STATISTICAL ANALYSIS PLAN

Sponsor: Quantum Genomics

Protocol: QGC001-2QG4

EudraCT number: 2018-003146-17

A Phase 2, Double-blind, Active-controlled, Dose-titrating Efficacy and Safety Study of Firibastat (QGC001) Compared to Ramipril Administered Orally, Twice Daily, Over 12 Weeks to Prevent Left Ventricular Dysfunction after Acute Myocardial Infarction

VERSION: Final 2.0

DATE: 20JUL2021

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ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
BID	Bis in die (twice daily)
CI	Confidence Interval
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
CMRI	Cardiac Magnetic Resonance Imaging
CRP	C-reactive Protein
CSR	Clinical Study Report
DB	Database
EOT	End-of-Treatment
ICH	International Conference of Harmonization
IA	Interim Analysis
IP	Investigational Product
ITT	Intent-To-Treat
mITT	Modified Intent-To-Treat
LVEF	Left Ventricular Ejection Fraction
MACE	Major Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NT-proBNP	N-terminal Pro B-type Natriuretic Peptide
PIIINP	Procollagen Type III Aminoterminal Peptide
PCI	Percutaneous Coronary Intervention
PP	Per-protocol
PT	Preferred Term
Q1	The first quartile
Q3	The third quartile

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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SBP	Systolic blood pressure
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

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INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses to be performed on the study, contains the definition of analysis populations and protocol deviations, specifies the primary and secondary endpoints to be analyzed and outlines the outputs (tables, listings and figures) to be compiled in the Clinical Study Report (CSR).

This analysis plan is based on the final versions of Study Protocol Final Version 1.0 dated 04-DEC-2018 (including local final versions: Final Version 4.0 for France dated 09-OCT-2019, Final Version 5.0 for Germany dated 10-OCT-2019, and Final Version for UK dated 09-OCT-2019) and the Global Amendment to the Study Protocol Version 3.0 dated 10-OCT-2019 and the electronic case report from (eCRF) Final Version 1.0 dated 12-JUL-2019. The analyses closely follow the ICH guidelines for industry on topic E3 (Structure and Content of CSRs) and E9 (Statistical Principles for Clinical Trials).

The SAP has to be finalized and approved before database (DB) lock and executed after DB lock. Protocol deviations have to be defined and subjects' disposition into analysis populations has to be approved before DB lock.

1. PLANNED CHANGES FROM STUDY PROTOCOL

A single futility interim analysis (IA) performed by the independent statistician of the independent data monitoring committee was to be planned for the primary efficacy endpoint for the comparison of firibastat 50 mg against ramipril when approximately 50% of the maximum number of subjects have completed the Day 84 primary endpoint assessment. Due to the dynamic of subject inclusion in the study, the time of delivery of IA results is deemed too close to the end of the recruitment period. Therefore, it was decided to not perform IA. To complete the primary objective, several exploratory subgroups were added.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the effects of BID (bis in die) oral administration of 2 doses of firibastat to those of BID oral administration of ramipril on the change from Baseline in left ventricular ejection fraction (LVEF) assessed by cardiac magnetic resonance imaging (CMRI) on Day 84.

2.2 SECONDARY OBJECTIVES

Secondary objectives include the following:

- To compare the effects of BID administration of firibastat and ramipril on the change from baseline to Day 84 in left-ventricular end-diastolic and end-systolic volumes assessed by CMRI
- To compare the effects of BID administration of firibastat and ramipril on the change from baseline to Day 84 in average peak of longitudinal and circumferential strain (assessed by CMRI) in the infarcted segments
- To compare the effects of BID administration of firibastat and ramipril on infarct mass (assessed by CMRI) at Day 84
- To compare the effects of BID administration of firibastat and ramipril on major cardiac event (MACE): combined clinical endpoint of cardiovascular death, new myocardial infarctions (MIs), and cardiac hospitalization over 84 days

- To compare the effects of BID administration of firibastat and ramipril on the change from Baseline to Day 84 in N-terminal pro b-type natriuretic peptide (NT-proBNP), procollagen type III aminoterminal peptide (PIIINP), and C-reactive protein (CRP)
- To compare the effects of BID administration of firibastat and ramipril on the slope of decrease in copeptin blood level change between baseline and Day 84
- To compare the safety of firibastat and ramipril

3. STUDY DESIGN

3.1 BRIEF DESCRIPTION OF STUDY DESIGN

This phase 2, multicenter, randomized, double-blind, active-controlled, dose-titration clinical study is designed to compare the efficacy and safety of firibastat with ramipril in the prevention of left ventricular dysfunction after acute anterior MI. A total of 294 male and female subjects are randomized at about 38 sites in Europe and in the US to obtain 264 evaluable subjects. Subjects must be at least 18 years of age and have a diagnosis of first acute anterior MI with primary percutaneous coronary intervention (PCI) of the index-MI-related artery no earlier than 3 hours after acute MI and within 24 hours after the MI.

Subjects are randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:

- Group 1: Subjects receive 50 mg firibastat BID for 2 weeks and then 100 mg BID for 10 weeks
- Group 2: Subjects receive 250 mg firibastat BID for 2 weeks and then 500 mg BID for 10 weeks
- Group 3: Subjects receive 2.5 mg ramipril BID for 2 weeks and then 5 mg BID for 10 weeks

98 subjects are randomized into each treatment group. The first capsule of the investigational product (IP) is administered on Day 1 as soon as possible after the CMRI, which is performed no later than 72 hours after MI. Subjects then take 1 capsule of the IP BID until the next visit. The maximum treatment duration for each subject is 87 days.

It should be noted that the subjects' dosage is up-titrated and/or down-titrated according a specific titration procedure described in the study protocol.

This clinical study is considered completed when the last subject's last study visit has occurred.

All subjects are informed that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons. The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable adverse events (AEs), intercurrent illness, non-compliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation are recorded on the appropriate page of the eCRF form. Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

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3.2 RANDOMIZATION

In this parallel-group randomized study, subjects who meet study entry criteria are randomly assigned in a 1:1:1 ratio to initially receive either 100 mg firibastat daily (Group 1), 500 mg firibastat daily (Group 2), or 5 mg ramipril daily (Group 3), respectively. The randomization schedule is computer-generated using a permuted block algorithm and randomly allocates IP to randomization numbers. The randomization numbers are assigned sequentially through a web-allocation system as subjects are entered into the study.

The randomization schedule is prepared by a subcontracted company before the start of the study. No one involved in the study performance has access to the randomization schedule before official unblinding of treatment assignment. No subject is randomized into this study more than once.

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, are blinded to treatment assignment with the exception of a specified independent, unblinded statistician and programmer, who has access to the randomization code for interim analysis needs. The unblinded study personnel do not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel with exception of the independent statistician. Unblinded personnel who are not otherwise involved in the study prepare the data for review.

Overall unblinding takes place at the end of the study only after DB lock has been achieved.

4. STUDY ENDPOINTS

4.1 DEMOGRAPHY AND BASELINE DATA

Demographic data include age, gender, height and weight. Baseline subject characteristics include medical history, clinical examination findings at Screening, results of the coronary angiography, acute MI details, and troponin peak test.

4.2 PRIMARY ENDPOINT

The primary efficacy endpoint is the change from baseline to Day 84 in LVEF assessed by CMRI (centralized reading).

4.3 SECONDARY ENDPOINTS

Secondary efficacy endpoints:

- Change from baseline to Day 84 in left-ventricular end-diastolic and end-systolic volumes assessed by CMRI (centralized reading)
- Change from baseline to Day 84 in average peak of longitudinal and circumferential strain in the infarcted segments assessed by CMRI (centralized reading)
- Infarct mass at end-of-treatment (EOT) (Day 84) assessed by CMRI (centralized reading)
- MACE (i.e., cardiovascular deaths, new MIs, and cardiac hospitalizations) as adjudicated by an independent committee
- Change from baseline in NT-proBNP, PIIINP, and CRP levels to Day 84
- Slope of decrease in copeptin over time

Safety endpoints:

- All AEs, AEs of special interest, which include allergic reactions and diabetes insipidus, and clinical laboratory evaluations

- Change from baseline in clinic systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate at each visit
- Change from baseline in sodium, potassium, aspartate aminotransferase, and alanine aminotransferase blood levels and estimated glomerular filtration rate (eGFR)

5. DEFINITIONS

Day 84 is the day of treatment discontinuation (i.e. 84 days [±3 days] after the Inclusion Visit [Day 1]) as long treatment discontinuation was not premature.

MACEs are defined as cardiovascular deaths, new MIs, and cardiac hospitalizations.

5.1 STUDY DATABASE AND EXTERNAL DATA

Data collected and validated in a study DB are analyzed.

The external data are transformed into format suitable for analysis (SAS datasets) and analyzed. The provider of external data is responsible for the quality of those data.

5.2 LABELS USED IN SAP AND IN STATISTICAL OUTPUTS

Labels used for study visits:

SCR Screening

BAS Baseline

V1 - V6 Visit 1 - Visit 6

EOT End-of-treatment

5.3 BASELINE VALUES

For CMRI data, baseline is defined as the last value reported before or within 8 hours of taking the first IP. For other data, baseline is defined as the last value before first IP.

6. ANALYSIS SETS

The following 4 analysis populations are defined in the study protocol (section 13.1.1):

- Safety population
- Intent-to-treat (ITT) population
- Modified intent-to-treat (mITT) population
- Per-protocol (PP) population

6.1 SAFETY POPULATION

The safety population consists of all subjects who receive at least 1 dose of the IP. This population is based on the treatment actually received by the subject and is used for the analysis of the safety endpoints.

6.2 ITT POPULATION

The ITT population consists of all randomized subjects. This population is based on the treatment to which the subject was randomized. Any subject who receives an allocated kit number is considered to have been randomized. Individual subject data listings will be generated on ITT population if all treated subjects are randomized, else these listings will be generated on randomized or treated subjects.

6.3 mITT POPULATION

The mITT population consists of all randomized subjects who receive at least 1 dose of the IP and who have at least 1 baseline (before or within 8 hours of taking the first IP) and 1 post-baseline efficacy assessment (LVEF). This population is based on the treatment to which the subject was randomized and is the primary population for the analysis of the efficacy endpoints.

6.4 PP POPULATION

The PP population consists of all subjects from the mITT population without any major protocol deviation. This population is considered for sensitivity analysis of the primary endpoint.

6.5 PROTOCOL DEVIATIONS

Details about handling of protocol deviations are included in the protocol deviation guidance plan.

Deviations from the protocol including violations of inclusion/exclusion criteria are defined and assessed as minor or major in cooperation with the sponsor during a blind review meeting before the DB lock, together with the determination of inclusion in the analysis populations.

6.6 EXPLORATORY SUBGROUPS

Exploratory Subgroups for the analysis of primary endpoint are defined as follows:

- Gender (male /female);
- Age group (≤65 years/ >65 years);
- Baseline eGFR level (≤60 mL/min/1.73m²/ >60 mL/min/1.73m²);
- PCI successful (Yes = TIMI 3/ No = TIMI 0, 1 or 2);
- Time from onset of MI to PCI (2 options to define categories: either ≤ median/> median or if not too imbalanced : <6h/ ≥ 6h);
- Baseline LVEF (<50%/ ≥50%);
- Diabetes mellitus (Yes / No, Yes= diabetes mellitus in medical history or any intake of anti-diabetic drug at baseline.).

Theses exploratory analyses will be performed only if the sample size in each category of subgroup is enough.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This section describes the data analysis in details. The statistical methods are planned in accordance with the study protocol (section 13) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

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7.1 GENERAL PRINCIPLES

Statistical package SAS (version 9.4) is used for analysis and for generation of tables, figures and listings.

Unless otherwise indicated, all testing of statistical significance is 2-sided, and a difference resulting in a p-value of ≤ 0.05 is considered statistically significant.

The acceptable risk of error for the statistical tests is set at 5%, except for treatment-by-covariates interactions. For those interactions, the level of significance is set at 10%.

Individual subject data listings are generated by treatment group, subject identifier, country and visit (if applicable).

7.1.1 Descriptive statistics

Continuous variables are summarized using descriptive statistics (number of observations, mean, standard deviation (SD), median, the first quartile (Q1), the third quartile (Q3), minimum, and maximum). Frequency distribution (counts and percentages) are summarized for the categorical variables (to be noted percentages are calculated on available data). When applicable, 95% confidence interval (CI) of the mean (or the median) is provided for continuous variables, and the 95% CI of the proportion is displayed for each modality of categorical variables.

Where appropriate, results are presented by treatment group as well as overall.

7.1.2 Rounding procedures

The following rounding procedures are used for all variables:

- for minimum and maximum the same number of decimal places as the original value is used;

- for mean, SD, median, Q1 and Q3, and 95% CI one more decimal place than the original value is used;

- p-values are displayed with four decimal places;

- all values reported as percentage are displayed with 1 decimal place (except no decimal place for 100%).

7.1.3 Unscheduled/ repeated assessments

For screening data, the last valid value is used for the analyses. For baseline data, the last valid value which meets the baseline definition is used for the analyses. For all other time points, the values at scheduled time points are used for calculation of summary statistics. Both unscheduled and scheduled measurements are listed in chronological order.

7.1.4 Missing data

In general, missing data are not imputed, i.e. complete case analyses are performed.

For the analysis of primary efficacy endpoint, a sensitivity analysis is performed using a multiple imputation method in subjects who discontinued the study prior to Day 84. If the potential impact of the missing data (i.e., data recorded at premature discontinuation visit) is substantial and may result into a biased outcome, i.e., the proportion of missing data is more than 40%, then the imputation and the corresponding sensitivity analysis is not performed.

7.1.5 Methods for handling of incomplete dates/ times

In general, if date and time are missing no imputation is applied.

If a start time is missing for AE, it is imputed with the time of the first IP intake if the start date equals the first IP intake date, otherwise "00:00".

If the start day is missing for MACE, it is imputed with the first day of the month.

7.1.6 Validation of statistical programming

Outputs and programs are to be reviewed by a second AIXIAL statistician.

Disposition of subjects into analysis populations is agreed with the sponsor.

Logs of all programs used for the analysis and data preparation are checked for errors and unexpected warnings.

Any undocumented updating of study data in statistical programs instead of change in clinical DB (or source data) is not allowed. Specifically, this refers to the cases where subjects or the data are added/ changed using a statistical program rather than updating the DB. This kind of hard coding can be proposed to correct deficiencies (missing values, wrong values, and wrong measurement units) in the DB when these errors are detected after DB lock.

No hard coding is done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after DB lock.

This policy ensures integrity of clinical data, since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial DB.

7.2 STUDY SUBJECTS

The numbers of subjects randomized, treated, completing, and withdrawing, along with reasons for withdrawal, are tabulated overall and by treatment group.

The number of subjects randomized is also tabulated by country, treatment group and overall. Pattern of study premature discontinuations including the profile of subjects and reason and time to withdrawal are presented in listings to assess potential impact of dropouts on treatment comparisons. The number of subjects in each analysis population is reported and tabulated overall and by treatment group.

Identified protocol deviations are listed together with indication whether they lead to exclusion from analysis populations. Major protocol deviations are summarized overall and by treatment group.

7.3 DESCRIPTION OF BASELINE CHARACTERISTICS

Demographic variables include calculated age, gender, height, and weight measured at Screening. The age is calculated in years as follows:

- year of screening – year of birth if month of birth is missing or if month of birth lower or equal to month of screening
- year of screening – year of birth -1 if month of birth higher than month of screening

Baseline subject characteristics include medical history, clinical examination findings, and results of the coronary angiography defining the success or not of the procedure (TIMI 3 or not), the MI-related data, and troponin peak test measured/performed at Screening.

Time between onset of pain and PCI is calculated as the difference between the date of PCI and the date of onset of MI symptoms in hours.

Demographics and baseline characteristics are listed and summarized overall and by treatment group on the mITT population using the standard sets of summary statistics as defined in Section 7.1.1.

Medical history is listed and summarized by treatment group, by the number and percentage of subjects having each medical history, classified using MedDRA dictionary (system organ class (SOC) and preferred term (PT)) on the mITT population. Previous medication is defined as any treatment taken and stopped prior to the first IP dose intake (the day before the first IP dose intake or the same day).

Concomitant medication is defined as any treatment taken at least once between the first IP dose intake and EOT Visit (Day 84) or Early Termination Visit, whichever occurs first (including those which started prior to the first IP dose intake and continued after that).

Prior and concomitant medications are listed and summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary ATC classes (pharmacological subgroup – ATC level 3) and PTs on the mITT population.

The status of active smoking, hypertension, diabetes and dyslipidemia are considered to be present at baseline if the medical history and concomitant medication meet the following conditions:

	MH			**Concomitant medication**	
	Preferred Term name	**Start date**	**End date**	**ATC code 3**	**Start date**
Active smocking	Tobacco user Nicotine dependence	Missing date Before or the same day first intake of IP	Missing After First IP Ongoing		
Hypertension	Essential hypertension Hypertension				
Diabetes	Diabetes mellitus Diabetic nephropathy Diabetic neuropathy Type 1 diabetes mellitus Type 2 diabetes mellitus			Blood Glucose Lowering Drugs, Excl. Insulins Insulins And Analogues	
Dyslipidaemia	Dyslipidaemia			Lipid Modifying Agents, Combinations Lipid Modifying Agents, Plain	Not Statin*: - Missing date - Before or the same day first intake of IP Statin*: Before the MI

*Statins are the treatment with the following PT name

- "Ezetimibe;Rosuvastatin Calcium"
- "Ezetimibe;Simvastatin"
- "Atorvastatin Calcium;Ezetimibe
- "Atorvastatin"
- "Atorvastatin Calcium"
- "Pravastatin Sodium"

- "Rosuvastatin"
- "Rosuvastatin Calcium"
- "Simvastatin"

7.4 EXPOSURE AND COMPLIANCE

For each subject mean and final dose, and the duration of exposure is calculated.

The duration of exposure is calculated in days as the number of days between the first and the last administration of IP (date of last intake – date of first intake + 1).

Final dose is considered to be the theoretical dose (see below the definition for the theoretical dose) of the last IP administered prior to EOT Visit (Day 84) or Early Termination Visit, whichever occurs first.

Mean dose is calculated according to the following algorithm:

Theoretical dose P1 = 50 mg of firibastat or 250 mg of firibastat or 2.5 mg of ramipril according to study group

Theoretical dose P2 =
- Theoretical dose P1 if no titration at V3
- Theoretical dose P1 * 2 if up titration
- 0 mg if treatment discontinuation

Theoretical dose P3 =
- Theoretical dose P2 if no titration at V4
- Theoretical dose P2 / 2 if down titration
- Theoretical dose P2 * 2 if up titration
- 0 mg if treatment discontinuation

Dose the day of V3 =
- Theoretical dose P1 if no titration or if up-titration and first dose of up/down titration equal morning
- Theoretical dose P1 / 2 + Theoretical dose P2 / 2 if up-titration and first dose of up/down titration equal evening

Dose the day of V4 =
- Theoretical dose P2 if no titration or if up-titration or down titration and first dose of up/down titration equal morning
- Theoretical dose P2 / 2 + Theoretical dose P3 / 2 if up-titration or down titration and first dose of up/down titration equal evening

Total dose =
Theoretical Dose P1 * (Date of [V3-1] – Date of first intake + 1) + Dose the day of V3 + Theoretical dose P2 * (Date of [V4-1] – Date of [V3+1] + 1) + Dose the day of V4 + Theoretical dose P3 * (Date of last intake – Date of [V4+1] +1).
Note: The day of first intake, this calculation considered that the full dose was taken. In case of withdrawal premature, the calculation will be performed until the last intake

Mean dose = Total dose / Duration of exposure

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Investigational product administration is summarized in terms of each subject's mean and final dose and in terms of duration of exposure. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, are provided by treatment group. Number of subjects who reached predefined/target doses at EOT Visit (Day 84) or Early Termination Visit, whichever occurs first and the schema of titration (No titration + No titration, No titration + Up titration, Up titration + No titration, Up titration + Down titration) are summarized by counts and percentages.

All intake details per subject are provided in data listings.

7.5 ANALYSES OF EFFICACY

The primary efficacy endpoint, i.e., the change from baseline in LVEF assessed by CMRI, is primarily analyzed on the mITT population. Sensitivity analyses is performed on the ITT and PP populations. Secondary efficacy endpoints are analyzed on the mITT population.

For efficacy variables, descriptive statistics are given by treatment group at each assessment time point. The change from baseline is also presented if applicable (both listed and summarized).

There is a single primary efficacy endpoint in the study – the change from baseline in LVEF assessed by CMRI on Day 84. The other efficacy endpoints are defined to be of secondary importance. Due to multiple treatment comparisons, a hierarchical step-down testing procedure is applied for the primary and secondary criteria to control the overall type I error rate. Only if superiority of firibastat 250 mg against ramipril is demonstrated at the 2-sided 5%-level, superiority of firibastat 50 mg against ramipril can be tested. Likewise, only if superiority of firibastat 50 mg against ramipril is demonstrated at the 2-sided 5%-level, superiority of firibastat 250 mg against firibastat 50 mg can be tested. The testing procedure stops as soon as a comparison is found to be not statistically significant at the 2-sided 5%-level.

For each analyzed efficacy parameter, the normality assumption of model residuals distribution is checked using graphical methods, skewness and kurtosis values, and Shapiro-Wilk's statistic. If there is a strong violation of the normality assumption (or violation of homogeneity of variances for analysis of covariance [ANCOVA]), a rank transformation is primarily done, and the statistical analysis model is applied to the ranks except for copeptin analysis. For copeptin analysis, a log base 10 transformation is preferred.

7.5.1 Primary efficacy endpoint

The absolute values and changes from baseline in LVEF are listed by subject and summarized with descriptive statistics. The changes from baseline are primarily analyzed using an ANCOVA. The ANCOVA includes treatment group as factor, baseline LVEF and country as covariates. For subjects who prematurely discontinue the study, measurements made at the time of study withdrawal are considered in the analysis.

The adjusted mean is presented by treatment group. The difference in adjusted mean between the treatment groups, associated 95% CI and p-value are also presented using a hierarchical step-down testing procedure to control the overall type I error.

Possible treatment-by-covariate interactions are investigated including the interaction term in the model for ANCOVA (1 separated model for each interaction). The adjusted mean difference between treatment groups will be computed. If the p-value is lower than 10% and the interaction is qualitative, then the main model will be performed by level of the covariate (in classes).

Sensitivity analyses of the primary efficacy endpoint:

While subjects missing Day 84 data but having earlier data are included in the primary analysis, the interpretability of the results from the primary model depends on the missing data satisfying the missing completely at random. This signifies that data is missing independently of observed (or unobserved) variables. To support the validity of the conclusions drawn from this analysis, sensitivity analyses are performed to explore possible impact of dropout pattern on treatment comparisons.

1. A complete case ANCOVA is performed on the values recorded on Day 84 (i.e., the measurement made at the time of the study premature discontinuation is not considered in the analysis)

2. A sensitivity analysis is performed on the values recorded on Day 84 and the data imputed using a multiple imputation method in subjects who prematurely discontinued the study. This means that the data from premature discontinuation visits are considered as missing and are discarded from the analysis. Multiple imputation is used to impute missing Day 84 data in subjects who prematurely discontinued the study.

The multiple imputation technique is a stepwise procedure. First, a plausible multivariable distribution for the missing values is estimated based on observed data. Missing values are then randomly drawn from this distribution resulting in a complete dataset. This procedure is repeated multiple times generating multiple datasets. The number of imputations is set to the proportion of missing data multiplied by 100. Second, the datasets are then analyzed separately producing multiple estimates, and third, the multiple estimates are pooled resulting in one single estimate.

The multiple imputation technique is a stepwise procedure. First, a plausible multivariable distribution for the missing values is estimated based on observed data. Missing values are then randomly drawn from this distribution resulting in a complete dataset. This procedure is repeated multiple times generating multiple datasets. The number of imputations is set to the proportion of missing data multiplied by 100. Second, the datasets are then analyzed separately producing multiple estimates, and third, the multiple estimates are pooled resulting in one single estimate.

The PROC MI procedure from SAS 9.4 is used under the MONOTONE REG option. The missing Day 84 data is imputed according to all the variables in the VAR statement. The number of imputations is automatically determined with the NIMPUTE = PCTMISSING option. A SEED value is used to guarantee the reproducibility of the multiple imputation. Lastly, PROC MIANALYZE is used to combine the adjusted means by treatment group and the adjusted mean differences. To be noted type III p-values cannot be combined with PROC MIANALYZE.

At the minimum, the regression model used to impute missing Day 84 data includes the baseline value, treatment group, and country as covariates. This imputation is performed under the assumption that Day 84 values are missing at random, meaning that their missingness depends on observed variables. To improve the accuracy of imputed values as well as of the efficiency of the estimates, auxiliary variables are considered in the imputation model. Auxiliary variables are variables that may be correlated with the missing data or be good predictors of missingness. These variables will also serve to strengthen the missing at random assumption. In addition to the primary covariates, four auxiliary variables will be considered for the multiple imputation model: age (≤ 65 years / > 65 years), time between onset of MI and PCI (<6h / ≥ 6h), PCI- Index MI-related artery (LAD / no LAD), and infarct mass (Yes / No). These variables have been associated with MI-related reduced LVEF.

Auxiliary variables are included in the imputation model if 1) they have no missing values in the primary analysis population and 2) if they are correlated with the observed Day 84 values or if they are predictors of missingness.

For continuous variables, the correlation between the observed Day 84 values and the potential auxiliary variables is computed using PROC CORR. If the correlation coefficient is more than 0.1 and the resulting p-value is less than 10%, then the variable is included in the imputation model. Should no correlation be found, a t-test is computed to compare the means of the continuous variable between subjects with different study completion statuses (i.e., subjects who prematurely discontinued the study and subjects who completed the study). If the conditions of normality and homoscedasticity are not verified, then a non-parametric Wilcoxon test is done instead. If the means differ at the level of 10%, then the variable is added to the imputation model.

For categorical variables, a t-test (or Wilcoxon test) is used to compare the means of observed Day 84 values amongst the different categories. Alternatively, a chi-square test can be done to test the association between the categorical variable and study completion status. If the p-value is less than 10%, then the variable will be included in the imputation model.

The primary analysis and the sensitivity analyses presented here above are repeated on the ITT and PP populations.

Below is a sample program to conduct the multiple imputation sensitivity analyses:

```
/* Imputation step */
proc mi data=<dataset_SA> nimpute = PCTMISSING seed=30185 out=<out_mi>;
/* use a version of the dataset where Day84 is missing */
  class <trt> <country> <categorial auxiliary variable(s)>;
  /* order of imputation - from most complete to least complete*/
  var <trt> <baseline> <country> <auxiliary variable1> <auxiliary variable2>
<auxiliary variable3> <auxiliary variable4> <Day84> ;
  monotone reg;
run;

/* Compute change from baseline with imputed data */
data <anal_mi>;
  set <out_mi>;
  <change> = <Day84> - <baseline> ;
run;

/* Analysis step */
ods output lsmeans=lsmeans type3=type3 estimates=diffs;
proc mixed data = anal_mi method=type3;
/* repeat the analysis for each imputed dataset */
  by _imputation_;
  class <country> <trt>(ref=last);
  model <change> = <baseline> <country> <trt>;
  LSMEANS <trt> /CL diff=all;

  estimate "High Dose(B) vs Reference(C)" <trt> 0 1 -1  /CL e;
  estimate "Low Dose(A) vs Reference(C)"  <trt>  1 0 -1 /CL e;
  estimate "High Dose(B) vs Low dose(A)"  <trt> -1 1 0  /CL e;
run;

/* Pooling step of adjusted means and mean differences */
```

```
/* Sort by a grouping variable i.e. trt for lsmeans or label for diffs*/
proc sort data = <output table>;
by <group variable> _imputation_;
run;

proc mianalyze data = <sorted output table>; by <group variable>;
modeleffects estimate;
stderr stderr;
ods output parameterestimates = <pooled_estimatename>;
run;
```

Exploratory Subgroup analysis of the primary efficacy endpoint:

The analysis of absolute values and changes from baseline in LVEF and the ANCOVA primary model (including the covariate of interest and the treatment-by-covariate interaction) are repeated on mITT for subgroups defined in Section 6.6. For subjects who prematurely discontinue the study, measurements made at the time of study withdrawal are considered in the analysis.

Forest plots for mean differences to ramipril and for mean differences between higher dose and lower dose of firibastat are created by corresponding subgroup if applicable.

Exploratory analysis of the primary efficacy endpoint:

The analysis of absolute values and changes from baseline in LVEF and the ANCOVA primary model (including the covariate of interest and the treatment-by-covariate interaction) are repeated on mITT with combining higher dose and lower dose of firibastat compared to ramipril. For subjects who prematurely discontinue the study, measurements made at the time of study withdrawal are considered in the analysis.

7.5.2 Secondary efficacy endpoint

As for the primary efficacy endpoint, a hierarchical step-down testing procedure is applied for each of the secondary efficacy endpoints in order to control the overall type I error due to multiplicity of treatment comparisons.

Change from baseline in left-ventricular end-diastolic and end-systolic volumes:

The absolute values and changes from baseline in left-ventricular end-diastolic and end-systolic volumes assessed by CMRI are listed by subject and summarized with descriptive statistics and analyzed using an ANCOVA as for the primary efficacy endpoint, i.e., considering the treatment group as factor, baseline value and country as covariates.

Change from baseline in average peak of longitudinal and circumferential strain:

The absolute values and changes from baseline in the average peak of longitudinal and circumferential strain in the infarcted segments assessed by CMRI are listed by subject and summarized with descriptive statistics and analyzed using an ANCOVA as for the primary efficacy endpoint, considering the treatment group as factor and baseline value and country as covariates.

Infarct mass:

The infarct mass assessed by CMRI at the end of the treatment is listed by subject and analyzed using an ANCOVA. The ANCOVA includes treatment group as factor and country as covariate.

MACE:

The MACE which occurred during the course of the study are adjudicated by an independent committee. The number of committee-confirmed events per subject are described per category (listed and summarized by PT). The time to first confirmed MACE is derived as the number of days elapsed from the first administration of study treatment to the first confirmed MACE onset. Descriptive statistics (mean, SD, median, Q1 and Q3, minimum and maximum) of this time is presented by treatment group on the safety population

If the number of subjects with confirmed MACE is sufficient (at least 5 subjects in at least one group), the time to first confirmed MACE is tested using censored data analysis. For the subjects without MACE, the subject is censored and the time to first confirmed MACE is the number of days elapsed from the first administration of study treatment to EOT Visit (Day 84) or Early Termination Visit, whichever occurs first. Median or Q1 time with 95% CI is estimated using the Kaplan-Meier method. Number and percentage of subjects who had an event or were censored are reported. A Kaplan-Meier survival curve is generated by treatment group.

Changes from Baseline in NT-proBNP, PIIINP, and CRP:

The absolute values and changes from baseline in NT-proBNP, PIIINP, and CRP are listed by subject and summarized with descriptive statistics, and analyzed using an ANCOVA as for the primary efficacy endpoint, considering the treatment group as factor and baseline value and country as covariates.

Slope of decrease in copeptin:

Copeptin is assessed at each visit. The change from baseline in copeptin are listed by subject and summarized with descriptive statistics; Copeptin is analyzed using a mixed model for repeated measures (MMRM) where intercept and slope considered as random. The model includes treatment group as a fixed factor, baseline value and country as covariates, and time, treatment group by time interaction, and baseline by time interaction. Time is calculated in days as date of copeptin assessment - date of first study treatment intake. The restricted maximum likelihood (REML) estimation approach is used, and the default covariance structure is unstructured.

Estimate of slope is presented by treatment group. Difference in slopes between the treatment groups and associated 95% CI are also presented. Comparison of slopes between the treatment groups is performed using the hierarchical step-down testing procedure.

The decrease of copeptin is graphically illustrated. The mean at each time point used for the figure is estimated from the model.

7.6 ANALYSES OF SAFETY

7.6.1 Adverse events

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of IP (firibastat and/or ramipril) and not more than 30 days after the last administration of IP.
Adverse events are coded using MedDRA dictionary version 21.1 or higher.

The number (%) of subjects reporting each treatment emergent AE (TEAE) are summarized by SOC and PT where subjects with more than one TEAE within a particular SOC and PT are counted only once for that SOC and PT. Percentages are based on the number of subjects actually receiving a given treatment (based on the safety population) within each treatment group. Separate summaries are given for all TEAEs, treatment-related AEs, Serious AEs (SAEs), and AEs leading to discontinuation of study treatment.

TEAEs are considered as related to the study treatment if for the question "Relationship to Study Drug?" the answer is "potentially related", "probably related" or "definitely related" or missing.

The following AEs of clinical and special interest are summarized separately:

- Skin reactions reviewed by the dermatologists
- Diabetes insipidus

For skin reaction, the number (%) of subjects are summarized by final diagnosis and relationship to IP according to dermatologist

Individual subject data listings of AEs including outcome, action taken, severity, relationship to IP, and seriousness are performed for overall AEs, SAEs, and drug-related SAEs.

7.6.2 Clinical examination findings

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline in weight are presented at each visit and by treatment group. Individual values of clinical examination findings are listed.

7.6.3 Vital signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline are presented at each visit and by treatment group for SBP, DBP, and HR.

For SBP the frequencies of values <100 mmHg are tabulated at each visit and by treatment group.

7.6.4 Clinical laboratory evaluations

All laboratory data are converted to standard units.

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values are presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges, are tabulated showing the change from baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit.

Laboratory values that are outside the normal range are also flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant are also shown in a data listing.

If laboratory values equal to «<x» or «>x», then the value x will be retained for the analysis.

The laboratory data are listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range, NV = Normal value, CS = Clinically significant, NCS = Not clinically significant).

7.6.5 Twelve-lead electrocardiogram

The number and percentage of subjects with normal and abnormal ECG findings (rhythm, QRS duration) is summarized for each treatment group at each time point.

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values are presented for QT duration for each treatment group at each time point.

7.7 INTERIM ANALYSES

The futility IA will not be performed (see Section 1).

7.8 DETERMINATION OF SAMPLE SIZE

The sample size determination is based on the primary efficacy endpoint (i.e., the change from baseline in LVEF assessed by CMRI on Day 84), on an equal randomization, using a 2-sided 5% nominal level of significance.

The SD of the primary efficacy variable is estimated to 10%.

Based on an estimated difference of 5% between the treatment groups on the primary efficacy variable, around 88 evaluable subjects per group are needed to achieve 90% power (accounting for the futility IA at 50% of the maximum information). Assuming of a dropout/non-evaluable rate of about 10%, 98 subjects per group are expected to be randomized, namely a total of 294 subjects.

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8. LIST OF TABLES, FIGURES AND LISTINGS

The table hereunder presents preliminary list of content of tables, figures and listings which will be integrated in study report. The structure and numbering are proposed according the ICH guidelines - E3: Structure and Content of CSRs.

8.1 Section 10 of CSR (STUDY SUBJECTS)

Output	Number	Title	Analysis population
	Section 10.1	***Disposition of subjects***	
Table	10.1.1	Disposition of subjects	ITT
Table	10.1.2	Reasons for discontinuation of study	ITT
Listing	10.1.1	Other reasons for discontinuation of study	ITT
Table	10.1.3	Subjects randomized by country	ITT
Table	10.1.4	Overview of analysis populations	All screened subjects
Table	10.1.5	Major protocol deviations	ITT
	Section 10.2	***Demographics and baseline characteristics***	
Table	10.2.1	Demographics and clinical examination findings at Baseline	mITT
Table	10.2.2	Acute MI details and troponin peak test	mITT
Table	10.2.3	Results of the coronary angiography, TIMI flow after PCI – Central reading	mITT
Table	10.2.4	Medical History	mITT
Table	10.2.5	Prior medications	mITT
Table	10.2.6	Concomitant medications	mITT
	Section 10.3	***Treatment exposure and compliance***	
Table	10.3.1	Treatment exposure and compliance	mITT

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8.3 Section 11 of CSR (EFFICACY EVALUATION)

Output	Number	Title	Analysis population
Section 11.1		***Primary efficacy endpoints***	
Table	11.1.1	Summary statistics of LVEF	mITT
Table	11.1.2	Changes from baseline in LVEF	mITT
Table	11.1.3	Primary efficacy model, treatment effects on changes from baseline in LVEF	mITT
Table	11.1.4	Sensitivity analysis on completed subjects: Primary efficacy model, treatment effects on changes from baseline in LVEF	mITT
Table	11.1.5	Sensitivity analysis, missing data imputed: Primary efficacy model, treatment effects on changes from baseline in LVEF	mITT
Table	11.1.6	Primary efficacy model, treatment effects on changes from baseline in LVEF, investigation of 'Treatment by Baseline' interaction	mITT
Table	11.1.7	Primary efficacy model, treatment effects on changes from baseline in LVEF, investigation of 'Treatment by country' interaction	mITT
Table	11.1.8	Summary statistics of LVEF	ITT
Table	11.1.9	Changes from baseline in LVEF	ITT
Table	11.1.10	Primary efficacy model, treatment effects on changes from baseline in LVEF	ITT
Table	11.1.11	Sensitivity analysis on completed subjects: Primary efficacy model, treatment effects on changes from baseline in LVEF	ITT
Table	11.1.12	Sensitivity analysis, missing data imputed: Primary efficacy model, treatment effects on changes from baseline in LVEF	ITT
Table	11.1.13	Summary statistics of LVEF	PP
Table	11.1.14	Changes from baseline in LVEF	PP
Table	11.1.15	Primary efficacy model, treatment effects on changes from baseline in LVEF	PP
Table	11.1.16	Sensitivity analysis on completed subjects: Primary efficacy model, treatment effects on changes from baseline in LVEF	PP
Table	11.1.17	Sensitivity analysis, missing data imputed: Primary efficacy model, treatment effects on changes from baseline in LVEF	PP

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Output	Number	Title	Analysis population
Section 11.2		***Primary efficacy endpoint – subgroup analyses***	
Table	11.2.X	Summary statistics of LVEF by <subgroup name>	mITT
Table	11.2.X	Changes from baseline in LVEF by <subgroup name>	mITT
Table	11.2.X	Primary efficacy model, treatment effects on changes from baseline in LVEF by <subgroup name>	mITT
Figure	11.2.1	Forest plot for the mean differences, firibastat higher dose vs ramipril	mITT
Figure	11.2.2	Forest plot for the mean differences, firibastat lower dose vs ramipril	mITT
Figure	11.2.3	Forest plot for the mean differences, firibastat higher dose vs firibastat lower dose	mITT
Section 11.3		***Primary efficacy endpoint – subgroup analyses***	
Table	11.3.X	Summary statistics of LVEF in two groups	mITT
Table	11.3.X	Changes from baseline in LVEF in two groups	mITT
Table	11.3.X	Primary efficacy model, treatment effects on changes from baseline in LVEF in two groups	mITT
Section 11.4		***Secondary efficacy endpoints***	
Table	11.4.1	Summary statistics of left-ventricular end-diastolic volume	mITT
Table	11.4.2	Changes from baseline in left-ventricular end-diastolic volume	mITT
Table	11.4.3	Treatment effects on changes from baseline in left-ventricular end-diastolic volume	mITT
Table	11.4.4	Summary statistics of left-ventricular end-systolic volume	mITT
Table	11.4.5	Changes from baseline in left-ventricular end-systolic volume	mITT
Table	11.4.6	Treatment effects on changes from baseline in left-ventricular end-systolic volume	mITT
Table	11.4.7	Summary statistics of average peak of longitudinal strain	mITT
Table	11.4.8	Changes from baseline in average peak of longitudinal strain	mITT
Table	11.4.9	Treatment effects on changes from baseline in average peak of longitudinal strain	mITT
Table	11.4.10	Summary statistics of average peak of circumferential strain	mITT
Table	11.4.11	Changes from baseline in average peak of circumferential strain	mITT

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Output	Number	Title	Analysis population
Table	11.3.12	Treatment effects on changes from baseline in average peak of circumferential strain	mITT
Table	11.4.13	Summary statistics of infarct mass	mITT
Table	11.4.14	Treatment effects on infarct mass	mITT
Table	11.4.15	Summary of MACEs adjudicated by treatment group, category and PT	Safety
Table	11.4.16	Summary of time to the first confirmed MACE adjudicated (days)	Safety
Table	11.4.17	Estimated median time to the first confirmed MACE adjudicated (days)	Safety
Figure	11.4.1	Kaplan-Meier curve of time to the first confirmed MACE adjudicated (days)	Safety
Table	11.4.18	Summary statistics of NT-proBNP	mITT
Table	11.4.19	Changes from baseline in NT-proBNP	mITT
Table	11.4.20	Treatment effects on changes from baseline in NT-proBNP	mITT
Table	11.4.21	Summary statistics of PIIINP	mITT
Table	11.4.22	Changes from baseline in PIIINP	mITT
Table	11.4.23	Treatment effects on changes from baseline in PIIINP	mITT
Table	11.4.24	Summary statistics of CRP	mITT
Table	11.4.25	Changes from baseline in CRP	mITT
Table	11.4.26	Treatment effects on changes from baseline in CRP	mITT
Table	11.4.27	Summary statistics of copeptin	mITT
Table	11.4.28	Changes from baseline in copeptin	mITT
Table	11.4.29	Treatment effects on copeptin	mITT
Figure	11.4.2	Decrease of copeptin	mITT

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8.4 Section 12 of CSR (SAFETY EVALUATION)

Output	Number	Title	Analysis population
	Section 12.1	***Adverse events***	
Table	12.1.1	Summary of all treatment-emergent adverse events by treatment group, primary SOC, and PT within primary SOC	Safety
Table	12.1.2	Summary of treatment-emergent adverse events related to study treatment by treatment group, primary SOC, and PT within primary SOC	Safety
Table	12.1.3	Summary of serious treatment-emergent adverse events by treatment group, primary SOC, and PT within primary SOC	Safety
Table	12.1.4	Summary of serious adverse events by treatment group, primary SOC, and PT within primary SOC	Safety
Table	12.1.5	Summary of treatment-emergent adverse events leading to discontinuation of study treatment by treatment group, primary SOC, and PT within primary SOC	Safety
Table	12.1.6	Summary of treatment-emergent skin reactions reviewed by the dermatologists by treatment group, final diagnosis and relationship to treatment according dermalotolist	Safety
Table	12.1.7	Summary of treatment-emergent diabetes insipidus by treatment group, primary SOC, and PT within primary SOC	Safety
Section 12.2		***Other safety endpoints***	
Table	12.2.1	Body weight: Summary statistics	Safety
Table	12.2.1	Body weight: Changes from baseline	Safety
Table	12.2.X	Vital signs, <SBP, DBP, HR>: Summary statistics	Safety
Table	12.2.X	Vital signs, <SBP, DBP, HR>: Changes from baseline	Safety
Table	12.2.X	Vital signs, SBP < 100 mmHg	Safety
Table	12.2.X	Laboratory evaluations, <parameter>: Summary statistics	Safety
Table	12.2.X	Laboratory evaluations, <parameter>: Changes from baseline	Safety
Table	12.2.X	Laboratory evaluations, <parameter>: Frequencies of abnormal values	Safety
Table	12.2.X	Laboratory evaluations, <parameter>: Shift table of change from baseline by visit	Safety

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Output	Number	Title	Analysis population
Table	12.2.X	12-lead ECG evaluations, Rhythm	Safety
Table	12.2.X	12-lead ECG evaluations, QRS duration	Safety
Table	12.2.X	12-lead ECG evaluations, QT duration: Summary statistics	Safety
Table	12.2.X	12-lead ECG evaluations, QT duration: Changes from baseline	Safety

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8.5 Appendix 16.2 of CSR (SUBJECT DATA LISTINGS)

All subjects included in clinical DB are listed (if not specified otherwise).

Listing Number	Title
Section 16.2.1	***Disposition and discontinued subjects***
16.2.1.1	Informed consent details
16.2.1.2	Populations
16.2.1.3	Study visits
16.2.1.4	Screening failures and withdrawals (prior or after to randomization)
Section 16.2.2	***Protocol deviations***
16.2.2.1	Protocol deviations
Section 16.2.3	***Subjects excluded from population***
16.2.3.1	Subjects excluded from Safety, ITT, m-ITT and PP sets
Section 16.2.4	***Demographic data and baseline characteristics***
16.2.4.1	Demographic and clinical examinations at baseline
16.2.4.2	Acute myocardial infarction details
16.2.4.3	TIMI flow after PCI – Central reading
16.2.4.4	Troponin peak test details
16.2.4.5	Medical history
16.2.4.6	Previous and concomitant medications
Section 16.2.5	***Study treatment compliance and exposure***
16.2.5.1	Study treatment administration
16.2.5.2	Dose titration details
16.2.5.3	Study treatment exposure and compliance
Section 16.2.6	***Individual efficacy response data***
16.2.6.1	CMRI: LVEF, absolute values and changes from baseline
16.2.6.2	CMRI: Left-ventricular end-diastolic and end-systolic volumes, absolute values and changes from baseline

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Listing Number	Title
16.2.6.3	CMRI: Average peak of longitudinal and circumferential strain, and infarct mass, absolute values and changes from baseline
16.2.6.4	MACEs
16.2.6.5	Biomarkers: NT-proBNP, PIIINP and CRP, absolute values and changes from baseline
16.2.6.6	Biomarkers: Copeptin, absolute values and changes from baseline
Section 16.2.7	***Adverse events listings***
16.2.7.1	Listing of all adverse events by subject
16.2.7.2	Adverse events – MedDRA coding details
Section 16.2.8	***Other safety endpoints***
16.2.8.1	Clinical examination data
16.2.8.2	Vital signs
16.2.8.3	Laboratory evaluations
16.2.8.4	12-lead ECG evaluations

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[1] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] Chen, Z. W., Yu, Z. Q., Yang, H. B., Chen, Y. H., Qian, J. Y., Shu, X. H., & Ge, J. B. (2016). Rapid predictors for the occurrence of reduced left ventricular ejection fraction between LAD and non-LAD related ST-elevation myocardial infarction. *BMC cardiovascular disorders*, *16*(1), 1-8.

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DOCUMENT HISTORY

Version	Date	Description of change	Performed by
Draft 0.1	03-APR-2020	First version of the document created.	Mariya Antonova
Draft 0.2	21-JUL-2020	SAP updated according to sponsor's comments	Mariya Antonova
Draft 0.3	25-JAN-2021	SAP updated according to sponsor's comments	Isabelle Josse
Final	04-MAR-2021	SAP updated according to sponsor's comments	Isabelle Josse
Final 2	20-JUL2021	Clarification on the sensitivity analysis with multiple imputations Addition of decision rules for baseline medical history (smoking, diabetes, hypertension, dyslipidemia) Addition of the definition of TEAE Addition of groupings for the relationships of AEs with the treatment of the study (Not related / Related) Completion of the definition of the mITT (baseline: before or within 8 hours of taking the first IP)	Isabelle Josse