited</p> <p>14. Patients unlikely to cooperate in the study or with inability or unwillingness to give informed consent</p> <p>15. Child-bearing period women without effective contraceptive measures, pregnancy and lactation</p> <p>16. Participation in another clinical trial within the past 30 days</p> <p>17. Other significant disease that in the Investigator's opinion would exclude the subject from the trial</p>
<b>Investigational Medicinal Product (s): dose/mode of</b>	Nicorandil (SIGMART® Tablets 5.0mg) / Oral / t.i.d, 12 weeks

<b>administration/ dosing schedule</b>	
<b>Reference therapy(ies): dose/mode of administration/dosing schedule</b>	<p>Patients have already received the current standard therapy strategy, if conditions permitted, aspirin/clopidogrel, ACEI/ARB, <math>\beta</math>-blockers, CCBs, and statins should be included;</p> <p>All the medicines mentioned above and other anti-angina medicines(except nitroglycerine) need to be stabilized at least two weeks before screening period;</p> <p>All subjects in treatment group will start taking nicorandil after enrollment. Subjects in standard treatment group will continue with all the medicines at the screening period. Nitroglycerine is allowed during the treatment period</p>
<b>Planned treatment duration per subject</b>	12 weeks
<b>Primary endpoint(s)</b>	Comparison of myocardial blood flow reserve(MFR) between baseline and after twelve-week treatment
<b>Secondary endpoint(s)</b>	<p>Comparison of below items between baseline and after twelve-week treatment</p> <p>1) MBF by rest and stress PET</p> <p>2) Parameters of heart function by Echocardiography:</p> <p>a) cardiac systolic function: Ejection Fraction (EF%), left ventricular end-systolic dimension (LVESD), left ventricular wall thickness</p> <p>b) cardiac diastolic function: E/A ratio</p> <p>3) Seattle Angina Questionnaire(SAQ) score</p>
<b>Statistical methods (includes sample size calculation)</b>	For primary endpoint, when a sample size of 15, considering 30% drop out rate, will have 80% power to detect a difference in means of -0.55, assuming a standard deviation of differences of 0.56, using a paired t-test with a 0.05 two-sided significance level.

## 2 Sponsor, Investigators and Trial Administrative Structure

### 2.1 Sponsor

Merck Serono Co., Ltd.

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

## 2.2 Trial center

The trial is planned to be performed in a single center:

Address: PPD

### Principal investigator

Name: PPD

Position: PPD

Address: PPD

## 2.3 Clinical trial leader

PPD, Merck Serono Co., Ltd., China development Centre, PPD

## 2.4 Trial Monitor

PPD

## 2.5 Global drug safety responsibility

PPD, Merck Serono, Global drug safety medicine, PPD

# 3 Background Information

## 3.1 Background

### 3.1.1 Non-obstructive CAD

At least 20%-40% of patients presenting with angina have no significant CAD on invasive coronary angiography <sup>[1,2]</sup>, when more women than men had no obstructive CAD (65% vs 32%)<sup>[3]</sup>. Patients with stable angina and non-obstructive CAD have elevated risks of MACE and all-cause mortality <sup>[3]</sup>. Non-obstructive CAD comprised two groups: normal coronary arteries and those with <50% stenosis in any epicardial coronary artery. As many as about 65% of patients with chest pain without obstructive CAD are believed to have coronary microvascular dysfunction (CMD) <sup>[4]</sup>.

### 3.1.2 Coronary microvascular dysfunction

#### 3.1.2.1 Definition of coronary microvascular dysfunction

Coronary microvascular dysfunction defines as a primary dysfunction of the small coronary arteries <500µm in diameter which may cause microvascular angina or not <sup>[5]</sup>. It is attracting



more and more attentions now. In 2013 ESC guidelines on the management of stable coronary artery disease, it is listed as one of mechanisms of myocardial ischemia, together with fixed or dynamic stenosis of pericardial coronary arteries and focal or diffuse pericardial coronary spasm<sup>[6]</sup>. The mechanism of CMD continues to be discussed. Functional abnormalities of the coronary microcirculation during stress, including abnormal dilator responses and a heightened response to vasoconstrictors, have been considered as potential mechanisms of chest pain and ischemic appearing ST-segment depression during exercise. Endothelial dysfunction is most probably only one of the components <sup>[5]</sup>

### 3.1.2.2 Patients with CMD have poor prognosis

Patients with CMD believed to have a poor prognosis, with higher rates of hospitalization and increase rates of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, congestive heart failure, and coronary revascularization. The WISE study at 5.4-year follow-up demonstrated adverse events including cardiac death (53% being sudden cardiac death), stroke, and new onset heart failure rather than myocardial infarction, in particular in women with reduced Coronary flow reserve(CFR) assessed by adenosine<sup>[7]</sup>. Murthy and his colleagues showed that a low myocardial flow reserve (MFR) (<1.5) was associated with a 5.6-fold increase in the risk of cardiac death in a population with 2783 patients <sup>[8]</sup>.

### 3.1.2.3 CFR by PET is considered to be golden standard of non-invasive method for CMD assessment

Quantification of myocardial blood flow (MBF) and MFR has incremental values in the evaluation of the prognosis for patients with cardiovascular disease. There has been significant variation in the diagnostic criteria used to define CMD. The current gold standards for clinically assessing microvascular function have been CFR using invasive testing and positron emission tomography (PET) <sup>[9]</sup>. A CFR<2.0 strongly suggests coronary microvascular disease, and related to patients CV outcomes. However, CFR may be preserved in mild forms of coronary microvascular disease <sup>[5]</sup>. The current published data suggests that CFR are continuous variables, and thus, any cutoff used will have varying specificities and sensitivities. Several important prognostic studies have used thresholds of 1.5 to 2.3 to define cutoff values based on prognostic data <sup>[7,8]</sup>. However, many treatment studies have included subjects with CFR values >3 in their analysis. This study use a CFR<3.0 as a cutoff value for judging whether patient has coronary microvascular disease..

### 3.1.2.4 Limited treatment options for CMD

It is mentioned in the 2013 ESC guideline for the management of stable CAD that, symptomatic treatment is empirical. The results of available therapeutic trials cannot be accepted as conclusive because of variable patient selection, small sample size, inadequate design and lack of demonstration of clinical improvement of microvascular disease. All patients should receive secondary prevention medications including aspirin and statins.  $\beta$ -blockers are recommended as a first line treatment. Calcium antagonists are recommended if  $\beta$ -blockers do not achieve sufficient symptomatic benefit or are not tolerated. ACEI is recommended in patients with refractory symptoms <sup>[6]</sup>. Nicorandil is also recommended by

the guideline with the evidence that improvement of exercise capacity has been observed in a small trial with nicorandil which will be described in section 3.1.3.2.

### 3.1.3 Nicorandil has special effect on microvascular function

#### 3.1.3.1 Mechanism of nicorandil's effect on microvascular function

Nicorandil is a unique dual pharmacological mechanism anti-anginal agent with adenosine triphosphate sensitive potassium ( $K_{ATP}$ ) channel agonist and nitrate-like properties. It opens  $K_{ATP}$  channels in the vascular smooth muscle cell, leading to  $K^+$  efflux and membrane hyperpolarization, which in turn reduces  $Ca^{2+}$  influx, including closing voltage-sensitive calcium channels (VOC). Its  $K_{ATP}$  channel opening effect also inhibits  $Ca^{2+}$  release from the sarcoplasmic membrane. The concentration of intracellular free  $Ca^{2+}$  then decreases. Arterial vasodilation is therefore predominant <sup>[16]</sup>.  $K_{ATP}$  channel is one of the most critical target spots that regulates the tone of coronary arterioles (with diameter <200 $\mu$ m) <sup>[17]</sup>.

#### 3.1.3.2 Evidences of nicorandil's effect on microvascular function

A study result on dogs showed that the vessels <100 $\mu$ m in diameter were more sensitive to nicorandil than vessels >100 $\mu$ m. ATP-sensitive potassium channels are involved in the nicorandil-induced dilation of vessels smaller than 100 $\mu$ m<sup>[18]</sup>.

In a study to assess the role of nicorandil in vasodilation of human coronary resistance vessels in vitro. Coronary resistance vessels were resected from the right atrial appendage of 27 patients undergoing open heart surgery. Nicorandil induced a concentration-dependent vasodilation in these coronary resistance vessels <sup>[19]</sup>.

In a randomized, double-blind, placebo-controlled, crossover study, 13 patients with microvascular angina, (defined as had chronic stable angina, an ischemia-like ECG during exercise, normal angiography, no evidence of coronary spasm, and coronary flow reserve <3.0 by invasive Doppler assessment), were studied to find out if their cardiac ischemia could be improved after 2 weeks of oral nicorandil (5mg, t.i.d). Treadmill exercise tests and 24-hour ambulatory electrocardiogram monitoring were performed. The results showed that both time to 1-mm ST depression and total exercise duration were significantly prolonged with nicorandil treatment compared with placebo, suggesting that nicorandil might have a direct vasodilatory effect on coronary microvasculatures in patients with microvascular angina <sup>[20]</sup>.

Till now, there were no clinical trials to investigate nicorandil's effect on microvascular function by intuitive, visible and quantitative imaging test.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, GCP) and the Japanese ministerial ordinance on GCP, and any other applicable regulations.

## 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 nicorandil, all patients need to undergo rest and stress PET test both at baseline and end of treatment. Cardiac PET is more and more widely used now for cardiac diagnosis, prognosis assessment and efficacy assessment of response to therapy<sup>[21]</sup>. The patient radiation exposure is significantly less with most PET perfusion radiotracers than SPECT. In our study, the radiotracer will be N-13 ammonia (dose for baseline/EOT: 10-20mCi), when 10 mCi of N-13 ammonia exposes the patients to only 1.5 mSv<sup>[21]</sup>. That is much less than the radiation dose of a CT coronary angiography exam (16 mSv is the average adult effective dose from a CT coronary angiography exam), or an interventional fluoroscopy (5-70 mSv)<sup>[22]</sup>. For the stress PET, ATP will be used as hyperemic agent. ATP has been approved with good safety and tolerability in previous trials<sup>[23,24]</sup>. For patients who suffer from angina with all current standard therapies but no obstructive coronary, the free test of microvascular function in this study may avoid them from further more coronary CTA or interventional coronary angiography;

## **4 Trial Objectives**

### **Primary**

To evaluate the improvement of microvascular function by positron emission tomography (PET) after twelve-week treatment of oral nicorandil in female non-obstructive CAD patients

### **Secondary**

- 1) To evaluate the improvement of myocardial blood flow (MBF) by rest and stress PET after twelve-week treatment of oral nicorandil
- 2) To evaluate the improvement of heart function by echocardiography after twelve-week treatment of oral nicorandil
- 3) To evaluate the improvement of angina attacks after twelve-week treatment of oral nicorandil

## **5 Investigational Plan**

### **5.1 Overall Trial Design and Plan**

The study is a single-center, interventional, pilot study.

#### **5.1.1 Major aspects of the trial**

There will be a 2-week screening period, when baseline lab tests, ECG, UCG and PET will be conducted in this period. Patients who met the inclusion criteria but not the exclusion criteria will be enrolled. Totally 11-20 patients will be enrolled in the study. The study period after enrollment is 12 weeks. The anticipated recruitment period is 12 months. The anticipated period of the whole study will be 15 months. According to the recruitment

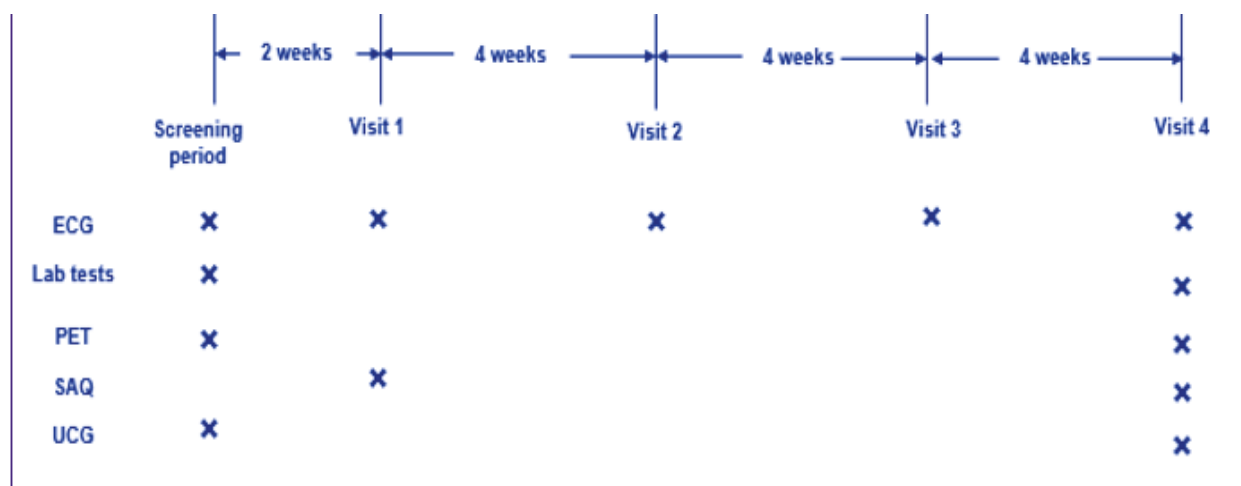
progress, if there have been 11 patients complete their following period, this study could be accomplished when meet the end of the anticipated period of the whole study.

Patients in the nicorandil group will start to take nicorandil 5mg, t.i.d from visit 1 for 12 weeks. All other cardiovascular medicines which need to be stabilized at least two weeks before screening period will be continued. Patients in standard treatment group will still take all the cardiovascular medicines stabilized at least two weeks before screening without any other newly added drugs. There will be a visit every four weeks. Symptoms and safety issues will be assessed at visit 2, visit 3. At visit 4 (week 12, end of treatment), lab tests, ECG, UCG, PET, symptoms and safety issues will all be re-assessed.

The primary endpoint is the MFR tested by PET at baseline and end of treatment; the secondary endpoints include the MBF by rest and stress PET at baseline and end of treatment, the heart function at baseline and end of treatment (based on UCG), symptom and quality of life at baseline and end of treatment (based on Seattle Angina Questionnaire).

In order to collect all the information in the inclusion and exclusion criteria for subjects' enrollment, medical history, physical examination, lab tests, ECG and UCG should be conducted in a 2-week screening period. As MFR by PET is also an inclusion criteria, rest and stress PET should also be conducted in subjects who have already met all other inclusion but not exclusion criteria in this 2-week screening period. If patients conducted lab tests, ECG or UCG in this period, but not especially for this trial, the result could also be used for the screening. 20 patients who meet the inclusion criteria but not the exclusion criteria will be enrolled in the study.

### 5.1.2 Schematic diagram of the study plan



## 5.2 Discussion of Trial Design

This is a single-arm, interventional, pilot study. PET is chosen for the assessment of primary endpoints. It is thought to be golden standard for the assessment of microvascular function due to its excellent image and able to quantification<sup>[9]</sup>. Nicorandil is believed to improve microvascular function due to its unique effect on  $K_{ATP}$  channel of vascular smooth muscle as

detailed described in section 3.1.3.1. Many Cardiologist also found nicorandil's good efficacy on patients with suspected coronary microvascular dysfunction in their clinical practice. However, there are few clinical evidences to show nicorandil's effect on microvascular function, especially by intuitive, quantitative imaging test. Also, PET is only limitedly used in CAD patients in China. As there was no MFR data test by PET in coronary microvascular dysfunction patients in China before, no reliable data could be provided for a RCT study design. In order to investigate nicorandil's effect on microvascular by PET, and to collect more information and parameters for further studies, this interventional, pilot study is designed.

### **5.2.1 Inclusion of Special Populations**

Only female patients are enrolled in this study, because women are more likely to suffer from non-obstructive coronary artery disease than men <sup>[3]</sup>. Some other studies focus on CMD, such as WISE study <sup>[7]</sup>, also only enrolled women in the study.

## **5.3 Selection of Trial Population**

### **5.3.1 Inclusion Criteria**

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

1. Female
2. Patients aged 18-70 years
3. Patients with typical stable angina but without coronary obstruction (defined as coronary occlusion <50%) by invasive coronary angiography or coronary computed tomography angiography (CTA) in recent three months
5. All other long acting cardiovascular disease medicines, including but not limited to aspirin/clopidogrel, CCB, ACEI/ARB,  $\beta$ -blockers, statins, ivabradine, trimetazidine, et al, should be stable taken for at least two weeks before screening period
6. For patients who met these five criteria above, MFR will be tested by stress PET. Patients whose MFR <3.0 could be included in the study

### **5.3.2 Exclusion Criteria**

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

1. Severe or uncontrolled hypertension (resting SBP  $\geq 160$ mmHg, or resting DBP  $\geq 100$ mmHg at screening period)
2. Patients with shock (including cardiogenic shock), or hypovolemia
3. Severe hypotension (resting SBP <90mmHg, or resting DBP <60mmHg)
4. Significant valvular heart disease, congenital heart disease or cardiomyopathy
5. Congestive heart failure (NYHA III-IV), echocardiographic ejection fraction <45%
6. Acute pulmonary edema;
7. Hepatic or renal dysfunction, defined as:
  - Serum Alanine Aminotransferase (ALT) > triple of the normal value upper limit;
  - Serum Aspartate Aminotransferase (AST) > triple of the normal value upper limit
  - Serum creatinine > twice of the normal value upper limit
8. Glaucoma
9. Active peptic ulcer or active skin ulcer

10. Taking glyburide, PDE-5 inhibitors, soluble guanylate cyclase stimulator(s)
11. Known to be hypersensitivity to nicorandil, nitrates, niacin, or any of the excipient
12. With contraindication to complete stress PET test
13. No legal ability and legal ability is limited
14. Patients unlikely to cooperate in the study or with inability or unwillingness to give informed consent
15. Child-bearing period women without effective contraceptive measures, pregnancy and lactation
16. Participation in another clinical trial within the past 30 days
17. Other significant disease that in the Investigator's opinion would exclude the subject from the trial

#### **5.4 Criteria for Initiation of Treatment with the Investigational Medicinal Product**

The inclusion and exclusion criteria examined at screening shouldn't be checked again before initiation of the treatment.

#### **5.5 Criteria for Subject Withdrawal**

##### **5.5.1 Withdrawal from the Trial**

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

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 assessments, the Investigator must determine and record the reasons and the circumstances as completely and accurately as possible.

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

##### **5.5.2 Withdrawal from the Investigational Medicinal Product**

The subject must be withdrawn in the event of any of the following:

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 anti-angina drugs that investigator believes would affect the function/perfusion of coronary microvascular, including but not limited to ACEI, ARB, Statins,  $\beta$ -blockers, CCB,



ivabradine, and trimetazidine, also other long-term Chinese traditional medicines for the treatment of angina.

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.

## **5.6 Premature Discontinuation 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 (applicable to trials with marketed products only).

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.

## **6 Investigational Medicinal Product and Other Drugs Used in the Trial**

The term "Investigational Medicinal Product" refers to the investigational drug undergoing trial.

### **6.1 Description of Investigational Medicinal Product**

Nicorandil (Sigmart® Tablets, 5mg), white plain tablets, with diameter 5mm, thickness 2mm, manufactured by PPD .



## **6.2 Dosage and Administration**

During the whole study duration, subjects in nicorandil group would take Sigmart® orally, 5mg, t.i.d. The whole tablet is to be swallowed with water, not chewed.

### Treatment of angina pectoris:

The usual adult dosage for oral use is 15 mg of nicorandil daily in three divided doses. The dosage may be adjusted according to the patient's condition.

In this study, according to the small sample size, single-arm design for primary endpoint, and the usual dose of Sigmart® in China, the dose is required not to change during the study duration.

## **6.3 Assignment to Treatment Groups**

After completion of all the screening evaluations, 20 eligible subjects will be enroll to treatment group.

Subject numbers should be unique (i.e. reallocation of subject numbers is not permitted).

## **6.4 Other Drugs to be used in the Trial**

No other drugs are mandatory in this trial.

For nicorandil group, all other long acting cardiovascular disease medicines, including aspirin/clopidogrel, CCB, ACEI/ARB,  $\beta$ -blockers, statins, ivabradine, trimetazidine, et al, should be stable taken for at least one month before screening period;

For standard treatment group, the standard treatment should include aspirin/clopidogrel, CCB, ACEI/ARB,  $\beta$ -blockers and statins if condition permits. They should also be taken for at least one month before screening period.

## **6.5 Concomitant Medications and Therapies**

### **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.

Patients should take all the current standard therapy for angina. It should include aspirine / clopidogrel, ACEI/ARB, statins,  $\beta$ -blockers and CCBs. Other medicines for angina treatment are also permitted, such as ivabradine, trimetazidine, and other Chinese traditional medicines, such as Tong Xin Luo capsule. However, all these medicines mentioned in this paragraph need to be stabilized before screening period. There should be no dose/form change during the trial.

Emergency medicines for sudden angina attacks such as nitroglycerin and Compound Danshen Dripping Pills, are permitted in the trial duration. Their usage is not restricted. But the dose and frequency should be recorded in the corresponding section of the CRF at every visit.

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 Non-permitted Medicines**

Glyburide, which may influence the efficacy of nicorandil;

PDE-5 inhibitors, such as sildenafil citrate, vardenafil hydrochloride hydrate and tadalafil. The coadministration of these medicines with nicorandil may enhance hypotensive effect;

Soluble guanylate cyclase stimulator(s), such as riociguat. The co-administration with nicorandil may enhance hypotensive effect.

Some evidences showed that ranolazine could effect coronary microvascular function. So it should not be used during the study period and one month before the screening period.

Some injections that might have efficacy on patients' microvascular function are also not permitted during the study, such as alprostadil injection.

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

### **6.5.3 Other Trial Considerations**

If the subjects undergone PCI or CABG 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**

Packaging: 5mg tablets, boxes of 100 tablets in PTP. One box would supply for 33 days.

Labeling: “use only for clinical study EMR200505\_506” will be labelled on the box by an independent company.

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

## **6.7 Preparation, Handling and Storage**

Nicorandil is freely soluble in methanol, ethanol (99.5), acetic acid (100); soluble in acetic anhydride; sparingly soluble in water. The melting point is about 92°C (to be decomposed). So the medicine 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 accountability for the IMP, including reconciliation of drugs and maintenance of drug 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 the IMP, the Storage Manager will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be archived in the Investigator Site File.

The dispensing of the IMP will be carefully recorded by the Storage Manager on the appropriate drug accountability forms provided by the 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 delivery to/receipt by the trial site.

- IMP accountability forms (provided by the Sponsor and completed at the site).

- The use of each dose by each subject.

- The return to the Sponsor or alternative disposition of unused IMP.

- Dates, quantities, batch numbers, expiry dates, formulation (for IMP prepared at the site), and the subjects' 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 IMPs provided by the Sponsor were fully reconciled.

The unused IMP must not be discarded or used for any purpose other than the present trial. IMP that has been dispensed to a subject must not 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 Method of Blinding**

NA

## **6.11 Emergency Unblinding**

NA

## **6.12 Treatment of Overdose**

An overdose is defined as any dose greater than the highest daily dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the CRF.

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).

The usual adult dosage for oral use is 15 mg of nicorandil daily in three divided doses. The dosage may be adjusted according to the patient's condition. Till now, there is no maximum dose for nicorandil. In a clinical trial conducted in European stable angina patients, the dose of nicorandil was 20mg, twice daily with a mean follow up of 1.6 years. Patients showed good tolerance of the medicine and less coronary events <sup>[25]</sup>.

If patients took more dose of nicorandil than 15mg/d, the investigators should use his/her clinical judgement treating such situations.

## **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.

## **7 Trial Procedures and Assessments**

### **7.1 Schedule of Assessments**

Day 1 is defined as the first day of enrollment.

The trial procedures and assessment contents are as follow:

1. Screening Visit -Day -14 to 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, waist circumference, current medical condition and past medical history, including concomitant therapies
- b) Perform physical examinations, including vital signs (blood pressure, heart rate)
- c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;
- d) Echocardiography
- e) Rest and stress PET
- f) Blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets), myocardial enzymes(CKMB), liver function (ALT, AST), renal function (Bun, Cr), fasting blood glucose and blood lipids (TC, TG, LDL-C and HDL-C), electrolyte (K, Na) (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) Signing the informed consent form
- i) AE
- j) Concomitant medication

2. Visit 1- Day 1±3: this visit entails the following:

- a) Enrollment.
- b) Perform physical examinations, including vital signs (blood pressure, heart rate)
- c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;
- d) Seattle Angina Questionnaire score;

- e) Cardiovascular events: cardiac death, hospitalization caused by heart failure/ACS/revascularization, stroke, cerebral hemorrhage;
- f) AE;
- g) Concomitant medication

3. Visit 2- Day 28±3: This visit entails the following:

- a) Perform physical examinations, including vital signs (blood pressure, heart rate
- b) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no),if yes, specify;
- c) Record adverse events, concomitant drugs and use of study drug;
- d) Cardiovascular events: cardiac death, hospitalization caused by heart failure/ACS/revascularization, stroke, cerebral hemorrhage;

4. Visit 3- Day 56±3: This visit entails the following:

- a) Perform physical examinations, including vital signs (blood pressure, heart rate)
- b) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy(yes/no); abnormal ST-T change(yes/no), if yes, specify;
- c) Record adverse events, concomitant drugs and use of study drug;
- d) Cardiovascular events: cardiac death, hospitalization caused by heart failure/ACS/revascularization, stroke, cerebral hemorrhage;

5. Visit 4- Day 84±3: This visit entails the following:

- a) Record height, weight and waist circumference
- b) Perform physical examinations, including vital signs (blood pressure, heart rate)
- c) ECG: heart rate; sinus rhythm/arrhythmia, specify; cardiac hypertrophy (yes/no); abnormal ST-T change(yes/no), if yes, specify;
- d) Echocardiography
- e) Rest and stress PET
- f) Seattle Angina Questionnaire score
- g) Blood tests: full blood count (white blood cells, neutrophils, red blood cells, hemoglobin and platelets), myocardial enzymes (CKMB), liver function (ALT, AST), renal function (Bun, Cr), fasting blood glucose and blood lipids (TC, TG, LDL-C and HDL-C), electrolyte (K, Na)

- h) Routine urine test (PH, Specific gravity, Protein, Glucose, Ketone, Nitrite, Leukocytes, Hemoglobin, Red blood cells, Bilirubin);
- i) Record adverse events, concomitant drugs and use of study drug;
- j) Cardiovascular events: cardiac death, hospitalization caused by heart failure/ACS/revascularization, stroke, cerebral hemorrhage;
- k) 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**

### **7.2.1 Demographic variables**

Major demographic information is as follows:

1. Birth date
2. Gender (according to the protocol, only female could be enrolled)
3. Race

### **7.2.2 Medical history**

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

#### **7.2.2.1 Angina pectoris**

1. Basic information: classification (stable or unstable); duration (total years suffering from angina); frequency of angina attacks in recent one month ( how many times/ week); previous treatment procedures (PCI or CABG), time of the procedure; result of CTA or coronary angiography in recent 3 months ( totally normal coronary/ coronary with occlusion <20%; which coronary branch, LM/LAD/LCX/RCA; the ratio of occlusion); history of MI or not, if yes, the time need to be recorded; result of ECG during exercise stress test or when angina attacks in recent three months; or results by myocardial nuclein perfusion imaging in recent three months;
2. Current medicine treatment at screening period of the study: name, dose, initiation date, frequency (month/year)
3. Emergency treatment: frequency and dose consumption of emergency medicine in recent one month (nitroglycerin or compound Danshen drip pill)

#### **7.2.2.2 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.



### 7.2.3 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  $> 5\text{mmHg}$ , 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 $^2(\text{m}^2)$

6. Measurement of waist circumference: At screening visit, under fasting, standing, calm breathing conditions, feet apart 25-30cm, waist circumference 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.

### 7.2.4 Lab test items

Lab examination should include at least the following items: hematological examination, echocardiography, rest and stress PET 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) Myocardial enzymes (CKMB)



g) Electrolyte (K, Na)

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

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

4. Echocardiography: to measure ejection fraction (EF%), left ventricular end systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (PWT) and E/A ratio

5. Rest and stress PET: MBF of both rest and stress PET, then  $MFR = MBF \text{ at stress} / MBF \text{ at rest}$  (the detailed description of PET test will be described in 7.3.1)

## **7.3 Assessment of Efficacy**

### **7.3.1 MFR by PET**

1. Radiation tracer:  $^{13}\text{N}$ -ammonia; Hyperemic agent: Adenosine (ATP);

2. Patients were instructed to strictly refrain from any caffeinated substances for 24h before testing; All subjects fasted for >6 h;

3. PET:  $^{13}\text{N}$ -ammonia PET was assessed in a 1-day protocol at rest and during Adenosine stress at a standard rate (0.12mg/min/kg) over 6 min. At rest, approximately 370~740 MBq of  $^{13}\text{N}$ -ammonia was injected into a peripheral vein of all subjects, followed by a 30 mL saline flush. Dynamic and gated acquisition was initiated just before injection, and was extended for 20 min. Adenosine stress test was performed more than 50 min (5 half-lives) after rest protocol. During this time,  $^{13}\text{N}$  activity at rest had physically decayed to about 3 % of its initial activity.  $^{13}\text{N}$  ammonia and adenosine were infused through the peripheral veins of both the right and left arms (2-route method) to prevent suspending adenosine infusion during administration of  $^{13}\text{N}$ -ammonia.  $^{13}\text{N}$ -ammonia of the same dose (370~740 MBq) was injected at the end of the 3 min of administration. Images were acquired in 3-dimensional list mode on a Siemens Biograph64 TrueV PET scanner (Siemens Medical Solution, USA, Inc.), with a field of view 21.6 cm. The optimal imaging position was determined on a CT scout scan. Dynamic acquisitions of the emission scans were performed using a standard protocol using list mode for 20 min. Low-dose CT images were used for attenuation correction. Images were reconstructed using ordered subset expectation maximization (OSEM) method, and for review the images were resliced in short-axis as well as in vertical and horizontal long-axis orientation;

4. Data analysis. Regional  $^{13}\text{N}$ -ammonia uptake was assessed using the 17-segment model and the semi quantitative scoring system of defect severity and extent, as recommended by the American Society of Nuclear Cardiology. A scan was considered normal if the summed stress score (SSS) was <4, mildly abnormal if the SSS was between 4 and 8, and moderately to severely abnormal if the SSS was >8, as previously reported in PET studies. Image interpretation according to these definitions was performed by 2 experienced readers. Diverging interpretations were resolved by consensus reading. Quantitative MBF

was determined using the PPD package developed and validated by PPD. A spherical region of interest was placed into the blood pool of the left ventricle. Myocardial and blood pool time-activity curves were generated from the dynamic frames and corrected for radioisotope decay. MBF was estimated by model fitting of the blood pool and myocardial time activity curves correcting for partial volume and spillover. MFR was calculated as the ratio of hyperemic to resting MBF.

### 7.3.2 Echocardiography

Ejection fraction (EF%), left ventricular end systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (PWT) and E/A ratio

### 7.3.3 Seattle angina questionnaire

1. The Seattle Angina Questionnaire is designed to quantify the physical and emotional effects of coronary artery disease. This instrument (Appendix II) is a 19-item self-administered questionnaire resulting in five scales that measure clinically important dimensions of coronary artery disease: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception;
2. The Seattle Angina Questionnaire is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing across items within each of the five scales. Scale scores are then transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. Because each scale monitors a unique dimension of coronary artery disease, no summary score is generated.
3. The Seattle Angina Questionnaire could be finished by a single page of paper. The answers will be copied in the eCRF by investigators as soon as it is completed. It is designed to be self-administered. For patients who can't read, investigators or other family persons could read the questions for them, then the patients could choose the most appropriate answers which the questioners tick them in the paper for the patients. For those who could read, they should complete it by themselves

## 7.4 Assessment of Safety

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

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any adverse event (AE), whether observed by the Investigator or reported by the subject (see Section 7.4.1.2, "Methods of Recording and Assessing Adverse Events").

The reporting period for adverse events is described in Section 7.4.1.3.

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

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

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

#### **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” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization.

Results in persistent or significant disability/incapacity.

Is a congenital anomaly/birth defect.

Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via the IMP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner 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 (e.g. 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 (e.g., 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.

### **Severity of AEs**

The Investigator is required to grade the severity of each adverse event.

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

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

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

The 5 general grades are:

**Grade 1:** Mild

**Grade 2:** Moderate

**Grade 3:** Severe

**Grade 4:** Life-threatening or disabling

**Grade 5:** Death related to AE\*

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the Investigator must also report the event as a serious adverse event (SAE; see definition below) as per Section 7.4.1.4. However, a laboratory abnormality with a

severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described above.

\*Note: Death (Grade 5 as defined by NCI-CTCAE version 4.0) is mainly regarded as an outcome, to be documented as described below.

In the case of death, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

### **Causal relationship of AEs to the IMP**

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

**Not related:** Not suspected to be 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:** Suspected to be 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 (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g. anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

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### **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 serious AEs or unexpected 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 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[s]) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

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 into the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period, defined as the complete of the last visit.

### **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 report to Merck Serono Global Drug Safety Department by telephone, by fax or by emails within a maximum 24 HOURS after becoming aware of the event.

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](mailto:GlobalDrugSafety@merckgroup.com)

**Fax:** 49(0) 6151 72 6914;

**Telephone:** 49 (0) 6151 72 8101;

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.

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). Other relevant pages from the CRF may also be provided (e.g., medical history, concomitant drugs).

The Investigator/reporter must respond to any request for follow-up information (e.g., 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 initial reports. This is necessary to ensure that the Sponsor promptly assesses the event and, where applicable, meets the regulatory timelines for expedited safety reporting.

Requests for follow-up will usually be made by the responsible Monitor. In exceptional cases where a particularly critical event occurs, the Global Drug Safety department may contact the Investigator directly for further information or discussion.



#### **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 report SAEs (particularly deaths) in accordance with applicable site-specific requirements to the IEC that approved the trial.

In accordance with the ICH GCP guidelines, the Sponsor will immediately inform all the trial Investigators and the Heads of the trial sites 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 immediately inform all the trial Investigators and the Heads of the trial sites 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). In addition, according to applicable regulations, the Sponsor will inform the trial Investigators and the Heads of the trial sites of all SAEs which were reported to the health authorities. The investigator should place copies of the safety reports in the Investigator Site File. The Head of the trial site should also maintain copies of safety reports appropriately.

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

#### **7.4.1.6 Monitoring of Subjects with Adverse Events**

Any AE that occurs during the course of a clinical trial and is considered to be possibly related to the IMP 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. The Sponsor will actively follow-up and collect information on any AE that occurs during the course of a clinical trial, however while this activity will continue for any serious AEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

#### **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 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 in case of abnormal outcome, the Adverse Event Safety Report Form (Clinical Trials) when the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form when 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 Laboratory Assessments**

All 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/Pharmacogenetics (PGX)**

*Not Applicable.*

### **7.7 Other Assessments**

*Not Applicable.*

## **8 Statistics**

### **8.1 Sample Size**

This is an open-label, single arm trial intended to evaluate the improvement of microvascular function (myocardial blood flow reserve, MFR) by positron emission tomography (PET) after twelve week treatment with oral nicorandil in female non-obstructive CAD patients. The null hypothesis is that there is no difference between MFR at baseline and MFR after twelve weeks treatment. The alternative hypothesis is that the MFR after twelve weeks treatment is higher than the MFR at baseline.



Suppose the difference of MFR follows normal distribution, and the following assumptions are made to determine the sample size:

The mean value of difference of MFR is 0.55.

The standard deviation of difference of MFR is 0.56.

Alpha=0.05(two sided).

Power=0.80.

A sample size of 11 patients will be required to reach this goal. Assuming a drop-out rate of 30%, then a total of 15 patients will be recruited into this study. According to the recruitment progress, if there have been 11 patients complete their following period, this study could be accomplished when meet the end of the anticipated period of the whole study.

## **8.2 Randomization**

Not available.

## **8.3 Endpoints**

### **8.3.1 Primary Endpoint**

The primary endpoint is the difference of MFR by stress PET between baseline and after twelve-week treatment.

### **8.3.2 Secondary Endpoints**

The secondary endpoints in this study include

The difference of myocardial blood flow (MBF) by rest PET between baseline and twelve weeks treatment.

The difference of myocardial blood flow (MBF) by stress PET between baseline and twelve weeks treatment.

The parameters of heart function by echocardiography: Cardiac systolic function: Ejection Fraction (EF%), left ventricular end systolic dimension (LVESD), left ventricular wall thickness. Cardiac diastolic function: E/A ratio

Seattle Angina Questionnaire score

### **8.3.3 Safety Endpoint**

Assessment of safety endpoints will include:

All deaths.

All AEs occurred during treatment period.

Vital signs (heart rate, and blood pressure).

Clinical laboratory assessments from hematology and biochemistry samples.

Drug exposure.

## **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.

### ***Intention-to-treat(ITT)***

The ITT population is the subset of screen population, and it should include all subjects who receive at least one dose of trial treatment.

### ***Per Protocol (PP)***

The PP population will be the subset of the ITT population that is compliant with the protocol and characterized by criteria such as:

- 1) Measurement of the primary endpoint both at baseline and after twelve week treatment.
- 2) Absence of any major protocol deviation.

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. It will be considered a secondary population.

### ***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 Further Endpoints of Interest**

No further endpoints of interest.

### **8.5.2 General Considerations**

Statistical analysis will be performed using CRF data obtained until all subjects have Completed (or discontinued) the trial. The ITT 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, these will be two-sided with a confidence probability of 95%, 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. Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the population of interest. 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.

### **8.5.3 Analysis of Primary Endpoint**

Paired t test will be used to evaluate the primary endpoint. The null hypothesis is that there is no difference between MFR at baseline and MFR after twelve week treatment. The alternative hypothesis is that the MFR after twelve week treatment is higher.

Furthermore, the mean value, standard deviation and two-sided 95% confidence interval (CI) will be calculated for the difference between MFR at baseline and after twelve week treatment.

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

### **8.5.4 Analysis of Secondary Endpoints**

For secondary endpoints such as MBF by rest PET, MBF by stress PET, ejection fraction (EF%), left ventricular end-systolic dimension (LVESD), left ventricular wall thickness, E/A ratio, paired t test will be used to compare the difference of these parameters between baseline and after twelve week treatment directly, furthermore, 95% confidence interval will also be calculated.

The Seattle angina questionnaire (SAQ) score will be classified into five dimensions: physical limitation (question 1), anginal stability (question 2), anginal frequency (question 3-4), treatment satisfaction (question 5-8) and disease perception (question 9-11). The sum of score in each dimension will be calculated respectively, and then transformed into the standard score between 0 and 100:

$$\frac{(\text{Sum of score} - \text{the minimum value of score in this dimension})}{(\text{the range of score in this dimension})} \times 100$$

For example:

Suppose the sum of score in dimension 1 is 43, and the minimum and maximum of score in this dimension is 1×9=9 and 6×9=54 respectively. So the standard score in this dimension is

$$\frac{43-9}{54-9} \times 100 = 75.55;$$

Suppose the sum of score in dimension 2 is 2 and the minimum and maximum of score in this dimension is 1 and 5 respectively. So the standard score in this dimension is  $\frac{2-1}{5-1} \times 100 = 25$

The paired t test will be used to compare the difference of standard score in each dimension, furthermore, the 95% confidence interval will also be calculated.

### **8.5.5 Safety Analyses**

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.

### **8.5.6 Analysis of Further Endpoints**

The MFR results of standard treatment will be shown by subjects.

### **8.6 Interim Analysis**

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 his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), the Chinese GCP (06/08/2003), and any other

applicable regulations. In particular, the Investigator must ensure that only subjects who have given their informed consent are included in the trial.

## **9.2 Subject Information and Informed Consent**

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

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). With the cooperation of the Sponsor, and in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator will prepare the informed consent form and other written information to be used in obtaining informed consent from the trial subjects. The Sponsor should provide the investigator with documents/information necessary for preparing the aforementioned written information and cooperate with the investigator to prepare it. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject of all pertinent aspects of the trial orally as well as in writing. The language used in the aforementioned oral and written information about the trial must be fully and readily understandable to lay persons.

Before consent may be obtained, the investigator should provide the prospective subject (the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative) with ample time and opportunity to inquire about details of the clinical trial and to decide whether or not to participate in the trial. In such cases, the investigator or the trial collaborator giving supplementary explanation should answer all questions about the trial to the satisfaction of the prospective subject (or of the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative).

Depending on national regulations, a person other than the Investigator may inform the subject about the trial and sign the Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and personally dated by the subject and the Investigator.

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

Whenever important new information becomes available that may be relevant to the subject's consent, the Investigator will revise the subject information sheet and any other written information provided to the subjects and submit them to the 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 his/her written consent for continued participation in the trial.

### **9.3 Subject Identification and Privacy**

A unique subject number will be assigned to each subject at inclusion, 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.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but the subject's 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 during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

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

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

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, s/he will answer any questions. Any subsequent action will follow the standard processes established for the 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**

The Sponsor is entirely responsible for AEs that are associated with this trial and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the trial site, and/or the subject. The Sponsor takes out insurance to fulfill the responsibility.

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

## **9.6 Independent Ethics Committee or Institutional Review Board**

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted, through the Head of the trial site, together with its associated documents (Informed Consent Form) to the responsible IRB for its favorable opinion/approval. The written favorable opinion/approval of the IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at Sponsor.

The Sponsor initiates the trial at a site after obtaining written approval from the Head of the trial site based on favorable opinion/approval from the concerned IRB. The IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, its membership list, and names of members who were present and voted at the meeting. Written favorable opinion/approval should clearly identify the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version that were reviewed at the meeting. Where possible, copies of the meeting minutes should also be obtained.

Plans for any substantial amendments to the clinical trial will also be submitted to the concerned IRB before they are implemented (see Section 10.5). Relevant safety information will be submitted to the IRB during the course of the trial in accordance with national regulations and requirements.

## **9.7 Health Authorities**

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

## **10 Trial Management**

### **10.1 Case Report Form Handling**

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

The data collected in the course of this trial must be documented in the CRFs and/or the Adverse Event Safety Report Form (Clinical Trials), and must be forwarded to Sponsor. They



will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations.

The Investigator must ensure that the CRFs and any other associated documents forwarded to Sponsor contain no mention of any subject names.

The paper CRFs must be filled in completely and legibly, using either black or blue ballpoint pen suitable for use on official documents. Any necessary amendments or corrections must be made, countersigned and dated by the Investigator. When corrections are made to errors in data entry, the original entries must remain legible and must not be deleted or obscured with correction aids. The Investigator must state his/her reasons for the correction of important data.

In the case of missing data or remarks, the entry spaces provided in the paper CRF should be cancelled out to avoid unnecessary follow-up inquiries.

The CRFs are essential trial documents and must be suitable for regulatory inspections and submissions.

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

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 EMR200505-506

Date of subject's inclusion into the trial (i.e. date of giving informed consent),

Subject number in the trial,



Dates of the subject's visits to the site,  
Any medical examinations and clinical findings predefined in the clinical trial protocol,  
All adverse events observed in the subject,  
Date of subject's end of trial, and  
Date of and reason for early withdrawal of the subject from the trial or from the IMP, if applicable.

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

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, PET scan images, ECG recordings, laboratory value listings, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

Certain data may be recorded directly in the CRF (or in a questionnaire, diary etc.) rather than entered into the subject's original medical file. In such cases there will be no record in the original subject file (either on paper or electronically) that corresponds to the entries in the CRF. In such cases, the data entered in the CRF will be considered source data. The clinical trial protocol should clearly and completely specify all those subject data in the CRF that will be considered source data. Data in the CRF that are not explicitly defined as source data will be entered in the subject's medical file.

### **10.3 Investigator Site File and Archiving**

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

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Head of the trial site 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), the Japanese ministerial ordinance on GCP, and any other applicable regulations. The Monitor will perform visits to the trial site at regular intervals.

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

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.

## **10.5 Changes to the Clinical Trial Protocol**

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the EC and to the relevant IRB through the Head of the trial site for approval or favorable opinion. In such cases, the amendment will be implemented only after written approval from the Head of the trial site based on favorable opinion/approval from the relevant IRB has been obtained.

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

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

## **10.6 Clinical Trial Report and Publication Policy**

### **10.6.1 Clinical Trial Report**

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor in consultation with the Principal Investigator.

### **10.6.2 Publication**

The first publication will be a publication of the results of the analysis of the primary endpoint that 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 pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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## 12 Appendices

### Appendix I Schedule of Assessments

	<b>Screening visit (Day -14 to 0)</b>	<b>Visit 1 (Day 1±3)</b>	<b>Visit 2 (Day 28±3)</b>	<b>Visit 3 (Day 56±3)</b>	<b>Visit 4 (Day 84±3)</b>
<b>Signing the ICF</b>	×				
<b>Demographic data</b>	×				
<b>Inclusion and exclusion criteria</b>	×				
<b>Medical history</b>	×				

<b>Body weight and height</b>	×				×
<b>Waist circumference</b>	×				×
<b>Vital signs</b>	×	×	×	×	×
<b>Physical examination</b>	×	×	×	×	×
<b>ECG</b>	×	×	×	×	×
<b>Full blood count</b>	×				×
<b>Hepatic and renal functions</b>	×				×
<b>Blood glucose and lipids</b>	×				×
<b>Echocardiography</b>	×				×
<b>Rest and stress PET</b>	×				×
<b>SAQ</b>		×			×
<b>Cardiovascular events</b>		×	×	×	×
<b>Sigmart® therapy (For treatment group only)</b>		×	×	×	×
<b>Adverse event record</b>	×	×	×	×	×
<b>Medication possession ratio (MPR)</b>	×				×
<b>Concomitant medicine</b>	×	×	×	×	×

## Appendix II

### *The Seattle Angina Questionnaire*

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks.**

Place an x in one box on each line.

Activity	Severely Limited	Moderately Limited	Somewhat Limited	A Little Limited	Not Limited	Limited, or did not do for other reasons
Dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking indoors on level ground	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Showering	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing a hill or a flight of stairs without stopping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gardening, vacuuming, or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking more than a block at a brisk pace	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Running or jogging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lifting or moving heavy objects (e.g. furniture, children)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Participating in strenuous sports (e.g. swimming, tennis)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Compared with 4 weeks ago, how often do you have chest pain, chest tightness, or angina when doing your **most strenuous** level of activity?

I have had chest pain, chest tightness, or angina...

<b>Much more often</b>	<b>Slightly more often</b>	<b>About the same</b>	<b>Slightly less often</b>	<b>Much less often</b>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Over the **past 4 weeks**, on average, how many times have you had chest pain, chest tightness, or angina?

I get chest pain, chest tightness, or angina...



4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Over the past 4 weeks, on average, how many times have you had to take nitros (nitroglycerin tablets) for your **chest pain, chest tightness, or angina**?  
I take nitros...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. How bothersome is it for you to take your pills for **chest pain, chest tightness or angina** as prescribed?

<b>Very bothersome</b>	<b>Moderately bothersome</b>	<b>Somewhat bothersome</b>	<b>A little bothersome</b>	<b>Not bothersome at all</b>	<b>My doctor has not prescribed pills</b>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. How satisfied are you that everything possible is being done to treat your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. How satisfied are you with the explanations your doctor has given you about your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. Overall, how satisfied are you with the current treatment of your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. Over the past 4 weeks, how much has your **chest pain, chest tightness, or angina** interfered with your enjoyment of life?

It has **severely**  
limited my  
enjoyment of  
life

☐

It has  
**moderately**  
limited my  
enjoyment of life

☐

It has **slightly**  
limited my  
enjoyment of  
life

☐

It has **barely**  
limited my  
enjoyment of  
life

☐

It has **not**  
limited my  
enjoyment of  
life

☐

10. If you had to spend the rest of your life with your **chest pain, chest tightness, or angina** the way it is right now, how would you feel about this?

Not satisfied  
at all

☐

Mostly  
dissatisfied

☐

Somewhat  
satisfied

☐

Mostly  
satisfied

☐

Highly  
satisfied

☐

11. How often do you worry that you may have a heart attack or die suddenly?

**I can't stop**  
worrying  
about it

☐

**I often think**  
or worry  
about it

☐

**I occasionally**  
worry about it

☐

**I rarely think**  
or worry  
about it

☐

**I never think**  
or worry  
about it

☐