PROTOCOL

PRODUCT NAME/NUMBER:	Firibastat (QGC001)
PROTOCOL NUMBER:	QGC001-2QG4
IND NUMBER:	145271
NCT NUMBER:	NCT03715998
EUDRACT NUMBER:	2018-003146-17
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	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 Short Title: Quantum Genomics Firibastat (QGC001) or Ramipril after Acute Myocardial Infarction for Prevention of Left Ventricular Dysfunction (QUORUM)
PROTOCOL DATES:	Final V1.0: 04-Dec-2018, Local V2.0 for France: 26-Feb-2019, Local V3.0 for France: 14-Mar-2019, Local V2.0 for Germany: 15-Apr-2019, Global Amendment V2.0: 09-Aug-2019, Local V4.0 for France: 09-Oct-2019, Local V2.0 for United Kingdom: 09-Oct-2019, Local V5.0 for Germany: 10-Oct-2019, Global Amendment V3.0: 10-Oct-2019
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1. APPROVAL SIGNATURES

PROTOCOL NUMBER: QGC001-2QG4

PROTOCOL TITLE: 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

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

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2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/ NUMBER	Firibastat (QGC001)
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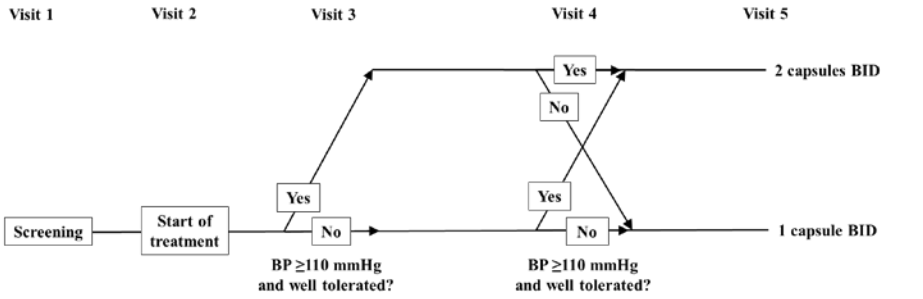
INDICATION	Prevention of left ventricular dysfunction after acute anterior myocardial infarction
OBJECTIVES	**Primary objective:** The primary objective of this study is to compare the effects of twice daily (bis in die [BID]) oral administration of 2 doses of firibastat to those of BID oral administration of ramipril on the change from Baseline in left ventricular ejection fraction (LVEF) assessed by cardiac magnetic resonance imaging (CMRI) on Day 84. **Secondary objectives:** • 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, myocardial infarction (MI), 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
RATIONALE	Heart failure (HF) is considered to be a complex clinical syndrome that could develop from multiple structural or functional cardiac and non-cardiac diseases. HF is often the result of a myocardial infarction (MI) or hypertension. HF is the leading cause of hospitalization for patients over 65 years old in western countries. It affects 1 to 5 persons in a thousand persons in industrialized countries, all ages considered, with a prevalence of 3 to 20 in a thousand persons. Although a large number of drugs is available to treat HF symptoms, half of the patients die in the 3 to 5 years following the onset of symptoms of HF. Thus, HF remains one of the major causes of cardiovascular death. The aim of this study is to assess the efficacy and the safety of firibastat compared to ramipril to prevent

	left ventricular dysfunction in subjects after acute MI. Firibastat targets the brain renin-angiotensin system. Through a triple mechanism of action, firibastat induces a simultaneous effect on the arteries, heart, and kidneys, offering promising perspectives in the treatment of HF. Latest data in post-myocardial infarction in mice and rats treated with oral doses of firibastat showed significant cardiac function improvement. Furthermore, a favorable safety profile of firibastat was observed in HF patients during a phase 2a clinical study (QUID-HF).
STUDY DESIGN	This is a multicenter, randomized, double-blind, active-controlled, dose-titrating phase 2 study to evaluate the safety and efficacy of firibastat administered orally BID (2 daily doses) versus ramipril administered orally BID over 12 weeks after acute anterior MI. Subjects will be followed for 12 weeks over 5 study visits (about 16 weeks over 6 study visits for women of childbearing potential). A total of 294 male and female subjects with a diagnosis of first acute anterior MI will be randomized. The subjects will need to have a primary percutaneous coronary intervention (PCI) of the index-MI-related artery within 24 hours after MI. Subjects will be randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio: • Group 1: Subjects will receive 50 mg firibastat BID for 2 weeks and then 100 mg BID for 10 weeks • Group 2: Subjects will receive 250 mg firibastat BID for 2 weeks and then 500 mg BID for 10 weeks • Group 3: Subjects will receive 2.5 mg ramipril BID for 2 weeks and then 5 mg BID for 10 weeks It should be noted that the subjects' dosage will be up-titrated and/or down-titrated according to a specific titration procedure. Baseline is defined as the day when the CMRI is performed and the first investigational product (IP) dose is taken. Day 84 will be the day of treatment discontinuation (i.e. 84 days [±3 days] after the Inclusion Visit [Day 1]). **Screening Visit (Visit 1; within 24 hours after acute MI [Day -2 – Day 1]):** The Screening Visit will occur within 24 hours after index acute MI, defined as the time of onset of symptoms, and after PCI is performed (no earlier than 3 hours after acute MI and within 24 hours after MI). Subjects will sign an informed consent form (ICF) prior to any study procedures being performed. Any standard-of-care procedures performed prior to ICF signature should not be repeated for the purpose of the study if already performed. Subjects may be screened even if the exclusion criterion 4 (SBP <100 mmHg) is not met at this time. **Inclusion Visit (Visit 2; within 72 hours after acute MI [Day 1]): This visit can be done on the same day as the Screening Visit:** Subjects who meet all of the inclusion criteria but none of the exclusion criteria (excluding exclusion criterion 4 [SBP <100 mmHg]) at the Screening Visit will undergo visit-specific procedures, and a baseline CMRI must be performed no later than 72 hours after the MI. As soon as possible after the CMRI is performed, the subject's blood pressure will be measured. If systolic blood pressure (SBP) is ≥100 mmHg, the subject's eligibility will be confirmed, and the site will connect on the treatment kits allocation web system available through the electronic data capture (EDC) system for randomization information. Subjects will be randomly assigned on Day 1 in a 1:1:1 ratio to receive either 50 mg firibastat BID (Group 1), 250 mg firibastat BID (Group 2), or 2.5 mg ramipril BID (Group 3). The first capsule of the IP will be administered on Day 1 as soon as possible after the CMRI, which will be performed no later than 72 hours after MI. Subjects will then take 1 capsule of the IP BID until the next visit. After the first administration occurring after

	the CMRI, next intake must not occur before 6 hours and if not possible, must be done on the next morning. **Safety Check (Day 3):** A safety check should be performed 3 days after first administration of the IP to ensure the good tolerance of the treatment by the subjects. In most of the cases, subjects will be still hospitalized at the site 3 days after the first IP administration, and the investigator will be able to continuously monitor the tolerance of the treatment and immediately react if non-tolerance is suspected. As there is no possibility to decrease the dose of the IP at this stage, in case of non-tolerance of the IP the subject will be withdrawn from the study. For subjects discharged early, i.e., before 3 days after the first IP administration, a phone call to the subject should be performed. If the investigator judges that there is a risk of non-tolerance according to the subject's answers (e.g., any suspicion or symptoms related to hyper- or hypotension), the subject will be asked to come to the site for an unscheduled visit. The investigator will then decide whether the subject should be withdrawn from the study. Details provided by the subject should be recorded in the subject's medical notes. In all cases, tolerability of the IP should be checked before subject discharge. **Titration Visit (Visit 3 [Day 14 ±2 days]):** Subjects will undergo visit-specific procedures. If SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock, the dose will be increased to 2 capsules of the IP BID. If SBP is <110 mmHg, the subject will remain on the same dose (1 capsule BID). If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study, and the event will be recorded as an adverse event (AE) leading to discontinuation. In case of any suspicion or symptoms related to hyper- or hypotension, the subjects should contact the site, attend an unscheduled visit, or visit their general practitioner or nearest cardiovascular unit, where a decision on any action with the IP can be made by the investigator or other physician seeing the subject. Note: the newly allocated dose will be administered as soon as possible after the visit is completed (i.e., on the evening of the day of the visit). **Treatment Visit (Visit 4 [Day 42 ±2 days]):** Subjects will undergo visit-specific procedures. If SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock, the dose will remain the same if the subject has already been treated with 2 capsules of the IP BID, or the dose will be increased to 2 capsules of the IP BID. If SBP is <110 mmHg and if the subject was being treated with 2 capsules of the IP BID, the dose will be decreased to 1 capsule of the IP BID. If SBP is <110 mmHg and if the subject was being treated with 1 capsule of the IP BID, the subject will remain on the same dose (1 capsule BID). If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study, and the event will be recorded as an AE leading to discontinuation. In case of any suspicion or symptoms related to hyper- or hypotension, the subjects should contact the site, attend an unscheduled visit, or visit their general practitioner or nearest cardiovascular unit, where a decision on any action with the IP can be made by the investigator or other physician seeing the subject. Note: the newly allocated dose will be administered as soon as possible after the visit is completed (i.e., on the evening of the day of the visit).

	End-of-Treatment Visit (Visit 5 [Day 84 ± 3 days]): Subjects will undergo End-of-Treatment (EOT) Visit-specific procedures, and the IP will be discontinued. In case of premature discontinuation (except if consent is withdrawn), a CMRI and all Visit 5 procedures, if possible, will be performed as soon as possible and no later than 72 hours after treatment discontinuation. **Follow-up Visit (Visit 6 [Day 114 (±3 days) or 30 Days after IP discontinuation]):** For females of childbearing potential only, a serum pregnancy test will be performed. A schematic presentation of the titration procedure for Groups 1, 2, and 3 is given below:  If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued.
PLANNED NUMBER OF SUBJECTS	A total of 294 subjects will be randomized to reach 264 evaluable subjects (88 subjects per group). Evaluable subjects are defined as those subjects who have a CMRI at both the Baseline and EOT Visits.
STUDY ENTRY CRITERIA	The population for this study corresponds to subjects with a first acute anterior MI. **Inclusion criteria:** 1. Subject must provide signed written informed consent. *Important Note: Subject must be willing and able to give informed consent for participation in the study.* 2. Men and women ≥18 years of age at Screening. 3. Diagnosis of first acute anterior MI (ST-elevation myocardial infarction) defined as chest pain >30 minutes and ST elevation ≥0.2 mV in at least 2 consecutive electrocardiogram (ECG) leads in the anterior area (DI, aVL, V1-V6). 4. Primary PCI of the index-MI-related artery within 24 hours after the MI. 5. Women of childbearing potential and non-surgically sterile male subjects who are sexually active must agree to use an approved highly effective form of contraception from the time of informed consent until 30 days post-dose. Approved forms of contraception include hormonal intrauterine devices, hormonal contraceptives (oral birth control pills, depot, patch, or injectable), together with supplementary double-barrier methods such as condoms or diaphragms with spermicidal gel or foam. Note: The following categories define women who are NOT considered to be of childbearing potential: o Premenopausal women with 1 of the following: • Documented hysterectomy • Documented bilateral salpingectomy • Documented bilateral oophorectomy OR

	○ Postmenopausal women, defined as having amenorrhea for at least 12 months without an alternative medical cause. 6. Women of childbearing potential must have a negative serum pregnancy test result at the Screening Visit. **Exclusion criteria:** 1. Body mass index>45 kg/m². 2. Subject is hemodynamically unstable or has cardiogenic shock. 3. Subjects with clinical signs of HF (Kilipp III and IV corresponding to severe HF). 4. Systolic blood pressure <100 mmHg at Inclusion Visit. 5. Early primary PCI of the index-MI-related artery performed within 3 hours after MI. *Important Note: the time of the PCI MUST NOT be delayed because of the protocol; if PCI is performed within 3 hours after MI, the subject is not eligible.* 6. Subjects who require treatment with angiotensin-converting-enzyme inhibitor (ACE-I), angiotensin-receptor blocker (ARB), or sacubitril/valsartan after the index magnetic resonance imaging. Note: if treatment was for HTN, ACE-I/ARB should be stopped right before index magnetic resonance imaging, and, if necessary, another therapeutic class can be prescribed for HTN. If the ACE-I/ARB was prescribed for congestive HF, the subject is not considered eligible; if the ACE-I/ARB prescribed for another reason cannot be stopped, the subject is not eligible for study inclusion. 7. Subjects scheduled for implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy, or pacemaker within the next 3 months. If an ICD is indicated for ventricular arrhythmia during the course of the study, a life vest, when possible, should be prescribed and the ICD scheduled after study completion. 8. Subjects with any contraindication related to the CMRI procedure (devices or metal foreign bodies, including pacemaker, defibrillator) including severe claustrophobia according to the lists/safety rules of the local MRI departments. 9. Female who is breast-feeding, pregnant, or planning to become pregnant during the study. 10. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years. 11. Alkaline phosphatase>3 × upper limit of normal (ULN), total bilirubin ≥1.5 × ULN, or direct bilirubin >ULN in subjects with Gilbert's syndrome at the Screening Visit. 12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at the Screening Visit. 13. History of any blood disorder, other than sickle cell trait, causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, hemolytic anemia, thalassemia, or sickle cell anemia). 14. Clinical evidence of thyroid disease, thyroid hormone therapy that is not stable ≥4 weeks prior to Screening, or a thyroid-stimulating hormone (TSH) level <0.75 × lower limit of normal or >1.5 × ULN. 15. History of alcohol or drug abuse within the 3 months prior to the Screening Visit that would interfere with study participation or lead to decreased compliance with study procedures or IP intake in the investigator's opinion.

	16. Participation in another clinical study involving an investigational drug within 30 days prior to Screening, or if a subject plans to participate in another clinical study within 30 days of discontinuation of the IP. 17. Any condition that in the opinion of the investigator would interfere with study participation, may pose a risk to the subject, or would make study participation not in the best interest of the subject. 18. Subjects with a life expectancy of less than 1 year per investigator's discretion. 19. Any subject who, in the opinion of the investigator, will not be able to follow the protocol. The contraindications of Ramipril as given in the summary of product characteristics must be checked before any inclusion to ensure that the subject has no contraindication to the administration of Ramipril; otherwise, the subject should be excluded from the study.
TEST PRODUCT	Name: firibastat (QGC001) Dose, route, and frequency: Subjects will receive either: • Group 1: 1 capsule of firibastat as 50 mg capsule orally BID (1 capsule in the morning and 1 capsule in the evening) from Day 1 to Day 14 (Day 14 morning only) and then 2 capsules BID (2 capsules in the morning and 2 capsules in the evening) from Day 14 (Day 14 evening only) to Day 84 (the subjects' dosage will be up-titrated and/or down-titrated according to a specific titration procedure) OR • Group 2: 1 capsule of firibastat as 250 mg capsule orally BID (1 capsule in the morning and 1 capsule in the evening) from Day 1 to Day 14 (Day 14 morning only) and then 2 capsules BID (2 capsules in the morning and 2 capsules in the evening) from Day 14 (Day 14 evening only) to Day 84 (the subjects' dosage will be up-titrated and/or down-titrated according to a specific titration procedure)
CONTROL PRODUCT	Name: ramipril Dose, route, and frequency: Subjects will receive: Group 3: 1 capsule of ramipril as 2.5 mg capsule orally BID (1 capsule in the morning and 1 capsule in the evening) from Day 1 to Day 14 (Day 14 morning only) and then 2 capsules BID (2 capsules in the morning and 2 capsules in the evening) from Day 14 (Day 14 evening only) to Day 84 (the subjects' dosage will be up-titrated and/or down-titrated according to a specific titration procedure).
TREATMENT REGIMENS	The IP will be administered orally as 1 capsule BID (1 capsule in the morning and 1 capsule in the evening) from Day 1 to Day 14. The dose will then be increased to 2 capsules BID (2 capsules in the morning and 2 capsules in the evening) from Day 14 if the subject has an SBP ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock. If the SBP is <110 mmHg, the subject will remain on the same dose (1 capsule BID). If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study. SBP will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting for 5 minutes at rest. In case of any suspicion or symptoms related to hyper- or hypotension, the subjects should contact the site, attend an unscheduled visit, or visit their general practitioner or nearest cardiovascular unit, where a decision on any action with the IP can be made by the investigator or other physician seeing the subject.

	On Day 42, if SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock, the dose will remain the same if the subject has already been treated with 2 capsules of the IP BID, or will be increased to 2 capsules of the IP BID. If SBP is <110 mmHg and if the subject was being treated with 2 capsules of the IP BID, the dose will be decreased to 1 capsule of the IP BID. If SBP is <110 mmHg and if the subject was being treated with 1 capsule of the IP BID, the subject will remain on the same dose (1 capsule BID). If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study.
COORDINATING/ PRINCIPAL INVESTIGATOR	Prof. Gilles Montalescot, MD, PhD Head of the Medical Cardiology Department Cardiology Institute, Hôpital Pitié-Salpêtrière 47 Boulevard de l'Hôpital 75013 Paris, France Telephone: +33 1 42 16 30 07 Fax: +33 1 42 16 29 31
PLANNED STUDY SITES	Approximately 38 study sites in Europe and the United States
CRITERIA FOR EVALUATION	**Efficacy endpoints:** *Primary efficacy endpoint:* The primary efficacy endpoint is the change from Baseline to Day 84 in LVEF assessed by CMRI (centralized reading). *Secondary 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 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:** Safety assessments will include all AEs, adverse events of special interest, which include allergic reactions and diabetes insipidus, and clinical laboratory evaluations and specifically: • Change from Baseline in clinic SBP, diastolic blood pressure (DBP), and heart rate (HR) at each visit • Change from Baseline in sodium, potassium, aspartate aminotransferase (AST), and ALT blood levels and eGFR Every effort should be made to follow up subjects who continue to experience an AE or a serious adverse effect (SAE) on completion of the study until the AE stabilizes or resolves.
INDEPENDENT DATA MONITORING COMMITTEE	An independent data monitoring committee (IDMC), consisting of independent physicians qualified to treat the study population will be established for the regular unblinded review of emerging safety data. The IDMC will also include an independent statistician who will be in charge of the interim analysis corresponding to efficacy and safety data.

STATISTICAL METHODS	**Analysis populations:** The following analysis populations will be considered: • Safety population: The safety population will consist of all subjects who receive at least 1 dose of the IP. This population will be based on the treatment actually received by the subject and will be used for the analysis of the safety endpoints. • Intent-to-treat (ITT) population: The ITT population will consist of all randomized subjects. This population will be based on the treatment to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized. • Modified intent-to-treat (mITT) population: The mITT population will consist of all randomized subjects who receive at least 1 dose of the IP and who have at least 1 baseline and 1 post-randomization efficacy assessment (CMRI) on treatment. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of the efficacy endpoints. • Per-protocol (PP) population: The PP population will consist of all subjects from the mITT population without any major protocol deviation. This population will be considered for sensitivity analysis of the primary endpoint. A single futility interim analysis (IA) is 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. **Subject characteristics and disposition:** The number of subjects in each analysis population will be provided overall and by treatment group. Demographics and baseline characteristics will be summarized overall and by treatment group on the mITT population. **Efficacy analyses:** The primary efficacy endpoint will be primarily analyzed on the mITT population. Sensitivity analyses will be performed on the ITT and PP populations. The secondary efficacy endpoints will be analyzed on the mITT population. *Primary analysis of the primary efficacy endpoint:* The change from Baseline in LVEF will be primarily analyzed using an analysis of covariance (ANCOVA). The ANCOVA will include treatment group as factor and baseline LVEF and country as covariates. For subjects who prematurely discontinue the study, measurements made at the time of study withdrawal will be considered in the analysis. Pattern of study premature discontinuations, including the profile of subjects and reason and time to withdrawal, will be presented to assess potential impact of dropouts on treatment comparisons. The adjusted mean will be presented by treatment group. Difference in adjusted mean between treatment groups, associated 95% confidence interval, and *P* value will be also presented using a hierarchical step-down testing procedure to control the overall type I error. *Sensitivity analysis of the primary efficacy endpoint:* A sensitivity analysis will be performed to explore possible impact of dropout pattern on treatment comparisons. *Secondary efficacy endpoints:* As for the primary efficacy endpoint, a hierarchical step-down testing procedure will be applied for each of the secondary efficacy endpoints in order to control the overall type I error due to multiplicity of treatment comparisons. **Safety analyses:** All safety analyses will be descriptive and performed on the safety population.

	Vital signs: The SBP, diastolic blood pressure (DBP), and heart rate (HR), as well as the corresponding changes from Baseline, will be described at each visit by treatment group. *Clinical laboratory data:* The blood level of sodium, potassium, AST, ALT, and the eGFR calculated value, as well as the corresponding changes from Baseline, will be described at each visit by treatment group. *Adverse events:* All AEs, whether serious or non-serious, will be reported from signing the ICF until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. For AE reporting, the verbatim term recorded in the electronic case report form by the investigators to identify AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities. Treatment-emergent AEs are defined as: • Adverse events with onset at the time of or following the start of treatment with IP through the EOT Visit • Adverse events starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the EOT Visit The following AEs of clinical and special interest will be summarized separately: • Allergic reactions • Diabetes insipidus
SAMPLE SIZE DETERMINATION	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 standard deviation 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, approximately 88 evaluable subjects per group are needed to achieve 90% power (accounting for the futility IA at 50% of the maximum information). Assuming an approximate 10% of dropout/non-evaluable rate, 98 subjects per group are expected to be randomized, i.e., a total of 294 subjects.
STUDY AND TREATMENT DURATION	The overall study duration is expected to be 19 months (16 months of active enrollment and 3 months of treatment). The sequence and maximum duration of the study periods will be as follows: 1. Screening: 1 day (+1 day) 2. Inclusion: 1 day 3. Titration Period: 42 days (±2 days) 4. Treatment Period: 42 days (±3 days) 5. Follow-up Visit for women of childbearing potential only: 1 day The maximum study duration is 119 days for women of childbearing potential and 89 days for all other subjects. The maximum treatment duration for each subject is 87 days.

2.2. Schedule of Events

Table 2-1: Schedule of Events

	Screening[a]	Inclusion[a]	Safety check[b]	Titration	Treatment	EOT[c]	Follow-up[m]
Visit	**Visit 1**	**Visit 2**	**On-site or via Telephone Call**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Day **Assessment**	**Day -2 to Day 1**	**Day 1**	**Day 3**	**Day 14 (±2 days)**	**Day 42 (±2 days)**	**Day 84 (±3 days)**	**Day 114 (±3 days) or 30 Days after Treatment Discontinuation**
Written informed consent[d]	X						
Inclusion/exclusion criteria	X	X					
Demographics	X						
Medical history	X						
Clinical examination[e]	X			X	X	X	
12-lead ECG[f]	X			X	X	X	
Blood pressure and HR measurement[g]	X	X		X	X	X	
Capture of troponin peak	X						
CMRI[h]		X				X	
Blood samples for local laboratory assessment (hematology and clinical chemistry)[i,j]	X				X	X	
Blood samples for central laboratory assessment (biomarkers)[k]		X		X[l]	X[l]	X	
Pregnancy test[m]	X				X	X	X
Randomization		X					
Dispense IP[n]		X		X	X		
Discontinue IP						X	
IP compliance check				X	X	X	
Concomitant medications	X	X		X	X	X	
AEs		X	X	X	X	X	

Abbreviations: AE = adverse event; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CMRI = cardiac magnetic resonance imaging; CRP = C-reactive protein; ECG= electrocardiogram; EOT = end of treatment; GFR = glomerular filtration rate; HR = heart rate; ICF = informed consent form; IP = investigational product; MI = myocardial infarction; NT-proBNP = N-terminal pro b-type natriuretic peptide; PCI = percutaneous coronary intervention; PIIINP = procollagen type III aminoterminal peptide; TSH = thyroid-stimulating hormone

a. The Screening Visit will occur within 24 hours after index acute MI, defined as the time of onset of symptoms and after PCI is performed (no earlier than 3 hours after acute MI and within 24 hours after MI). If possible, the Screening (Visit 1) and the Inclusion (Visit 2) Visits could be performed on the same day; procedures applicable for both visits should not be duplicated.
b. A safety check should be performed 3 days after first administration of the IP to ensure the good tolerance of the treatment by the subjects. If a subject is discharged early (i.e., before 3 days after the first IP administration), the site will contact the subject by telephone. If the investigator judges that there is a risk of non-tolerance such as any suspicion or symptoms related to hyper- or hypo-tension, the subject will be asked to come to the site for an unscheduled visit. The investigator will then decide whether the subject should be withdrawn from the study.
c. For subjects completing the study, EOT will be at Visit 5. For subjects who are withdrawn from the study prior to completion, all Visit 5 procedures will be performed at an Early Termination Visit that should be conducted as early as possible after treatment discontinuation.
d. The subject will sign an ICF before any study-specific procedures are performed. Any standard-of-care procedures performed prior to ICF signature should not be repeated for the purpose of the study if already performed.
e. Clinical examination will also include the measurement of height (at Screening only) and weight. If the subject provided consent for this, the subject's coronary angiography performed after MI at Screening will be captured using the CMRI electronic repository as part of the subject's study documentation.
f. The subject must rest in a supine position for at least 5 minutes before the 12-lead ECG recording.
g. The blood pressure will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting for 5 minutes at rest.
h. The CMRI must be performed within 72 hours after MI.
i. Blood sample analysis for hematology will include red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.
j. Blood sample analysis for clinical chemistry will include sodium, chloride, potassium, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glucose, albumin, bicarbonate, creatinine kinase, TSH, direct bilirubin, and total bilirubin. Estimated GFR will be calculated using the CKD-EPI formula.
k. The blood samples should be shipped to the central laboratory for analysis of biomarkers (NT-proBNP, copeptin, PIIINP, and CRP).
l. At Visits 3 and 4, assessment of copeptin only.
m. For females of childbearing potential only; serum pregnancy tests will be performed at the Screening Visit, Treatment Visit 4, EOT Visit, and Follow-up Visit (or 30 days after treatment discontinuation).
n. The first capsule of the IP will be administered on Day 1 as soon as possible after CMRI is performed, with a maximum of 72 hours after MI.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

The following changes were introduced due to a deficiency letter of the Medicines and Healthcare Products Regulatory Agency:

1. Exclusion criterion 11 was modified to exclude any subjects with severe liver impairment (total bilirubin ≥1.5 upper limit of normal [ULN]) or Gilbert's syndrome (direct bilirubin >ULN). Furthermore, the restriction regarding alanine aminotransferase (ALT) was removed from exclusion criterion 11 since following acute MI as a result of myocardium cytolysis, a transient increase in ALT is frequently observed. Therefore, it does not make sense to exclude patients with an elevation of ALT at Screening or randomization visits (within 72 hours after acute MI).
2. Section 10.3.2.1.1 and Table 10-1, which describe blood collection volumes, was updated to clarify expected blood draws during Visit 6.

SUMMARY OF AMENDED SECTIONS

This is a substantial protocol amendment.

Section 2.1 Synopsis – Study Entry Criteria

Text formerly read: Exclusion criteria:

11. **Alanine aminotransferase (ALT) or** alkaline phosphatase >3 x upper limit of normal (ULN) **or a** total bilirubin ≥**2** x ULN **(unless secondary to** Gilbert's syndrome**)** at the Screening Visit.

Now reads: Exclusion criteria:

11. Alkaline phosphatase >3 x upper limit of normal (ULN), total bilirubin ≥**1.5** x ULN, **or direct bilirubin >ULN in subjects with** Gilbert's syndrome at the Screening Visit.

Section 8.2.2 Exclusion Criteria

Text formerly read: Exclusion criteria:

11. **Alanine aminotransferase (ALT)** or alkaline phosphatase >3 × upper limit of normal (ULN) or a total bilirubin **≥2** × ULN (unless secondary to Gilbert's syndrome) at the Screening Visit.

Now reads: Exclusion criteria:

11. Alkaline phosphatase >3 × upper limit of normal (ULN), total bilirubin **≥1.5** × ULN, **or direct bilirubin >ULN in subjects with** Gilbert's syndrome at the Screening Visit.

Section 10.3.2.1.1 Clinical Laboratory Tests to be Performed

Text formerly read: Each blood sample will be 3.0 to 21.5 mL in volume. The total amount of blood to be drawn during the study will be **55.0** mL per subject, including samples for assessment of hematology, clinical chemistry, biomarkers, and pregnancy testing. The blood volumes to be collected at each visit are specified in Table 10 1.

Now reads: Each blood sample will be 3.0 to 21.5 mL in volume. The total amount of blood to be drawn during the study will be **60.0** mL per subject, including samples for assessment of hematology, clinical chemistry, biomarkers, and pregnancy testing. The blood volumes to be collected at each visit are specified in Table 10 1.

Addition: Table 10-1: Blood Sample Collection Volumes

A 5.0 mL blood sample for pregnancy test was added at the Follow-up Visit 6 (Day 114 [±3 days] or 30 days after treatment discontinuation).

Footnotes a (referring to clinical chemistry) and c (referring to pregnancy test) were added to the table:

a. The pregnancy test for females of childbearing potential will be performed from the blood samples collected for clinical chemistry at Visits 1, 4, and 5, but a separate blood sample for pregnancy testing will be collected at Visit 6.

c. For females of childbearing potential only; a serum pregnancy test will be performed at the Follow-up Visit (or 30 days after treatment discontinuation). The blood volume will depend on the site standard up to a maximum of 5.0 mL.

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ACE-I	angiotensin-converting-enzyme inhibitor
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AOBP	automatic office blood pressure
APA	aminopeptidase A
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
BAPAI	brain aminopeptidase A inhibitor
BID	bis in die
BP	blood pressure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMRI	cardiac magnetic resonance imaging
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
DBP	diastolic blood pressure
DI	diabetes insipidus
DOCA	deoxycorticosterone acetate
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HF	heart failure
HR	heart rate
HTN	hypertension
IA	interim analysis
IB	investigator brochure

ABBREVIATION	EXPLANATION
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major cardiac event
MI	myocardial infarction
MMRM	mixed model for repeated measures
MR	mineralocorticoid receptor
NT-proBNP	N-terminal pro b-type natriuretic peptide
PCI	percutaneous coronary intervention
PD	pharmacodynamics
PIIINP	procollagen type III aminoterminal peptide
PK	pharmacokinetics
PT	preferred term
RAAS	renin-angiotensin aldosterone
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SHR	spontaneously hypertensive rat
STEMI	ST-elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
$T_{½}$	plasma elimination half-life
T_{max}	time to reach the maximum plasma concentration
TSH	thyroid-stimulating hormone
UADR	unexpected adverse drug reaction
UAE	unexpected adverse event
ULN	upper limit of normal

5. INTRODUCTION

5.1. Background and Rationale

5.1.1 Heart Failure

Heart failure (HF) is considered to be a complex clinical syndrome that could develop from multiple structural or functional cardiac and non-cardiac diseases. From a population-based study in 220 patients with new onset of HF, primary etiologies were reported as coronary heart disease (36%), unknown (34%), hypertension (HTN) (14%), valve disease (7%), atrial fibrillation alone (5%), and other (5%).[1] In western developed countries, coronary artery disease and HTN seem to be the most common causes of HF. HF is often the result of a myocardial infarction (MI). In the Framingham Heart Study, coronary artery disease and HTN (either alone or in combination) were implicated as the cause in over 90% of the cases of HF. HTN has been associated with an increased risk of HF; it was reported as the cause of HF (either alone or in association with other factors) in over 70% of the cases.[2] HF is the leading cause of hospitalization for patients over 65 years old in western countries. It affects 1 to 5 persons in a thousand in industrialized countries, all ages considered, with a prevalence of 3 to 20 in a thousand. The total estimated direct and indirect cost of HF in the US for 2010 was $39.2 billion.[3]

HF is characterized by increased activity of the renin-angiotensin aldosterone system (RAAS), by enhanced sympathetic tonus, and withdrawal of parasympathetic control. This autonomic imbalance is recognized as an important mediator of increased mortality and morbidity in HF.[4] The sustained increase of sympathetic drive, along with reduced parasympathetic activity and activation of the RAAS in HF, also contribute to progressive left ventricular (LV) dysfunction, progressive LV remodeling, end-organ damage, and ultimately death.[5,6] In addition, several studies have shown a significant elevation in mean values of plasma vasopressin in populations of patients with HF and/or LV dysfunction.[7-9]

Very few pharmacological innovations have been recorded in the past decade for HF. The current evidence-based guideline interim analysis (IA) recommended medicines for HF with reduced ejection fraction are mainly RAAS-acting molecules such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), mineralocorticoid receptor (MR) antagonists, β-adrenergic receptor blocking agents, and diuretics. The combination valsartan/sacubitril (brand name Entresto™, previously known as LCZ696) consists of the ARB valsartan and the neprilysin inhibitor sacubitril in a 1:1 ratio by molecule count. It is also available for the treatment of symptomatic HF with reduced ejection fraction if HF is still symptomatic and if left ventricular ejection fraction (LVEF) is ≤35% despite therapy combining an ACE inhibitor, a β-adrenergic receptor blocker, and a MR antagonist.

Although a large number of drugs is available, HF has still a poor prognosis as the 1-year survival, all stages considered, is about 65%. HF remains one of the first causes of cardiovascular death. Consequently, there is still an unmet medical need to develop new efficient and safe classes of drugs acting on alternative pathways, specifically those preventing activation of brain neuromodulatory pathways that may lead to more optimal and specific strategies to improve the treatment of HF.

5.1.2 ST-segment Elevation Myocardial Infarction

ST-segment elevation myocardial infarction (STEMI) is a very serious type of heart attack, which is characterized by a blockade of one of the heart's major arteries detected as an abnormality on the 12-lead electrocardiogram (ECG). It is considered as a cardiology emergency requiring immediate recognition and treatment aimed at successful and early reperfusion to ensure optimal outcomes. It is a significant public health problem in both industrialized and developing countries, which is associated with significant morbidity and mortality. The annual incidence of STEMI ranged between 44 and 142/100 000 in European countries in 2010[10], and it was shown to be 73/100 000 in the United States in 2011.[11]

Rapid and timely reperfusion is recommended after STEMI for all eligible patients, presenting within 12 hours of symptom onset to LVEF deterioration and remodeling. Primary percutaneous coronary intervention (PCI) is considered the reperfusion strategy of choice. After acute MI, cardiac remodeling can lead to changes in size, shape, and function of the heart, which is recognized as an important aspect of cardiovascular disease progression.

Activation of the renin-angiotensin system (RAS) is considered to play an important role in remodeling since its inhibition improves the long-term clinical outcomes after a successful PCI.[12] In patients following acute MI, ACE-inhibitors were successfully studied: The results from the Survival And Ventricular Enlargement (SAVE) study showed a benefit of captopril, suggesting that ACE inhibitors should be routinely administered to patients with impaired left ventricular function after MI.[13] In the TRAndolapril Cardiac Evaluation (TRACE) study, the long-term treatment of patients with reduced left ventricular function with trandolapril resulted in a significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe HF.[14] The effect of ramipril on mortality and morbidity of survivors of acute MI with clinical evidence of HF was analyzed in the Acute Infarction Ramipril Efficacy (AIRE) study. The investigators showed that the treatment resulted in a substantial reduction in premature death from all causes.[15] Based on these studies, ACE-inhibitors are recommended after MI in patients with low LVEF and/or clinical signs of HF. Nevertheless, all of these drugs were tested before the era of early revascularization, and it is unclear if the benefit remains the same when used after early PCI.

5.2. Firibastat

Quantum Genomics is developing the molecule firibastat as the first drug candidate of a new class of centrally acting agents, brain aminopeptidase A inhibitors (BAPAIs).

Firibastat ([3S,3'S]-4,4'-dithiobis-[3-aminobutane-1-sulfonic acid]), previously named RB150 or QGC001) is a prodrug of EC33 ([3S]-3-amino-4-sulfanylbutane-1-sulfonic acid, a specific and selective inhibitor of aminopeptidase A (APA), a membrane-bound zinc metalloprotease of the RAS that generates angiotensin III from angiotensin II. The design of firibastat is based on a previously demonstrated approach that causes an increase of the brain penetration of free sulfide-containing molecules by blocking the thiol group under a disulfide form.[16] Firibastat, obtained by disulfide bridge-mediated dimerization of EC33, is known to be stable in plasma but to be reduced in the brain by a physiologically dependent process, releasing 2 active molecules of EC33 into the brain.

The mechanism of action of firibastat is displayed in Figure 5-1. Following oral administration, firibastat crosses the intestinal, hepatic, and blood-brain barriers. On entry into the brain, it is cleaved by brain reductases to generate 2 active molecules of EC33, which inhibit brain APA activity and block the formation of brain angiotensin III, and this process further results in a decrease in sympathetic tone and a reduction in arginine-vasopressin release from the posterior pituitary into the bloodstream in experimental animal models of HTN and HF.

Because there is supportive evidence that overactivity of the brain RAS plays a major role in the activation of peripheral mechanisms contributing to progressive cardiac remodeling and dysfunction after a MI and that targeting vasopressin release and sympathetic tone could be of interest for the treatment of HF, firibastat appears to be a reasonable drug candidate to treat patients with HF. Thus, firibastat represents a new therapeutic approach that may specifically prevent activation of brain neuromodulatory pathways and lead to a more optimal and specific strategy to improve the treatment of HF.

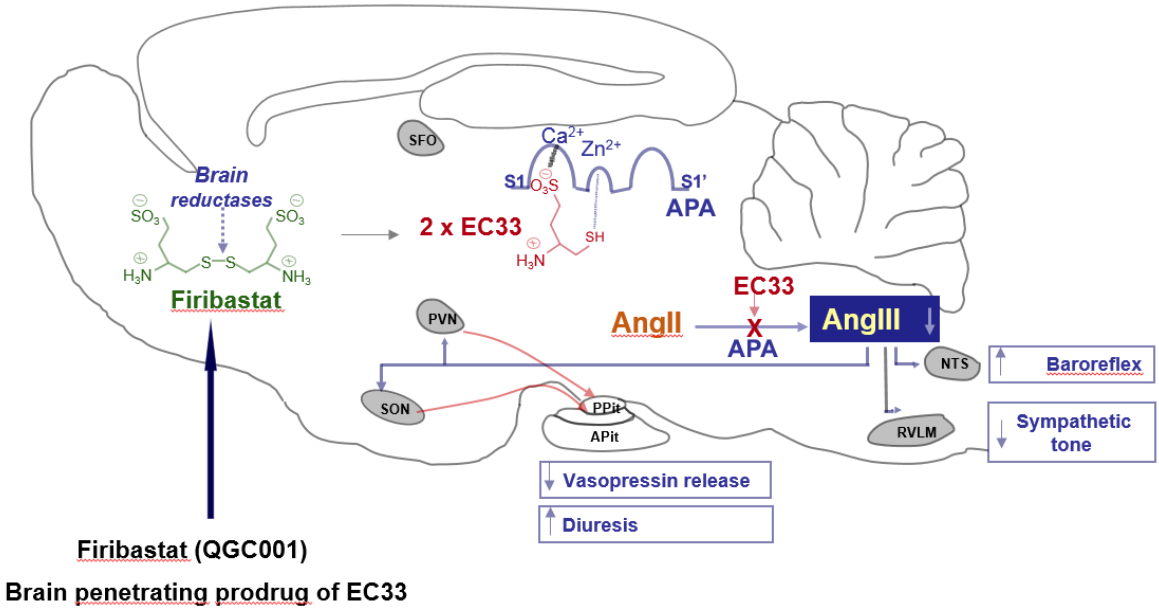


Figure 5-1: Mechanism of Action of Firibastat

(Firibastat = QGC001/RB150; adapted from Gao et al., 2014)[17]

5.2.1 Preclinical Experience

When administered intravenously to deoxycorticosterone acetate (DOCA)-salt rats, firibastat can penetrate into the brain, block the brain RAS activity through APA inhibition, and markedly reduce blood pressure (BP) in conscious hypertensive DOCA-salt rats.[17] The antihypertensive effect of firibastat was further demonstrated in hypertensive DOCA-salt and in spontaneously hypertensive rats (SHRs) after single oral dosing at 15 mg/kg.[19,1] Firibastat was found to act as an antihypertensive drug and not as a hypotensive drug since it has no significant effect on BP and heart rate (HR) in normal normotensive rats at 15 mg/kg.

In acute MI animal models (coronary artery ligation in rats and mice), APA activity rapidly increases. When infused intracerebroventricularly early after MI in rats, firibastat prevents the MI-induced increase in APA activity, improves baroreflex function and LV function, prevents enhanced sympatho-excitatory and pressor responses to air stress, and seems to be more effective than losartan.[21] Firibastat was also found to improve the left ventricular end diastolic pressure and the LVEF without lowering BP levels after 4 weeks in post-MI rats treated daily by oral route with firibastat.[22]

Similarly, firibastat oral treatment given in mice post MI was found to normalize brain APA hyperactivity to control values measured in sham-operated animals after 2 weeks. After 6 weeks post MI, mice treated daily by oral route with firibastat exhibited significant lower LV end-diastolic pressure, LV end-systolic diameter and volume, and higher LVEF (data on file). Firibastat treatment (150 mg/kg/day) was found to be as effective as enalapril (1 mg/kg/day) alone. However, oral treatment combining firibastat (150 mg/kg/day) with enalapril (1mg/kg/day) was found less effective on LVEF improvement in mice post MI than the treatment of each compound alone, suggesting that dual blockade of brain RAS and systemic RAS may not be optimal after MI (data on file). Firibastat treatment (150 mg/kg/day) alone was found to also reduce significantly messenger ribonucleic acid expressions of several HF biomarkers (β-myosin heavy chain, brain natriuretic peptide, and atrial natriuretic factor) and the fibrosis biomarkers connective tissue growth factor, collagen type I and collagen type III in the peri-infarct area (data on file).

In conclusion, experimental data support that chronic oral administrations of firibastat in mice and rats post MI normalize brain APA activity, prevent cardiac dysfunction, attenuate cardiac hypertrophy, and potentially reduce fibrosis.

5.2.2 Clinical Experience

Five clinical studies evaluating the safety, tolerability, efficacy, pharmacokinetics (PK), and/or pharmacodynamics (PD) of firibastat have been completed so far.[23]

5.2.3 Phase 1 Studies in Healthy Volunteers

Study QGC001/1QG1 was a phase 1, double-blind, placebo-controlled, ascending single-dose, safety, tolerability, and PK study of firibastat in 56 healthy male volunteers. Study QGC001/1QG2, was a phase 1, double-blind, placebo-controlled, ascending, repeated-dose study. Firibastat was administered orally as a single ascending dose (Part 1) or as multiple ascending doses (Part 2) to 69 healthy male volunteers to assess the safety, tolerability, PK, and PD. In these 2 phase 1 studies, the administration of a single oral dose of firibastat up to 2000 mg was found to be safe and well-tolerated. No withdrawal due to adverse events (AEs) occurred; no serious adverse events (SAEs) or important medical events were recorded. A total of 5 treatment-emergent adverse events (TEAEs) of mild or moderate intensity and possibly related to treatment were reported by 3 subjects of the firibastat groups; the other TEAEs were considered to be unlikely related to the investigational product (IP). All the subjects recovered without sequelae.

After repeated doses, the most common TEAEs were diarrhea in 4 patients (44%) and rash in 4 patients (44%). These events occurred at the highest tested dose (1000 mg twice daily [bis in die, BID]). All the subjects recovered without sequelae.

All firibastat doses (500 mg, 750 mg, and 1000 mg BID) were rapidly absorbed (time to reach the maximum plasma concentration [T_{max}] range: 3-5 hours) and converted to EC33 within 3-5 hours. The peak plasma concentrations and area under the curve of firibastat and EC33 increased with the dose. There was a mild accumulation of firibastat and EC33 and increase in plasma elimination half-life ($T_{½}$) with time. When compared to placebo, firibastat did not significantly change renin, aldosterone, and cortisol plasma concentrations, or levels of plasma copeptin in any treatment group. No change in heart rate, nor in systolic/diastolic blood pressure was observed.

Food intake had no influence on the safety and the tolerability of firibastat after single oral administration of 1000 mg in healthy male subjects in study QGC001/1QG2. There was no significant influence of food intake on the T_{max}. The $T_{½}$ of firibastat remained around 2.5 hours and 2 hours in fed and fasted conditions, respectively. A moderate decrease in the firibastat plasma peak (30%) and exposure (15%) was observed when the IP was taken with food, while food intake had no influence on the PK parameters of EC33.

5.2.4 Phase 2 Studies

The phase 2a study QGC001/2QG1 compared the oral administration of firibastat with placebo over 4 weeks in a multicenter, randomized, double-blind, 2-period, placebo controlled, forced titration, proof-of-concept crossover design in 34 patients with Grade I or II HTN. The dose of firibastat in this study was 250 mg BID for 1 week followed by 500 mg BID for 3 weeks. The ambulatory daytime systolic blood pressure (SBP) (primary endpoint) was decreased, by 2.69 mmHg compared to placebo (P = 0.16), and clinic SBP by 4.65 mmHg (P = 0.15). The decrease was directly correlated with the initial BP level, i.e., a higher initial BP was associated with a larger decrease in SBP. The non-significant BP-lowering effect of firibastat may be of multifactorial origin, including the small sample size of the study, the short duration of exposure to firibastat (4 weeks), the relatively low level of HTN (mean baseline clinic SBP of 144 mmHg), and the large between-patient variability in BP levels.

Firibastat administration in this study did not influence the HR, or plasma/urine hormones, including renin, aldosterone, copeptin, apelin, and adrenocorticotrophic hormone. No significant laboratory abnormalities were reported, particularly no change in sodium and potassium blood levels, and no change in renal function were observed. Firibastat administration was well tolerated, with the exception of occurrence of 3 SAEs: 1 episode of macular rash and periorbital oedema each, which were considered to be probably related to firibastat and AEs of special interest (AESIs), and a case of vestibular disorder, considered to be possibly related to firibastat. The case of macular rash was the only TEAE that occurred during the treatment with firibastat that was considered to be probably related to the IP. Other than the case of vestibular disorder, TEAEs occurring during treatment with firibastat and considered possibly related to the IP were arthralgia (leading to study withdrawal), blood creatinine increased, chest pain, headache, and hypertriglyceridemia, reported only in 1 patient each. All these AEs were of mild intensity, except the arthralgia and vestibular disorder, which were of moderate intensity.

Study QGC001/2QG3 NEW-HOPE is "A Phase 2, Open-Label, Dose-Titrating Safety and Efficacy Study of QGC001 Administered Orally, Twice Daily, Over 8 Weeks in Hypertensive Overweight Subjects of Multiple Ethnic and Racial Groups in the United States". The aim of the study was to assess the safety and efficacy of firibastat administered orally BID over 8 weeks in overweight patients with HTN of multiple ethnic groups. 256 patients were enrolled in this study. Results showed that 8 weeks of treatment with firibastat (250 mg twice-a-day orally for 2 weeks, then 500 mg twice-a-day if automatic office blood pressure [AOBP] was >140/90 mmHg; hydrochlorothiazide 25 mg once daily could be added after 1 month if systolic AOPB was ≥160 mmHg and/or diastolic AOBP was ≥100 mmHg) led to a statistically significant decrease of 9.7 mmHg in systolic AOBP from Baseline (P <0.0001), which was the primary endpoint of the trial. Overall, firibastat was well-tolerated. The most common side effects were skin reactions and headaches, with occurrence frequencies of 4% and 3%, respectively. No angioedema was reported. No changes in serum potassium or sodium levels were observed. Blood glucose levels and renal function remained stable.

Study QGC001/QUID-HF is "A Phase II randomized, placebo controlled, double-blind, multi-centre study to assess safety and efficacy of incremental doses of QGC001 in patients with NYHA class II/III chronic heart failure with left ventricular systolic dysfunction". Recruitment was completed, and 23 patients were enrolled in this study. No efficacy results were available at the time of protocol writing for this study, QGC001-2QG4, but no major safety concerns occurred during the study.

5.2.5 Rationale for Using Firibastat after Acute Myocardial Infarction and for the Conduct of the Study

- The RAS is activated after acute MI and has deleterious effects on remodeling. Blockade of the RAS demonstrated efficacy (ACE-I, angiotensin receptor-neprilysin inhibitors). Firibastat is a RAS inhibitor at the brain level.
- Animal data showed a rapid increase in brain APA activity after MI, and firibastat (as the first APA inhibitor) prevents this activation.
- After MI in animal models (rats and mice), firibastat improves LVEF, as compared to sham, increases contractility and decreases filing pressures without any decrease in systemic blood pressure.
- There is no evidence that a dual blockade of both cerebral and peripheral RAS is useful. Some data suggest that, since this is an adaptive mechanism, indeed a high blockade of the RAS may be deleterious. Some experimental data with combination of enalapril and firibastat may support this hypothesis.
- It is currently unclear if a beneficial effect of ACE inhibitors after acute MI remains when an early revascularization is performed.

5.3. Summary of Potential Risks and Benefits

During the phase 1 clinical study (QGC001/1QG2) conducted in healthy normotensive adult male subjects, the administration of a multiple oral doses of QGC001 (500 mg BID, 750 mg BID, and 1000 mg BID) for 7 consecutive days was safe and well-tolerated up to 750 mg BID. At the 1000 mg BID dose, 4 subjects had liquid stools, and 4 cases of probable skin allergy were observed. All cases remained of mild intensity and regressed spontaneously.

Following this observation, the French competent authority, the Agence Nationale de Sécurité du Médicament et des Produits de Santé, requested that all allergic reactions should be collected and analyzed as AESIs by Quantum Genomics. This additional special safety-related reporting requirement was put in place in the frame of the Phase 2a clinical study in HTN (QGC001/2QG1). No other actions have been taken by Quantum Genomics and/or any regulatory authority during the reporting period up to 13-Nov-2016.

Cumulatively, 12 SAEs, collected in 9 different SAE case reports, occurred during the clinical studies program:

- Three SAEs were reported from study QGC001/2QG1, among which 2 SAEs were experienced by the same subject and during treatment with QGC001. There was 1 case of a vestibular disorder, considered possibly related to the IP, which led to treatment discontinuation and hospitalization; the patient recovered with 48 hours. The 2 other SAEs were experienced by the same subject and were a macular rash and periorbital oedema, thought to be a drug-induced toxidermia and probably related to the IP. The treatment was discontinued, and the subject was hospitalized and treated with an antihistamine. The subject recovered within 4 days. These 2 SAEs were classified as AESIs. Two other AESIs of pruritic rash occurred in another subject in Study 2QG1, but both events occurred whilst the subject was treated with placebo.
- Three SAEs were experienced by the same subject from study QGC001/QUID-HF: ventricular tachycardia, cardiac failure, and pneumonia. These events were assessed as unrelated and were not unblinded.
- Six SAEs occurred during the NEW-HOPE study (QGC001/2QG3) and were all experienced by different subjects. There were 4 cases assessed as unrelated, 1 case of squamous cell carcinoma, 1 case of umbilical hernia, 1 case of myocardial infarction, and 1 case of lung nodule. Two cases of erythema multiforme occurred and were also reported as AESIs: the first was assessed as reasonable possibility to be related to the IP and the second as related to the IP. The subjects recovered.

Cumulatively, 14 AESIs were collected from all studies during the clinical studies program:

- Four AESIs were collected from study QGC001/2QG1, among which 2 nonserious AESIs of pruritic rash occurred during the placebo treatment phase, and 2 serious AESIs of rash macular and periorbital oedema occurred in the same subject during the IP treatment phase and were also considered as a suspected unexpected serious adverse reaction (SUSAR).
- Ten AESIs were collected from study QGC001/2QG3, among which 2 reports of erythema multiforme were serious and considered as SUSARs. The 8 nonserious AESIs included 3 AEs of rash, 2 AEs of eczema, and 3 AEs of drug hypersensitivity, all experienced by different subjects.

Data obtained from a non-clinical 13-week toxicity study conducted in dogs suggest that high doses of QGC001 (100 mg/kg or more) could affect hematological parameters, such as the platelet count. However, available clinical safety data from clinical studies (phase 1 study QGC001/1QG2: exposure to QGC001 in humans dosed at 500 mg BID for 7 consecutive days; phase 2 study QGC001/2QG1: exposure to QGC001 in humans dosed at 250 mg BID for 1 week and then 500 mg BID for 3 weeks) did not put in evidence any effect on hematological parameters in humans. Based on the PK analysis of the phase 1 clinical study QGC001/1QG2, QGC001 exposure

in humans dosed for 7 consecutive days with QGC001 500 mg BID is below 200 ng h/mL, which is more than 100-times lower than the exposure found in the 13-week non-clinical study in dogs, which were dosed at 100 mg/kg.

As mentioned above, the clinical development is currently limited to 2 phase 1 studies, conducted in 125 healthy male volunteers, a completed phase 2a study in 34 hypertensive patients, a completed phase 2b study in 256 hypertensive patients, and a completed phase 2 study in 23 patients with HF. Currently, 438 patients and healthy volunteers have been enrolled into the QGC001 clinical development program; and 398 subjects have received QGC001.

The data obtained so far imply a good safety profile of QGC001 for the treatment of HTN and HF. As mentioned earlier, allergic reactions have been identified as a potential risk for QGC001, although 4 allergic reactions that occurred in clinical studies were considered as serious. Due to the low number of subjects treated so far in the development program, no frequency calculation has been established for allergic reactions. The sponsor has put in place relevant measures to closely monitor, collect, and assess all allergic reactions occurring in the development program. Any allergic skin reaction must be reported as an AESI.

The subjects participating in the clinical studies should be informed by the investigator at site that, as noted in the informed consent form (ICF), in case of occurrence of skin lesions, they must inform their site investigator as soon as possible. In cases where a skin reaction is concomitant to fever or blisters on the skin and/or the mucous membranes of the mouth, nose, eyes, and genitals, and peeling and shedding skin, which may suggest erythema multiforme or Stevens-Johnson syndrome, subjects must immediately stop their investigational treatment and inform their site investigator. In this case, the subject should be managed by an experienced team and receive the appropriate symptomatic treatment. All subjects with skin reactions must be referred to a dermatologist as soon as possible for precise diagnosis, to document the case, to take pictures, and to perform a skin biopsy (for central reading). Skin biopsy samples should be sent to the referent for central reading. In addition, all the cases will be reviewed by a referent dermatologist.

Overall, although the efficacy data are currently limited, accumulating safety data from the completed clinical studies suggest that the overall risk-benefit balance for QGC001 remains favorable and supports the continued development of QGC001.

A summary of the pharmaceutical properties and known potential risks of firibastat is provided in the current version of the IB.[23] The investigator must become familiar with all sections of the IB and the prescribing information for ramipril before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to compare the effects of BID 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.

6.2. 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 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

7. STUDY DESIGN

7.1. Overall Study Design and Plan

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 LV dysfunction after acute anterior MI. A total of 294 male and female subjects will be randomized 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 PCI of the index-MI-related artery no earlier than 3 hours after acute MI and within 24 hours after the MI. The definition of MI is chest pain >30 minutes and ST elevation ≥0.2 mV in at least 2 consecutive ECG leads in the anterior area (DI, aVL, V1-V6). Subjects will not be eligible if they have a body mass index of >45 kg/m², are hemodynamically unstable or have cardiogenic shock, or have clinical signs of HF (Kilipp II and III).

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

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

Approximately 98 subjects will be randomized into each treatment group. The maximum treatment duration for each subject is 87 days. Women of childbearing potential will have an additional Follow-up Visit with a pregnancy test on Day 114 (±3 days). For all other subjects, the last study visit will be the EOT Visit (Visit 5) on Day 84 (±3 days).

It should be noted that the subjects' dosage will be up-titrated and/or down-titrated according a specific titration procedure.

Baseline is defined as the day when the CMRI is performed and the first IP dose is taken. Day 84 will be the day of treatment discontinuation (i.e. 84 days [±3 days] after the Inclusion Visit [Day 1]). A schematic representation of the timing of study procedures and assessments is provided in Figure 7-1.

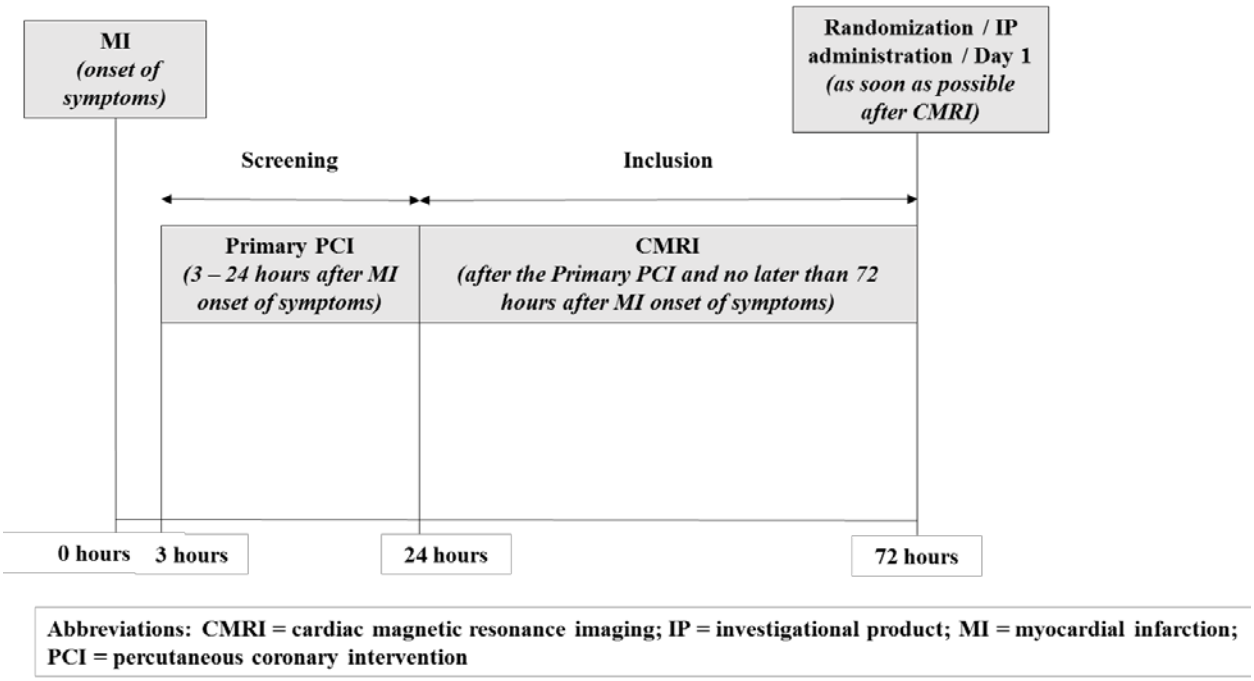


Figure 7-1: Timing of Study Procedures at Screening and Inclusion Visits

Screening Visit (Visit 1; within 24 hours after acute MI [Day -2 -Day 1]):

The Screening Visit will occur within 24 hours after index acute MI defined as the time of onset of symptoms and after primary PCI is performed (no earlier than 3 hours after acute MI and within 24 hours after MI). Subjects will sign an informed consent form (ICF) prior to any study procedures being performed. Any standard-of-care procedures performed prior to ICF signature should not be repeated for the purpose of the study if already performed. Subjects may be screened even if excluding exclusion criterion 4 (SBP <100 mmHg) is not met at this time (see Section 8.2.2).

Inclusion Visit (Visit 2, within 72 hours after acute MI [Day 1]): This visit can be done on the same day as the Screening Visit:

Subjects who meet all of the inclusion criteria but none of the exclusion criteria (excluding exclusion criterion 4 [SBP <100 mmHg]) at the Screening Visit will undergo visit-specific procedures, and a baseline CMRI must be performed no later than 72 hours after the MI.

As soon as possible after the CMRI is performed, the subject's blood pressure will be measured. If SBP is ≥100 mmHg, the subject's eligibility will be confirmed, and the site will connect on the treatment kits allocation web system available through the electronic data capture (EDC) system for randomization information. Subjects will be randomly assigned on Day 1 in a 1:1:1 ratio to receive either 50 mg firibastat BID (Group 1), 250 mg firibastat BID (Group 2), or 2.5 mg ramipril BID (Group 3).

The first capsule of the IP will be administered on Day 1 as soon as possible after the CMRI, which will be performed no later than 72 hours after MI. Subjects will then take 1 capsule of the IP BID until the next visit. After the first administration occurring after the CMRI, the next intake must not occur within 6 hours, and if not possible, must be done on the next morning.

Safety Check (Day 3):

A safety check should be performed 3 days after first administration of the IP to ensure the good tolerance of the treatment by the subjects.

In most of the cases, the subjects will be still hospitalized at the site 3 days after first administration of the IP. The investigator will be able to continuously monitor the tolerance of the IP and immediately react if non-tolerance is suspected. As there is no possibility to decrease the dose of the IP at this stage, in case of non-tolerance of the IP, the subject will be withdrawn from the study.

For subjects discharged early, i.e., before 3 days after the first IP administration, a telephone call to the subject should be performed. If the investigator judges that there is a risk of non-tolerance according to the subject's answers e.g. any suspicion or symptoms related to hyper- or hypotension, the subject will be asked to come to the site for an unscheduled visit. The investigator will then decide whether the subject should be withdrawn from the study.

In all cases, tolerability of the IP should be checked before subject discharge.

Titration Visit (Visit 3 [Day 14 ±2 days]):

Subjects will undergo visit-specific procedures.

If SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock, the dose will be increased to 2 capsules of the IP BID. The BP will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting for 5 minutes at rest.

If SBP is <110 mmHg, the subject will remain on the same dose (1 capsule BID).

If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study, and the event will be recorded as an AE leading to discontinuation.

In case of any suspicion or symptoms related to hyper- or hypotension, the subjects should contact the site, attend an unscheduled visit, or visit their general practitioner or nearest cardiovascular unit, where a decision on any action with the IP can be made by the investigator or other physician seeing the subject.

Note: the newly allocated dose will be administered as soon as possible after the visit is completed (i.e., on the evening of the day of the visit).

Treatment Visit (Visit 4 [Day 42 ±2 days]):

Subjects will undergo visit-specific procedures.

If SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock, the dose will remain the same if the subject has already been treated with 2 capsules of the IP BID, or the dose will be increased to 2 capsules of the IP BID.

If SBP is <110 mmHg and if the subject was being treated with 2 capsules of the IP BID, the dose will be decreased to 1 capsule of the IP BID.

If SBP is <110 mmHg and if the subject was being treated with 1 capsule of the IP BID, the subject will remain on the same dose (1 capsule BID).

If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study, and the event will be recorded as an AE leading to discontinuation.

In case of any suspicion or symptoms related to hyper- or hypotension, the subjects should contact the site, attend an unscheduled visit, or visit their general practitioner or nearest cardiovascular unit, where a decision on any action with the IP can be made by the investigator or other physician seeing the subject.

Note: the newly allocated dose will be administered as soon as possible after the visit is completed (i.e., on the evening of the day of the visit).

End-of-Treatment Visit (Visit 5 [Day 84 ± 3 days]):

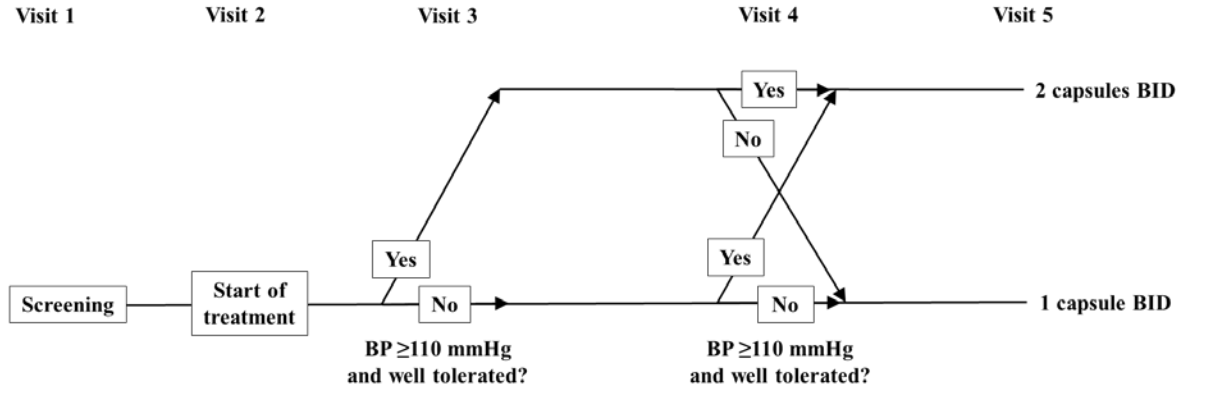
Subjects will undergo End-of-Treatment (EOT) Visit-specific procedures, and the IP will be discontinued. In case of premature discontinuation (except if consent is withdrawn), a CMRI and all Visit 5 procedures, if possible, will be performed as soon as possible and no later than 72 hours after treatment discontinuation.

Follow-up Visit (Visit 6 [Day 114 (±3 days) or 30 days after IP discontinuation]):

For females of childbearing potential only, a serum pregnancy test will be performed.

A schematic presentation of the titration procedure for Groups 1, 2, and 3 is given in Figure 7-2.

Figure 7-2: Study Titration Scheme



If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued.

Efficacy will be assessed by measurement of LVEF, left-ventricular end-diastolic and end-systolic volumes, average peak of longitudinal and circumferential strain in the infarcted segments, and infarct mass by respectively cine and late gadolinium enhancement CMRI all measured with centralized core laboratory reading. In addition, blood levels of biomarkers (NT-proBNP, PIIINP, and CRP) and the slope of decrease in copeptin will be measured, and any MACE (cardiovascular death, new MIs, and cardiac hospitalization) will be documented.

Safety will be assessed by evaluating TEAEs and AESIs (allergic reactions and diabetes insipidus [DI]), clinical laboratory test results (including sodium and potassium blood levels and estimated glomerular filtration rate [eGFR]), vital sign measurements (SBP, diastolic blood pressure [DBP], and HR), 12-lead ECGs, and clinical examination findings.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through Visit 5) will be documented.

A single futility IA is 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.

7.2. Rationale and Discussion of Study Design

This is a randomized, double-blind, active-controlled, dose-titrating study to compare the efficacy and safety of 2 doses of the test product firibastat against that of the approved ACE inhibitor ramipril.

The study population will consist of subjects following first acute anterior MI. It is planned that 294 subjects within 24 hours after acute MI will be randomized at about 38 sites in Europe and in the US.

The primary endpoint of the study will be the change from Baseline in LVEF assessed by CMRI; secondary endpoints will include CMRI regional strain in the infarcted segments and infarct mass, cardiac events, functional status, and change in HF biomarkers. The efficacy and safety assessments in this study are considered as standard in this subject population.

The study is designed to show superiority of the test treatment to the active control. A hierarchical testing procedure will be applied to control the type I error rate since failure to appropriately control the type I error rate can lead to false-positive conclusions.[24]

7.3. Selection of Doses in the Study

According to the clinical studies conducted in healthy subjects, PK results demonstrated good dose proportional exposure to firibastat after repeated oral administration.

The maximal dose of 500 mg BID is expected to be safe since no SAE, no TEAEs, and no important medical event were recorded after repeated oral administrations up to 500 mg BID for 7 consecutive days in healthy male subjects. Firibastat was safe and well-tolerated following oral administration of multiple doses up to 750 mg BID to healthy subjects for 7 consecutive days. Furthermore, in post-MI animal models, after coronary artery ligation, rats were treated daily for 4 weeks with vehicle (peanut butter 5 to 6 g) or QGC001 (150 mg/kg/day) on peanut butter. At 4 weeks post-MI, the left ventricular end diastolic pressure was increased and EF, and the maximum rate of pressure change in the left ventricle (dP/dt_{max}) and left ventricular pulse systolic pressure were decreased as compared to sham-operated rats. The dose of 150 mg/kg of firibastat, which was pharmacologically active in this model, corresponds to a human-equivalent dose of 1440 mg daily normalized to the body surface area and using a conversion factor of 0.16 and a mean body weight in humans of 60 kg. The sponsor, therefore, proposes a maximal dose of 500 mg BID (1000 mg daily), which was a safe diose in healthy volunteers and which was the dose used in phase 2 clinical studies in hypertensive patients.[23]

Ramipril dosing will be done according to the approved summary of product characteristics. The drug is considered to have a favorable cost profile compared to other ACE inhibitors and belongs the preferred ACE inhibitors recommended for the treatment of HF by the European Society of Cardiology[25,26] and the American College of Cardiology Foundation/American Heart Association.[27]

7.4. Study Sites

The study will take place at approximately 38 sites in Europe and in the US. Each site is anticipated to screen a sufficient number of subjects to randomize a total of 294 subjects. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrollment.

7.5. Point of Contact

A point of contact will be identified to provide guidance to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the ICF.

7.6. End of Study Definition

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

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

As specified in Section 13.2, 294 total subjects (98 subjects per treatment group) with a first acute anterior MI will be randomized to achieve a total of 264 evaluable subjects (88 subjects per treatment group).

Subjects who do not meet all of the eligibility criteria will not be enrolled.

A screening log of potential study candidates and an enrollment log must be maintained at each study site.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Subject must provide signed written informed consent. *Important Note: Subject must be willing and able to give informed consent for participation in the study.*
2. Men and women ≥18 years of age at Screening.
3. Diagnosis of first acute anterior MI (STEMI) defined as chest pain >30 minutes and ST elevation ≥0.2 mV in at least 2 consecutive ECG leads in the anterior area (DI, aVL, V1-V6).
4. Primary PCI of the index-MI-related artery within 24 hours after the MI.
5. Women of childbearing potential and non-surgically sterile male subjects who are sexually active must agree to use an approved highly effective form of contraception from the time of informed consent until 30 days postdose. Approved forms of contraception include hormonal intrauterine devices, hormonal contraceptives (oral birth control pills, depot, patch, or injectable), together with supplementary double-barrier methods such as condoms or diaphragms with spermicidal gel or foam.

   Note: The following categories define women who are NOT considered to be of childbearing potential:

   - Premenopausal women with 1 of the following:
     - Documented hysterectomy
     - Documented bilateral salpingectomy
     - Documented bilateral oophorectomy

     OR
   - Postmenopausal women, defined as having amenorrhea for at least 12 months without an alternative medical cause.
6. Women of childbearing potential must have a negative serum pregnancy test result at the Screening Visit.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Body mass index >45 kg/m².
2. Subject is hemodynamically unstable or has cardiogenic shock.
3. Subjects with clinical signs of HF (Kilipp III and IV corresponding to severe HF).
4. Systolic blood pressure <100 mmHg at Inclusion Visit.
5. Early primary PCI of the index-MI-related artery performed within 3 hours after MI. *Important Note: the time of the PCI MUST NOT be delayed because of the protocol; if PCI is performed within 3 hours after MI, the subject is not eligible.*
6. Subjects who require treatment with angiotensin-converting-enzyme inhibitor (ACE-I), ARB, or sacubitril/valsartan after the index magnetic resonance imaging. Note: if treatment was for HTN, ACE-I/ARB should be stopped right before index magnetic resonance imaging, and, if necessary, another therapeutic class can be prescribed for HTN. If the ACE-I/ARB was prescribed for congestive HF, the subject is not considered eligible; if the ACE-I/ARB prescribed for another reason cannot be stopped, the subject is not eligible for study inclusion.
7. Subjects scheduled for implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy, or pacemaker within the next 3 months. If an ICD is indicated for ventricular arrhythmia during the course of the study, a life vest, when possible, should be prescribed and the ICD scheduled after study completion.
8. Subjects with any contraindication related to the CMRI procedure (devices or metal foreign bodies, including pacemaker, defibrillator) including severe claustrophobia according to the lists/safety rules of the local MRI departments.
9. Female who is breast-feeding, pregnant, or planning to become pregnant during the study.
10. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years.
11. Alkaline phosphatase >3 × upper limit of normal (ULN), total bilirubin ≥1.5 × ULN, or direct bilirubin >ULN in subjects with Gilbert's syndrome at the Screening Visit.
12. Estimated glomerular filtration rate <30 mL/min/1.73 m², as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula at the Screening Visit.
13. History of any blood disorder, other than sickle cell trait, causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, hemolytic anemia, thalassemia, or sickle cell anemia).
14. Clinical evidence of thyroid disease, thyroid hormone therapy that is not stable ≥4 weeks prior to Screening, or a thyroid-stimulating hormone (TSH) level <0.75 × lower limit of normal or >1.5 × ULN.
15. History of alcohol or drug abuse within the 3 months prior to the Screening Visit that would interfere with study participation or lead to decreased compliance with study procedures or IP intake in the investigator's opinion.

16. Participation in another clinical study involving an investigational drug within 30 days prior to Screening or if a subject plans to participate in another clinical study within 30 days of discontinuation of the IP.
17. Any condition that in the opinion of the investigator would interfere with study participation, may pose a risk to the subject, or would make study participation not in the best interest of the subject.
18. Subjects with a life expectancy of less than 1 year per investigator's discretion.
19. Any subject who, in the opinion of the investigator, will not be able to follow the protocol.

Section 9.7.3 provides a listing of the contraindications of Ramipril as given in the summary of product characteristics. These restrictions must be checked before any inclusion to ensure that the subject has no contraindication to the administration of Ramipril; otherwise, the subject should be excluded from the study.

8.3. Premature Subject Withdrawal

All subjects will be informed that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw their consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

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 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 will be recorded on the appropriate page of the electronic case report form (eCRF). 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.

8.4. Discontinuation of Study Intervention

If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment will be discontinued for the remainder of the study, and the event will be recorded as an AE leading to discontinuation.

In case a skin reaction is concomitant to fever, blisters on the skin, and/or the mucous membranes of the mouth, nose, eyes and genitals, peeling and shedding skin, which may suggest erythema multiforme or Stevens-Johnson syndrome, the treatment must be immediately discontinued. In this case, the subject should be managed by an experienced team and receive the appropriate symptomatic treatment. All subjects with a skin reaction must be referred to a dermatologist as soon as possible for precise diagnosis, to document the case, to take pictures, and to perform a skin biopsy (for central reading). Skin biopsy samples should be sent to the referent for central reading.

In addition, all the cases will be reviewed by a referent dermatologist. Any allergic skin reaction must be reported as an AESI.

Discontinuation from treatment with firibastat or ramipril does not necessitate discontinuation from the study, and remaining study procedures and all future visits should be completed as indicated in the schedule of events in Section 2.2. If a clinically significant finding is identified (including, but not limited to changes in the subject's health status from Day 1 after enrollment), the investigator or qualified designee will determine whether any change in subject management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation are detailed in the schedule of events in Section 2.2.

8.5. Subject Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression that requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject is unable to receive firibastat/ramipril for a total of 14 consecutive or non-consecutive days during the study

If an allergic reaction, symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment with firibastat or ramipril will be immediately discontinued for the remainder of the study.

A safety check should be performed 3 days after first administration of the IP to ensure the good tolerance of the treatment by the subjects.

In most of the cases, the subjects will be still hospitalized at the site 3 days after first administration of the IP. The investigator will be able to continuously monitor the tolerance of the treatment and immediately react if non-tolerance is suspected. As there is no possibility to decrease the dose of the IP at this stage, in case of non-tolerance of the IP, the subject will be withdrawn from the study.

For subjects discharged early, i.e., before 3 days after the first IP administration, a telephone call to the subject should be performed. If the investigator judges that there is a risk of non-tolerance according to the subject's answers e.g. any suspicion or symptoms related to hyper- or hypotension, the subject will be asked to come to the site for an unscheduled visit. The investigator will then decide whether the subject should be withdrawn from the study.

In all cases, tolerability of the IP should be checked before subject discharge.

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the ICF and are randomized but do not receive the IP may be replaced. Subjects who sign the ICF, are randomized, and receive the IP, and subsequently withdraw or are withdrawn or discontinued from the study, will not be replaced.

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. Details on subject replacement criteria are provided in Section 8.6.

A subject will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study
- Before a subject is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8.6. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study must not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Products

9.1.1 Test Product

Firibastat (QGC001), is a prodrug, a dimer of EC33 ([3S]-3-amino-4-sulfanylbutane-1-sulfonic acid), a selective inhibitor of APA. Firibastat (50 mg or 250 mg) will be provided in opaque white hard hydroxypropyl methylcellulose size-1 capsules. It has been mixed with the following well-known excipients that are all described in the current edition of the European Pharmacopoeia and the US Pharmacopoeia:

- Lactose anhydrous (specific grade "direct tableting high velocity") as diluent
- Povidone 90 (Kollidon 90) as a binder in wet granulation
- Magnesium stearate as lubricant
- Silica, dental type (specific grade RxCIPIENTS GL100, precipitated) as glidant

9.1.2 Reference Product

The active comparator ramipril (Triatec, manufacturer: Sanofi S.p.A., Scoppito [AQ], Italy) will be provided in the form of opaque white hard hydroxypropyl methylcellulose size-1 capsules capsules (2.5 mg each) by the sponsor. The active substance is ramipril; the other ingredients are:

- Hypromellose
- Pregelatinised maize starch
- Microcrystalline cellulose
- Sodium stearyl fumarate
- Yellow ferric oxide (E172)

9.2. Selection of Timing of Dose for Each Subject

Firibastat and ramipril should be taken twice daily, i.e., in the morning and in the evening around the same time each day, with or without food. Details on the IP dosing are provided in Sections 7.1 and 7.3.

9.3. Dose Adjustment Criteria

The IP dose will be increased to 200 mg firibastat daily (Group 1), 1000 mg firibastat daily (Group 2), and 10 mg ramipril daily (Group 3), respectively, if the subject is tolerating the IP and the following criteria are met:

- At Visit 3, if SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock
- At Visit 4, if SBP is ≥110 mmHg without any symptoms of hypotension and/or cardiogenic shock (if the subject is already treated with 2 capsules of the IP BID, the dose will remain the same)

If symptomatic hypotension, symptomatic orthostatic hypotension, or cardiogenic shock occur, the treatment with firibastat or ramipril will be discontinued for the remainder of the study.

Note: the newly allocated dose will be administered as soon as possible after the visit is completed (i.e., on the evening of the day of the visit).

9.4. Treatment Compliance

Study personnel will assess treatment compliance with IP regimens via capsule counts of returned IP and by questioning the subject, if necessary, at every post-randomization visit. A subject who is not compliant (taken <80% or >120% of IP) will be counseled at each visit on the importance of taking the IP as instructed.

9.5. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be 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 will be computer-generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a web-allocation system as subjects are entered into the study.

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

9.6. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified independent, unblinded statistician and programmer, who will have access to the randomization code for interim analysis needs. The unblinded study personnel will 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. A single futility interim analysis is 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. Unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, the study personnel will use the treatment kits allocation web-system available through the EDC system. If the investigator is not able to discuss treatment unblinding in advance with the medical monitor, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate CRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Overall unblinding will take place at the end of the study only after database lock has been achieved.

9.7. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.7.1 Permitted Therapies

Subjects can continue to receive treatment and management for their condition(s) unless the drug and procedure is prohibited by the protocol. Concomitant medications should be limited to those medications considered necessary. Gadolinium chelates will be administered during the CMRI examination for infarct imaging and mass quantification at doses and protocols recommended in standard-of-care CMRI procedures.

9.7.2 Prohibited Therapies

The following therapies are prohibited during the study:

- Subjects who have had treatment with ACE-Is, ARBs, or sacubitril/valsartan prior to index MRI are not allowed to participate in the study. If the treatment was for HTN, ACE-I/ARB should be stopped, and, if necessary, another therapeutic class can be prescribed for HTN. If the ACE-I/ARB or sacubitril/valsartan was prescribed for congestive HF, the subject is not considered eligible; if the ACE-I/ARB prescribed for another reason cannot be stopped, the subject is not eligible for study inclusion. There are no other prohibited concomitant medications to treat HTN other than ACE-I/ARB.
- Subjects who are scheduled for an ICD, cardiac resynchronization therapy, or pacemaker within the next 3 months are not allowed to participate in the study. If an ICD is indicated for ventricular arrhythmia during the course of the study, a life vest, when possible, should be prescribed and the ICD scheduled after study completion.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study, at the discretion of Quantum Genomics, the investigator, and the medical monitor.

9.7.3 Restrictions

The following contraindications as given in the ramipril summary of product characteristics should be taken into account:

- Hypersensitivity to the active substance, to any of the excipients, or any other ACE inhibitors
- History of angioedema (hereditary, idiopathic, or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists)
- Concomitant use of sacubitril/valsartan therapy
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Second and third trimesters of pregnancy
- Ramipril must not be used in patients with hypotensive or hemodynamically unstable states
- The concomitant use of ramipril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m^2)

Investigators and study teams should refer to the section "Contraindications" and "Special warnings and precautions for use" of the current Summary of Product Characteristics.

9.8. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.9. Dispensing and Storage

The IP is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator or designee (e.g., site pharmacist) is responsible for dispensing the IP according to the dosage scheme described in this protocol and for ensuring proper storage of the IP. The acknowledgement of receipt of the IP will be managed via the IP-allocation system.

Until the IP is dispensed to the subjects, it must be stored in a securely locked area, only accessible to authorized personnel, at room temperature (15 to 25°C/59 to 77°F).

9.10. Drug Accountability

The investigator or designee must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received the IP. The investigator or designee will not supply the IP to any person except those named as sub-investigators, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed. The IP may not be relabeled or reassigned for use by other subjects. If any of the not dispensed IPs, are lost, stolen, unusable, or are received in a damaged condition, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (partly used, unused, and empty packaging, e.g., empty bottles) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.11. Labeling and Packaging

Labeling and packaging of the IPs will be performed by Amatsigroup SAS (Saint-Gély-du-Fesc, France).

9.11.1 Labeling

The following information will be included on the label; other information may be included as needed.

- Protocol number
- Unique bottle identifier
- Subject number (record at the time of dispensing)
- Expiry date
- Directions for use
- Package contents (quantity)
- Storage instructions
- Caution: "For clinical trial use only", "Keep out of reach of children" and "New Drug – Limited by United States Law to Investigational Use" (US-specific information).
- Sponsor name and address

Sites should keep all empty packaging and unused IP for accountability and final disposition by the sponsor or site pharmacy.

9.11.2 Packaging

Investigational products will be packaged in white high-density polyethylene child-resistant closure 50 mL bottles of 35 capsules each. In this double-blind study, firibastat and ramipril will be packaged so as to be blinded to the investigator, the study clinic personnel, and subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

The overall study duration is expected to be 19 months (16 months of active enrollment and 3 months of treatment for the last subject included).

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: 1 day (+1 day)
2. Inclusion: 1 day
3. Titration Period: 42 days (±2 days)
4. Treatment Period: 42 days (±3 days)
5. Follow-up Visit for women of childbearing potential only: 1 day

The maximum study duration for each subject is 119 days for women of childbearing potential and 89 days for all other subjects.

The maximum treatment duration for each subject is 87 days.

10.2. Study Visits

Procedures and assessments will be performed at each visit as given in the schedule of assessments in Section 2.2.

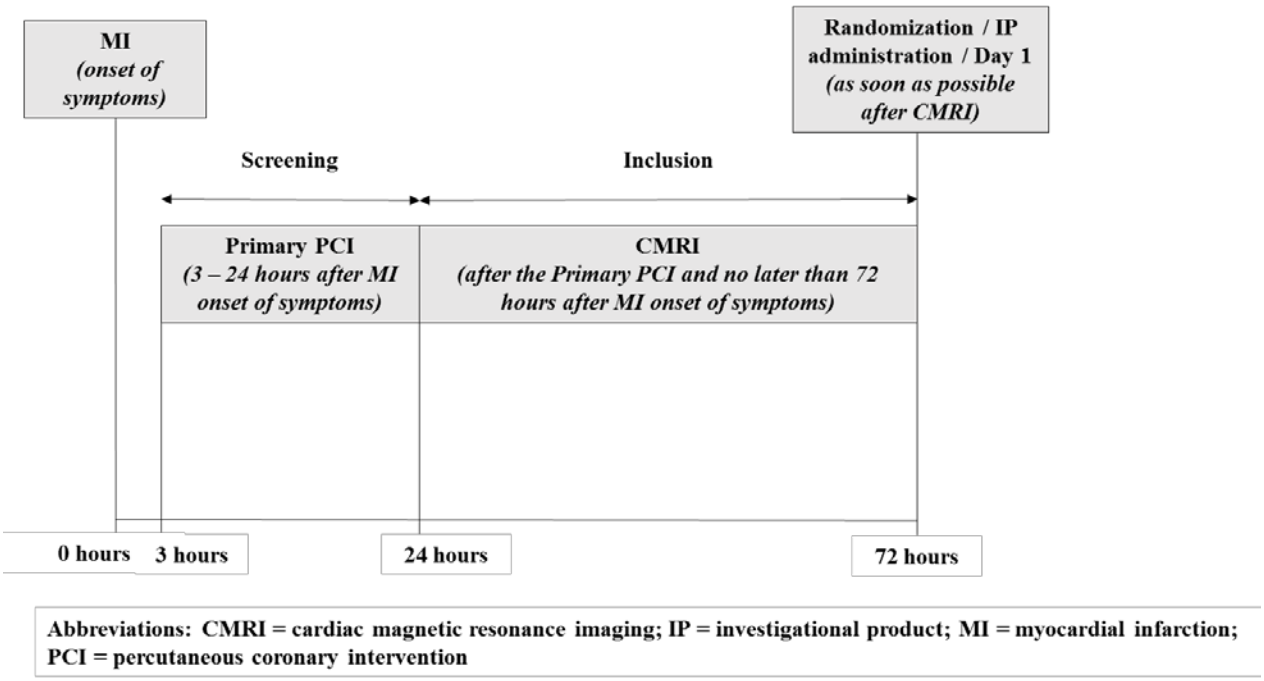


Figure 10-1: Timing of Study Procedures at Screening and Inclusion Visits

10.2.1 Screening Visit (Visit 1; within 24 Hours after Acute Myocardial Infarction [Day -2 - Day 1])

The Screening Visit will occur within 24 hours after index acute MI, defined as the time of onset of symptoms and after primary PCI is performed (no earlier than 3 hours after acute MI and within 24 hours after MI). The subject will sign an ICF before any study-specific procedures are performed. Any standard-of-care procedures performed prior to ICF signature should not be repeated for the purpose of the study if already performed. Subject may be screened even if exclusion criterion 4 (SBP <100 mmHg) is not met at this time (see Section 8.2.2). The following procedures will be performed:

1. Obtain written informed consent and record concomitant medications
2. Assess inclusion/exclusion criteria
3. Collect demographic information
4. Record medical history, including current therapies (e.g., prescription and non-prescription medications)
5. If the subject provided consent for this, capture the subject's coronary angiography performed after MI using the CMRI electronic repository as part of the subject's study documentation
6. Perform a clinical examination, including measurement of height and weight
7. Perform a 12-lead ECG

8. Measure vital signs (SBP, DBP, and HR); the blood pressure will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting for 5 minutes at rest
9. Blood samples for local laboratory assessments (hematology and clinical chemistry, including capture of troponin peak)
10. Conduct a serum pregnancy test for females of childbearing potential

10.2.2 Inclusion Visit (Visit 2; within 72 Hours after Acute Myocardial Infarction [Day 1])

This visit can be done on the same day as the Screening Visit. If the Screening (Visit 1) and the Inclusion (Visit 2) are performed on the same day, procedures applicable for both visits should not be duplicated.

Subjects who meet all the inclusion criteria but none of the exclusion criteria (excluding exclusion criterion 4 [SBP <100 mmHg]) (see Section 8.2.2) will undergo visit-specific procedures, and a baseline CMRI must be performed no later than 72 hours after the MI.

As soon as possible after the CMRI is performed, the subject's blood pressure will be measured, and after confirmation that the subject is eligible (SBP ≥100 mmHg), the site will connect on the treatment kits allocation web system available through the EDC system for randomization information. Subjects will be randomly assigned (Day 1) in a 1:1:1 ratio to receive either 50 mg firibastat BID (Group 1), 250 mg firibastat BID (Group 2), or 2.5 mg ramipril BID (Group 3).

The first capsule of the IP will be administered on Day 1 as soon as possible after CMRI, which will be performed no later than 72 hours after MI. Subjects will then take 1 capsule of the IP BID until the next visit. The following procedures will be performed:

1. Re-assess inclusion/exclusion criteria
2. Measure vital signs (SBP, DBP, and HR); the blood pressure will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting for 5 minutes at rest
3. Conduct CMRI for LVEF, left-ventricular end-diastolic and end-systolic volumes longitudinal and circumferential strain, and infarct mass assessment no later than 72 hours after primary MI
4. Blood samples for central laboratory assessments (biomarkers NT-proBNP, copeptin, PIIINP, and CRP)
5. Connect on the treatment kits allocation web system available through the EDC system for randomization information and treatment kit allocation after CMRI is performed
6. Dispense IP
7. Assess and record AEs and concomitant medications

10.2.3 Safety Check (Day 3)

A safety check should be performed 3 days after first administration of the IP to ensure the good tolerance of the treatment by the subjects.

In most of the cases, subjects will be still hospitalized at the site 3 days after first administration of the IP, and the investigator will be able to continuously monitor the tolerance of the treatment and immediately react if non-tolerance is suspected. As there is no possibility to decrease the dose of the IP at this stage, in case of non-tolerance of the IP the subject will be withdrawn from the study.

For subjects discharged early, i.e., before 3 days after the first IP administration, a phone call to the subject should be performed. If the investigator judges that there is a risk of non-tolerance according to the subject answers to his/her investigation such as any suspicion or symptoms related to hyper- or hypotension, the subject will be asked to come to the site for an unscheduled visit. The investigator will then decide whether the subject should be withdrawn from the study.

In all cases, tolerability of the IP should be checked before subject discharge.

10.2.4 Titration Visit (Visit 3 [Day 14 ± 2 days])

Titration of the IP dose will be done as described in Section 7.1. In addition, the following procedures will be performed:

1. Perform a clinical examination, including measurement of weight
2. Perform a 12-lead ECG
3. Measure vital signs (SBP, DBP, and HR)
4. Blood samples for central laboratory assessments (biomarker copeptin only)
5. Connect on the treatment kits allocation web system available through the EDC system for treatment kits allocation
6. Dispense IP
7. Perform IP compliance check
8. Assess and record AEs and concomitant medications

10.2.5 Treatment Visit (Visit 4 [Day 42 ± 2 days])

Titration of the IP dose will be done as described in Section 7.1. In addition, the following procedures will be performed:

1. Perform a clinical examination, including measurement of weight
2. Perform a 12-lead ECG
3. Measure vital signs (SBP, DBP, and HR)
4. Blood samples for local laboratory assessments (hematology and clinical chemistry)
5. Blood samples for central laboratory assessments (biomarker copeptin only)
6. Connect on the treatment kits allocation web system available through the EDC system for treatment kits allocation
7. Dispense IP
8. Perform IP compliance check
9. Assess and record AEs and concomitant medications

10. Conduct a serum pregnancy test for females of childbearing potential only

10.2.6 End-of-Treatment Visit (Visit 5 [Day 84 ± 2 days])

The following procedures will be performed:

1. Perform a clinical examination, including measurement of weight
2. Perform a 12-lead ECG
3. Measure vital signs (SBP, DBP, and HR)
4. Conduct CMRI for LVEF, left-ventricular end-diastolic and end-systolic volumes, longitudinal and circumferential strain, and infarct mass assessment as soon as possible and no later than 72 hours after treatment discontinuation
5. Blood samples for local laboratory assessments (hematology and clinical chemistry)
6. Blood samples for central laboratory assessments (biomarkers NT-proBNP, copeptin, PIIINP, and CRP)
7. Conduct a serum pregnancy test for females of childbearing potential
8. Discontinuation of IP
9. Perform IP compliance check
10. Assess and record AEs and concomitant medications

10.2.7 Follow-up Visit (Visit 6 [Day 114 ± 3 days] or 30 days after Treatment Discontinuation)

The visit will be performed for females of childbearing potential only. The following procedures will be performed:

1. Conduct a serum pregnancy test for females of childbearing potential

10.3. Assessments

The efficacy variables selected are standard for this indication/subject population.

10.3.1 Efficacy Variables

10.3.1.1 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging is a non-invasive imaging technique in cardiovascular disease that allows a clear delineation of the cardiac anatomy, detailed tissue characterization, and a comprehensive evaluation of global and regional cardiac function. It is considered as the gold standard for evaluating cardiac structure and function along with non-invasive tissue characterization. More specifically, it is widely established as a reference method for the diagnosis and management of ischemic heart disease thanks to its ability to precisely study regional cardiac deformation and provide non-invasive infarct depiction and quantification in clinical practice and research.[28] CMRI has demonstrated the best inter-study reproducibility of all methods for measurement of chamber volumes, ejection fraction and mass, making it an important tool now considered as the gold standard for clinical studies.[29]

CMRI reading and quantitative image post-processing will be performed centrally in a CMRI Core Laboratory. The measurement of LVEF, left-ventricular end-diastolic and end-systolic volumes, longitudinal and circumferential strain, and infarct mass by CMRI will be conducted at the time points detailed in the schedule of events in Section 2.2.

10.3.1.1.1 Left Ventricular Ejection Fraction Measurement by Cardiac Magnetic Resonance Imaging

LVEF is considered as the main imaging prognostic marker after a STEMI. The measurement of LVEF is a strong predictor of mortality in patients with LV dysfunction and has become one of the most common primary endpoints in cardiovascular studies after STEMI.[30] LVEF measurement with CMRI is considered as the gold standard in care and clinical research.[31,32] LVEF will be calculated from end-diastolic and end-systolic LV volumes measured with a semi-automated method and expert validation reading and manual adjustments as necessary.

10.3.1.1.2 Measurement of Left-ventricular End-diastolic and End-systolic Volumes by Cardiac Magnetic Resonance Imaging

The difference between end-diastolic and end-diastolic volumes determine the stroke volume or output of blood by the heart during the cardiac cycle. Impairment of global systolic LV function is the major predictor of mortality after acute MI, which is also indicated by changes in the end-systolic and end-diastolic volumes. End-systolic and end-diastolic volumes have also been related to mortality after MI.[33] To quantify LV volumes and mass, cine acquisitions will be made using retrospectively ECG steady-state free-precession sequences. Two- and 4-chamber long axis cine magnetic resonance images will be acquired and used to prescribe a complete stack of 12 to 14 short axis cine loops, acquired from above the mitral valve plane to the left ventricular apex. LV end-diastolic and end-systolic endocardial and epicardial contours will be semi-automatically traced using established methods with expert validation reading and manual adjustments as necessary. Measurements and readings will be centralized in the CMRI core laboratory.

10.3.1.1.3 Strain Measurement by Cardiac Magnetic Resonance Imaging

Estimating the cardiac ejection fraction is a widely performed global assessment of myocardial function, but many cardiac diseases initially affect the myocardium regionally rather than globally. Myocardial strain analysis is a widely performed technique to quantify the regional myocardial wall motion as a normalized measure of deformation. Initially, tagged-CMRI methods have been considered the non-invasive gold standard to measure myocardial deformation[34], but they require specific and not widely available acquisition sequences. Recently, CMRI feature tracking methods have been proposed to measure strain and were validated in the general population including by our group (REFS).[35,36] This method may be considered as a practical reference for the measurement of regional myocardial strain free from issues related to echogenicity.[37] The validated CARDIO-TRACK (Sorbonne University license) software will be used to study regional average peak longitudinal and circumferential strain in the infarcted segments. Measurements and readings will be centralized in the CMRI core laboratory.

10.3.1.1.4 Measurement of Infarct Mass by Cardiac Magnetic Resonance Imaging

Following MI, multiple large studies have demonstrated that infarct mass measured by CMRI is a stronger predictor of outcome than either LV volumes or ejection fraction.[38,39] Infarct size, measured within 1 month after primary PCI, was shown to be strongly associated with all-cause mortality and hospitalization for HF within 1 year. Therefore, infarct size may be useful as an endpoint in clinical studies and as an important prognostic measure when caring for patients with STEMI.[40] CMRI is the reference non-invasive method to detect and quantify myocardial infarction using late gadolinium enhancement in T1-weighted inversion recovery images. A segmental classification of MI transmurality will be provided as well as infarcted mass in grams and mass indexed to global LV mass in %.[41] Measurements and readings will be centralized in the CMRI core laboratory.

10.3.1.2 Major Cardiac Events

The term 'MACE' is a commonly used endpoint for cardiovascular research. Generally, MACE are defined in studies as a composite of various secondary outcomes, including death, cardiac death, MI, Q-wave MI, stent thrombosis, target lesion revascularization; target vessel revascularization, coronary artery bypass graft surgery, and stroke, whichever occurred first.[42]

For the purpose of this trial, MACE will be defined as cardiovascular deaths, new MIs, and cardiac hospitalizations and will be recorded in the eCRF and adjudicated by an independent committee between the treatment groups.

10.3.1.3 Assessment of Biomarkers

Cardiac biomarkers are cardiac enzymes and cell contents (e.g., troponin I, troponin T, and myoglobin), which are released into the bloodstream after myocardial cell necrosis. The markers appear at different times after injury, and the levels decrease at different rates. Sensitivity and specificity for myocardial cell injury vary significantly among these markers, but the troponins (cTn) are the most sensitive and specific and are now the markers of choice.[43] The consensus guidelines from the European Society of Cardiology and the American College of Cardiology recommend that cardiac markers should be measured at presentation in patients with suspected MI and cardiac troponin should be used for diagnosis of acute MI due to its superior sensitivity and accuracy.[1,44-45]

Blood samples for the determination of biomarkers (NT-proBNP, PIIINP, CRP, and copeptin) will be collected at the specified time points in the schedule of events in Section 2.2 and shipped to the central laboratory for analysis. Details are provided in the laboratory manual.

10.3.2 Safety Variables

Safety will be assessed by evaluating TEAEs and AESIs (allergic reactions, and DI), clinical laboratory test results (including sodium, potassium, AST, and ALT blood levels and eGFR), vital sign measurements (SBP, DBP, and HR), 12-lead ECGs, and clinical examination findings.

10.3.2.1 Clinical Laboratory Safety Assessments

10.3.2.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 2.2).

Hematology:	Red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count
Clinical chemistry:	Sodium, chloride, potassium, blood urea nitrogen, creatinine, ALT, aspartate aminotransferase (AST), alkaline phosphatase, glucose, albumin, bicarbonate, creatinine kinase, TSH, direct bilirubin, and total bilirubin; eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
Biomarkers	NT-proBNP, PIIINP, copeptin, and CRP
Pregnancy test (serum)	For women of childbearing potential only, a serum pregnancy test will be performed at the Screening Visit, Treatment Visit 4 (Day 42), EOT Visit (Day 84), and Follow-up Visit (or 30 days after treatment discontinuation)

If possible, all blood samples for the clinical chemistry tests must be taken in a fasting state, approximately 8 hours after the previous meal.

Each blood sample will be 3.0 to 21.5 mL in volume. The total amount of blood to be drawn during the study will be 60.0 mL per subject, including samples for assessment of hematology, clinical chemistry, biomarkers, and pregnancy testing. The blood volumes to be collected at each visit are specified in Table 10-1.

Table 10-1: Blood Sample Collection Volumes (mL)

	Screening	Inclusion	Titration	Treatment	EOT	Follow-up
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study Day **Panel**	**Day -2 to Day 1**	**Day 1**	**Day 14 (± 2 days)**	**Day 42 (± 2 days)**	**Day 84 (± 3 days)**	**Day 114 (±3 Days) or 30 Days after Treatment Discontinuation**
Hematology	3.0	-	-	3.0	3.0	-
Clinical chemistry[a]	5.0	-	-	3.0	5.0	-
NT-proBNP	-	3.0	-	-	3.0	-
PIIINP	-	5.0	-	-	5.0	-
Copeptin[b]	-	3.0	3.0	3.0	3.0	-
CRP	-	2.5	-	-	2.5	-
Pregnancy test[c]	-	-	-	-		5.0
Total blood volume	8.0	13.5	3.0	9.0	21.5	5.0

Abbreviations: CRP = C-reactive protein; EOT = end-of-treatment; NT-proBNP = N-terminal pro b-type natriuretic peptide; PIIINP = procollagen type III aminoterminal peptide

a. The pregnancy test for females of childbearing potential will be performed from the blood samples collected for clinical chemistry at Visits 1, 4, and 5, but a separate blood sample for pregnancy testing will be collected at Visit 6.
b. The volume required for copeptin assay may need to be updated. The central laboratory will provide the final volume requirement upon validation of the assay.
c. For females of childbearing potential only; a serum pregnancy test will be performed at the Follow-up Visit (or 30 days after treatment discontinuation). The blood volume will depend on the site standard up to a maximum of 5.0 mL.

Laboratory specimens for hematology, clinical chemistry, and pregnancy tests will be analyzed at local laboratories, according to the site's procedures. Blood samples for biomarker measurement will be sent to a central laboratory for analysis, as specified in the central laboratory manual.

10.3.2.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic samples. Procedures and regulations for the packaging and shipping of infectious samples should follow the site's procedures and will be detailed in the central laboratory manual (biomarkers). The investigator or designee is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of biomarkers will be transported to the central laboratory (for address, see laboratory manual).

10.3.2.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Quantum Genomics prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.2.2 Clinical Assessments

10.3.2.2.1 Vital Signs

The SBP and DBP, together with the HR, will be measured at each visit and recorded in the eCRF. The blood pressure will be calculated as the average of 3 measurements (with intervals of 1 to 2 minutes), which will be performed after the subject has been sitting at 5 minutes at rest.

10.3.2.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, initials, date, and time of the recording and will be attached to the subject's notes.

10.3.2.2.3 Clinical Examination

A complete clinical examination (excluding the genitourinary examination) will be performed at each visit and recorded in the eCRF. In addition, height (at Screening only) and weight will be measured.

10.3.2.2.4 Other Safety Variables

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that 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, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity or a change in the quality of the disease or condition (worsening of a preexisting condition is considered an AE).

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an IP related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to an investigational product" means that a causal relationship between an IP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possible" or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were "possible".

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product).

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

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

- Results in death
- Is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-emergent 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.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care or upon review by a study monitor.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Actions Taken

Actions taken may consist of:

Dose increased	An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount.
Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than 1 AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven).

Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Potentially related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related	An AE with evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Definitely related	An AE occurring in a plausible time relationship to IP administration and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate (the period of observation for the study is described in Section 11.2).

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double- or triple-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. Every effort should be made to follow up subjects who continue to experience an AE or an SAE on completion of the study until the AE stabilizes or resolves. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to the contract research organization (CRO) within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the CRO by one of the following methods:

European contact details for 24-hours immediate reporting:

Fax number: +1 215 972 8765
Email: globalPV-US@premier-research.com

US contact details for 24-hours immediate reporting:

Fax number: +421 2 6820 3713
Email: PVDS-ROW@premier-research.com

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- AE term
- Date of occurrence of the event

- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, AE, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the CRO Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Non-serious Adverse Events

A non-serious AE is any AE that does not fulfill the definition of an SAE. All non-serious AEs will be recorded in the eCRF.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

For AESIs with immediate notification, the sponsor is to be informed immediately (i.e., within 24 hours of the investigator's first knowledge), as per SAE notification guidelines, even if a seriousness criterion is not met and whatever its severity grade is. Subjects that report an AESI will be followed until the full disappearance of symptoms. The events described in the following subsections are considered AESIs for this study.

11.3.1.1 Allergic Reactions

Drug reactions deemed to be allergic or have an allergic component that require consultation with another physician for further evaluation of hypersensitivity/allergy, as per the investigator's medical judgment, should be reported as an AESI with immediate notification.

Adverse events that may constitute an allergic reaction could be generalized as itch, nasal itch, flushing, hives, swelling at lips, eyes, face, tongue, hands, or feet, lump in throat, difficulty swallowing, hoarseness, change in pitch of voice, inability to speak, wheezing, chest tightness, stridor, cutaneous reaction, pruritus, etc.

The subjects participating in the clinical studies should be informed by the investigator at site that, as noted in the informed consent form (ICF), in case of occurrence of skin lesions, they must inform their site investigator as soon as possible. In cases where a skin reaction is concomitant to fever or blisters on the skin and/or the mucous membranes of the mouth, nose, eyes, and genitals, and peeling and shedding skin, which may suggest erythema multiforme or Stevens-Johnson syndrome, subjects must immediately stop their investigational treatment and inform their site investigator. In this case, the subject should be managed by an experienced team and receive the appropriate symptomatic treatment. All subjects with skin reactions must be referred to a dermatologist as soon as possible for precise diagnosis, to document the case, to take pictures, and to perform a skin biopsy (for central reading). Skin biopsy samples should be sent to the referent for central reading. Any allergic skin reaction must be reported as an AESI.

The investigator should evaluate the subject for possible etiologies and extra-cutaneous symptoms and signs. Additional blood tests will be performed if necessary according to the guidance of the dermatologist or allergist.

In the setting of skin lesions, whenever possible, the site will take photographs of the skin lesions after receiving the subject's consent. If photos are obtained, then copies should be kept as source documents that may later be collected by the sponsor, and these photos will be forwarded to the dermatologist by the sponsor for a specific opinion. The identity of the subject will be preserved, and his/her face will not be shown on photographs, except for lesions occurring at the level of the subject's face. In this case, the subject's face will be partly masked to avoid identification.

Adverse events with cutaneous involvement that are obviously of allergic origin should be evaluated by a dermatologist as soon as possible and preferably within 7 days of the investigator's first knowledge.

The full report of the dermatologist should include at least a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [e.g., scattered, grouped, or linear], distribution, color, consistency, presence of pruritus or pain, and other clinical signs), and, if a skin biopsy (including histopathology and immunofluorescence) is performed (if deemed necessary as per the dermatologist's or investigator's medical judgment), the results of this investigation with, if applicable, a specific diagnosis for the biopsy. The full report should be sent by the dermatologist to the investigator. Skin biopsy samples should be sent to the referent for central reading.

In case of potential allergic reactions (including delayed hypersensitivity), whatever the intensity of the observed symptoms is, the administration of the tested drug will be immediately stopped, and a symptomatic treatment will be started if needed. This treatment may include oral antihistaminic drugs, oral or intravenous steroids, β2-agonists, or adrenaline if needed.

11.3.1.2 Diabetes Insipidus

One consequence of the inhibition of APA is the decrease of vasopressin. Although not observed in any animal or human subject during the study of firibastat, the suppression of vasopressin holds a theoretical risk for the development of central DI. Symptoms of DI include polyuria, nocturia, and polydipsia. In the setting of suspected DI, the investigator should proceed with a diagnostic evaluation to establish the diagnosis as well as any subsequent management at their discretion. All suspected DI, as per the investigator's medical judgment, should be reported as an AESI with immediate notification.

11.3.2 Pregnancy

Fertility and teratology studies with firibastat have been conducted, and the results indicate that women of childbearing potential could participate provided that they are using an appropriate form of contraception (as defined in inclusion criterion 5 in Section 8.2.1).

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential at Screening, Visit 4 (Day 42), EOT Visit, and Follow-up Visit (or 30 days after treatment discontinuation). A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A female subject who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy of a female study subject, as well as a male subject's female partner, as if it were an SAE within 24 hours of learning of the pregnancy to the CRO Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an Exposure in Utero form/SAE and AE form (entering the event temporarily as non-serious on both forms)/other designated form provided by the CRO.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form/SAE and AE form/other designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.3 Overdose

At present, there are no data available for overdose in humans. If overdose does occur in humans, administration of firibastat should be discontinued, and necessary measures should be taken for support of vital functions.

The maximal dose of firibastat should not be exceeded during the study. Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated

individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, subject identification, IP, dose, action taken (e.g., supportive measures or therapy), and any comments.

12. INDEPENDENT DATA MONITORING COMMITTEE

Safety oversight will be under the direction of an independent data monitoring committee (IDMC), composed of individuals with the appropriate expertise, including cardiology. It will also include an independent statistician who will be in charge of the interim analysis corresponding to efficacy and safety data. Members of the IDMC will be independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The IDMC will meet at least semi-annually to assess safety data on each arm of the study (unblinded for treatment). The IDMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the IDMC prior to the start of the study. At this time, each data element that the IDMC needs to assess will be clearly defined. The interim analysis, planned to assess futility, will be performed when approximately 50% of the maximum number of subjects have completed the Day 84 primary endpoint assessment, for the comparison of firibastat 50 mg against ramipril. Details are provided in Section 13.1.6.

The IDMC will provide its input to Quantum Genomics. In case of significant safety concerns, the IDMC may recommend stopping recruitment in a particular dose group. The IDMC may also recommend dropping the firibastat 50 mg arm if a substantially low treatment effect compared to ramipril is demonstrated as the outcome of futility interim analysis.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock. Any changes from the planned analyses will be described and justified in the final clinical study report (CSR).

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

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

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 will be 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.

Continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum). Frequency distribution (counts and percentages) will be summarized for the categorical variables. When applicable, 95% confidence interval (CI) of the mean (or the median) will be provided for continuous variables, and the 95% CI of the proportion will be displayed for each modality of categorical variables.

For each analyzed parameter, the normality assumption of model residuals distribution will be 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 will be primarily done, and the statistical analysis model will be applied to ranks.

13.1.1 Analysis Populations

The following 4 analysis populations are planned for this study:

- Safety population: The safety population will consist of all subjects who receive at least 1 dose of the IP. This population will be based on the treatment actually received by the subject and will be used for the analysis of the safety endpoints.
- Intent-to-treat (ITT) population: The ITT population will consist of all randomized subjects. This population will be based on the treatment to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.

- Modified intent-to-treat (mITT) population: The mITT population will consist of all randomized subjects who receive at least 1 dose of the IP and who have at least 1 baseline and 1 post-randomization efficacy assessment (CMRI) on treatment. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of the efficacy endpoints.
- Per-protocol (PP) population: The PP population will consist of all subjects from the mITT population without any major protocol deviation. This population will be considered for sensitivity analysis of the primary endpoint.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.1.2.2 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The non-compliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the relevant regulatory bodies as applicable and sponsor. Protocol deviations must be sent to the reviewing IRB/IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

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

13.1.2.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment group on the mITT population.

Demographic variables will include age, gender, height, and weight.

Baseline subject characteristics will include medical history, clinical examination findings, and results of the coronary angiography defining the success or not of the procedure (TIMI 3 or not).

If the subject provided consent for this, the subject's coronary angiography performed after MI at Screening will be captured using the CMRI electronic repository as part of the subject's study documentation. Coronary angiography reading will be performed centrally in a core laboratory.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms (PTs).

13.1.3 Exposure and Compliance

Investigational product administration will be 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, will be provided by treatment group.

All intake details per subject will be provided in data listings.

13.1.4 Efficacy Analysis

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

For efficacy variables, descriptions will be given by treatment group at each assessment time. The change from Baseline will be also presented if applicable.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint:

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

Secondary endpoints:

- Change from Baseline to Day 84 in left-ventricular end-diastolic and end-systolic volumes assessed by CMRI
- Change from Baseline to Day 84 in average peak of longitudinal and circumferential strain in the infarcted segments assessed by CMRI
- Infarct mass at EOT (Day 84) assessed by CMRI
- 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

13.1.4.2 Primary Efficacy Endpoint Analysis

The analysis of the primary efficacy endpoint will be based on the mITT population.

Primary analysis of the primary efficacy endpoint:

The change from Baseline in LVEF will be primarily analysed using an ANCOVA. The ANCOVA will include 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 will be considered in the analysis. Pattern of study premature discontinuations including the profile of subjects and reason and time to withdrawal will be presented to assess potential impact of dropouts on treatment comparisons.

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

Model assumptions checking:

Assumptions underlying ANCOVA (residuals distribution normality, heteroscedasticity, etc.) will be checked using graphical methods, skewness and kurtosis values, and Shapiro-Wilk's statistic.

Possible treatment-by-covariate interactions will be investigated including the interaction term in the model for ANCOVA (1 separated model for each interaction).

Sensitivity analyses of the primary efficacy endpoint:

While subjects missing Day 84 data but having earlier data will be included in the primary analysis, the interpretability of the results from the primary model will depend on the missing data satisfying the missing at random. To support the validity of the conclusions drawn from this analysis, sensitivity analyses will be performed to explore possible impact of dropout pattern on treatment comparisons.

1. An ANCOVA will be performed on the value recorded on Day 84 (i.e., the measurement made at the time of the study premature discontinuation will not be considered in the analysis)
2. A sensitivity analysis will be performed using a multiple imputation method that will be further detailed in the SAP

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

13.1.4.3 Secondary Efficacy Endpoints Analyses

Secondary efficacy endpoints will be analyzed on the mITT population.

As for the primary efficacy endpoint, a hierarchical step-down testing procedure will be 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 change from Baseline in left-ventricular end-diastolic and end-systolic volumes assessed by CMRI will be 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 change from Baseline in the average peak of longitudinal and circumferential strain in the infarcted segments assessed by CMRI will be 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 will be analyzed using an ANCOVA. The ANCOVA will include treatment group as factor and country as covariate.

MACE:

The MACE (i.e., cardiovascular deaths, new MIs, and cardiac hospitalizations) which occurred during the course of the study will be adjudicated by an independent committee. The number of committee-confirmed events per subject will be described per category. The time to first confirmed MACE will be tested using censored data analysis. Median time with 95% CI will be estimated using the Kaplan-Meier method. Number and percentage of subjects who had an event or were censored will also be reported. A Kaplan-Meier survival curve will be generated by treatment group.

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

The change from Baseline in NT-proBNP, PIIINP, and CRP will be 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 will be assessed at each visit. The change from Baseline in copeptin will be analyzed using a mixed model for repeated measures (MMRM) where intercept and slope will be considered as random. The model will include treatment group as fixed factor, Baseline value and country as covariates, and time, treatment group by time interaction, and Baseline by time interaction. Time will be calculated in days as date of copeptin assessment - date of first study treatment intake. The restricted maximum likelihood (REML) estimation approach will be used, and the default covariance structure will be unstructured.

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

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

13.1.5 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1). Safety variables include TEAEs, clinical laboratory values, vital signs (SBP, DBP, and HR measurement), 12-lead ECG readings, and clinical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.1.5.1 Adverse Events

All AEs, whether serious or non-serious, will be reported from signing the ICF until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. For AE reporting, the verbatim term recorded in the eCRF by the investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities, Version 21.1 or higher.

Treatment-emergent AEs are defined as:

- Adverse events with onset at the time of or following the start of treatment with IP through the EOT Visit (Day 84) or Early Termination Visit, whichever occurs first, or
- Adverse events starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first

The AEs will be summarized by frequency and proportion of subjects by treatment group, by SOC, and PT. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment.

The following AEs of clinical and special interest will be summarized separately:

- Allergic reactions
- Diabetes insipidus

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

13.1.5.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be 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, will be 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 will also be 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 will also be shown in a data listing.

Blood level in sodium, potassium, AST, and ALT and the eGFR calculated value, as well as corresponding changes from Baseline, will be described at each visit by treatment group.

13.1.5.3 Vital Signs

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

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from Baseline (shift tables) for each parameter by treatment group and by study visit.

13.1.5.4 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point.

13.1.5.5 Clinical Examination Findings

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline in weight will be presented at each visit and by treatment group.

13.1.6 Interim Analysis

One single futility IA is 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. However, if the dynamic of subject inclusion in the study is faster than expected, it could be decided to not perform the IA if the time of delivery of IA results is deemed too close to the end of the recruitment period.

This futility IA was put in to allow for dropping firibastat 50 mg arm if a substantially low treatment effect compared to ramipril is demonstrated. The futility stopping rule is based on a group-sequential design using the beta-spending O'Brien-Fleming approach. If firibastat 50 mg does not pass the futility boundaries (i.e., if futility of firibastat 50 mg against ramipril is demonstrated), then the treatment arm will be dropped due to lack of efficacy.

The IA to assess futility of firibastat 50 mg will be performed by an independent data monitoring committee (IDMC) using the primary model of analysis. Additional details of the IA will be provided in an IDMC charter that will be written and validated before the IA database lock.

13.2. Sample Size Determination

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.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Quantum Genomics agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The study will be conducted in accordance with ICH GCP and applicable regulations. The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, documented approval from the IRB/IEC, except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed human subject's protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IPs, and their specific duties within the context of the study. Investigators are responsible for providing Quantum Genomics with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, institutional policies, or sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at Aixial. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Aixial research staff will be secured and password protected.

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee
3. The study site has a clinical trial agreement in place
4. Study site personnel, including the principal investigator, have participated in a study initiation visit or have been trained appropriately if visit attendance is not possible

14.3. Screen/Randomization Failures

Due to the nature of the study population (subjects to be randomized at a maximum of 24 hours after acute MI), rescreening will not be possible.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. Randomization failures are defined as subjects who were randomized but not treated. A minimal set of information is required to ensure transparent reporting of those subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Quantum Genomics for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject, and written documentation of informed consent is required prior to starting intervention/administering study intervention. The ICF and subject's card are submitted as consent materials with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/IEC-approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below:

- Signed original protocol (i.e., investigator's agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the local and central laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Any other relevant GCP documents

The regulatory and GCP documents must be received from the investigator and reviewed and approved by Quantum Genomics or its designee before the study site can initiate the study and before Quantum Genomics will authorize shipment of IP to the study site. Copies of the investigator's regulatory and GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the firibastat IB, eCRF completion guidelines, copies of regulatory correspondence and approvals, copies of IRB/IEC correspondence and approvals, and IP accountability records should also be retained as part of the investigator's regulatory and GCP documents. It is the investigator's responsibility to ensure that copies of all required regulatory and GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the investigator's agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF/EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the eCRF/EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

The following data are to be recorded directly on the eCRFs (i.e., no prior written or electronic record of data) and considered to be source data: hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Quantum Genomics and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Quantum Genomics and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Quantum Genomics personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review the following items:

- Regulatory documents, directly comparing entries in the eCRF system with the source documents
- Consenting procedures

- AE procedures
- Storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study plan. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the investigator's agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Quantum Genomics or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan.

14.5.2 Data Management

Quantum Genomics or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study plan.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Quantum Genomics or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., protocol and/or CSR)

Quantum Genomics or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Quantum Genomics immediately.

14.6. Study Termination

The study may be terminated at Quantum Genomics' discretion at any time and for any reason.

The IDMC may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Quantum Genomics or designee will notify the IRBs/IECs and regulatory authorities on the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Quantum Genomics, IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Quantum Genomics or its designee will notify the IRBs/IECs and regulatory authorities on the premature termination as required according to national laws and regulations. Quantum Genomics or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform study subjects, the IRB/IEC, and sponsor and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or regulatory authority.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Quantum Genomics may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Non-compliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

After completing the study, Quantum Genomics will receive the original CRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at the central laboratory either in Europe or the USA, depending on the biomarker to be analyzed. After the study is completed, the archived data will be transmitted to and stored at Quantum Genomics for use by other researchers, including those outside of the study. Permission to transmit data to Quantum Genomics will be included in the informed consent.

These samples could be used to provide information on the diagnosis of MI and risk stratification, to assess the degree of damage and assist in deciding management, as well as to reflect the repair process and scar formation after MI.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Quantum Genomics. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning firibastat, Quantum Genomics' operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Quantum Genomics or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Quantum Genomics. Electronic case report forms also remain the property of Quantum Genomics. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Quantum Genomics in connection with the continued development of firibastat and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Quantum Genomics. Publication or other public presentation of firibastat data resulting from this study requires prior review and written approval of Quantum Genomics. Abstracts, manuscripts, and presentation materials should be provided to Quantum Genomics for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Quantum Genomics has reviewed and commented on such a presentation or manuscript for publication. This study will be registered at ClinicalTrials.gov and ClinicalTrialsRegister.eu, and results information from this study will be submitted to both databases.

15. FINAL CLINICAL STUDY REPORT

Quantum Genomics will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results, based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

See Appendix B for regulation and guidelines.

16.2. Subject Information and Informed Consent and/or Assent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Quantum Genomics, and/or the sponsor's designee. Collection of informed consent has to be documented on the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

For IND studies, the minimum standards of conduct and requirements for informed consent and/or assent are defined in the Food and Drug Administration (FDA) regulations.

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor form, IRB/IEC approval form, or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Quantum Genomics before implementation. This written approval will consist of a completed IRB/IEC approval form or written documentation from the IRB/IEC containing the same information.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER: QGC001-2QG4

PROTOCOL TITLE: 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

FINAL PROTOCOL: Global Amendment V3.0, 10-Oct-2019

The undersigned acknowledges possession of and has read the product information (e.g., the IB) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Quantum Genomics.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Quantum Genomics within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Quantum Genomics and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name:

Signature: _____

Date: _____

Investigator's name and address (stamp) _____

APPENDICES

A. Study-specific Requirements

Killip Classification for HF

The Killip classification[46] is widely used in patients presenting with acute MI for the purpose of risk stratification, as follows:

- Killip class I includes individuals with no clinical signs of heart failure
- Killip class II includes individuals with rales or crackles in the lungs, an S_3 gallop, and elevated jugular venous pressure
- Killip class III describes individuals with frank acute pulmonary edema
- Killip class IV describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure <90 mmHg), and evidence of low cardiac output (oliguria, cyanosis, or impaired mental status)

B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf