Statistical Analysis Plan

Clinical Trial Protocol Identification No.	EMR200505_506
Title	An interventional, pilot study to evaluate the efficacy of oral nicorandil on improving microvascular function in female non - obstructive CAD patients (SPET study)
Trial Phase	Phase IV
Investigational Medicinal Product	Nicorandil (SIGMART® Tablets 5.0 mg) / Oral / t.i.d, 12 weeks
Clinical Trial Protocol Version	Protocol Amendment <III> / 15 Apr 2018
Statistical Analysis Plan Author	PPD, Study Statistician
Statistical Analysis Plan Date and Version	13FEB2019 /Version 2.0
Statistical Analysis Plan Reviewers	**MakroCare** 1. PPD 2. PPD **Merck Serono** 1. PPD

1. Signature Page

Statistical Analysis Plan: EMR200505_506

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

PPD

Signature

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Date of Signature

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3. List of Abbreviations and Definition of Terms

ACEI	Angiotensin-Converting Enzyme Inhibitor(s)
AE	Adverse Event
ALT	Alanine Transaminase
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CFR	Coronary Flow Reserve
CI	Confidence Intervals
CKMB	Myocardial Enzymes
CMD	Coronary Microvascular Dysfunction
CREAT	Creatinine
CRF	Case Report Form
CTR	Clinical Trial Report
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EF	Ejection Fraction
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ITT	Intention to Treat
IVST	Interventricular Septum Thickness

K_{ATP}	Potassium
LDL	Low Density Lipoprotein
LVESD	Left Ventricular End Systolic Diameter
MedDRA	Medical Dictionary for Regulatory Activities
MBF	Myocardial Blood Flow
MFR	Myocardial Blood Flow Reserve
MPR	Medication Possession Ratio
NYHA	New York Heart Association
PET	Positron Emission Tomography
PP	Per Protocol
PT	Preferred Term
PWT	Posterior Wall Thickness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQ	Seattle Angina Questionnaire
SAS	Statistical Analysis System
SBP	Systolic Blood pressure
SEM	Standard Error of Mean
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
UCG	Ultrasound Cardiogram
VOC	Voltage-sensitive Calcium Channels

4. Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
0.1	23 DEC 2016	PPD	Baseline Version
1.0	11 APR 2017	PPD	Final Version
1.1	27 SEP 2018	PPD	Based on the amended protocol and CRF
1.2	16 OCT 2018	PPD	Based on client comments
1.3	22 NOV 2018	PPD	Based on client comments
2.0	26 NOV 2018	PPD	Final Version
2.0	04 FEB 2019	PPD	Final Version
2.0	04 FEB 2019	PPD	Based on client comments
2.0	13 FEB 2019	PPD	Final Version

5. Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for protocol EMR200505_506. Results of the analyses described in this SAP will be included in the Clinical Trial Report (CTR). Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective SAP will be clearly identified in the CTR.

The SAP is based upon trial protocol and protocol amendments and is prepared in compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guidelines. The SAP focused on the improvement of microvascular function by positron emission tomography (PET) after twelve-week treatment of oral nicorandil in female non obstructive CAD patients. Statistical analyses for other variables such as the improve of myocardial blood flow (MBF) by rest and stress PET, the improve of heart function by echocardiography, the improve of angina attacks after twelve-week treatment of oral nicorandil and safety variables are also added in this version of SAP.

6. Summary of Clinical Trial Features

Study Title	An interventional, pilot study to evaluate the efficacy of oral nicorandil on improving microvascular function in female non obstructive CAD patients (SPET study)
Study number	EMR200505_506
Study Phase	IV
Study Center(s)/Country(ies)	1 (hospital)/1 (country)
Study Background	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). A CFR<2.0 strongly suggests coronary microvascular disease, and related to patients CV outcomes. 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 decease. 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. K_{ATP} channel is one of the most critical target spots that regulates the tone of coronary arterioles (with diameter <200 μm)
Study objectives	Primary objective: 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 objectives: • To evaluate the improve of myocardial blood flow (MBF） by rest and stress PET after twelve-week treatment of oral nicorandil • To evaluate the improve of heart function by echocardiography after twelve-week treatment of oral nicorandil • To evaluate the improve of angina attacks after twelve-week treatment of oral nicorandil
Primary endpoint(s)	Comparison of myocardial blood flow reserve (MFR) between baseline and after twelve-week treatment

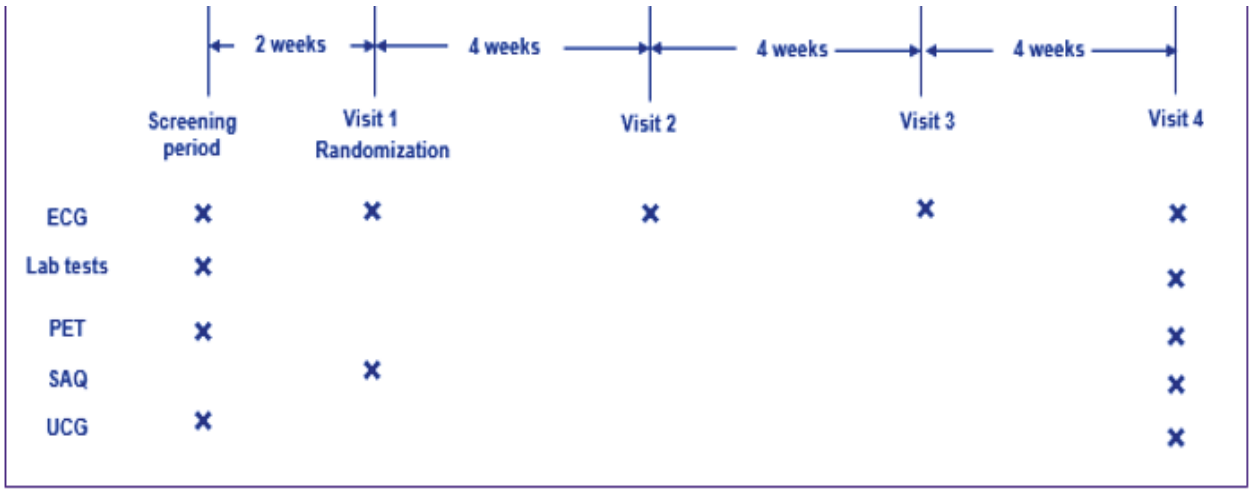
Secondary endpoint(s)	Comparison of below items between baseline and after twelve-week treatment
	• MBF by rest and stress PET
	• Parameters of heart function by Echocardiography:
	  o Cardiac systolic function: Ejection Fraction (EF%), left ventricular end-systolic dimension (LVESD), left ventricular wall thickness
	  o Cardiac diastolic function: E/A ratio
	• Seattle Angina Questionnaire (SAQ) score

Study Design	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
Planned number of subjects	11-20
Schedule of visits and assessments	Screening visit: ECG, lab tests, MFR by rest and stress PET, UCG; Visit 1 (week 0): ECG, SAQ; Visit 2 (week 4): ECG; Visit 3 (week 8): ECG; Visit 4 (week 12): ECG, lab tests, MFR by rest and stress PET, UCG
Eligibility Criteria	**Inclusion criteria:** • Female • Patients aged 18-70 years • 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 • All other long acting cardiovascular disease medicines, including but not limited to aspirin/clopidogrel, CCB, ACEI/ARB, β -blockers, statins, ivabradine, trimetazidine, et al, should be stable taken for at least two weeks before screening

	period • For patients who met these four criteria above, MFR will be tested by stress PET. Patients whose MFR <3.0 could be included in the study **Exclusion criteria:** • Severe or uncontrolled hypertension (resting SBP ≥ 160 mmHg, or resting DBP ≥ 100 mmHg at screening period) • Patients with shock (including cardiogenic shock), or hypovolemia • Severe hypotension (resting SBP < 90 mmHg, or resting DBP < 60 mmHg) • Significant valvular heart disease, congenital heart disease or cardiomyopathy • Congestive heart failure (NYHA III-IV), echocardiographic ejection fraction < 45% • Acute pulmonary edema • Hepatic or renal dysfunction, defined as: o Serum Alanine Aminotransferase (ALT) > triple of the normal value upper limit; o Serum Aspartate Aminotransferase (AST) > triple of the normal value upper limit o Serum creatinine > twice of the normal value upper limit • Glaucoma • Active peptic ulcer or active skin ulcer • Taking glyburide, PDE-5 inhibitors, soluble guanylate cyclase stimulator(s) • Known to be hypersensitivity to nicorandil, nitrates, niacin, or any of the excipient

	• With contraindication to complete stress PET test • No legal ability and legal ability is limited • Patients unlikely to cooperate in the study or with inability or unwillingness to give informed consent • Child-bearing period women without effective contraceptive measures, pregnancy and lactation • Participation in another clinical trial within the past 30 days • Other significant disease that in the Investigator's opinion would exclude the subject from the trial
Investigational Medicinal Product (s): dose/mode of administration/ dosing schedule	Nicorandil (SIGMART® Tablets 5.0 mg) / Oral / t.i.d, 12 weeks
Reference therapy(ies): dose/mode of administration/dosing schedule	Patients have already received the current standard therapy strategy, if conditions permitted, aspirin/clopidogrel, ACEI/ARB, β-blockers, CCBs, and statins should be included; All the medicines mentioned above and other anti-angina medicines (except nitroglycerine) need to be stabilized at least two weeks before screening period; All subjects will start taking nicorandil after enrollment.

Schematic diagram of the study plan:



Schedule of Assessments

	Screening visit (Day -14 to 0)	Visit 1 (Day 1±3)	Visit 2 (Day 28±3)	Visit 3 (Day 56±3)	Visit 4 (Day 84±3)
Signing the ICF	X				
Demographic data	X				
Inclusion and exclusion criteria	X				
Medical history	X				
Body weight and height	X				X
Waist circumference	X				X
Vital signs	X	X	X	X	X
Physical examination	X	X	X	X	X
ECG	X	X	X	X	X
Full blood count	X				X
Hepatic and renal functions	X				X
Blood glucose and lipids	X				X
Echocardiography	X				X
Rest and stress PET	X				X
SAQ		X			X
Cardiovascular events		X	X	X	X
Sigmart® therapy (For treatment group only)		X	X	X	X
Adverse event record	X	X	X	X	X
Medication possession ratio (MPR)	X				X
Concomitant medicine	X	X	X	X	X

7. Sample Size

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 follow-up period, this study could be accomplished when meet the end of the anticipated period of the whole study.

8. Overview of Planned Analyses

This SAP describes final analysis of the study. No interim analyses are planned for this study.

9. Changes to the Planned Analyses in the Observational Study Protocol

The statistical methods as described in the protocol were adopted.

10. Analysis Sets

Screening 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) Population

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

Per Protocol (PP) Population

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.

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 Population

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

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. The safety population will be used to summarize the safety data.

11. General Specifications for Statistical Analyses

Statistical analysis will be made utilizing Statistical Analysis System (SAS) version 9.1.3 or higher.

Descriptive statistics such as

- Number of subjects (n), number of subjects with missing values (Missing),
- Mean, Standard Deviation (SD),
- Median, First Quartile (Q1), Third Quartile (Q3),
- Minimum and Maximum

will be provided for all continuous variables.

Mean, Median, Q1 and Q3 will have more than one decimal place than the raw data and SD will have 2 decimal places more than the raw data. The decimal place for minimum and maximum values will be same as the raw data.

The frequency (n) and percentage (%) will be calculated for all categorical variables including missing observations and the percentages will be rounded off to one decimal place.
95% Confidence Interval (CI) will be provided wherever applicable.
If day is missing for any date variable then it will be replaced by 1st day of the month. Similarly, missing month will be replaced by 1st month of the year.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or higher terminology for System Organ Class (SOC) and Preferred Term (PT).

Handling of missing data

Missing information will be captured for quantitative as well as qualitative variables by the category "Missing" in the summary statistics. If there are no missing values this will be indicated by „0". Unless otherwise specified missing data will not be replaced.

12. Trial Subjects

12.1 Disposition of Subjects and Discontinuations

A table with

- Number of subjects screened
- Number of screen failure subjects
- Number of subjects enrolled in the study
- Number of subjects in ITT population
- Number of subjects in PP population
- Number of subjects in safety population
- Number of subjects (ITT population) who completed the study

- Number of subjects (ITT population) who discontinued from the study together with primary reason for study discontinuation (Adverse event/ Lost to follow-up/ Lack of efficacy/ Death/ Withdrew Consent/ Study reached predefined end/ Other)

will be summarized as number and percentage.

12.2 Outliers

Listing will be provided for subjects with outliers (if data available). Extreme data that are not explainable from clinical point of view are considered as outliers. Subjects with such outliers will be identified before the database lock. These outlier data will not be included in the analysis.

13. Demographics and Other Baseline Characteristics

13.1 Demographics

The quantitative variable

- Age (years)

will be summarized by descriptive statistics from ITT Population.

The age variable will be calculated by using below formula:

Age (years) = (Date of Informed consent - Date of Birth) + 1

If day is missing for any date variable then it will be replaced by 1st day of the month. Similarly, missing month will be replaced by 1st month of the year.

The qualitative variables

- Sex (Female)
- Race (Asian/ Other)

will be summarized as number and percentage from ITT Population.

13.2 Medical History

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

History of Hypertension/Heart Failure/Diabetes

Listing will be provided for History of Hypertension/Heart Failure/Diabetes for ITT Population.

Other Medical History

Listing will be provided for history of any other medical conditions for ITT Population.

History of Angina Pectoris

The quantitative variables

- Duration of Angina Pectoris (Years)
- Frequency of angina attacks in recent one month per week

will be summarized by descriptive statistics from ITT Population.

The qualitative variable

- Classification (Stable/ Unstable)

will be summarized as number and percentage from ITT Population.

14. Previous or Concomitant Medications/Procedures

Listings will be provided for Prior and Concomitant Medications and Concomitant Procedures for all individual subjects for ITT Population.

15. Treatment Compliance and Exposure

Treatment Compliance

The quantitative variables

- Number of tablets to be taken
- Number of tablets taken
- Percentage (%)

will be summarized using descriptive statistics from Safety Population.

The qualitative variable

- Compliance (Good (80%-100%) / Insufficient (<80% or >100%))

will be summarized as number and percentage from Safety Population.

SIGMART® Administration

The quantitative variables

- Total duration of Sigmart® administration (Days)
- Total dose of Sigmart® administration (mg)

will be summarized using descriptive statistics from Safety Population.

Total duration of Sigmart® administration will be calculated by using below formula:
Total duration Sigmart® Administration (Days) = (Last dose of SIGMART® Administration End date – First dose of SIGMART® Administration Start date) + 1.

Total dose (mg) of Sigmart® administration will be calculated by using below formula:
Total dose (mg) of Sigmart® Administration = Sum of (Daily dose of Sigmart® Administration * number of treatment days for the dose).

The qualitative variables

- Change in dose (No change/ Dose adjusted/ No dose)
- Reason for dose adjustment (Adverse event/ Titration/ Other)
- Reason for no dose (Adverse event/ Missed dose/ Other)

will be summarized as number and percentage from Safety Population.

16. Endpoint Evaluation

16.1 Primary Endpoint Analyses

The primary endpoint is comparison of myocardial blood flow reserve (MFR) between baseline and after twelve-week treatment. 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.

The quantitative variable

- Myocardial blood flow reserve (MFR)

will be summarized using descriptive statistics at baseline, visit 4 (week 12) and change from baseline from ITT and PP populations. Two-sided 95% confidence interval (CI) will be calculated for the difference between MFR at baseline and after twelve week treatment.

Paired T-test or Wilcoxon Signed Rank test will be used to compare the myocardial blood flow reserve (MFR) between baseline and after twelve-week treatment based on the normality assumption of the data.

16.2 Secondary Endpoint Analyses

MBF by rest and stress PET

The quantitative variables

- Rest PET-MBF (ml/gm/min)
- Stress PET-MBF (ml/gm/min)

will be summarized using descriptive statistics at baseline, visit 4 (week 12) and change from baseline from ITT and PP populations. The same analysis as mentioned for primary endpoint (MFR) will be performed for MBF by rest and stress PET.

Echocardiography

The quantitative variables

- Ejection Fraction (EF) (%)
- Left ventricular end systolic dimension (LVESD) (mm)
- Interventricular septum thickness (IVST) (mm)
- Left ventricular posterior wall thickness (PWT) (mm)
- E/A Ratio

will be summarized using descriptive statistics at baseline, visit 4 (week 12) and change from baseline from ITT and PP populations. The same analysis as mentioned for primary endpoint (MFR) will be performed for all Echocardiography variables.

Seattle angina questionnaire (SAQ)

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:

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

For example: Suppose the sum of score in dimension 1 is 43, and the minimum and maximum of score in this dimension is 1 x 9=9 and 6 x 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 scores for the following dimensions

- Physical limitation
- Anginal stability
- Anginal frequency
- Treatment satisfaction
- Disease perception

will be summarized using descriptive statistics at visit 1 (week 0), visit 4 (week 12) and change from visit 1 (week 0) from ITT and PP populations. The same analysis as mentioned for primary endpoint (MFR) will be performed for each dimension.

17. Safety Evaluation

Safety evaluation includes the summary of safety endpoints such as AEs, TEAEs, SAEs, laboratory tests, ECG parameters and vital signs during the study based on safety population.

17.1 Adverse Reactions / Events

AEs will be summarized per subject using number and percentage by SOC and PT from Safety Population. If an AE is reported for a subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated. Listings will also be provided for all the AEs.

AEs will be coded using MedDRA version 21.0 or above.

17.1.1 All Adverse Events

All AEs and Treatment Emergent Adverse Events (TEAE) will be summarized using number and percentage by MedDRA-SOC and PT within SOC for severity, relationship, causality factors other than study treatment, action taken with study medication and outcome. The AEs and TEAEs reported under the category „Related" will be considered as treatment-related AEs and TEAEs. Missing will also be considered as related to the treatment. PT within SOC and primary SOC will be given in alphabetical order from safety population.

TEAE period: Occurrence of AE in nicorandil period, which means from day 0 to last visit.

17.1.2 Adverse Events Leading to Trial or Treatment Discontinuation

AEs leading to study termination will be summarized by MedDRA-SOC and PT within SOC.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

If any death is reported it will be presented as case narrative.

Listings will also be provided.

17.2.2 Serious Adverse Events

Serious adverse events (SAEs) will be summarized per subject using number and percentage by SOC and PT from safety population.

All SAEs will be summarized using number and percentage by MedDRA-SOC and PT within SOC for severity, relationship, causality factors other than study treatment, action taken with study medication and outcome. The SAEs reported under the category „Related" will be considered as treatment-related SAEs. Missing will also be considered as related to the treatment. PT within SOC and primary SOC will be given in alphabetical order from safety population.

17.3 Clinical Laboratory Evaluation

Hematology

The quantitative variables

- Hemoglobin (HGB) (g/dL)
- Erythrocytes (RBC) (10^9/L)
- White blood cells (WBC) (K/ul)
- Neutrophils (NEUT) (10^3/mcL)
- Platelet count (PLAT) (10^3/mcL)

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at baseline, visit 4 (week 12) and change from baseline from Safety Population.

Unit conversion for Hematology will be done at the time of analysis appropriately.

Bio Chemistry

The quantitative variables

- Alanine Aminotransferase (ALT) (IU/L)
- Aspartate aminotransferase (AST) (IU/L)
- Blood Urea Nitrogen (BUN) (mg/dL)
- Creatinine (CREAT) (mg/dL)
- Total Cholesterol (mmol/L)

- Triglycerides (µmol/l)
- HDL cholesterol (µmol/l)
- LDL Cholesterol (µmol/l)
- Potassium (mEq/L)
- Sodium (mEq/L)
- Myocardial Enzymes (CKMB) (IU/L)

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at baseline, visit 4 (week 12) and change from baseline from Safety Population.

Unit conversion for Bio Chemistry will be done at the time of analysis appropriately.

Routine Urine Test (Urinalysis)

The quantitative variables

- pH
- Specific gravity

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at baseline, visit 4 (week 12) and change from baseline from Safety Population.

Shift tables for below mentioned qualitative Routine Urine Test (Urinalysis) variables will be summarized with number and percentage of change among the results Normal, Trace/+, ++, +++ & ++++ at Baseline and Visit 4 (Week 12) from safety population.

- Protein
- Glucose
- Ketone
- Nitrite

- Leukocytes
- Hemoglobin
- Red blood cells
- Bilirubin

Other Lab Tests

The quantitative variable

- Fasting Blood Glucose (µmol/l)

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at baseline, visit 4 (week 12) and change from baseline from Safety Population.

Unit conversion for Fasting Blood Glucose will be done at the time of analysis appropriately

Shift tables for below mentioned qualitative Other Lab Tests variables will be summarized with number and percentage of change among the results Positive and Negative at Baseline and Visit 4 (Week 12) from safety population.

- Urine Pregnancy Test (Positive / Negative)

Listings will also be provided for all the Clinical Laboratory parameters.

17.4 Electrocardiogram (ECG)

The quantitative variable

- Heart Rate (beats/min)

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at baseline, visit 4 (week 12) and change from baseline from Safety Population.

The qualitative variables

- Rhythm (Sinus rhythm/ Arrhythmia)
- Cardiac hypertrophy (Yes/ No)
- ST-T Change (Abnormal) (Yes/ No)

will be summarized as number and percentage at all available visits from Safety Population. Listings will also be provided for ECG Parameters.

Vital Signs

The quantitative variables

- Systolic Blood pressure in Sitting Position (mmHg)
- Diastolic Blood pressure in Sitting Position (mmHg)
- Resting Heart rate (beats/minute)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) (Auto calculated in database)
- Waist circumference (cm)

will be summarized using descriptive statistics including standard error of mean (SEM) and 95% confidence interval at all available visits and change from baseline from Safety Population.

Conversion formula for Waist circumference: cm = inches * 2.54.

Listings will also be provided for Vital Signs Parameters.

17.5 Physical Examination

All abnormalities occurring or worsening in physical examination after putting signature in the informed consent will be recorded in the Adverse Events section unless otherwise stated by the protocol. Hence, physical examination parameters will not be summarized separately.

18. Benefit risk assessment

Not applicable.

19. References

1. Protocol Number: EMR200505_506, Dated 15 APR 2018, Protocol Amendment <III>

2. Case Report Form Version 4.0 dated 23 JAN 2019

3. ICH E3 - “Structure and Content of Clinical Study report” and E9- “Statistical Principles for Clinical Trials”.

20. Appendices

Not applicable.