SYNOPSIS

Name of Sponsor/Company: Quantum Genomics	Individual Study Table Referring to Part of the Dossier Volume: 1 Page: 387	
Name of Finished Product: Not applicable		
Name of Active Ingredient: Firibastat (QGC001)		

Title of Study:
A phase 3, double-blind, placebo-controlled, efficacy and safety study of firibastat (QGC001) administered orally, twice daily, over 12 weeks in difficult-to-treat/resistant hypertensive subjects

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Study centers:
This study was conducted at 75 centers in 11 countries (8 in Brazil, 4 in Bulgaria, 11 in Canada, 5 in Czech Republic, 3 in France, 6 in Germany, 3 in Hungary, 1 in Mexico, 12 in Poland, 4 in Spain and 18 in USA)

Publication (reference): Not applicable

Studied period (years): 2.25 years **Date of first enrolment:** 25 June 2020 **Date of last patient last visit:** 20 September 2022	**Phase of development:** 3

Rationale:
Firibastat (QGC001) is a first-in-class brain aminopeptidase A inhibitor that centrally blocks the brain renin-angiotensin system [1-3]. Firibastat combined with current chronic antihypertensive treatment may be a therapeutic strategy for improving blood pressure (BP) control and preventing cardiac dysfunction in patients with hypertension (HTN). The study's primary objective was to assess the effects of oral firibastat, 500 mg twice daily over 12 weeks, in hypertensive subjects despite being treated with 2 (difficult-to-treat) or ≥3 (resistant) antihypertensive classes at their maximally tolerated doses.
At study design, firibastat had previously been assessed in two phase 2 studies: the proof-of-concept cross-over placebo-controlled study (QGC001/2QG1) in a "standard" hypertensive population and the open-labeled, uncontrolled NEW-HOPE study (QGC001/2QG3; NCT03198793) in a high-risk, diverse population of hypertensive subjects. The NEW-HOPE study enrolled 256 overweight or obese hypertensive subjects with 54% black or hispanic.[1] After an initial 2-week washout period, where all antihypertensive treatments were stopped, subjects were then treated for 8 weeks with oral firibastat twice daily (initially at 250 mg for 2 weeks, then at 500 mg if automated office blood pressure was [AOBP], after 1 month hydrochlorothiazide [25 mg once daily] was added if AOBP was ≥160/110 mmHg). After 8 weeks, there were significant decreases in both systolic AOBP (by 9.5 mmHg; $p<0.0001$) and diastolic AOBP (by 4.2 mmHg; $p<0.0001$). Thus, firibastat, as monotherapy, has proven efficacy to reduce BP in overweight or obese hypertensive subjects.

A preclinical study in hypertensive rats also showed that firibastat combined with enalapril and hydrochlorothiazide reduced BP [4]. Furthermore, in unpublished work, firibastat showed a synergic effect for reducing BP when combined with valsartan and losartan.

In terms of safety, firibastat was well tolerated by healthy subjects in a single dose of up to 2000 mg and at multiple daily doses of up to 750 mg twice daily over 7 days. Moreover, the pilot, randomized, double-blind, phase 2 QUID-HF study (NCT02780180) assessed firibastat (up to 500 mg twice daily), combined with standard heart failure treatment, in 23 subjects with chronic congestive heart failure. During the study, no firibastat-related serious adverse events (SAEs) were reported. The standard heart failure treatments included a diuretic (100% of subjects), an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (100%), a beta-blocker (96%), and a mineralocorticoid receptor antagonist (91%). However, the changes in BP were not different in subjects treated with firibastat compared to placebo.

No safety signals have been observed, during monotherapy and combined with standard treatments for BP and heart failure, and it was decided to move to a randomized placebo-controlled phase 3 to assess the benefit of adding 12-weeks of treatment with oral firibastat (500 mg twice daily) in subjects with uncontrolled hypertensive despite chronic antihypertensive therapies.

Objectives:

- **Primary Objective**

The primary objective was to assess the effects of oral firibastat, at a dosage of 500 mg twice daily, on BP over 12 weeks in subjects with uncontrolled primary HTN despite being treated with at least 2 classes of antihypertensive therapies, at the maximum tolerated doses (MTDs), according to the systolic AOBP.

- **Secondary Objectives**
  - ✓ To assess the effect of firibastat, at a dosage of 500 mg twice daily, on BP over 12 weeks in subjects with uncontrolled primary HTN despite being treated with at least 2 classes of antihypertensive therapies, at the maximum tolerated doses (MTDs), according to the following:
    - Change in diastolic AOBP after 12 weeks.
    - Change in systolic and diastolic AOBP after 4 and 8 weeks.
    - Change in mean 24-h ambulatory systolic BP (SBP) and diastolic BP (DBP) after 12 weeks.
    - Percentage of controlled subjects after 12 weeks, as defined by the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines [5].
    - Percentage of controlled subjects after 12 weeks, as defined by the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines [6].
    - Predictive factors for controlled subjects after 12 weeks.
    - Change from baseline in plasma concentration of biomarker N-terminal pro-B-type natriuretic peptide (NT-ProBNP).
  - ✓ To assess the safety of firibastat (QGC001)

Methodology:

The FRESH study was designed as a double-blind, placebo-controlled, multicenter, efficacy and safety study. The study assessed the effect on blood pressure of adding firibastat (QGC001) to current HTN treatment in subjects with uncontrolled, chronic HTN despite baseline treatment.

Adults older than 18 years of age, with uncontrolled primary HTN despite:

- For treatment-resistant subjects, being treated with at least 3 classes of antihypertensive therapies at the maximum tolerated doses, including a diuretic.
- For difficult-to-treat subjects, being treated with 2 classes of antihypertensive therapies (with or without a diuretic) at the maximum tolerated doses.

Subjects were randomly allocated, in a 1:1 ratio to investigational product (IP) and receivedeither firibastat (QGC001) or matching placebo in addition to their current chronic antihypertensive treatments. During the study, firibastat (500 mg) or placebo was administered twice daily for 12 weeks.

Number of patients (planned and analyzed)

To show a difference between firibastat (QGC001) and placebo in change from baseline in systolic AOBP of 5 mmHg with a phase 2 hypotheses of standard deviation (SD) of 14.3 mmHg, α=5% and 95% power, 213 subjects per group were required. To allow for a 15% drop-out rate, 251 subjects were planned in each group for a total of 502 subjects.

Finally, Overall, 515 subjects were randomized in the study and 514 were analyzed in the full analysis set (255 subjects were enrolled in the Firibastat group and 259 in the Placebo group) .and in the Safety Set.

Diagnosis and main criteria for inclusion:

- **Inclusion criteria**

Subjects who met all of the following criteria were eligible to participate in the study:

1) Able to understand, and willing to provide written informed consent and able to comply with the study procedures and restrictions.
2) Men and women ≥18 years of age at Screening.
3) Diagnosis of primary HTN for at least 6 months prior to Screening and:
   - Currently treated with 2 antihypertensive classes of drug (difficult-to-treat subjects), or currently treated with at least 3 antihypertensive classes of drug including a diuretic (treatment-resistant subjects), at the maximum tolerated doses of those medications (i.e., the subject can tolerate the current dose of each medication but higher doses have caused or may worsen side effects), with no change in their antihypertensive regimen (drug dose or schedule) for at least 6 weeks and with medication adherence >80% during the run-in period.
   - Have a systolic AOBP between 140 mmHg and 180 mmHg (inclusive) at Screening while on their current chronic antihypertensive treatments.
   - Have a successful ambulatory blood pressure monitoring (ABPM) measurement with a mean systolic daytime ambulatory blood pressure (ABP) >135 mmHg after the run-in period while on their current chronic antihypertensive treatments. An ABPM was successful if at least 21 daytime readings and 6 nighttime readings were successfully recorded.
4) Women of childbearing potential and nonsurgically sterile male subjects who are sexually active that agreed to use an approved highly effective form of contraception from the time of informed consent until 30 days postdose. Approved forms of contraception included hormonal intrauterine devices, hormonal contraceptives (oral birth control pills, depo, patch, or injectable) together with supplementary barrier method such as condoms or diaphragms with spermicidal gel or foam.
5) Women of childbearing potential required a negative serum pregnancy test result at screening and a negative urine pregnancy test result at the inclusion visit (Visit 2, Day 1).

- **Exclusion criteria**

Subjects who met any of the following criteria were excluded from participating in the study:

1) Known or suspected secondary HTN (e.g., hyperaldosteronism, renovascular HTN, pheochromocytoma, Cushing's disease).
2) Automated office SBP >180 mmHg or DBP >110 mmHg at the Screening or Inclusion Visit (Visit 2, Day 1) and confirmed by a second measurement within 30 min to 1 hour.
3) Known hypertensive retinopathy (Keith-Wagener Grade 3 or Grade 4) and/or hypertensive encephalopathy.
4) Upper arm circumference that was outside the limits of the study-provided BP cuff associated with either the ABPM and/or AOBP measurement device.
5) History of spontaneous or drug-induced angioedema.
6) History of drug-related allergy or hypersensitivity to any components of the IP (firibastat [QGC001] or placebo).
7) Known severe aortic stenosis (symptomatic or asymptomatic with valvular indexed surface <0.5 cm^2/m^2).
8) Subjects with severe symptomatic heart failure (New York Heart Association [NYHA] Class III or Class IV).
9) History of acute coronary syndrome (non-ST elevation myocardial infarction [MI], ST elevation MI, and unstable angina pectoris), stroke, or transient ischemic attack within 6 months prior to Screening.
10) Known history of malabsorption syndrome, or has undergone gastrointestinal surgery, including bariatric procedures, that induce chronic malabsorption, within 2 years of Screening.
11) Treatment with anti-obesity drugs or procedures 3 months prior to Screening (i.e., surgery, aggressive diet regimen, etc.), leading to unstable body weight.
12) Female who was breastfeeding, pregnant, or planning to become pregnant during the study period.
13) Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 3 years.
14) Shift workers who routinely sleep during the daytime and/or whose work hours include midnight.
15) Subjects with moderate to severe hepatic impairment (Child-Pugh A, B, or C); alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >3×upper limit of normal (ULN), or a total bilirubin ≥1.5×ULN (unless secondary to Gilbert's syndrome), or direct bilirubin >ULN in subjects with Gilbert's syndrome at Screening.
16) Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CDK-EPI) formula [7] at screening.
17) History of any blood disorder, other than sickle cell trait, causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, hemolytic anemia, thalassemia, sickle cell anemia).
18) Subjects with documented diabetes insipidus.
19) Subjects with Type 1 diabetes mellitus.
20) Subjects with Type 2 diabetes mellitus who were:

- ✓ Poorly controlled, defined as glycosylated hemoglobin A1c (HbA1c) >9% at screening, OR
- ✓ Taking short-acting insulin. Use of a stable dose (≥12 weeks prior to screening) of the following medications is permitted: glucagon-like peptide-1 analog, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, metformin plus sulfonylurea, metformin plus dipeptidyl peptidase-4 inhibitor, single basal insulin, sodium-glucose co-transporter 2 (SGLT2) inhibitors and pioglitazone.

21) Routine or anticipated treatment with any systemic corticosteroid. Use of topical, inhaled, intra-articular or nasal corticosteroids were permitted.
22) Clinical evidence of thyroid disease, thyroid hormone therapy that was not stable ≥4 weeks prior to Screening, or a thyroid-stimulating hormone (TSH) level 1.5×ULN at Screening.
23) History of alcohol or drug abuse (including opioid overuse/misuse) within the 3 months prior to Screening that would interfere with study participation or lead to decreased compliance to study procedures or IP intake in the investigator's opinion.
24) Participation in another clinical study involving an investigational drug within 30 days prior to Screening or plans to participate in another clinical study within 30 days of discontinuation of IP.
25) Any other condition that precludes adequate understanding, cooperation, and compliance with study procedures, or any condition that could pose a risk to the subject's safety, as per the investigator's judgment.
26) Subjects with a life expectancy of less than 1 year per investigator's discretion.
27) Legal incapacity or limited legal capacity.
28) Previous participation in this study.

Test product, dose and mode of administration, batch number:
Firibastat (QGC001)
Dose: 2 x 250 mg capsules twice daily
Mode of administration: Oral capsules
Batch numbers: 19084520087; 19084520160; 19084520206; 19084521070

Duration of treatment: 12 weeks

Reference therapy, dose and mode of administration, batch number:
Placebo
Dose: 2 capsules twice daily
Mode of administration: Oral capsules
Batch numbers: 19084520042; 19084520127; 19084520232; 19084521069

Criteria for evaluation:

- **Primary Efficacy Endpoint**

The primary efficacy endpoint was the change in systolic AOBP from baseline to Week 12 (Visit 5, Day 84).

- **Secondary Efficacy Endpoints**

The secondary endpoints included the following:

- ✓ Change in diastolic AOBP from baseline to Week 12 (Visit 5, Day 84).
- ✓ Change in systolic and diastolic AOBP from baseline to Week 4 (Visit 3, Day 28) and Week 8 (Visit 4, Day 56).

- ✓ Change in mean 24-h ambulatory SBP and DBP from baseline to Week 12 (Visit 5, Day 84).
- ✓ Percentage of controlled subjects: defined as subjects with normalized AOBP, i.e., <140/90 mmHg, at Week 12 (Visit 5, D 84), as per the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines [5].
- ✓ Percentage of controlled subjects: defined as subjects with normalized AOBP, i.e., <130/90 mmHg, at Week 12 (Visit 5, D 84), as per the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines [6].
- ✓ Predictive factors for controlled subjects at Week 12 (Visit 5, Day 84)
- ✓ Change from baseline in plasma concentration of biomarker N-terminal pro-B-type natriuretic peptide (NT-ProBNP).

- **Safety Endpoints**

Safety assessments were:

- ✓ All adverse events (AEs)
- ✓ Vital signs
- ✓ Electrocardiogram (ECG)
- ✓ Laboratory parameters
- ✓ Concomitant treatments

Statistical methods:

Data are presented by treatment group using descriptive statistics: number of observations, number of missing data, mean, SD, median, minimum, and maximum for continuous variables, and counts, percentages (excluding missing data), and number of missing data for categorical variables. Inferential tests were performed 2-sided, with an alpha risk at 5%. No interim analysis was planned.

- **Primary endpoint analyses**

The main criterion was analyzed using a mixed model with repeated measures (MMRM) at Weeks 4, 8, and 12, with an unstructured matrix of covariance. The main analysis was planned in the Full Analysis Set, with a sensitivity analysis planned in the Per-Protocol Set.

- **Secondary endpoints analyses**

To check the homogeneity of the efficacy results, a forest plots of the estimates, at 12 weeks, for the global population and each modality of each subgroup (age, sex, body mass index [BMI], ethnicity, estimated glomerular filtration rate (eGFR), and treatment-resistant/difficult-to-treat) was planned. The analyses of the changes from baseline to Week 4 and 8 of systolic and diastolic AOBP, using the same model as for the main criterion, were planned. A description of the changes from baseline of AOBP to Week 12 for SBP and DBP, for daytime, nighttime, and during the 24-h ambulatory blood pressure monitoring (ABPM), were planned. These criteria were to be analyzed using an analysis of covariance (ANCOVA) with baseline as covariate.
The proportion of Controlled subjects at Week 12 were to be analyzed using a logistic regression with baseline systolic AOBP and baseline diastolic AOBP as covariates. The same analysis was planned for each modality of each subgroup. A forest plot of the estimates (odds ratios), at 12 weeks, for the global population and for the subgroups was planned.
The analysis of the change in NT-ProBNP levels from baseline to end of treatment (EOT) was planned, using an ANCOVA with baseline as covariates.

- **Safety Analysis**

AEs reported were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The results are presented according to the primary system organ class (SOC) and preferred terms.

Laboratory data, vital signs, and ECG parameters values and changes from baseline will be described.

Summary - Conclusion

Efficacy results:

514 subjects were analyzed for efficacy (Full Analysis Set).

- **Change in mean systolic AOBP after 12 weeks (84 days) (primary endpoint)**

The change in mean systolic AOBP (from baseline to Day 84) was -8.1 mmHg (SD: 17.2) in the Firibastat group and was -7.4 mmHg (SD: 16.6) in the Placebo group (see Appendix Table 14.2.1.1). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was 0.03 (standard error [SE]: 1.40, 95% CI of difference [-2.72 to 2.78], p=0.9844), see Appendix Table 14.2.1.3. Results were similar on the Per Protocol Set, see Appendix Table 14.2.1.6.

- **Change in mean diastolic AOBP after 12 weeks (84 days)**

The change in mean diastolic AOBP from baseline to Visit 5 (Day 84) was -4.6 mmHg (SD: 10.8) in the Firibastat group and by -3.8 mmHg (SD: 10.5) in the Placebo group (see Appendix Table 14.2.2.3). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was -0.79 (SE: 0.93, 95% CI of difference [-2.62 to 1.05], p=0.3990), see Appendix Table 14.2.2.4.

- **Change in mean systolic AOBP after 4 weeks**

The change in mean systolic AOBP from baseline to Visit 3 (Day 28) was -3.2 mmHg (SD: 16.7) in the Firibastat group and -2.9 mmHg (SD: 15.2) in the Placebo group (see Appendix Table 14.2.1.1). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was 0.25 (SE: 1.31, 95% CI of difference [-2.33 to 2.82], p=0.8501), see Appendix Table 14.2.1.3.

- **Change in mean systolic AOBP after 8 weeks**

The change in mean systolic AOBP from baseline to Visit 4 (Day 56) was -6.2 mmHg (SD: 17.6) in the Firibastat group and -5.0 mmHg (SD: 16.1) in the Placebo group (see Appendix Table 14.2.1.1). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was -0.25 (SE: 1.40, 95% CI of difference [-3.01 to 2.51], p=0.8609), see Appendix Table 14.2.1.3.

- **Change in mean diastolic AOBP after 4 weeks**

The change in diastolic AOBP from baseline to Visit 3 (Day 28) was -1.7 mmHg (SD: 9.9) in the Firibastat group and was -1.8 mmHg (SD: 9.3) in the Placebo group (see Appendix Table 14.2.2.3). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was 0.17 (SE: 0.83, 95% CI of difference [-1.46 to 1.80], p=0.8379), see Appendix Table 14.2.2.4.

- **Change in mean diastolic AOBP after 8 weeks**

The change in mean diastolic AOBP from baseline to Visit 4 (Day 56) was -3.7 mmHg (SD: 10.2) in the Firibastat group and -2.3 mmHg (SD: 10.2) in the Placebo group (see Appendix Table 14.2.2.3). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was -1.48 (SE: 0.90, 95% CI of difference [-3.25 to 0.29], p=0.1010), see Appendix Table 14.2.2.4.

- **Change in mean 24-h ambulatory SBP after 12 weeks**

At 12 weeks, the mean 24-h ambulatory SBP had decreased by -5.0 mmHg (SD:13.3) in the Firibastat group and by -6.5 mmHg (SD: 13.7) in the Placebo group (see Appendix Table 14.2.2.7). This decrease was not significantly different in the Firibastat group compared to the

Placebo group: after adjusting of means the difference from placebo was 1.28 (95% CI of difference [-1.28 to 3.84]), see Appendix Table 14.2.2.9.

- **Change in mean 24-h ambulatory DBP after 12 weeks**

At 12 weeks, the mean 24-h ambulatory DBP had decreased by -3.1 mmHg (SE: 8.5) in the Firibastat group and by -3.8 mmHg (SE: 8.6) in the Placebo group (see Appendix Table 14.2.2.7). This decrease was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was 0.45 (95% CI of difference [-1.14 to 2.04]), see Appendix Table 14.2.2.9.

- **Percentage of controlled subjects after 12 weeks, as defined by the 2018 ESC and ESH guidelines [5]**

At 12 weeks, 116/206 (56.3%) in the Firibastat group and 116/219 (53.0%) in the Placebo group had controlled AOBP, with a AOBP ≤140/90 (see Appendix Table 14.2.2.10).

- **Analysis of the percentage of controlled subjects after 12 weeks, as defined by the 2017 ACC and AHA guidelines[6]**

At 12 weeks, 41/206 (19.9%) in the Firibastat group and 51/219 (23.3%) in the Placebo group had controlled AOBP, with a AOBP ≤130/80 (see Appendix Table 14.2.2.10).

- **Predictive factors for controlled subjects after 12 weeks.**

The multivariate analyses found no parameter to be significantly associated with controlled subjects at 12 weeks , neither defined by the 2018 ESC and ESH guidelines [5] (AOBP ≤140/90) nor by the 2017 ACC and AHA guidelines [6] (AOBP ≤130/80), see the Forest plots in Appendix Figure 14.2.2.11.

- **Change from baseline in plasma concentration of biomarker N-terminal pro-B-type natriuretic peptide (NT-ProBNP).**

The change in mean NT-proBNP levels AOBP from baseline to Visit 5 (Day 84) was 0.99 pmol/L (SD: 15.95) in the Firibastat group and 3.78 pmol/L (SD: 40.09) in the Placebo group (see Appendix Table 14.2.2.12). This change was not significantly different in the Firibastat group compared to the Placebo group: after adjusting of means the difference from placebo was -2.43 (95% CI of difference [-8.38 to 3.52], p=0.4227), see Appendix Table 14.2.2.13.

Safety results:

514 subjects were analyzed for safety (Safety Set) (see Appendix Table 14.3.1.1).

- 261 (50.8%) reported ≥1 AE.
- 10 (1.9%) reported ≥1 SAE.
- 246 (47.9%) reported ≥1 TEAE.
- 54 (10.5%) reported ≥1 drug-related TEAE.
- No patient reported ≥1 drug-related SAE (see Appendix Table 14.3.1.8)
- 1 (0.2%) died from a TEAE: a COVID-19 related pneumonia.
- 23 (4.5%) reported an AE of special interest, all were skin reactions.

The drug-related TEAE reported in ≥1% of subjects in the overall population (n=514) or in the treatment groups are shown in Appendix Table 14.3.1.5. In the Firibastat group (n=255), 16 subjects (6.3%) reported a skin or subcutaneous tissue disorder, 6 (2.4%) a vascular disorder, 6 (2.4%) a gastrointestinal disorder, and 6 (2.4%) a nervous system disorder.
In the Firibastat group (n=255), 12 subjects (4.7%) reported an adjudicated skin reaction versus 1 (0.4%) in Placebo group (n=259), see Appendix Table 14.3.1.12.

No safety signals were identified during the analyses of the vital signs, the ECGs, the laboratory parameters, nor the concomitant treatments.

Conclusion

The study failed to show that 12-weeks of oral firibastat, at a dosage of 500 mg twice daily, significant reduced systolic AOBP, compared to placebo, in subjects with uncontrolled primary HTN despite being treated with 2 classes of antihypertensive therapies, at the MTDs,. Firibastat, combined with standard antihypertensive treatment, was well tolerated: no new safety signals beyond the already known skin reactions were identified during the study.

Date of report:

Version 1 (20 January 2023)

References:

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