# SYNOPSIS

**Title of the study:** 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 (QUORUM) (QGC001-2QG4).

**Indication:** Prevention of left ventricular dysfunction after acute anterior myocardial infarction.

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**Study centers:** 33 European active centers (i.e., with patients randomized), within 7 countries (France, Germany, Hungary, Poland, Spain, Slovakia, UK).

**Publications (reference):** N.A.

**Study period:**

Date first patient enrolled: 04-JUN-2019
Date last patient enrolled: 12-APR-2021
Date last patient completed: 08-JUL2021

**Phase of development:** Phase II

**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 amino-terminal 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 myocardial infarction (MI) or hypertension (HTN). 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 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 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 patients 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. The 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).

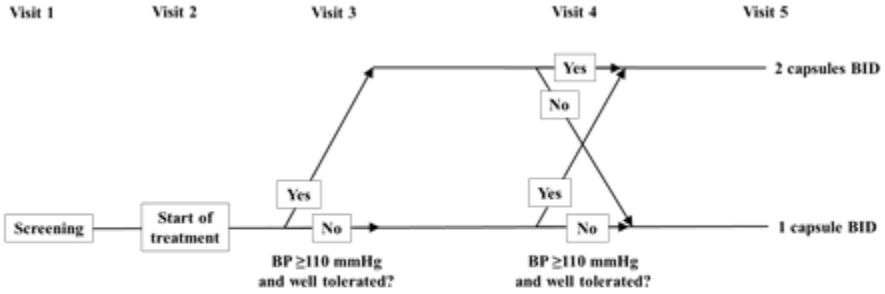
**Methodology:** This was a multicenter, randomized, double-blind, active-controlled, dose-titrating phase 2 study to evaluate the safety and efficacy of BID firibastat administered orally (2 daily doses) *vs* BID ramipril administered orally over 12 weeks after acute anterior MI. Patients were followed for 12 weeks over 5 study visits (about 16 weeks over 6 study visits for women of childbearing potential). A total of 295 male and female patients with a diagnosis of first acute anterior MI were randomized. The patients had a primary percutaneous coronary intervention (PCI) of the index-MI-related artery within 24 hours after MI. Patients were randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:

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

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

Baseline was defined as the day when the CMRI was performed, and the first investigational product (IP) dose was taken. Day 84 was the day of treatment discontinuation (i.e., 84 days [±3 days] after the Inclusion Visit [Day 1]).

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 had to be discontinued.

**Number of patients:** Planned: 294 randomized patients to reach 264 evaluable patients (88 patients *per* group).

Randomized: 295 patients.

Treated: 294 patients.

**Study entry criteria:** The population for this study corresponds to patients with a first acute anterior MI treated with primary PCI.

Inclusion criteria:

1. Patient must provide signed written informed consent (ICF). *Important Note: Patient 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 patients 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:*

*- 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. Patient is hemodynamically unstable or has cardiogenic shock.

3. Patients with clinical signs of HF (Killip 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 patient is not eligible.*

6. Patients 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 patient is not considered eligible; if the ACE I/ARB prescribed for another reason cannot be stopped, the patient is not eligible for study inclusion.*

7. Patients 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. Patients 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 Magnetic Resonance Imagery (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 x upper limit of normal (ULN), total bilirubin ≥1.5 x ULN, or direct bilirubin >ULN in patients with Gilbert's syndrome at the Screening Visit.

12. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2, 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 (i.e., 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 x lower limit of normal or >1.5 x 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 patient 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 patient, or would make study participation not in the best interest of the patient.

18. Patients with a life expectancy of less than 1 year per investigator's discretion.

19. Any patient 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 patient has no contraindication to the administration of Ramipril; otherwise, the patient should be excluded from the study.

**Study treatments**

**Investigational medicinal product (IMP): firibastat (QGC001)**

Patients received either:

- Group 1: one 50 mg capsule of firibastat 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 patients' dosage was up-titrated and/or down-titrated according to a specific titration procedure).

OR

- Group 2: one 250 mg capsule of firibastat 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 patients' dosage was up-titrated and/or down-titrated according to a specific titration procedure).

**Control product: ramipril**

Patients received:

- Group 3: one 2.5 mg capsule of ramipril 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 patients' dosage was up-titrated and/or down-titrated according to a specific titration procedure).

**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 89 days for all patients – except 119 days for women of childbearing potential.

The maximum treatment duration for each patient is 87 days.

**Criteria for evaluation:**

**Efficacy endpoints:**

*Primary efficacy endpoint:*

The primary efficacy endpoint was 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 to Day 84 in NT proBNP, PIIINP, and CRP levels.
- Slope of decrease in copeptin over time.

**Safety endpoints:**

Safety assessments included:

- All AEs, adverse events of special interest (AESIs), which include allergic reactions and diabetes insipidus, and clinical laboratory evaluations.
- Change from baseline in clinic systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at each visit.
- Change from baseline in sodium, potassium, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) blood levels and eGFR.

Every effort was made to follow up patients who continued to experience an AE or a serious adverse effect (SAE) on completion of the study until the AE stabilized or resolved.

**Independent data monitoring committee:** An independent data monitoring committee (IDMC), consisting of independent physicians qualified to treat the study population was established for the regular unblinded review of emerging safety data.

**Adjudication Committee for Allergic Skin Reaction:** An independent committee consisting of 3 independent physicians qualified in dermatology was established for the review and the adjudication of all skin reaction events.

**Adjudication Committee for Major Cardiovascular Events (MACE):** An independent committee consisting of independent physicians qualified in cardiology was established for the review and the adjudication of all MACE.

**Statistical methods**

**Analysis populations:**

The following analysis populations were considered:

- Safety population: the safety population consisted of all patients who received at least 1 dose of the IP. This population was based on the treatment actually received by the patient and was used for the analysis of the safety endpoints.
- Intention-to-treat (ITT) population: the ITT population consisted of all randomized patients. This population was based on the treatment to which the patient was randomized. Any patient who received an allocated kit number was considered to have been randomized.
- Modified intention-to-treat (mITT) population: the mITT population consisted of all randomized patients who received at least 1 dose of the IP, and who had at least 1 baseline (before or within 8 hours of taking the first IP) and 1 post-randomization efficacy assessment (LVEF). This population was based on the treatment to which the patient was randomized and was the primary population for the analysis of the efficacy

endpoints.

- Per-protocol (PP) population: the PP population consisted of all patients from the mITT population without any major protocol deviation. This population was considered for sensitivity analysis of the primary endpoint.

**Patient characteristics and disposition:**

The number of patients in each analysis population was provided overall and by treatment group. Demographics and baseline characteristics were summarized overall and by treatment group on the mITT population.

**Efficacy analyses:**

The primary efficacy endpoint was primarily analyzed on the mITT population. Sensitivity analyses were performed on the ITT and PP populations. The secondary efficacy endpoints were analyzed on the mITT population.

*Primary analysis of the primary efficacy endpoint:*

The change from baseline in LVEF was primarily analyzed using an analysis of covariance (ANCOVA). The ANCOVA included treatment group as factor and baseline LVEF and country as covariates. For patients who prematurely discontinued the study, measurements made at the time of study withdrawal were considered in the analysis.

The adjusted mean was presented by treatment group. Differences in adjusted mean between treatment groups, associated 95% confidence interval, and P value were 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 was performed to explore the possible impact of dropout pattern on treatment comparisons.

*Secondary efficacy endpoints:*

As for the primary efficacy endpoint, a hierarchical step-down testing procedure was 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 were descriptive and performed on the safety population.

*Vital signs:*

The SBP, DBP, and heart rate (HR), as well as the corresponding changes from baseline, were 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, were described at each visit by treatment group.

*Adverse events:*

All AEs, whether serious or non-serious, were 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 was coded using the latest version of Medical Dictionary for Regulatory Activities (Version 23.0).

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.

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

- Skin reactions reviewed by the dermatologists.
- Diabetes insipidus (DI).

**Summary:**

**Analysis populations:**

| N (%) | Firibastat 100 mg BID | Firibastat 500 mg BID | Ramipril 5 mg BID | Total |
|---|---|---|---|---|
| Randomized patients | | | | 295 |
| ITT population | 98 (100%) | 99 (100%) | 98 (100%) | 295 (100%) |
| Safety population | 98 (100%) | 98 (99.0%) | 98 (100%) | 294 (99.7%) |
| mITT | 72 (73.5%) | 77 (77.8%) | 80 (81.6%) | 229 (77.6%) |
| PP | 56 (57.1%) | 48 (48.5%) | 66 (67.3%) | 170 (57.6%) |

ITT= Intention-to-treat; mITT= modified intention-to-treat; PP= Per protocol; N= Number of patients in the treatment group; %= Percentage of patients based on available data; BID= Bis In Die.

**Population characteristics:**

Patients' demographic and clinical characteristics at baseline were well balanced between the treatment groups in the mITT population. The mean age of patients was 58.2 ±10.8 years, and there was a male predominance (76.0% of the mITT population). The mean BMI was 27.86 ±4.43 kg/m$^2$, 25.3% of the patients were obese (BMI >30 kg/m$^2$). Hypertension was the leading cardiovascular risk factor in 54.1% of patients followed by dyslipidemia in 40.6% of patients. 217 (94.8%) patients were Killip class I and the remaining 12 (5.2%) patients were Killip class II. RAS blockers were taken by 89 (38.9%) patients before enrollment. Most of the patients (93.8%) had normal baseline eGFR >60 mL/min/1.73 m$^2$.

Most of the patients had an antero-septal (V1-V3) MI (95.6%) with Left anterior descending (LAD) arteries lesions (96.9%). 96.5% of patients underwent successful PCI with TIMI (thrombolysis in myocardial infarction) III flow (according to the investigator) and 91.2 % according to the central reading. The mean time from onset of MI to PCI was 6.2 ±4.9 hours (<6 hours for 66.4% of patients). The mean troponin peak concentration at baseline was 30.65 ±60.63 µg/L.

**Efficacy results:**

**Primary efficacy endpoint**

The change in LVEF from baseline to EOT (Day 84) assessed by CMRI, was primarily analyzed on the mITT population. Sensitivity analysis was performed on the PP population.

<u>mITT population</u>

LVEF increased from baseline to EOT in all three groups:

• The mean change was 6.55 ±6.32% in the firibastat 100 mg BID group (95%CI= 5.07;8.04), 6.32 ±9.65% in the firibastat 500 mg BID group (95%CI= 4.13;8.51), and 7.20 ±9.10% with ramipril (95%CI= 5.17;9.22).

• Using ANCOVA model with treatment, treatment group as factor, baseline LVEF and country as covariates, the adjusted mean change in LVEF from baseline to EOT was 5.62 ±1.16% in the firibastat 100 mg BID group, 5.31 ±1.11% in the firibastat 500 mg BID group, and 5.66 ±1.12% with ramipril. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in LVEF from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was -0.36 ±1.32% (95%CI= -2.97;2.26, p=0.789).

<u>PP population</u>

LVEF increased from baseline to EOT in all three groups:

• The mean change was 7.12 ±6.34% in the firibastat 100 mg BID group (95%CI= 5.42;8.82), 7.16 ±9.96% in the firibastat 500 mg BID group (95%CI= 4.27;10.05), and 6.67 ±9.30% with ramipril (95%CI= 4.38;8.95).

• The adjusted mean change was 4.94 ±1.43% in the firibastat 100 mg BID group, 5.23 ±1.51% in the firibastat 500 mg BID group, and 4.08 ±1.36% with ramipril. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in LVEF from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 1.15 ±1.58% (95%CI= -1.96;4.26, p=0.466).

**Secondary efficacy endpoint**

The secondary efficacy results presented below pertain to the mITT population.

**Change in left-ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) from baseline to EOT**

**LVEDV**

LVEDV increased from baseline to EOT in all three groups:

• The mean change was 14.92 ±30.45 mL in the firibastat 100 mg BID group (95%CI= 7.76;22.08), 12.90 ±31.96 mL in the firibastat 500 mg BID group (95%CI= 5.64;20.15), and 9.68 ±32.36 mL with ramipril (95%CI= 2.48;16.89).

• The adjusted mean change was 14.17 ±4.50 mL in the firibastat 100 mg BID group, 12.66 ±4.28 mL in the firibastat 500 mg BID group, and 9.37 ±4.35 mL with ramipril. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in LVEDV from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 3.29 ±5.13 mL (95%CI= -6.81;13.39, p=0.521).

**LVESV**

LVESV decreased from baseline to EOT in all three groups:

• The mean change was -1.99 ±21.89 mL in the firibastat 100 mg BID group (95%CI= -7.13;3.16), -1.74 ±25.46 mL in the firibastat 500 mg BID group (95%CI= -7.52;4.04), and -4.84±23.23 mL with ramipril (95%CI= -10.02;0.32).

• The adjusted mean change was -0.45 ±3.34 mL in the firibastat 100 mg BID group, -0.39 ±3.19 mL in the firibastat 500 mg BID group, and -3.14 ±3.24 mL with ramipril. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in LVESV from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 2.75 ±3.82 mL (95%CI= -4.79;10.28, p=0.473).

**Infarct mass at EOT**

• The mean myocardial infarct mass at EOT was 21.31 ±15.67 g in the firibastat 100 mg BID group, 25.38 ±16.57 g in the firibastat 500 mg BID group and 25.32 ±17.70 g in the ramipril group.

• The adjusted mean myocardial infarct mass at EOT was 22.76 ±2.72 g in the firibastat 100 mg BID group, 27.19 ±2.79 g in the firibastat 500 mg BID group, and 27.15 ±2.59 g in the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on myocardial infarct mass at EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 0.04 ±3.08 g (95%CI= -6.04;6.12, p=0.991).

**Major adjudicated cardiac events (MACEs) over 84 days**

• Overall, 10 MACEs occurred in 8 (8.2%) patients in the firibastat 100 mg BID group, 8 MACEs in 6 (6.1%) patients in the firibastat 500 mg BID group, and 6 MACEs in 5 (5.1%) patients in the ramipril group. No MACE was considered as treatment-related.

• 5 cardiovascular events leading to death were reported in the study for 4 patients (i.e., one patient had 2 MACEs reported as concomitant events, fatal outcome was reported for both events).

• New MIs happened in 3 patients both in the firibastat 100 mg BID and ramipril groups (none in the firibastat 500 mg BID group).

• Hospitalization due to MACE was recorded for 6 patients (6.1%) both in the firibastat 100 mg and 500 mg BID groups, and 2 patients (2.0%) in the ramipril group.

**Change in biomarkers from baseline to EOT**

**NT-proBNP**

NT-proBNP level decreased from baseline to EOT in all three groups:

• The mean change was -1360.0 ±1381.7 pg/mL in the firibastat 100 mg BID group (95%CI= -1710.8;-1009.1), -1596.4 ±2279.6 pg/mL in the firibastat 500 mg BID group (95%CI= -2136.0; -1056.8), and -1735.6 ±2326.5 pg/mL in the ramipril group (95%CI= -2290.3;-1180.8).

• The adjusted mean change was -1618.7 ±113.1 pg/mL in the firibastat 100 mg BID group, -1467.2 ±104.2 pg/mL in the firibastat 500 mg BID group and -1741.0 ±107.3 pg/mL in the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in NT-proBNP from baseline to EOT, but there was a trend in favor of ramipril as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 246.8 ±127.0 pg/mL (95%CI= 3.6;497.3, p=0.053).

**CRP**

CRP level decreased from baseline to EOT in all three groups:

• The mean change was -26.97 ±39.30 mg/L in the firibastat 100 mg BID group (95%CI= -36.63;-17.30), -29.12 ±42.44 mg/L in the firibastat 500 mg BID group, and -32.13 ±39.37 mg/L in the ramipril group (95%CI= -41.38;-22.87).

• The adjusted mean change was -29.63 ±0.97 mg/L in the firibastat 100 mg BID group, -29.92 ±0.90 mg/L in the firibastat 500 mg BID group, and -30.10 ±0.94 mg/L in the ramipril group. The adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 0.18 ±1.10 mg/L (95%CI= 1.99;2.35, p=0.870).

**Change from baseline to EOT in copeptin blood level and copeptin slope value**

• Copeptin blood level decreased from baseline to EOT in all three groups: the mean change was -1.07 ±5.56 pmol/L in the firibastat 100 mg BID group (95%CI= -2.85;0.71), -1.56 ±6.77 pmol/L in the firibastat 500 mg BID group (95%CI= -3.70;0.57), and -1.23 ±6.82 pmol/L in the ramipril group (95%CI= -3.33;0.87).

• The slope values for each group decreased: -0.0005 in the firibastat 100 mg BID group, -0.0008 in the firibastat 500 mg BID group, and -0.0005 in the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on the evolution of copeptin as the adjusted slope difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was -0.0004 (95%CI= -0.0013;0.0006, p=0.473).

**Subgroup efficacy analyses**

**Change in LVEF from baseline to EOT in the subgroup of patients with baseline LVEF <50%**

LVEF increased from baseline to EOT in all three subgroups:

• The mean change was 6.51 ±6.99% within the firibastat 100 mg BID group (95%CI= 3.95;9.08), 8.85 ±10.04% within the firibastat 500 mg BID group (95%CI= 5.46;12.25), and 7.83 ±9.27% within the ramipril group (95%CI= 4.94;10.72).

• The adjusted mean change was 2.67 ±1.76% within the firibastat 100 mg BID group, 5.23 ±1.68% within the firibastat 500 mg BID group and 3.51 ±1.64% within the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in LVEF from baseline to EOT in this subgroup as the adjusted mean difference in LVEF for firibastat 500 mg BID *vs* ramipril 5 mg BID was 1.72 ±1.88% (95%CI= -1.97;5.42, p=0.358).

**Change in LVEF from baseline to EOT in other exploratory subgroups**

The exploratory subgroups analyses for gender; age group; time from onset of MI to PCI; baseline LVEF ≥50%; and diabetes mellitus presented no differences.

**Post-Hoc analyses**

**Change in average peak in longitudinal and circumferential strains from baseline to EOT**

**Longitudinal peak of strain**

• The mean change in longitudinal peak of strain from baseline to EOT was 4.96 ±3.48% in the firibastat 100 mg BID group (95%CI= -6.02; -3.91), -3.45 ±3.50% in the firibastat 500 mg BID group (95%CI= -4.73; -2.17), and 3.49 ±3.85% in the ramipril group (95%CI= -4.58; -2.39, p=0.847).

• The adjusted mean change in longitudinal peak of strain from baseline to EOT was -4.19 ±0.73% in the firibastat 100 mg BID group, -2.29 ±0.88% in the firibastat 500 mg BID group, and -2.45 ±0.77% in the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in longitudinal peak of strain from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 0.16 ±0.83% (95%CI= -1.48;1.80, p=0.847).

**Circumferential peak of strain**

• The mean change in circumferential peak of strain from baseline to EOT was -4.21 ±2.85% in the firibastat 100 mg BID group (95%CI= -5.08;-3.35), -4.03 ±4.19% in the firibastat 500 mg BID group (95%CI= -5.57;-2.50), and -3.91 ±4.57% in the ramipril group (95%CI= -5.21;-2.61).

• The adjusted mean change in circumferential peak of strain from baseline to EOT was -4.22 ±0.79% in the firibastat 100 mg BID group, -4.05 ±0.95% in the firibastat 500 mg BID group, and -3.78 ±0.83% in the ramipril group. There was no statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in longitudinal peak of strain from baseline to EOT as the adjusted mean difference for firibastat 500 mg BID

*vs* ramipril 5 mg BID was -0.27 ±0.90% (95%CI= -2.05;1.50, p=0.761).

**Change in PIIINP from baseline to EOT**

PIIINP increased from baseline to EOT in all three groups:

• The mean change was 1.19 ±1.58 ng/mL in the firibastat 100 mg BID group (95%CI= 0.80;1.58), 1.46 ±1.37 ng/mL in the firibastat 500 mg BID group (95%CI= 1.13;1.79), and 0.88 ±1.56 ng/mL in the ramipril group (95%CI= 0.51;1.25).

• The adjusted mean change was 0.88±0.23 ng/mL in the firibastat 100 mg BID group, 1.17±0.21 ng/mL in the firibastat 500 mg BID group, and 0.67±0.22 ng/mL in the ramipril group. There was a statistical difference between firibastat 500 mg BID and ramipril 5 mg BID on change in PIIINP from baseline to EOT in favor of ramipril as the adjusted mean difference for firibastat 500 mg BID *vs* ramipril 5 mg BID was 0.50 ±0.24 ng/mL (95%CI= 0.02;0.98, p=0.040) but there was no statistical difference between firibastat 100 mg BID and ramipril 5 mg BID (difference: 0.21±0.25 ng/mL [95%CI= -0.27;0.70], p= 0.385).

**Safety results:**

The safety population comprised of 294 patients (99.7% of the randomized population) who received at least one dose of study treatment, with 98 patients in each treatment groups.

Overall, firibastat (2 doses) has a global safety profile similar to that of the reference treatment ramipril 5 mg BID.

**Treatment-emergent adverse events (TEAEs)**

• Over the study, TEAEs were reported at a similar incidence and rate in the firibastat group (100 mg BID: 99 TEAEs in 49 [50.0%] patients – 500 mg BID: 129 TEAES in 63 [64.3%] patients) and in the ramipril group (133 TEAEs in 54 [55.1%] patients). The majority of the reported TEAEs were non-serious, mild or moderate in severity, considered not related to study treatment by the investigator, and most events were recovered by the end of the study.

• The SOC with the most frequently reported TEAEs was *Cardiac disorders* (14 events in 10 [10.2%] patients in the firibastat 100 mg BID group, 15 events in 11 [11.2%] patients in the firibastat 500 mg BID group and 21 events in 16 [16.3%] patients in the ramipril group). The incidence of TEAEs in the *Gastrointestinal disorders* SOC was slightly higher with ramipril (17 events in 14 [14.3%] patients) *vs* firibastat (100 mg BID= 5 events in 5 [5.1%] patients; 500 mg BID= 8 events in 6 [6.1%] patients), and vice versa in the *Skin and subcutaneous tissue disorders* SOC (firibastat 100 mg BID= 13 events in 11 [11.2%] patients; 500 mg BID= 21 events in 20 [20.4%] patients; ramipril= 5 events in 5 [5.1%] patients).

• The SOC with the highest frequency of TEAEs considered related to study treatment was *Skin and subcutaneous tissue disorders* in >5% patients in any treatment group (6 events in 5 [5.1%] patients in the firibastat 100 mg BID group, 14 events in 13 [13.3%] patients in the firibastat 500 mg BID group, and 5 events in 5 [5.1%] patients in the ramipril group).

**Deaths, other serious adverse events, and other clinically important events**

**Deaths**

4 patients died during the study: 2 cases in the firibastat 100 mg BID group (1 patient with PT '*Death*' [unknown reason], and 1 patient with both PTs '*Ventricle rupture*' and '*Cardiac tamponade*' considered both as leading cause of death), 1 case in the firibastat 500 mg BID group (1 patient with PT '*Cardiac failure acute*') and 1 case in the ramipril 5 mg BID group (1 patient with both PTs '*Vascular stent thrombosis*' and '*Cardiac arrest*' considered both as leading cause of death).

**Other serious adverse events**

• Overall, 53 Serious AEs in 41 patients (13.9%, N=294 – safety population) were reported during the study. Of these SAEs, almost all were TEAEs (50 events in 39 patients). Serious TEAEs were reported at a similar incidence and rate in the firibastat groups (100mg BID: 14 events in 11 [11.2%] patients – 500 mg BID: 21 events in 18 [18.4%] patients) and in the ramipril group (15 events in 10 [10.2%] patients).

• 2 Serious TEAEs were considered probably related to study treatment (1 PT of '*Drug eruption*' Recovered/Resolved in the firibastat 500 mg BID group and 1 PT of '*Rash maculopapular*' Recovered/Resolved in the ramipril group) – no other Serious TEAEs were assessed as related to study treatment.

• Almost all patients reporting Serious TEAE(s) (other than death) recovered from the event(s), except 1 patient with an event of *Anemia* (in the ramipril group) reported as 'unknown'. The Serious TEAEs of *Acute myocardial infraction* and *Vascular stent thrombosis* (in the firibastat 100 mg BID group), 2 events of *Ischemic stroke*

(1 event in each of the firibastat groups) and 1 event of *Cerebrovascular accident* in the firibastat 500 mg BID group had resolved with sequelae.

• 11 Serious TEAEs led to drug withdrawal (see below).

**Discontinuations Due to Adverse Events**

• 36 TEAEs led to treatment discontinuation – including 1 case of pregnancy: 13 TEAEs in 10 (10.2%) patients in the firibastat 100 mg BID group, 15 TEAEs in 14 (14.3%) patients in the firibastat 500 mg BID group and 8 TEAEs in 7 (7.1%) patients in the ramipril group. 11 of these TEAEs were Serious: 4 events in the firibastat 100 mg BID group (PTs of 'Aortic valve incompetence', 'Coronary artery disease', 'Covid-19 pneumonia' and 'Ischemic stroke'), 5 events in the firibastat 500 mg BID group (PTs of 'COVID-19' [2 events], 'Spinal pain', 'Cerebrovascular accident' and 'Drug eruption') and 2 events in the ramipril group (PTs of 'Pericardial effusion' and 'Rash maculopapular'). Almost all the events were considered not related to study treatment (except for the events of 'Drug eruption' and 'Rash maculo-papular' [probably related]), and their outcome was all reported as 'recovered/ resolved' (with sequelae for the events of 'Ischemic stroke' and 'Cerebrovascular accident').

**Treatment-emergent Adverse Events of Special Interest (TEAESIs)**

• 28 skin reactions were reported in the study. Only 13 of these TEAESIs were considered related to study treatment by the skin reaction adjudication committee (3 events in 3 (3.1%) patients in the firibastat 100 mg BID group, 7 events in 7 (7.1%) patients in the firibastat 500 mg BID group, and 3 events in 3 (3.1%) patients in the ramipril group). The most common skin reaction was '*Rash maculopapular*' with 9 events reported.

• No AESIs related to diabetes insipidus were reported in the study.

**Pregnancy**

1 patient in the firibastat 100 mg BID group had positive pregnancy tests during the study which led to treatment discontinuation *per* protocol.

**Vital signs**

Based on available data, no clinically relevant changes in vital signs were reported in any group in the treatment period, with no marked differences between the treatment groups.

**Clinical laboratory evaluation**

Based on available data, the mean and mean changes of clinical laboratory values showed minor fluctuations within the normal reference ranges or expected fluctuations after acute MI during the study and with no clinically relevant differences between treatment groups from baseline to EOT period.

Overall, few abnormalities were reported as AEs in all treatment groups and no pronounced differences were seen between firibastat and ramipril treatment groups. There were few cases of worsening renal and urinary functions (9 events) or hyperkalemia (6 events) with no significant between-group differences.

**Other safety assessments**

ECG investigations over the treatment period gave mainly normal findings in all groups when compared with the patients' baseline evaluations. Abnormal ECG investigations in the treatment period were infrequent with no marked differences between the treatment groups.

**Conclusions:**

In conclusion, firibastat 100 and 500 mg BID did not show a different efficacy from that of reference treatment ramipril 5 mg BID in the prevention of left-ventricular dysfunction after first acute anterior MI. Global safety profile was similar in the 3 groups as well. Interestingly, both doses of firibastat showed a trend to a better hemodynamic safety profile in comparison to ramipril. Similar results for efficacy and safety were found in a subgroup of patients with LVEF <50% at baseline as compared to the total population. In these patients, because of a favorable hemodynamic tolerance without any blood pressure decrease, firibastat could represent an alternative treatment.

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