

CLINICAL STUDY PROTOCOL

Title: 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

Short title: Firibastat in treatment-RESistant Hypertension (FRESH)

Protocol number: QGC001-3QG1

Study phase: Phase 3

Test product: Firibastat (QGC001)

EudraCT number: 2019-004509-29

IND number: 129994

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Protocol version and date: 4.0, 31 Mar 2021

This study will be performed in compliance with the principles of Good Clinical Practice.

This document is a confidential communication of Quantum Genomics. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein shall be published or disclosed without prior written approval, except that this document will be disclosed to the appropriate Institutional Review Board(s)/Independent Ethics Committee(s) under the condition that they keep it confidential.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Quantum Genomics representative(s):

Bruno Besse, MD

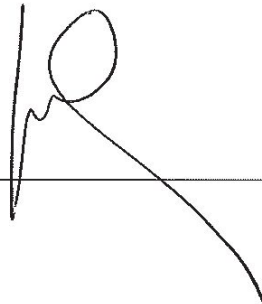
Chief Medical Officer

Print Name

Title

Signature

Date

A handwritten signature in black ink, appearing to be 'Bruno Besse', written over a horizontal line.

March 31st, 2021

PROTOCOL SIGNATURE PAGE – CONTRACT RESEARCH ORGANIZATION

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

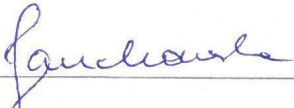
PRA Health Sciences representatives:

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PROTOCOL SIGNATURE PAGE – COORDINATING INVESTIGATOR

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Coordinating investigator:

Professor George Bakris, MD

Professor of Medicine

Print Name

Title

AHA Comprehensive Hypertension Center, University of Chicago Medicine

Institution



Digitally signed by George L. Bakris
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Date: 2021.04.06 07:25:17 -05'00'
Adobe Acrobat version: 2021.001.20145

April 6, 2021

Signature

Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Quantum Genomics and given approval/favorable opinion by the IRB/IEC, and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Quantum Genomics or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Quantum Genomics. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Quantum Genomics, and inspection by the appropriate regulatory authorities.

I agree to make my subjects' study records available to Quantum Genomics personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered into the case report forms (eCRFs). I will retain the study-related essential documents until Quantum Genomics indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Quantum Genomics.

I understand that Quantum Genomics may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Quantum Genomics.

Investigator:

Print Name

Title

Institution

Signature

Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 4.0, 31 Mar 2021 Global Amendment 3 The following changes are incorporated into Version 4.0 of the protocol.
Description of change and rationale for change: Eligible systolic automated office blood pressure (AOBP) range updated from 140-170 mmHg to 140-180 mmHg. Section(s) of the protocol affected: Protocol Summary: Inclusion Criteria #3 and Exclusion Criteria #2, Section 4.2, Section 5.1, Section 5.2
Description of change and rationale for change: Footnote c (“Visit 2, Day -1 will correspond to the last day of the Run-in Period.”) was deleted and the Footnotes were reordered to clarify that the Run-in Period should be at least 28 days and no more than 33 days. Section(s) of the protocol affected: Study schematic Figure 1 and, Schedule of Assessments Table 1 Footnote d
Description of change and rationale for change: Updated barrier method requirement. Section(s) of the protocol affected: Protocol summary Inclusion Criteria #4, Section 5.1
Description of change and rationale for change: Removed “at least” from text in reference to the number of current antihypertensive therapies required for inclusion. Section(s) of the protocol affected: Protocol Summary: Objectives, Inclusion Criteria#3, Section 2.1, Section 5.1, Section 8.7.1
Description of change and rationale for change: Added additional text to clarify that the Run-in Period will end once the subject has completed the Inclusion Visit and is randomized to study treatment. Section(s) of the protocol affected: Section 4.1.2
Description of change and rationale for change: Removed the Day number from Visit 2 to prevent subjects being randomized too early. Section(s) of the protocol affected: Section 4.1.3

Description of change and rationale for change: Updated screen failures, to allow for rescreening, which will include a new subject number and a new signed Informed Consent; all study-specific assessments will be repeated. However, previously randomized subjects cannot be rescreened. Section(s) of the protocol affected: Protocol summary: Study design, Section 5.3
Description of change and rationale for change: Antihypertensive treatments detailed in full in Inclusion Criteria #3 have been updated throughout the protocol to distinguish between the use of diuretics in difficult-to-treat subjects and treatment-resistant subjects. Section(s) of the protocol affected: Protocol summary: Objectives, Study design, Target population and Inclusion Criteria #3, Section 1.1, Section 1.3, Section 2.1, Section 4.1, Section 4.2, Section 5.1, Section 8.1.3, Section 8.7.1
Description of change and rationale for change: Updated text to allow investigators discretion to be used in the case of premature discontinuations of investigational product in symptomatic hypotension or symptomatic orthostatic hypotension. Section(s) of the protocol affected: Section 5.4.1
Description of change and rationale for change: Clarified the operation of the AOBP device and that there is an initial single reading. Section(s) of the protocol affected: Section 6.2.1
Description of change and rationale for change: Clarified the time the subject needs to be in the supine position when measuring orthostatic blood pressure. Section(s) of the protocol affected: Section 6.2.1
Description of change and rationale for change: Added text to clarify that dose reductions are not allowed. Section(s) of the protocol affected: Section 8.4.3 (new section)

Description of change and rationale for change:

Definition of an overdose included.

Section(s) of the protocol affected:

Section 8.8

Version 3.0, 27 Oct 2020

Global Amendment 2

The following changes are incorporated into Version 3.0 of the protocol

Description of change and rationale for change:

Updated Inclusion Criteria #3. Medication adherence for antihypertensive drugs updated from >80% to $\geq 80\%$ during the Run-in Period.

Section(s) of the protocol affected:

Protocol Summary: Study design and inclusion criteria #3, Schedule of Assessments footnote i (previously h), Section 4.1.3, Section 5.1

Description of change and rationale for change:

Exclusion Criteria #15 updated to include Child-Pugh A.

Section(s) of the protocol affected:

Protocol Summary: Exclusion Criteria, Section 5.2

Description of change and rationale for change:

Exclusion Criteria #20 altered to remove restriction of sodium-glucose co-transporter 2 (SGLT2) inhibitors, providing the subject has been receiving a stable dose [≥ 12 weeks prior to Screening]. SGLT2 inhibitors added to Permitted Medications list in Section 8.7.1.

Section(s) of the protocol affected:

Protocol Summary: Exclusion Criteria, Section 5.2, Section 8.7.1, Section 8.7.2

Description of change and rationale for change:

Added Exclusion Criteria #29, to exclude subjects with any history of documented allergic reactions or allergic diseases with the exception of documented seasonal allergies.

Section(s) of the protocol affected:

Protocol Summary: Exclusion Criteria, Section 5.2

Description of change and rationale for change:

Removed requirement for successful ambulatory blood pressure monitoring (ABPM) measurement during the Run-in Period to have at least 70% of all ABPM readings to be considered successful, prior to randomization.

Section(s) of the protocol affected:

Protocol Summary: Study Design, Inclusion Criteria #3, Schedule of Assessments footnote k (previously j), Section 6.2.2.1

Description of change and rationale for change:

Added that a duration of less than 24 hours (eg, 23 hours and 30 minutes) would be acceptable for a successful ABPM recording as long as it successfully confirms 21 daytime and 6 nighttime successful readings.

Section(s) of the protocol affected:

Protocol Summary: Study design, Section 6.2.2, Section 6.2.2.1

Description of change and rationale for change:

Clarified blood pressure (BP) measurements must be performed prior to investigational product (IP) administration as compulsory at Visit 2, Day 1, and recommended at all other following visits where blood pressure measures are taken. Removed reference to blood pressure measures taken in the morning as dosing may occur at any time of day.

Section(s) of the protocol affected:

Schedule of Assessments footnote h (previously g), Section 6.2.1

Description of change and rationale for change:

Added new discontinuation Criteria #7: Any of the following laboratory assessments will result in IP discontinuation and study withdrawal; ALT >3×ULN, AST >3×ULN, ALP >3×ULN, total bilirubin $\geq 1.5 \times \text{ULN}$ unless secondary to Gilbert's syndrome, direct bilirubin >ULN, in subjects with Gilbert's syndrome and eGFR <30 mL/min/1.73m², as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Section(s) of the protocol affected:

Section 5.4.1

Description of change and rationale for change:

Added that any incipient allergic skin reaction (as outlined in Section 6.3.3.1) must result in IP discontinuation and the investigator has the right to terminate participation of a subject from the study following any incipient allergic skin reaction. Subjects will be advised to contact the investigator or their general practitioner in the event of any incipient allergic skin reactions.

Section(s) of the protocol affected:

Section 5.4.1, Section 5.4.2, Section 6.3.3.1, Section 9.1.3 (new section)

Description of change and rationale for change:

End of Treatment (EOT) Visit: Removed that the IP will be discontinued “only” if ABPM measurements meet requirements, and clarified ABPM measurements must meet requirements per Section 6.2.2.1.

Section(s) of the protocol affected:

Section 8.4

Description of change and rationale for change:

Updated process for subjects who discontinue IP prematurely whereby subjects will have the Follow-up Visit 30 days after last dose of IP unless consent is also withdrawn for follow-up, whereby the reason for consent withdrawal must be recorded. For subjects who are physically unable to provide written consent withdrawal, the site should document and sign the reason for the subject’s failure to provide written withdrawal of consent. Updated Section 4.1.7 and added footnote to Schedule of Assessments clarifying Follow-up Visit 30 days after last dose.

Section(s) of the protocol affected:

Schedule of Assessments footnote c (new footnote), Section 4.1.7, Section 5.4.1

Description of change and rationale for change:

New section added outlining IP delivery directly to subjects who cannot attend site for planned assessments due to regional/local coronavirus disease 2019 (COVID-19) restrictions (Section 8.4.1).

Section(s) of the protocol affected:

Section 7, Section 8.4.1 (new section)

Description of change and rationale for change:

Since the study is an international, multicenter, placebo-controlled study, and since significant side effects (skin toxicities) may occur, in accordance with the Guideline on Data Monitoring Committees EMEA/CHMP/EWP/5872/03 Corr, an independent data monitoring committee (IDMC) should be implemented in order to ensure the safety of the trial participants. A new section entitled independent data monitoring committee was added to the protocol. The statement that IDMC may recommend the termination of the study if they find evidence of unacceptable risk to subjects was added to the Study Start and Termination section (Section 17) of the protocol.

Section(s) of the protocol affected:

Protocol Summary: Independent data monitoring committee (new section), Section 4.1, Section 10 (new section), Section 17

Description of change and rationale for change:

Clarified reporting process for serious adverse events (SAEs) during the study and after the final dose of IP.

Section(s) of the protocol affected:

Schedule of Assessments: footnote u (previously t), Section 9.4

Description of change and rationale for change:

Clarified wording for reporting of adverse events (AEs), in that all AEs “serious or not” will begin following provision of informed consent.

Section(s) of the protocol affected:

Schedule of Assessments: footnote u (previously t), Section 9.3

Description of change and rationale for change:

Clarified that if photographs are obtained for reporting of adverse events of special interest (AESIs) of allergic skin reactions, that these should be uploaded in the electronic data capture (EDC) portal for adjudication.

Section(s) of the protocol affected:

Section 6.3.3.1

Description of change and rationale for change:

Clarified process for the Adjudication Committee for Allergic Skin Reaction and process for reviewing symptoms and signs of allergic skin reactions during the course of the study.

Section(s) of the protocol affected:

Section 12.4.2

Description of change and rationale for change: Added clarification for handling AEs of COVID-19 infection whereby the local health authority recommendations regarding treatment should be followed and the event should be reported as an AE/SAE depending on the seriousness of infection. Section(s) of the protocol affected: Section 9.1.1
Description of change and rationale for change: Updated ECG recording process: ECGs will be recorded prior to any IP administration and time since last IP dose will be recorded. Added additional ECG recording for Visit 6, Day 112 prior to IP administration. Section(s) of the protocol affected: Protocol Summary: Study Design, Schedule of Assessment footnote g (previously f), Section 4.1.7, Section 6.3.6
Description of change and rationale for change: Removed requirement that subjects must take their current chronic hypertensive drug and the IP in front of the investigator during the 12-week Treatment Period. Section(s) of the protocol affected: Section 4.1.4
Description of change and rationale for change: Added clarification that the Visit 5, Day 83 should be scheduled for the morning (eg, between 8:00 am and 10:00 am) in order to avoid strict time constraints for the following visit on Day 84. Section(s) of the protocol affected: Protocol Summary: Study Design, Schedule of Assessments footnote j (previously i), Section 4.1.5
Description of change and rationale for change: New section added for COVID-19 mitigation to clarify handling of local/regional lockdowns, which might prevent subjects visiting for planned assessments, including wider allowed visit windows, instructions for home visits or remote assessments, and other necessary adjustments. It is added that any protocol non-adherence will be recorded as a protocol deviation related to COVID-19. Section(s) of the protocol affected: Section 7 (new section)

Description of change and rationale for change: Removed statement that visit-specific procedures for Day 84 will be performed prior to the last dose of IP to clarify that assessments will be performed following the last dose of IP. Section(s) of the protocol affected: Schedule of Assessments: footnote f (previously e), footnote g (previously f), footnote h (previously g), footnote l (previously k), and footnote m (previous l), Section 4.1.5
Description of change and rationale for change: New section added to provide a justification of the selected dosage taking into consideration the pharmacodynamics, the safety margins of the preclinical findings, the possible interactions with the base medications and the clinical side effects that have occurred so far, according to the Guideline for Good Clinical Practice (CPMP/ICH/135/95). Section(s) of the protocol affected: Section 1.3 (new section)
Description of change and rationale for change: Clarified secondary efficacy endpoint refers to “Change from baseline in plasma concentration of biomarker NT-ProBNP”. Section(s) of the protocol affected: Protocol Summary: Secondary efficacy endpoints, Section 3.2, Section 11.4.2
Description of change and rationale for change: Descriptive statistics for baseline characteristics updated to include comorbidities. Section(s) of the protocol affected: Protocol Summary: Analysis of Safety, Section 11.4.5
Description of change and rationale for change: Revision of statistical methods for primary and secondary endpoints, including clarification that the analysis of the main criterion with a mixed model with repeated measures (MMRM) will be performed at Week 4, 8, and 12, with an unstructured matrix of covariance. Removal of the Wilcoxon nonparametric test at Week 12 for the primary secondary endpoints. Removed paragraph from general procedures describing parametric and nonparametric analyses (due to change in statistical analyses). Section(s) of the protocol affected: Protocol Summary: Statistical methods, Section 11.1, Section 11.4.1, Section 11.4.2

Description of change and rationale for change: Clarified process for handling missing values for statistical methods. Sensitivity analyses (including multiple imputations) will no longer be used. Missing data will be accommodated by the use of MMRM with restricted maximum likelihood. Section(s) of the protocol affected: Protocol Summary: Statistical Methods, Section 11.4.7
Description of change and rationale for change: Removed requirement for subjects in the Full Analysis Set to have baseline and Week 12 systolic automated office blood pressure (AOBP) measurements. Section(s) of the protocol affected: Protocol Summary: Main analysis populations, Section 11.2
Description of change and rationale for change: New section describing site monitoring during the COVID-19 pandemic, outlining the process for remote monitoring visits if the contract research organization (CRO) monitor is unable to attend site due to regional/local restrictions or if the site is unable to accommodate a monitor for an on-site monitoring visit. Monitoring mitigations implemented due to COVID-19 will be included in the Clinical Management Plan. Section(s) of the protocol affected: Section 14.3 (new section)
Description of change and rationale for change: Clarified process for emergency unblinding. Section(s) of the protocol affected: Section 8.2
Description of change and rationale for change: Added references 42 and 43 to reference list Section(s) of the protocol affected: Section 19

Description of change and rationale for change:

Editorial updates including: update of Table of Contents for the inclusion of new sections, section renumbering, updates of cross-references due to section renumbering, added “2018” for European Society of Cardiology/European Society of Hypertension guidelines, the inclusion of abbreviations AUC (area under curve), IDMC (Independent Data Monitoring Committee), and COVID-19 (coronavirus disease 2019), removal from abbreviation list of AIC (Akaike information criterion), and updated Sponsor’s project manager details.

Section(s) of the protocol affected:

Table of contents, List of Abbreviations, New sections: Section 1.3, Section 5.4.1, Section 7, Section 8.4.1, Section 9.1.3, Section 10, and Section 14.3, Section 3.2 (additional year reference), cross-reference updates and section renumbering from Section 7 onwards, Appendix 20.1

Version 2.0, 30 Jan 2020

Global Amendment 1

The following changes are incorporated into Version 2.0 of the protocol:

Description of change and rationale for change:

Added ‘Subjects with moderate to severe hepatic impairment (Child-Pugh B or C)’ to exclusion criteria #15.

Section(s) of the protocol affected:

Protocol Summary, Section 5.2

Description of change and rationale for change:

Added blood sample for coagulation test (prothrombin time) at Screening to enable assessment of Child-Pugh classification of hepatic impairment.

Section(s) of the protocol affected:

Table 1, Section 6.3.4, Section 9.4.4, Section 11.4.2

Description of change and rationale for change:

Deleted the requirement for the investigator to measure the QT interval ‘3 times on 3 different complexes’. Added that the investigator will report the results as normal or abnormal in EDC, and that all ECGs will be collected for subsequent central reading of the QT/QTc interval.

Section(s) of the protocol affected:

Table 1 footnote (f), Section 6.3.6

Description of change and rationale for change: Revised to indicate that ambulatory blood pressure monitoring (ABPM) measurements will be read locally. A printed report will be filed in the subject's record for source verification, and ABPM data will be reported in the eCRF. Section(s) of the protocol affected: Section 6.2.2, Section 11.4.1
Description of change and rationale for change: Deleted analysis of blood samples for the biomarkers TNFR1 and copeptin. Section(s) of the protocol affected: Protocol Summary, Table 1 (and footnote [m]), Section 3.2, Section 4.2, Section 6.2.3, Section 9.4.2, Section 11.4.2
Description of change and rationale for change: Removed the details of the Central Laboratory as not required in the protocol, and clarified that the names and addresses of laboratories involved in the study will be provided in the laboratory manual. Section(s) of the protocol affected: Appendix 1
Description of change and rationale for change: Added Therapeutic Expert to Pierre Martineau's name to clarify his role in the study. Section(s) of the protocol affected: Appendix 1
Version 1.0, 16 Dec 2019
Initial creation

PROTOCOL SUMMARY

Protocol number: QGC001-3QG1
Protocol title: 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
Short title: <u>F</u> iribastat in treatment- <u>RES</u> istant <u>H</u> ypertension (FRESH)
Sponsor: Quantum Genomics
Coordinating investigator: George Bakris, MD
Study phase: Phase 3
Indication: Treatment of hypertension (HTN) in difficult-to-treat and/or treatment-resistant subjects.
Study sites: It is planned to recruit subjects from 70 sites across Europe, and North and Latin America.
Objectives: The primary objective of this study is to assess the effects of administration of firibastat (QGC001) 500 mg oral (po) twice daily (bis in die [bid]) on blood pressure (BP) over 12 weeks in subjects with uncontrolled primary HTN despite being treated with 2 classes of antihypertensive therapies, at the maximum tolerated doses (MTDs). The secondary objective is to assess the safety of firibastat (QGC001).
Study design: This is a double-blind, placebo-controlled, multicenter, efficacy and safety study of firibastat (QGC001) administered po bid over 12 weeks in male and female subjects ≥ 18 years of age at Screening, with uncontrolled primary HTN despite being treated with at least 3 classes of antihypertensive therapies, including a diuretic, for treatment-resistant subjects, or 2 classes of antihypertensive therapies, (including or not including a diuretic) for difficult-to-treat subjects at the MTDs. Subjects will be randomized 1:1 to investigational product (IP) and will receive either firibastat (QGC001) or matching placebo on top of their current chronic antihypertensive treatments. The study will include a Screening Visit (Visit 1, Day -28), a Run-in Period of at least 28 days and no more than 33 days duration, an Inclusion Visit (Visit 2, Day -1, and Visit 2, Day 1), and a 12-week blinded Treatment Period, during which subjects will receive a Safety Phone Call on Day 14 (± 3 d), and attend the site for 2 visits (Visit 3, Day 28 [± 3 d]) and Visit 4, Day 56 [± 3 d]). At the end of the Treatment Period, subjects will attend an End of Treatment (EOT) Visit (Visit 5, Day 83 [± 3 d], and Visit 5, Day 84). If systolic BP (SBP) is >180 mmHg or diastolic BP (DBP) >110 mmHg at any visit during the study, subjects will be withdrawn from the study and will receive appropriate treatment. Subjects will also attend a safety Follow-up Visit (Visit 6, Day 112 [± 3 d]). Screening assessments will be performed at Visit 1, Day -28. Eligible subjects will then enter the Run-in Period, during which medication adherence will be assessed via a subject medication diary. Subjects who are screen failures can be rescreened and will be given a new subject number and sign a new Informed Consent; all study specific assessments will be done again at the rescreening. Subjects previously randomized in the study cannot be rescreened. At Visit 2, on Day -1 (corresponding to the last day of the Run-in Period), an ambulatory BP monitoring (ABPM) device will be set up for each subject who has successfully completed the Run-in Period with a medication adherence $\geq 80\%$, and remains eligible to participate in the study. The ABPM will be set to record for at least 24 hours, with the measurement frequency set at 30-minute intervals during the day (8:00 am to 10:00 pm [theoretically 28 readings, 2 per hour]) and 60-minute intervals at night (10:00 pm to 8:00 am [theoretically 10 readings, 1 per hour]). Subjects must have a successful ABPM measurement prior to being randomized and starting treatment with IP at Visit 2, Day 1. An ABPM recording is considered successful if at least 21 daytime readings and 6 nighttime readings have been successfully recorded. A duration of less than 24 hours (eg, 23 hours and 30 minutes) would be acceptable for a successful ABPM recording providing the number of readings successfully recorded are the same as the

above (21 daytime readings and 6 nighttime readings). If the ABPM recording is not successful, 2 further attempts are permitted. Following a successful ABPM recording, subjects who still meet the inclusion/exclusion criteria, and who have a mean daytime systolic ambulatory BP (ABP) >135 mmHg, will undergo visit-specific assessments and will be randomized 1:1 to receive blinded treatment with IP on top of their current chronic antihypertensive treatments.

During the 12-week Treatment Period, the investigator (or designee) will call subjects by telephone on Day 14 (± 3 d) to collect any potential adverse events (AEs) and record any concomitant medications. Subjects will return to the site for Visit 3, Day 28 (± 3 d) and Visit 4, Day 56 (± 3 d). At each study visit, automated office BP (AOBP), orthostatic BP, and heart rate (HR) will be measured and other visit-specific procedures will be performed, including electrocardiograms (ECG), clinical laboratory evaluations, clinical examinations, collection of blood for the biomarker N-terminal pro-B-type natriuretic peptide (NT-ProBNP), monitoring of AEs, and concomitant medications. Allergic reactions, and/or diabetes insipidus (DI) are considered as adverse events of special interest (AESIs) with immediate notification.

At the EOT Visit (Visit 5, Day 83 [± 3 d]), a 24-hour ABPM device will be set up in the morning after IP intake. Subjects must have a successful ABPM measurement prior to discontinuing IP at Visit 5, Day 84. If the ABPM measurement is not successful, the subject should continue to take IP and repeat the ABPM measurement within 24 hours of the first measurement. Visit-specific procedures (including discontinuation of IP) will be delayed until a successful ABPM recording has been obtained. If required, a third attempt to obtain a successful ABPM may only be performed if IP has not previously been discontinued.

Subjects who discontinue the study early should undergo an Early Termination Visit and complete the assessments indicated at the EOT Visit.

At the safety Follow-up Visit (Visit 6, Day 112 [± 3 d]), assessments will include automated office blood pressure (AOBP), orthostatic BP, HR, ECG, AE monitoring, concomitant medications, and clinical laboratory assessments.

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. 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. 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 first IDMC meeting for the study. At that time, each data element that the IDMC needs to assess will be clearly defined. The IDMC will submit its recommendations to the Steering Committee and to Quantum Genomics. In case of significant safety concerns, the IDMC may recommend temporary interruption of subject recruitment as well as the termination of the study.

Study duration: The start of the study will be the date when the first subject provides informed consent; the end of the study will be the date of the last subject's last assessment.

The total duration of participation for each subject will be approximately 140 days from Screening (Visit 1, Day -28) to the final safety Follow-up (Day 112 [± 3 d]).

Planned number of subjects: It is planned to enroll approximately 502 subjects (251 per treatment group) in order to obtain 213 evaluable subjects in each treatment group, assuming a 15% drop-out rate.

Target population: Subjects with uncontrolled primary HTN despite being treated with at least 3 classes of antihypertensive therapies, including a diuretic, for treatment-resistant subjects or 2 classes of antihypertensive therapies (including or not including a diuretic), for difficult-to-treat subjects at the MTDs.

Inclusion criteria:

Subjects who meet all of the following criteria will be 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 MTDs of those medications (ie, 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 ABPM measurement with a mean systolic daytime ABP >135 mmHg after the Run-in Period while on their current chronic antihypertensive treatments. An ABPM is successful if at least 21 daytime readings and 6 nighttime readings have been successfully recorded.
4. Women of childbearing potential and nonsurgically 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, depo, patch, or injectable) together with supplementary barrier method such as condoms or diaphragms with spermicidal gel or foam.
5. Women of childbearing potential must have 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 meet any of the following criteria will be excluded from participation in the study:

1. Known or suspected secondary HTN (eg, 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 minutes to 1 hour.
3. Known hypertensive retinopathy (Keith-Wagener Grade 3 or Grade 4) and/or hypertensive encephalopathy.
4. Upper arm circumference that is 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 cm²/m²).
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 (ie, surgery, aggressive diet regimen, etc.), leading to unstable body weight.
12. Female who is 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) $>3 \times$ upper limit of normal (ULN), or a total bilirubin $\geq 1.5 \times$ 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 m², as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey AS, et al. 2009) at Screening.
17. History of any blood disorder, other than sickle cell trait, causing hemolysis or unstable red blood cells (eg, malaria, babesiosis, hemolytic anemia, thalassemia, sickle cell anemia).
18. Subjects with documented DI.
19. Subjects with Type 1 diabetes mellitus.
20. Subjects with Type 2 diabetes mellitus who:
 - Are poorly controlled, defined as glycosylated hemoglobin A1c (HbA1c) $>9\%$ at Screening; OR
 - Are 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 is permitted.
22. Clinical evidence of thyroid disease, thyroid hormone therapy that is not stable ≥ 4 weeks prior to Screening, or a thyroid-stimulating hormone (TSH) level $<0.75 \times$ lower limit of normal or $>1.5 \times$ 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.

29. Subjects with any history of documented allergic reactions or allergic diseases, with the exception of documented seasonal allergies (per the investigator's decision).
Test product: Name: Firibastat (QGC001) Dose: 500 mg (2×250 mg capsules) bid Mode of administration: Oral
Control Product: Matching oral placebo
Endpoints: Primary: The primary efficacy endpoint is the change in systolic AOBP from baseline to Week 12 (Visit 5, Day 84). Secondary efficacy endpoints include: • 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-hour ambulatory SBP and DBP from baseline to Week 12 (Visit 5, Day 84) • Percentage of controlled subjects (defined as subjects with normalized AOBP, ie, <140/90 mmHg at Week 12 [Visit 5, Day 84]) (as per 2018 European Society of Cardiology [ESC]/European Society of Hypertension [ESH] guidelines) • Percentage of controlled subjects (defined as subjects with normalized AOBP, ie, <130/80 mmHg at Week 12 [Visit 5, Day 84]) (as per 2017 American College of Cardiology [ACC]/American Heart Association [AHA] guidelines) • Predictive factors for controlled subjects at Week 12 (Visit 5, Day 84) • Change from baseline in plasma concentration of biomarker NT-ProBNP Safety endpoints: All AEs, vital signs, ECG, laboratory parameters, and concomitant treatments.
Statistical methods: All data will be presented by treatment group. Descriptive statistics (number of observations, number of missing data, mean, SD, median, minimum, and maximum) will be provided for continuous variables, and counts, percentages (excluding missing data) and number of missing data will be presented for categorical variables. Inferential tests will be performed 2-sided, with an alpha risk at 5%. Main analysis populations: • Full Analysis Set (FAS): all randomized subjects who received at least 1 dose of IP. The FAS will be used for analyses of the primary efficacy endpoint and all secondary efficacy endpoints and will be analyzed according to planned treatment. • Safety Set (SS): all subjects who receive at least 1 dose of IP. The SS will be analyzed according to actual treatment and will be used for summaries of safety data. • Per Protocol Set (PPS): all subjects in the FAS without any major deviation to the present protocol. The PPS will be used for sensitivity analyses and will be analyzed according to planned treatment. Primary endpoint analyses: The main criterion will be analyzed with a mixed model with repeated measures (MMRM) at Weeks 4, 8, and 12, with an unstructured matrix of covariance. A mixed model uses restricted maximum likelihood to estimate all unknown variance-covariance parameters, whereas a linear model uses method of moments estimators on transformed data. The advantage of the likelihood-based approach of the mixed model is that it can accommodate data that are missing at random, in contrast with linear model, which must ignore data from all subjects which have missing repeated measures. The other advantage of this approach is the ability to be robust to the

normality, associated with the sample size of 500 subjects, and provide a contrast and estimates of difference versus placebo, suitable in treatment of BP. The main analyses will be performed on the FAS, and on the PPS as a sensitivity analysis.

Secondary endpoints analyses: To check the homogeneity of the efficacy results, forest plots at Week 12 of the estimates will be provided for each modality of each subgroup (age, sex, body mass index [BMI], ethnicity, eGFR, and treatment-resistant/difficult-to-treat) and for the global population in the same graph. Change from baseline to Week 4 and 8 of systolic and diastolic AOBP will be analyzed from the same model as for the main criterion. Change from baseline of ABP to Week 12 will be described for SBP and DBP, for daytime, nighttime, and all along the 24 hours. These criteria will be analyzed through an analysis of covariance (ANCOVA) with baseline as covariate

Controlled subjects (defined as systolic AOBP <140 mmHg and diastolic AOBP <90 mmHg as per 2018 ESC/ESH guidelines, and systolic AOBP <130 mmHg and diastolic AOBP <80 mmHg as per 2017 ACC/AHA guidelines) at Week 12 will be analyzed using a logistic regression with baseline of systolic AOBP and baseline of diastolic AOBP as covariates. The same analysis of controlled subjects at Week 12 will be repeated for each modality of each subgroup. Forest plots at Week 12 of the estimates (odds-ratios) will be provided for each subgroup and for the global population in the same graph.

Biomarker NT-ProBNP: Change from baseline to EOT in plasma concentration will be analyzed with the same strategy as for the ABP (ANCOVA).

Analysis of safety: Adverse events' reported terms will be coded with the Medical Dictionary for Regulatory Activities (MedDRA); primary system organ class (SOC) will be used to report results. An AE will be considered as treatment-emergent if it begins the day of, or after the first IP administration. A summary table will present the incidence of all AEs in terms of the number of subjects (subjects with at least 1 AE) and events with: all AEs, all serious AEs, all treatment-emergent AEs (TEAEs), TEAEs by intensity, all serious TEAEs, drug-related TEAEs (and by intensity), all TEAEs leading to discontinuation, all TEAEs leading to death, and all AESIs. In addition, the number of subjects with at least 1 of the following types of AEs will be summarized according to SOC and preferred term (PT): all AEs, TEAEs, TEAEs according to the intensity of AE, drug-related TEAEs (and by intensity), serious TEAEs, TEAEs leading to a discontinuation, TEAEs leading to death, and AESIs.

Laboratory data, vital signs, and ECG parameters values and changes from baseline will be presented descriptively, as well as clinical significance. Prior and concomitant medications reported names will be coded in Anatomic Therapeutic Chemical (ATC) codes with World Health Organization (WHO)-Drug; the number of subjects with at least 1 prior medication (ended before the first IP administration) will be summarized.

Demographic and baseline characteristics (including height, weight, BMI, hip and weight circumference, disease characteristics, and comorbidities) will be presented descriptively, for subjects difficult-to-treat, resistant subjects, and all subjects. No inferential statistics is planned on baseline characteristics.

Subgroup analyses: To explore the uniformity of the detected overall treatment effect on the primary, and when applicable, key secondary efficacy endpoints, subgroup analyses may be performed for: resistance status (difficult-to-treat or resistant), age (<65 years, ≥65 years), ethnicity (Black, non-Black), eGFR: <60 mL/min/1.73 m², ≥60 mL/min/1.73 m², BMI (<25 kg/m², ≥25 kg/m²), and sex.

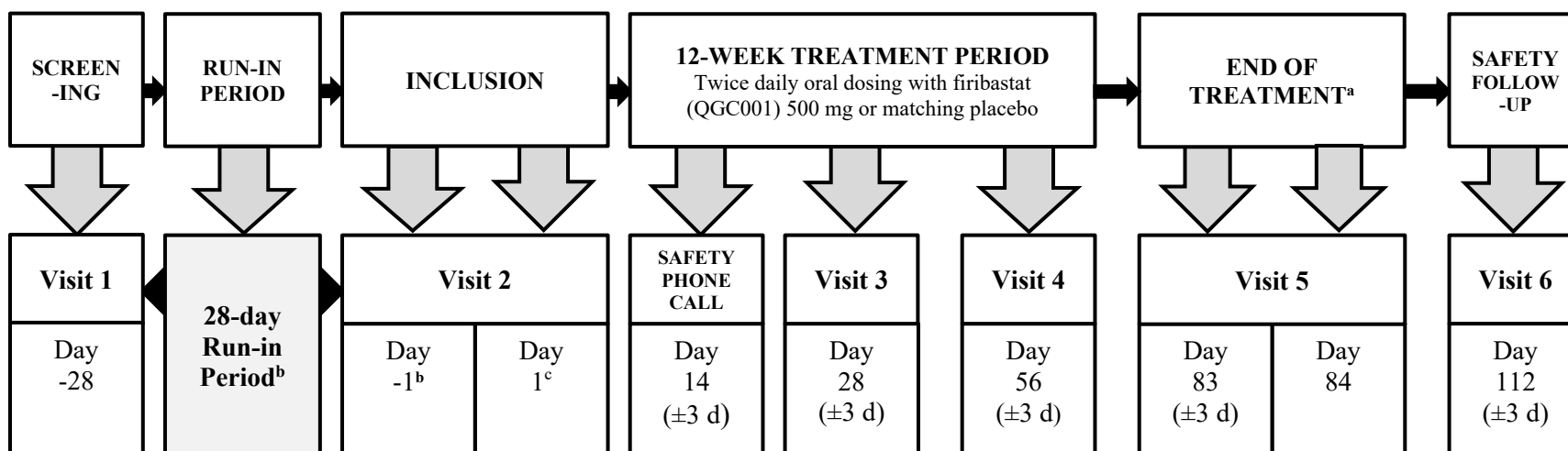
To examine the impact of intermediate missing values and missing values after premature termination of IP, missing data will be accommodated by the use of MMRM with restricted maximum likelihood.

No interim analysis is planned.

Protocol version and date: 4.0, 31 Mar 2021

STUDY SCHEMATIC

Figure 1 Study Schematic



ABPM=ambulatory blood pressure monitoring; bid=twice daily; d=day; DBP=diastolic blood pressure; IP=investigational product; po=oral(ly); SBP=systolic blood pressure.

Note: If SBP is >180 mmHg or DBP >110 mmHg at any visit during the study, subjects will be withdrawn from the study and will receive appropriate treatment.

^a Subjects who discontinue the study early should undergo the Visit 5 assessments at an Early Termination Visit.

^b The Run-in Period must be at least 28 days and no more than 33 days in duration.

^c Following a successful ABPM recording, subjects will be randomized and receive their first dose of IP (either 2 capsules of firibastat [QGC001] 250 mg po bid or 2 capsules of matching placebo po bid) on Visit 2, Day 1.

SCHEDULE OF ASSESSMENTS

Table 1 **Schedule of Assessments**

Assessment	Screening	Run-in Period ^a	Inclusion		12-week Treatment Period			End of Treatment (EOT)/ Early Termination Visit ^b	Follow-up ^c	
Visit/ Phone Call	Visit 1	NA	Visit 2		Safety Phone Call	Visit 3	Visit 4	Visit 5	Visit 6	
Study Day	Day -28	←----→	Day -1 ^d	Day 1 ^e	Day 14 (±3 d)	Day 28 (±3 d)	Day 56 (±3 d)	Day 83 (±3 d)	Day 84	Day 112 (±3 d)
Informed consent	X									
Inclusion/exclusion criteria	X		X	X						
Demographics	X									
Medical history	X									
Clinical examination ^f	X			X		X	X		X	X
12-lead ECG ^g				X					X	X
AOBP, orthostatic BP, and HR measurements ^h	X			X		X	X		X	X
Subject medication diary ⁱ	X	X	X							
Set up of 24-hour ABPM device ^j			X					X		
Return ABPM device and review 24-hour ABPM measurements ^k				X					X	

Table 1 Schedule of Assessments

Assessment	Screening	Run-in Period ^a	Inclusion		12-week Treatment Period			End of Treatment (EOT)/ Early Termination Visit ^b	Follow-up ^c	
Visit/ Phone Call	Visit 1	NA	Visit 2		Safety Phone Call	Visit 3	Visit 4	Visit 5	Visit 6	
Study Day	Day -28	←----→	Day -1 ^d	Day 1 ^e	Day 14 (±3 d)	Day 28 (±3 d)	Day 56 (±3 d)	Day 83 (±3 d)	Day 84	Day 112 (±3 d)
Blood sample for laboratory assessment (hematology) ^l	X					X	X		X	X
Blood sample for laboratory assessment (chemistry) ^m	X			X		X	X		X	X
Blood sample for coagulation (prothrombin time only)	X									
Blood samples for biomarker NT-ProBNP ⁿ				X					X	
Urine pregnancy test				X		X	X		X	
Serum pregnancy test	X									X
Continue chronic antihypertensive medication ^o	X-----									X
Randomization				X						
Dosing with IP ^p				X-----					X	
Dispense IP ^q				X		X	X			

Table 1 Schedule of Assessments

Assessment	Screening	Run-in Period ^a	Inclusion		12-week Treatment Period			End of Treatment (EOT)/ Early Termination Visit ^b	Follow-up ^c	
Visit/ Phone Call	Visit 1	NA	Visit 2		Safety Phone Call	Visit 3	Visit 4	Visit 5	Visit 6	
Study Day	Day -28	←----→	Day -1 ^d	Day 1 ^e	Day 14 (±3 d)	Day 28 (±3 d)	Day 56 (±3 d)	Day 83 (±3 d)	Day 84	Day 112 (±3 d)
IP compliance check ^r					X	X	X		X	
Assessment of hypotensive events ^s			X			X	X		X	X
Discontinue IP ^t									X	
Adverse events ^u	X-----									X
Concomitant medication	X-----									X

ABPM=ambulatory blood pressure monitoring; AESI=adverse event of special interest; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AOBP=automated office blood pressure; AST=aspartate aminotransferase; bid=twice daily; BP=blood pressure; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; d=day; DBP=diastolic blood pressure; DI=diabetes insipidus; ECG=electrocardiogram; EDC=electronic data capture; eGFR=estimated glomerular filtration rate; EOT=End of Treatment; GP=general practitioner; HbA1c=hemoglobin A1c; HR=heart rate; IP=investigational product; NA=not applicable; NT-ProBNP=N-terminal pro-B-type natriuretic peptide; po=oral(ly); RBC=red blood cell count; SBP=systolic blood pressure; TSH=thyroid-stimulating hormone; WBC=white blood cell count.

- ^a Subjects will enter a Run-in Period, which must be at least 28 days and no more than 33 days in duration. During the Run-in Period, subjects will continue to take their current chronic antihypertensive medications.
- ^b The EOT for subjects completing the study is Visit 5. For subjects who are withdrawn from the study prior to completion, all Visit 5 procedures should be performed at an Early Termination Visit (except in the case of consent withdrawal).
- ^c The Follow-up Visit (Visit 6, Day 112) will be performed 30 days after the last dose for subjects who prematurely discontinue the IP, unless consent has been withdrawn.
- ^d The Run-in Period must be at least 28 days and no more than 33 days in duration. The Run-in Period ends with randomization .
- ^e The day the subject starts treatment with IP will be nominated Visit 2, Day 1.
- ^f Clinical examination includes height, weight, and hip and waist circumference measurements. At Visit 2, Day 1, and Visit 3, Day 28 (±3 d), clinical examination will be performed prior to any IP administration. At and Visit 5, Day 84, clinical examination will be performed after IP administration. Height will be recorded at Screening only.
- ^g Subjects must rest in a supine position for at least 5 minutes before the ECG recording. ECG recordings must be performed prior to blood sampling procedures. At Visit 2, Day 1, ECG will be recorded prior to any IP administration and after IP administration on Day Visit 5, Day 84, and time since last IP dose will be recorded. At Visit 6, Day 112, time since last IP dose will also be recorded. The QT will be measured and reported as normal or abnormal in EDC. All ECGs will be collected for subsequent central reading of the QT/QTc interval.

- h If systolic AOBP is >180 mmHg or DBP >110 mmHg at any visit during the study, subjects will be withdrawn from the study and will receive appropriate treatment. If SBP >180 mmHg or DBP >110 mmHg at Visit 3 or Visit 4, it should be repeated and confirmed within 30 minutes. All BP measurements will be performed on the nondominant arm and, if possible, by the same person. BP measures must be taken prior to any blood being drawn or any IP being administered: compulsory at Visit 2, Day 1, recommended at Visit 3, Day 28 (± 3 d), Visit 4, Day 56 (± 3 d) and Visit 5, Day 84.
- i Subjects will complete a self-reported medication adherence diary during the Run-in Period. At Visit 2, Day -1, subjects must have a medication adherence $\geq 80\%$ to remain eligible to participate in the study.
- j A 24-hour ABPM device will be set up to record for at least 24 hours, with the measurement frequency set at 30-minute intervals during the day (8:00 am to 10:00 pm [theoretically 28 readings, 2 per hour]) and 60-minute intervals at night (10:00 pm to 8:00 am [theoretically 10 readings, 1 per hour]). For the Visit 5, Day 83 visit, the device should be set to begin recording in the morning immediately following IP dosing in the morning (between 8:00 and 10:00 am).
- k Subjects will return to the site 24 hours later to have the ABPM device removed, and the 24-hour ABPM measurements reviewed. Subjects must have a successful ABPM measurement prior to receiving IP. If the ABPM measurement is not successful, the subject may repeat the ABPM measurement within 24 hours of the first measurement. The ABPM measurement is considered successful if at least 21 daytime readings and 6 nighttime readings are successful.
- l Hematology will include hematocrit, hemoglobin, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils [manual microscopic review will be performed only if WBC and/or differential values are out of reference range]). At Visit 3, Day 28 (± 3 d), and Visit 4, Day 56 (± 3 d), samples for hematology will be obtained prior to any administration of IP. At Visit 5, Day 84, samples will be obtained after IP administration.
- m Clinical chemistry will include albumin, ALP, ALT, AST, bicarbonate, BUN, calcium, creatine kinase, creatinine, direct bilirubin, eGFR (calculated using the CKD-EPI formula [Levey AS, et al. 2009]), glucose, potassium, serum triglycerides, sodium, total bilirubin, total cholesterol, and uric acid; with the addition of HbA1c at Screening and Visit 5, Day 84 only, and TSH at Screening only. At Visit 2, Day 1, Visit 3, Day 28 (± 3 d), Visit 4, Day 56 (± 3 d), and Visit 5, Day 84, samples for clinical chemistry will be obtained prior to any administration of IP.
- n Blood samples will be collected for analyses of biomarker NT-ProBNP.
- o Subjects will continue to take their chronic antihypertensive treatments throughout the study. During the Run-in Period, medication adherence will be assessed by subject medication diary.
- p Following randomization, all subjects who have successful ABPM measurements will start dosing with IP for the 12-week Treatment Period; IP consists of either 2 capsules fribastat (QGC001) 250 mg po bid or 2 capsules of matching placebo po bid. For subjects randomized to fribastat (QGC001), the dose will remain unchanged at each visit.
- q Subjects will receive supplies of IP at Visit 2, Day 1, Visit 3, and Visit 4.
- r Compliance with IP administration will be checked by IP capsule count at each visit. Subjects will be asked about compliance during the Safety Phone Call at Day 14 (± 3 days).
- s Hypotensive events will be assessed at each visit and are defined by the following:
- SBP <90 mmHg; or
 - DBP <60 mmHg; and/or
 - Any BP with symptoms of hypotension (eg, lightheadedness, dizziness).
- At Visit 2, Day -1, any subject reporting symptoms of hypotension (eg, lightheadedness, dizziness) during the Run-in Period should be assessed by the investigator and treated as necessary; the subject must not continue with Visit 2 procedures. During the Treatment Period, any symptomatic hypotension or symptomatic orthostatic hypotension must lead to IP discontinuation. In case of any suspicion or symptoms related to hypotension, the subject will be advised to immediately contact the investigator or the subject's GP. Hypotensive events will be recorded as AEs.
- t If the 24-hour ABPM measurement is successful at Day 84, all visit-specific procedures will be performed and the IP will be discontinued. If the ABPM measurement is not successful, the subject should continue to take IP and repeat the ABPM measurement within 24 hours of the first measurement. Visit-specific procedures (including discontinuation of IP) will be delayed until completion of the second ABPM recording. If the second ABPM recording is not successful, a third attempt to obtain a successful ABPM may only be performed if IP has not previously been discontinued. Visit-specific procedures (including discontinuation of IP) will be further delayed until completion of the third ABPM recording.
- u Reporting of AEs (serious or not) will begin when the subject has provided informed consent and will continue until study participation is complete. Subjects will be informed by the investigator that in case of occurrence of any allergic reactions, skin lesions, or DI, they must inform their site investigator as soon as possible. Allergic reaction and DI are considered as AESIs with immediate notification (ie, within 24 hours of the investigator's first knowledge). Immediate reporting of SAEs will continue up to 30 days after the last administration of IP.

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LIST OF ABBREVIATIONS

ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	angiotensin I converting enzyme
ACTH	adrenocorticotrophic hormone
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Ang II	angiotensin II
Ang III	angiotensin III
AOBP	automated office blood pressure
APA	aminopeptidase A
APN	aminopeptidase N
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AT1	angiotensin II receptor Type 1
AT2	angiotensin II receptor Type 2
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
AVP	arginine-vasopressin
β-hCG	beta human chorionic gonadotrophin
BAPAI	brain aminopeptidase A inhibitor
BCRP	breast cancer resistance protein
bid	bis in die (twice daily)
BMI	body mass index

BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
DBP	diastolic blood pressure
DI	diabetes insipidus
DOCA	deoxycorticosterone acetate
EAPA	Europe, Asia-Pacific, and Africa
ECE-1	endothelin-converting enzyme
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	general practitioner
HbA1c	glycosylated hemoglobin A1c
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HTN	hypertension
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
LV	left ventricular
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model with repeated measures
MTD	maximum tolerated dose
NEP	neutral endopeptidase
NT-ProBNP	N-terminal pro-B-type natriuretic peptide
NTS	nucleus of the tractus solitarius
NYHA	New York Heart Association
OBP	office blood pressure
OVL	organum vasculosum of the lamina terminalis
PK	pharmacokinetic(s)
po	oral(ly)
PPS	Per Protocol Set
PT	preferred term
PVN	paraventricular nucleus
QD	once daily
QTL	quality tolerance limit
RAS	renin-angiotensin system
RVLM	rostral ventrolateral medulla
SAE	serious adverse event

SAP	statistical analysis plan
SBP	systolic blood pressure
SFO	subfornical organ
SGLT2	sodium-glucose co-transporter 2
SHR	spontaneously hypertensive rat
SI	Système International
SOC	system organ class
SON	supraoptic nucleus
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	plasma elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum plasma concentration
TMF	trial master file
TSH	thyroid-stimulating hormone
UGT	uridine glucuronyl transferase
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Arterial hypertension (HTN) is a global public health issue. It affects approximately 1 billion individuals worldwide and it is one of the leading risk factors for coronary heart disease, heart failure (HF), stroke, and renal insufficiency.¹

Despite decades of research efforts, the specific mechanisms involved in mediating the elevation in blood pressure (BP) that characterizes HTN are still poorly understood. Essential HTN is a multifactorial and polygenic disorder, in which various mechanisms contribute to a greater or lesser extent to increasing BP.

All antihypertensive drugs lower BP in patients with HTN and this decline is the best determinant of cardiovascular risk reduction. However, differences between drug classes and drugs themselves exist with respect to the reduction of target-organ disease and prevention of major cardiovascular events. Despite the availability of effective and safe antihypertensive drugs, HTN and its concomitant risk factors remain uncontrolled in most patients. Indeed, 2 out of 3 patients diagnosed with HTN do not have their BP controlled (<140/90 mmHg).^{2,3,4,5} The current antihypertensive drugs are also less effective in patients of African ancestry, and patients with diabetes mellitus or renal insufficiency in whom high BP is associated with low renin levels. In these patients, antihypertensive drugs must be used at higher doses and, consequently, significant adverse effects may be induced, leading to the interruption of the treatment. Therefore, most hypertensive patients need 2 or more drugs for BP control. Despite the availability of more than 75 antihypertensive agents distributed over as many as 9 different classes, the overall incidence of HTN resistant to at least 3 antihypertensive drugs (including a diuretic, if applicable) is estimated to be approximately 15% of the hypertensive population.^{6,7} Consequently, there is still an unmet medical need to develop new effective and safe classes of antihypertensive drugs acting through alternative pathways to further improve BP control and reduce the associated cardiovascular risk in patients.

Drugs targeting the systemic renin-angiotensin system (RAS) pathway, such as angiotensin 1 converting enzyme (ACE) inhibitors and angiotensin II Type 1 (AT1) receptor antagonists have been shown to be clinically effective in lowering BP and preventing cardiovascular and renal morbidity and mortality in a broad range of patients.

Recent evidence supports the hypothesis that a functional RAS controlling cardiovascular functions and body fluid homeostasis is also present in the brain.^{8,9} Hyperactivity of the brain RAS and particularly aminopeptidase A (APA, EC 3.4.11.7) and aminopeptidase N (APN, EC 3.4.11.2), 2 membrane-bound zinc metalloproteases involved in vivo in the metabolism of brain angiotensin II (Ang II) and angiotensin III (Ang III), respectively, play a critical role in mediating BP levels in various animal models of HTN, including the deoxycorticosterone acetate (DOCA)-salt rats and the spontaneously hypertensive rats (SHRs).^{10,11} Although the specific mechanisms by which increased brain RAS activity

results in HTN are still not well understood, they include increases in vasopressin release, sympathetic vasomotor tone, and impaired arterial baroreflex function.

Angiotensinergic neurons originate from hypothalamic circumventricular organs like the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT), and project to the preoptic area, the hypothalamic paraventricular nucleus (PVN), and the supraoptic nucleus (SON). Originating in the PVN, another pathway projects to the medulla oblongata in the nucleus of the tractus solitarius (NTS) and the rostral ventrolateral medulla (RVLM) and terminates in the spinal cord. The brain RAS controls BP via 3 different mechanisms: an increase in arginine-vasopressin (AVP) release into the bloodstream, an activation of sympathetic premotor neurons' activity at the level of the RVLM (a key BP regulatory center that contains the neurons generating the vasomotor tone), and an inhibition of the baroreflex at the level of the NTS. Several studies suggest that Ang III may be the true effector of the brain RAS in the central control of BP. ^{12,13,14,15} Indeed, brain Ang III was shown to exert a tonic central stimulatory action on BP even in hypertensive rats, and central injections of an APA inhibitor, by blocking the formation of Ang III in the brain, decreased BP in alert hypertensive rats. Therefore, brain APA, the enzyme generating Ang III from Ang II in the brain RAS, constitutes a promising therapeutic target for treatment of arterial HTN.

1.1.1 Investigational Product

Firibastat (previously named QGC001 or RB150) is a new molecular entity (3S-amino-4-[2S-amino-4-sulfobutyl]disulfanyl]-butane-1-sulfonic acid) and the first drug-candidate of a new class of centrally acting agents, brain aminopeptidase A inhibitors (BAPAI). Firibastat (QGC001) is currently being developed for the treatment of HTN, and in parallel for the treatment of HF.

Firibastat (QGC001) is a prodrug of EC33 ([3S]-3-amino-4-sulfanylbuthane-1-sulfonic acid), a selective inhibitor of APA, the enzyme that generates Ang III from Ang II. Firibastat (QGC001) can be referred to as the dimer of EC33 obtained through a disulfide bridge formation. When crossing the blood brain barrier, firibastat (QGC001) is cleaved, releasing 2 molecules of the active APA inhibitor EC33 into the brain which inhibit the activity of APA at the brain level and block the production of brain Ang III, known to exert a tonic stimulatory action on the control of BP.

Firibastat's (QGC001) antihypertensive effect is partly due to a decrease in AVP release in the blood circulation, increasing diuresis which reduces the size of the body fluid compartment, and to a reduction in the sympathetic tone leading to a subsequent decrease in vascular resistance.

Evidence suggests that targeting these 2 biological pathways could also be of interest for the treatment of HF. Therefore, firibastat (QGC001) may be a potentially beneficial drug-candidate to address the needs of HF patients.

1.1.2 *Nonclinical Studies*

Firibastat (QGC001) and its metabolite EC33 show a high selectivity for human APA compared to other receptors and enzymes involved in BP regulation, such as AT1, angiotensin II Type 2 (AT2) receptors, endothelin A, and endothelin B receptors, ACE, ACE-2, endothelin-converting enzyme (ECE-1) and neutral endopeptidase (NEP) and APN.

Firibastat (QGC001), administered by the intravenous route (IV; 1 mg/kg), or by the oral route (po; 15 mg/kg) was found to block the brain RAS activity and to markedly reduce BP in conscious hypertensive DOCA-salt rats which are characterized by low plasma renin activity and a resistance to drug treatments targeting the systemic RAS. Oral administration of firibastat (QGC001) (15 mg/kg) in DOCA-salt hypertensive rats also decreased vasopressin release in the blood circulation and increased diuresis. The antihypertensive effects of firibastat (QGC001) were also demonstrated after oral administration (15 mg/kg) in SHR, which is considered to be a relevant model of essential HTN, sensitive to systemic RAS blockers.

Firibastat (QGC001) (po; 15 mg/kg) had no significant effect on mean arterial BP or heart rate (HR) of conscious normotensive Wistar Kyoto rats or Sham rats. Firibastat (QGC001) administered po at doses up to 1000 mg/kg had no effect on behavior, body temperature, or on respiratory parameters in conscious rats and no effect on arterial BP, HR, body temperature, or cardiac conduction time in conscious dogs.

In mice and rats post-myocardial infarction (MI), repeated oral administration of firibastat (QGC001) was found to normalize brain APA hyperactivity and to prevent cardiac dysfunction by improving left ventricular (LV) end-diastolic pressure and ejection fraction.^{16,17}

The risk of adverse events (AEs) due to drug-drug interactions is limited since none of the human recombinant cytochrome P450s (CYPs) (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) were significantly inhibited by firibastat (QGC001), by EC33, or by QGC515 when tested in vitro at 100 µmol/L. Additionally, firibastat (QGC001) was found not to inhibit activities of uridine glucuronyl transferases (UGTs) UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, as well as transport mediated via P-gp and breast cancer resistance protein (BCRP), or via OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1, and MATE2-K.

No pharmacokinetic (PK) interactions were noted between firibastat (QGC001) and enalapril when both drugs were co-administered in rats.

Firibastat (QGC001) was not genotoxic in any of the 3 regulatory tests performed according to International Council for Harmonisation (ICH) S2R1 standards. Firibastat (QGC001) has not yet been tested for carcinogenic activity as per ICH S1 and ICH M3 (R2) at this stage of development.

Preclinical fertility and teratology studies with oral fribastat (QGC001) in rats and rabbits found no evidence of maternal or fetal toxicity at 1000 mg/kg/day in rats and at 400 mg/kg/day in rabbits. Since the calculation of the Human Estimated Doses of 1000 mg/kg/day in rats and of 400 mg/kg/day in rabbits gives, by using standard conversion factors (0.162 for rats and 0.324 for rabbits), doses far above the maximum daily dose considered in the clinical trials (10,000 mg/day for rats, [1000 mg/kg/day x 0.162 x 62 kg]; and 8000 mg/day for rabbits [400 mg/kg/day x 0.324 x 62 kg]), women of childbearing potential may participate in clinical trials provided they are using an appropriate form of contraception.

1.1.3 Clinical Studies

Quantum Genomics intends to market fribastat in resistant/difficult-to-treat hypertensive patients. Nevertheless, for safety reasons, the stepwise strategy was to get first a proof-of-concept in a “standard” hypertensive population (QGC001/2QG1), then demonstrate efficacy in a high-risk, diverse population (QGC001/2QG3 – NEW-HOPE)¹⁸ before moving to resistant/difficult-to-treat patients in Phase 3 (QGC001/3QG1).

Currently, 473 patients and healthy volunteers have been enrolled into the fribastat (QGC001) clinical development program, and at least 415 subjects have received fribastat (QGC001).

The clinical development of fribastat includes 6 completed clinical studies: 3 completed Phase 1 studies conducted in 137 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. One Phase 2 study in post-MI and one Phase 1 study are ongoing. Two additional studies (one Phase 1 study and the current Phase 3 in hypertensive patients) are currently planned.

According to the clinical studies conducted in healthy subjects, PK analysis demonstrated good dose proportional exposure to fribastat (QGC001) after repeated oral administration.

Pharmacokinetic parameters were assessed after repeated doses in 36 normotensive male volunteers: 500 mg, 750 mg, and 1000 mg twice a day (bid [bis in die]) of QGC001 (n=9/dose) or placebo (n=3/dose) for 7 days.

All QGC001 doses were rapidly absorbed (time to reach maximum plasma concentration [$t_{\max}$] range: 3-5 h) and converted to EC33 within 3.5 to 5 h. Maximum plasma concentration ($C_{\max}$) and area under the curve (AUC) of QGC001 and EC33 increased with the dose. There was a mild accumulation of QGC001 and EC33 and increase in plasma elimination $t_{1/2}$ with time. The median AUC accumulation ratio of QGC001 was 1.3, 1.6, 2.7 and that of EC33 was 1.6, 1.5, 2.1 for the 500 mg, 750 mg and 1000 mg bid doses. The median $t_{1/2}$ of QGC001 increased from <2 h on Day 1 to >5 h on Day 7 and that of EC33 increased from <3.1 to >7.7 h. Steady state was reached on Day 4 for both QGC001 and EC33 for the 750 mg bid and 1000 mg bid dose groups. For the 500 mg bid dose group, steady state was reached on Day 2 only for EC33.

Efficacy in HTN was assessed in two Phase 2 clinical trials (QGC001/2QG1 and QGC001/2QG3):

- In study QGC001/2QG1, 34 patients with Grade 1 or Grade 2 essential HTN were randomized to 4 weeks of treatment with each of oral QGC001 (250 mg bid for 1 week followed by 500 mg bid for 3 weeks) and placebo, in a crossover design. Ambulatory daytime systolic blood pressure (SBP) (primary endpoint), decreased by 2.7 mmHg with QGC001 compared to placebo ($p=0.16$) and office SBP by 4.7 mmHg. QGC001 did not influence HR, or plasma/urine hormones, including renin, aldosterone, copeptin, apelin, and adrenocorticotrophic hormone (ACTH).
- In the NEW-HOPE study (QGC001/2QG3), a diverse population of overweight and obese patients with primary HTN were treated with fribastat for 8 weeks. On completion of the Run-in Period, eligible subjects received oral fribastat (QGC001) 250 mg bid, which was adjusted to 500 mg bid po on Day 14 or Day 28 depending on BP measurements. Additionally, oral hydrochlorothiazide 25 mg was added (only for eligible subjects) to the dosing regimen on Day 28 or Day 35, depending on BP measurements. Subjects continued treatment until Day 56. The statistically significant improvements (by 9.5 ± 14 mmHg) in office SBP at Week 8 (primary endpoint) was supported by statistically significant differences in all secondary efficacy endpoints and by prespecified subgroup (race and body mass index [BMI]).¹⁸

More detailed information can be found in the Investigator's Brochure (IB).

1.1.3.1 Adverse Events

During the Phase 1 clinical trial (QGC001/1QG2) conducted in healthy normotensive adult male subjects, the administration of multiple oral doses of fribastat (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; however, all cases remained of mild intensity and resolved spontaneously.

Cumulatively 12 serious adverse events (SAEs) have occurred during all completed studies.

In the Phase 2a study QGC001/2QG1 in hypertensive patients, 3 SAEs occurred in 2 subjects during treatment with fribastat (QGC001); 1 subject experienced a vestibular disorder, considered possibly related to study medication, which led to treatment discontinuation and hospitalization; the patient recovered within 48 hours. The other subject experienced a macular rash and periorbital edema, thought to be a drug-induced toxidermia and probably related to study medication. Treatment was discontinued and the subject was hospitalized and treated with an antihistamine. The subject recovered within 4 days. These 2 SAEs were also classified as adverse events of special interest (AESIs).

In the Phase 2a study QUID-HF (QGC001/2QG2) in patients with New York Heart Association (NYHA) Class II/III chronic HF, 3 unrelated SAEs (ventricular tachycardia, cardiac failure, and pneumonia) occurred in the same subject.

In the Phase 2 study NEW-HOPE (QGC001/2QG3) in hypertensive patients, 6 SAEs were reported in 6 subjects: 4 SAEs were unrelated to study treatment: squamous cell carcinoma, umbilical hernia, MI, and lung nodule. Two cases of erythema multiforme were also reported as AESIs related to study medication. Both patients recovered fully.¹⁸

Cumulatively, 14 AESIs were collected across all studies:

- QGC001-2QG1: 4 AESIs were collected, among which 2 nonserious AESIs of pruritic rash occurred during the placebo treatment phase and 2 serious AESIs of macular rash and periorbital edema occurred in the same patient during the study drug treatment phase and were also considered a suspected unexpected serious adverse reaction (SUSAR).
- QGC001/2QG3: 10 AESIs were collected, among which 2 reports of erythema multiforme were serious and considered as SUSARs. The 8 nonserious AESI reports included 3 reports of rash, 2 reports of eczema, and 3 reports of drug hypersensitivity, all experienced by different patients.

1.2 Study Rationale

Firibastat (QGC001) offers a potential alternative therapeutic strategy for improving BP control of hypertensive patients and preventing cardiac dysfunction.

Due to its unique mechanism of action, firibastat (QGC001) represents an alternative therapeutic approach that may interfere with the mechanisms involved in the genesis and maintenance of elevated BP in hypertensive patients. Firibastat (QGC001) could prove beneficial to treat hypertensive patients resistant to current therapeutic drugs such as ACE inhibitors or AT1 receptor antagonists, and poorly controlled patients such as patients with low plasma renin and high vasopressin levels and/or with salt-sensitive HTN, a condition prevalent among African American, Asian, and Hispanic populations.

The primary objective of this study is to assess the effects of administration of firibastat (QGC001) 500 mg po bid on BP over 12 weeks in patients who are hypertensive despite being treated with 2 (difficult-to-treat) or 3 or more (resistant) antihypertensive classes at maximally tolerated doses.

This population is different from those enrolled in the completed Phase 2 studies, QGC001/2QG1 and QGC001/2QG3. Nevertheless, in the QGC001/2QG3 (NEW-HOPE) study, a high cardiovascular risk population, likely to be difficult-to-treat or resistant, was recruited. All patients enrolled were overweight (BMI>25 kg/m²) and 65% of the subjects were obese (BMI>30 kg/m²).¹⁸ Obesity increases the risk of resistant HTN by 5-fold.¹⁹ Moreover, in obese patients, impaired natriuresis is a key etiologic factor for HTN.²⁰ A

similar decrease in systolic automated office blood pressure (AOBP) (primary endpoint) was observed in obese subjects (-10.2 ± 14.5 mmHg, $p < 0.0001$) versus overweight subjects (-8.3 ± 13.9 mmHg, $p < 0.001$) following 8-week treatment with firibastat (QGC001) in NEW-HOPE. Because of its mode of action leading to a decrease in vasopressin release and increasing natriuresis, as demonstrated in hypertensive DOCA-salt rats,²¹ firibastat (QGC001) may be particularly useful in a hypertensive obese population. Even if obesity is not proposed as a criteria for inclusion in the Phase 3 study, the latter should include a significant proportion of obese patients, given obesity's contribution to treatment resistance.

Fifty-three percent of the subjects enrolled in NEW-HOPE were self-identified as minorities (Black or Hispanic), with 38% Blacks.¹⁸ HTN is less often controlled in Blacks.²² Blacks are more likely to suffer from salt-sensitive HTN,²³ and they are less responsive to angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs).^{24,25} Firibastat (QGC001) demonstrated to be effective in reducing BP in both SHR, an experimental model of essential HTN, and in DOCA-salt rats, an experimental model of HTN associated with salt sensitivity and low plasma renin levels, known to be poorly responsive to systemic RAS blockers.²⁶ In NEW-HOPE, decrease in systolic AOBP was similar (p value for interaction=0.40) in Blacks (-10.5 ± 14.7 mmHg, $p < 0.0001$) as in nonBlacks (-8.9 ± 14.1 mmHg, $p < 0.0001$).¹⁸

Although in previous clinical trials firibastat (QGC001) was not formally investigated in the population targeted in QGC001/3QG1 study, its efficacy to lower BP and its safety was demonstrated in the NEW-HOPE trial in a high-risk population sharing epidemiologic characteristics with resistant or difficult-to-treat subjects (such as obesity and ethnic origin), which may support the population targeted in this Phase 3 study QGC001/3QG1.

Firibastat (QGC001) was evaluated in hypertensive patients as a monotherapy in the QGC001/2QG1 and QGC001/2QG3 Phase 2 studies.^{19,20} Efficacy has not been assessed yet using combination therapies. Combination with existing therapies such as ACE-Is/ARBs, beta-blockers, and calcium channel blockers may be of interest in term of efficacy (additive or synergistic effect) and should be safe:

- Firibastat (QGC001), the first brain APA inhibitor acts through a new mechanism of action (central RAS blockade), different from those of existing classes, therefore an additive effect may be expected when firibastat (QGC001) is combined with these existing classes.
- In the preclinical development, combination of firibastat (QGC001) and enalapril was synergistic and safe in SHR. Firibastat (QGC001) showed also an additive effect with valsartan and losartan (internal data).²⁷

No specific concerns are expected regarding safety:

- Firibastat (QGC001) and its metabolite EC33 are not metabolized through the CYP450 system and UGT isoforms.^{28,29} In addition, firibastat (QGC001) does not

interfere with major drug transporters: fribastat (QGC001) is not an inhibitor of transport mediated via P-gp and BCRP, or via OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1, and MATE2-K. Drug-drug interaction related to such interaction is unlikely.

- The combination of fribastat (QGC001) and enalapril maleate (50:1) administered po in rats at the doses 125:2.5, 550:11, and 1000:20 mg/kg by the oral route for 28 consecutive days did not induce mortality, clinical signs, or change in body weight or food consumption.³⁰ No difference in fribastat (QGC001) PK parameters were noted between rats treated by fribastat (QGC001) 550 mg/kg and rats treated with the combination of fribastat (QGC001) (550 mg/kg) and enalapril maleate (11 mg/kg). Furthermore, Co-administration in rats of fribastat (QGC001: 50 mg/kg, IV) with enalapril maleate (0.5 mg/kg, IV) induced no significant change in the primary PK parameters of fribastat (QGC001), enalapril, and enalaprilat. The only significant change was a slight decrease (30%) of EC33 exposure.³¹
- In the QGC001/2QG3 (NEW-HOPE) study, 39 patients (15%) whose systolic/diastolic AOBP was still above 160/100 mmHg after 1-month treatment with fribastat (QGC001) monotherapy received a combined treatment with fribastat (QGC001) 500 mg bid and hydrochlorothiazide 25 mg once daily (QD) for one month with a good safety profile.
- In study QGC001/2QG2 (QUID-HF) conducted in a different indication (HF), fribastat (QGC001) or placebo was given on top of the standard of care treatment for congestive HF for 1 month. Twenty-three enrolled patients (and 14 patients treated with fribastat [QGC001]) were treated with diuretics (100%), ACE-Is or ARBs (100%) (87% ACE-Is and 13% ARBs), or mineralocorticoid receptor antagonists (91%). No related SAE was reported, and importantly, no difference between placebo and fribastat (QGC001) in change from baseline in sodium, potassium, and creatinine blood level was observed.

1.3 Justification of the Selected Dose

The primary objective of the study is to assess the effects of oral administration of fribastat (500 mg bid) on BP over 12 weeks in subjects with uncontrolled primary HTN despite being treated with at least 3 classes of antihypertensive therapies, including a diuretic in the case of treatment-resistant subjects or 2 classes of antihypertensive therapies (including or not including a diuretic), in the case of difficult-to-treat subjects. The daily oral dose and the frequency of fribastat administration (500 mg bid) were selected based on the current nonclinical pharmacodynamics and toxicokinetics data, and the clinical pharmacokinetics, safety, and efficacy data available.

Indeed, nonclinical pharmacology and toxicity studies showed that:

- An oral dose of 50 mg/kg of fribastat was found to be a relevant pharmacologically active dose in hypertensive DOCA-salt rats leading to a significant decrease in BP.²⁶ The conversion of this pharmacologically active dose in rats to human estimated dose

in mg/kg, gives 8.1 mg/kg by using a conversion factor of “0.162” (human estimated dose = 50 mg/kg x 0.162 = 8.1 mg/kg) and 506 mg by considering a human bodyweight of 62.5 kg.

- The no observed adverse effect level found in the 91-day toxicokinetic studies was 550 mg/kg in rat and 30 mg/kg in dog. Yet, exposures (AUC values) and C_{max} of firibastat and its metabolite EC33 found in rats treated at the dose of 550 mg/kg or in dogs treated at the dose of 30 mg/kg, were all at least 10× greater than those found in humans who received 500 mg bid of firibastat for 7 days.
- Based on in vitro and in vivo studies, risk of adverse side effects due to drug-drug interactions is limited. Indeed, none of the human recombinant CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) or the major drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1, and MATE2-K) were significantly inhibited by firibastat or its metabolites (EC33 and QGC515) when tested even at a high concentration (100 µmol/L). Also, neither firibastat, nor EC33 or QGC515 induced CYP1A2, CYP2B6, and CYP3A4 metabolic activities. Finally, co-administration in rats of firibastat (50 mg/kg, IV) with enalapril maleate (0.5 mg/kg, IV) induces no significant change in the primary pharmacokinetic parameters of firibastat, enalapril, and enalaprilat.

Also, clinical data showed that:

- In healthy subjects, firibastat was well tolerated after a single oral dose up to 2000 mg and after multiple daily oral doses up to 750 mg bid for 7 days.
- In the Phase 2 NEW-HOPE study, an oral 8-week treatment of firibastat (250 mg bid for 2 weeks, then 500 mg bid if AOBP was >140/90 mmHg) induced a significant decrease in BP levels in 256 overweight or obese hypertensive patients of multiple ethnic origins (decrease from baseline by 9.5 mmHg [$p<0.0001$] for systolic AOBP and by 4.2 mmHg for diastolic AOBP [$p<0.0001$])¹⁸. Firibastat was well tolerated in the study; the most common AEs were headaches (4%) and skin reactions (3%).
- In the pilot Phase 2 study QUID-HF conducted in patients with chronic congestive heart failure, no drug-related SAE was reported by patients treated with firibastat at doses up to 500 mg bid on top of HF standard of care which included a diuretic (100% of patients), an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (100%), a beta-blocker (96%), and a mineralocorticoid receptor antagonist (91%). Despite these concomitant treatments, changes in BP was not different with firibastat compared to placebo.
- No clinically relevant change in hematology, blood chemistry, and urinary parameters, was observed in subjects enrolled in the previous Phase 1 and 2 clinical trials and treated with firibastat at a daily dose of 500 mg bid.

1.4 Benefit/Risk Assessment

The data obtained so far imply a good safety profile of firibastat (QGC001) for the treatment of HTN and HF.

The most common side effects are allergic reactions. It has been identified as a potential risk for firibastat (QGC001). The sponsor has put in place relevant measures to closely monitor, collect, and assess all allergic reactions occurring in the clinical development program.

The maximal dose of 500 mg bid is expected to be safe since no SAEs, no treatment-emergent adverse events (TEAEs), and no important medical events were reported after repeated oral administration up to 500 mg bid for 7 consecutive days in healthy male subjects. Firibastat (QGC001) was also safe and well-tolerated following oral administration of multiple doses up to 750 mg bid in healthy subjects for 7 consecutive days. Doses of 250 mg bid for 1 week followed by 500 mg bid for 3 weeks were well tolerated in the Phase 2a clinical trial (QGC001/2QG1) in HTN and the nonsignificant BP lowering effect of firibastat (QGC001) observed in that study may be due in part to the short duration of exposure to firibastat (QGC001).

The sponsor believes that the risk of hypotension with firibastat (QGC001) treatment is unlikely according to the following findings:

1. BP did not decrease in normotensive animals, nor in healthy human subjects treated with firibastat (QGC001), even at high doses (1000 mg/kg in rat and dog and 1000 mg bid in humans).^{32, 33}
2. In the Phase 2 trials (QGC001/2QG1^{34,35} and QGC001/2QG3 – NEW-HOPE^{36,37}) conducted in hypertensive patients, the decrease in BP induced by firibastat (QGC001) treatment (500 mg bid) was correlated with the baseline initial BP level.
3. In rodent models, after MI induced by coronary artery ligation, firibastat (QGC001) improved left ventricular ejection fraction (LVEF) and decreased filling pressures, without any decrease in systemic BP.¹⁶
4. In humans, 23 patients with chronic congestive HF were enrolled in the QGC001/2QG2 (QUID-HF) study³⁸ and 14 subjects were randomized and treated with firibastat (QGC001) in addition to their standard of care treatment. In fact, all patients were co-treated with ACE-I or ARBs and diuretics, 96% with beta-blockers, and 91% with mineralocorticoid antagonists. Despite all these concomitant treatments, no significant decrease in BP was observed in the firibastat (QGC001) group and no significant difference in change from baseline in BP was observed between firibastat (QGC001) and placebo groups. After 1 month of treatment, SBP increased by 2 ± 14 mmHg in the firibastat (QGC001) group and by 3 ± 18 mmHg ($p=0.68$) in the placebo group, and diastolic BP (DBP) decreased by -1 ± 8 mmHg in firibastat (QGC001) group and

- increased by 1 ± 10 mmHg ($p=0.93$) in the placebo group (primary safety endpoint). Only 1 patient (out of 14) reported 1 non-serious hypotension AE.
5. Only a few hypotension events were reported as AEs in the previous clinical trials conducted in HTN:
- No hypotension event occurred in the Phase 2a study QGC001/2QG1 in 34 treated patients. ^{34,35}
 - Five patients out of 255 treated patients (2%) in QGC001/2QG3 (NEW-HOPE) study. ^{36,37}

One consequence of APA inhibition is the decrease of vasopressin release. Although not observed in any animal or human subject during the study of QGC001, the suppression of vasopressin holds a theoretical risk for the development of central diabetes insipidus (DI). Symptoms of DI include polyuria, nocturia, and polydipsia. The sponsor has put in place a procedure to collect any suspected DI and to report the event as an AESI with immediate notification, although no AESI related to DI has been observed so far.

Currently there are no known contraindications to firibastat (QGC001) and its metabolite EC33, as there is no potential for inhibition of CYP450 enzymes at the therapeutic doses to be tested.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of firibastat (QGC001) can be found in the IB.

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

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the effects of administration of firibastat (QGC001) 500 mg po bid on BP over 12 weeks in subjects with uncontrolled primary HTN despite being treated with 2 classes of antihypertensive therapies, at the maximum tolerated doses (MTDs).

2.2 Secondary Objectives

The secondary objective is to assess the safety of firibastat (QGC001).

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

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

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include 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-hour ambulatory SBP and DBP from baseline to Week 12 (Visit 5, Day 84)
- Percentage of controlled subjects (defined as subjects with normalized AOBP, ie, <140/90 mmHg at Week 12 [Visit 5, Day 84]) (as per 2018 European Society of Cardiology [ESC]/European Society of Hypertension [ESH] guidelines)³⁹
- Percentage of controlled subjects (defined as subjects with normalized AOBP, ie, <130/80 mmHg at Week 12 [Visit 5, Day 84]) (as per 2017 American College of Cardiology [ACC]/American Heart Association [AHA] guidelines)⁴⁰
- 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) (see [Section 6.2.3](#))

3.3 Safety Endpoints

Safety assessments are:

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

4 STUDY PLAN

4.1 Overall Study Design and Plan

This is a double-blind placebo-controlled, multicenter, efficacy and safety study of firibastat (QGC001) administered po bid over 12 weeks in difficult-to-treat and/or resistant hypertensive subjects not at goal despite treatment.

Approximately 502 male and female subjects ≥ 18 years of age at Screening, with uncontrolled primary HTN despite treatment-resistant subjects being treated with at least 3 classes of antihypertensive therapies, including a diuretic, or 2 classes of antihypertensive therapies, (including or not including a diuretic) for difficult-to-treat subjects at the MTDs. Enrollment will be from approximately 70 sites across Europe, and North and Latin America. Subjects will be randomized 1:1 to receive either firibastat (QGC001) or placebo on top of their current chronic antihypertensive treatments.

The study design is outlined in [Figure 1](#). Details of the visit schedule and planned assessments at each visit are detailed in [Table 1](#). Study assessments are described in [Section 6](#), efficacy assessments are described in [Section 6.2](#), and safety assessments are described in [Section 6.3](#).

Subjects will attend 6 study visits and will be followed for 12 weeks while on study treatment. The study will include a Screening Visit, a Run-in Period of at least 28 days and no more than 33 days duration, an Inclusion Visit, a 12-week blinded Treatment Period including a Safety Phone Call and 2 clinic visits, an End of Treatment (EOT) Visit, and a safety Follow-up Visit.

Subjects will continue to take their current chronic antihypertensive treatments for the duration of the study and will complete subject medication diaries during the Run-in Period. If SBP is >180 mmHg or DBP >110 mmHg at any visit during the study, subjects will be withdrawn from the study and will receive appropriate treatment.

The start of the study will be the date when the first subject provides informed consent, and the end of the study will be the date of the last subject's last assessment.

The total duration of participation for each subject will be approximately 140 days from the Screening Visit at Day -28 to the final safety Follow-up Visit at Day 112.

Subjects who discontinue the study early should undergo an Early Termination Visit (see [Section 4.1.6](#)), except in the case of consent withdrawal.

Study safety oversight will be under the direction of an independent data monitoring committee (IDMC). Details are provided in [Section 10](#).

Key details of the study visits are provided below.

4.1.1 Screening Visit (Visit 1, Day -28)

At the Screening Visit (Visit 1, Day -28), subjects will undergo the screening assessments detailed in [Table 1](#), such that all of the results of the screening tests will be available at the time that subject eligibility is reconfirmed prior to dosing.

The investigator will obtain signed informed consent from the subject before any study procedures are performed. For further details regarding the informed consent process, see [Section 12.3](#).

4.1.2 Run-in Period (Day -28 to Visit 2, Day -1)

Following Screening, eligible subjects will enter a Run-in Period of at least 28 days and no more than 33 days duration. During the Run-in Period subjects will continue to take their current chronic antihypertensive medications and will complete subject medication diaries.

The Run-in Period will end on Visit 2, Day 1, when the subject has successfully completed the Inclusion Visit assessments and is randomized to study treatment.

4.1.3 Inclusion Visit (Visit 2, Day -1, and Visit 2, Day 1)

At Visit 2, subjects will attend the site and take their current chronic antihypertensive drugs in front of the investigator (or designee). Each subject's eligibility to participate in the study will be checked.

At Visit 2, Day -1, any subject reporting symptoms of hypotension (eg, lightheadedness, dizziness) during the Run-in Period should be assessed by the investigator and treated as necessary; the subject must not continue with Visit 2 procedures.

Subject medication diaries will be assessed at Visit 2, Day -1. A 24-hour ambulatory BP monitoring (ABPM) device will be set up for each subject who has a medication adherence $\geq 80\%$ and remains eligible to participate in the study.

The subject will be instructed to return to the site approximately 24 hours later (Visit 2, Day 1) in order to have the 24-hour ABPM device removed and the ABPM measurements reviewed (see [Section 6.2.2](#)).

Subjects must have a successful ABPM measurement prior to being randomized and starting treatment with the investigational product (IP).

The criteria for a successful ABPM are detailed in [Section 6.2.2.1](#). If the first ABPM measurement is not successful, the subject will repeat the ABPM measurement within 24 hours of the first measurement. If required, a third attempt is permitted.

Following a successful ABPM recording, subjects who:

- Have successfully completed the Run-in Period with medication adherence $\geq 80\%$
 - Still meet the inclusion/exclusion criteria
 - Have a mean daytime systolic ambulatory BP (ABP) >135 mmHg
- will undergo Visit 2, Day 1 specific procedures ([Table 1](#)).

At Visit 2, Day 1, eligible subjects will be randomized to receive blinded treatment with IP (either fribastat [QGC001] 500 mg bid or matching placebo) on top of their current chronic antihypertensive treatments.

Visit 2, Day 1 assessments (including blood sample collection) will be performed prior to administration of any IP.

The day the subject starts treatment with IP will be nominated Visit 2, Day 1, and will be the start of the 12-week blinded Treatment Period.

See [Section 8.3](#) for further details of the method of assigning subjects to the treatment groups. Study treatments are described in [Section 8](#). See [Section 8.4](#) for further details on administration of fribastat (QGC001) and placebo.

The investigator, site personnel, the sponsor and their representatives involved in monitoring and conducting the study, and the subjects will be blinded to the IP administered. See [Section 8.2](#) for details on access to the treatment codes in the event of emergency unblinding.

4.1.4 12-week Treatment Period

During the 12-week Treatment Period subjects will continue their blinded treatment with IP on top of their current chronic antihypertensive treatments.

Subjects will be telephoned at Day 14 (± 3 d) and will return to the site for 2 visits on Visit 3, Day 28 (± 3 d) and Visit 4, Day 56 (± 3 d).

4.1.4.1 Safety Phone Call (Day 14 [± 3 d])

The investigator (or designee) will call subjects by telephone to collect any potential AEs and record any concomitant medications. Subjects will be asked about IP compliance.

4.1.4.2 Visit 3, Day 28 (± 3 d) and Visit 4, Day 56 (± 3 d)

At each visit, visit-specific procedures will be performed, including AOBP, orthostatic BP, and HR, and laboratory safety assessments. All visit-specific assessments will be performed prior to administration of any IP.

Compliance with IP administration will be checked and supplies of IP will be dispensed to the subject (see [Section 8.4](#)).

If systolic AOBP >180 mmHg or DBP >110 mmHg (and repeated and confirmed within 30 min) at Visit 3 or Visit 4, subjects will be withdrawn from the study and will receive appropriate treatment.

4.1.5 *End of Treatment Period Visit (Visit 5, Day 83 [± 3 d] and Visit 5, Day 84 [± 3 d])*

At Visit 5, on Day 83 (± 3 d), subjects will take their current chronic antihypertensive drugs and the blinded IP in front of the investigator (or designee), after which a 24-hour ABPM device will be set up. The 24-hour ABPM device should be set up to start immediately after IP intake (eg, between 8:00 and 10:00 am). As a consequence, Visit 5, Day 83 should be scheduled in the morning.

Subjects will return to the site 24 hours later on Visit 5, Day 84 to have their 24-hour ABPM device removed and the ABPM measurements reviewed.

- If the ABPM measurement is successful (see [Section 6.2.2.1](#)), the visit-specific procedures will be performed, and the investigator will discontinue the subject's IP.
- If the ABPM measurement is not successful, the subject should continue to take IP and repeat the ABPM measurement within 24 hours of the first measurement. Visit-specific procedures (including discontinuation of IP) will be delayed until completion of the second ABPM recording.
 - If the second ABPM recording is not successful, a third attempt to obtain a successful ABPM may only be performed if IP has not previously been discontinued. Visit-specific procedures (including discontinuation of IP) will be further delayed until completion of the third ABPM recording.

Administration of IP will be discontinued on Day 84 (± 3 d), once a successful ABPM measurement has been recorded (maximum of 3 attempts). Other visit-specific procedures for the Day 84 EOT Visit will be performed following the last dose of IP (see [Table 1](#)).

Subjects will continue to take their current chronic antihypertensive treatments.

4.1.6 *Early Termination Visit*

Subjects who discontinue the study prior to completion will be encouraged to undergo an Early Termination Visit at which the assessments described for the EOT Visit ([Section 4.1.5](#)) will be performed.

4.1.7 Follow-up Visit (Visit 6, Day 112 [± 3 d])

Visit-specific assessments will be performed, including AOBP, orthostatic BP, and HR, ECG, and clinical laboratory assessments ([Section 6.3.4](#)). Adverse events will be monitored and any concomitant medications will be recorded. For subjects who prematurely discontinue the IP, the Follow-up Visit will be performed 30 days after the last dose.

4.2 Discussion of Study Design

The study is randomized and double-blinded with regard to fribastat (QGC001) and placebo in order to prevent bias in treatment allocation and in the assessment of treatment effect.

As per Food and Drug Administration (FDA) guidance, placebo-controlled or active-controlled studies are required to demonstrate the efficacy of an antihypertensive drug.

The population for this study is men and women ≥ 18 years of age at Screening, with uncontrolled primary HTN despite being treated with at least 3 classes of antihypertensive therapies, including a diuretic, for treatment-resistant subjects or 2 classes of antihypertensive therapies (including or not including a diuretic), for difficult-to-treat subjects at the MTDs. Subjects must have a systolic AOBP between 140 mmHg and 180 mmHg inclusively, at Screening and at the Inclusion Visit and a successful ABPM measurement (as outlined in [Section 6.2.2.1](#)) with a mean systolic daytime ABP > 135 mmHg after the Run-in Period while on their current chronic antihypertensive treatments.

If SBP is > 180 mmHg or DBP > 110 mmHg at any visit during the study (and repeated and confirmed within 30 min at Visit 3 or Visit 4), subjects will be withdrawn from the study and will receive appropriate treatment.

Many blood biomarkers have been identified that may shed light on the underlying processes involved in the development and progression of HTN. In this study, blood samples will be collected for analyses of the biomarker N-terminal pro-B-type natriuretic peptide ([Section 6.2.3](#)).

Due to previous reports of probable skin allergy, all allergic reactions will be collected and analyzed as AESIs, and any suspected cases of DI will be reported as an AESI with immediate notification.

To ensure that posttreatment-BP data is captured and AEs are monitored and reported, subjects will attend a safety Follow-up Visit, 28 days after the EOT Visit, ie, at Day 112 (± 3 d).

4.3 End of Study

A subject is considered to have completed the study if he/she has completed all study visits.

The end of the study is defined as the date of the last visit or last procedure of the last subject in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects who meet all of the following criteria will be 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 MTDs of those medications (ie, 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 ABPM measurement according to the criteria in [Section 6.2.2.1](#), with a mean systolic daytime ABP >135 mmHg after the Run-in Period while on their current chronic antihypertensive treatments.
4. Women of childbearing potential and nonsurgically 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, depo, patch, or injectable) together with supplementary barrier method 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.
5. Women of childbearing potential must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test result at the Inclusion Visit (Visit 2, Day 1).

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Known or suspected secondary HTN (eg, 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 minutes to 1 hour.
3. Known hypertensive retinopathy (Keith-Wagener Grade 3 or Grade 4) and/or hypertensive encephalopathy.
4. Upper arm circumference that is 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 cm²/m²).
8. Subjects with severe symptomatic HF (NYHA Class III or Class IV).
9. History of acute coronary syndrome (non-ST elevation 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 (ie, surgery, aggressive diet regimen, etc.), leading to unstable body weight.
12. Female who is 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) $>3 \times$ upper limit of normal (ULN), or a total bilirubin $\geq 1.5 \times$ 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 m², as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)⁴¹ formula at Screening.
17. History of any blood disorder, other than sickle cell trait, causing hemolysis or unstable red blood cells (eg, malaria, babesiosis, hemolytic anemia, thalassemia, sickle cell anemia).
18. Subjects with documented DI.
19. Subjects with Type 1 diabetes mellitus.
20. Subjects with Type 2 diabetes mellitus who:
 - Are poorly controlled, defined as glycosylated hemoglobin A1c (HbA1c) $>9\%$ at Screening; OR
 - Are taking short-acting insulin. Use of a stable dose (≥ 12 weeks prior to Screening) of medications listed in [Section 8.7.1](#) is permitted.
21. Routine or anticipated treatment with any systemic corticosteroid. Use of topical, inhaled, intra-articular, or nasal corticosteroids is permitted.
22. Clinical evidence of thyroid disease, thyroid hormone therapy that is not stable ≥ 4 weeks prior to Screening, or a thyroid-stimulating hormone (TSH) level $<0.75 \times$ lower limit of normal or $>1.5 \times$ 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.
29. Subjects with any history of documented allergic reactions or allergic diseases, with the exception of documented seasonal allergies per the investigator's decision.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet 1 or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure 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 SAEs.

Screen-failed subjects will be replaced.

Individuals who are screen failures can be rescreened. Subjects will be given a new subject number and sign a new Informed Consent; all study-specific assessments will be done again at the rescreening. Subjects previously randomized in the study cannot be rescreened.

5.4 Premature Discontinuation

5.4.1 *Premature Discontinuation of Investigational Product*

Subjects should discontinue the IP and be withdrawn from the study if any of the following occurs:

1. The subject withdraws consent or requests discontinuation from the study for any reason.

2. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
3. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the investigator that continued participation is not in the best interest of the subject.
4. Skin reaction as described in [Section 6.3.3.1](#), or any incipient allergic skin reaction as described in [Section 9.1.3](#).
5. Any symptomatic hypotension or symptomatic orthostatic hypotension as defined in [Section 6.3.2](#), as per the investigator's discretion.
6. Severe HTN:
 - If SBP >180 mmHg or DBP >110 mmHg at any visit (and repeated and confirmed within 30 min at Visit 3 or Visit 4); or
 - Symptoms of severe HTN
7. Any of the following:
 - ALT >3×ULN
 - AST >3×ULN
 - ALP >3×ULN
 - Total bilirubin $\geq 1.5 \times \text{ULN}$, unless secondary to Gilbert's syndrome
 - Direct bilirubin >ULN, in subjects with Gilbert's syndrome
 - eGFR <30 mL/min/1.73m², as calculated using the CKD-EPI⁴¹ formula
8. Any clinical manifestation of severe allergy (eg, angioedema, anaphylactic shock, severe skin reaction, severe bronchospasm, asthma).
9. Pregnancy.
10. The subject takes prohibited medications as defined in this protocol.
11. Subject failure to comply with protocol requirements or study-related procedures; or
12. Termination of the study by the sponsor or the regulatory authority.

If IP is prematurely discontinued, the subject will have the Follow-up Visit 30 days after the last dose of IP, unless consent is also withdrawn for follow-up. In that case, the subject will also be discontinued from the study and the reason for withdrawal of consent must be recorded. In the case that the subject or subject's representative refuses or is physically unable to provide consent withdrawal in writing then the site staff should document and sign the reason for the subject's failure to provide written withdrawal of consent.

Subjects who discontinue IP prematurely will not be replaced.

5.4.2 *Premature Discontinuation from the Study*

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason, without any reprisal.

The investigator has the right to terminate participation of a subject for any of the following reasons:

- Premature discontinuation of IP
- Difficulties in obtaining blood samples
- Violation of the protocol
- Severe AEs or SAEs
- Any incipient allergic skin reaction
- Any other reason relating to the subject's safety or integrity of the study data

If a subject is withdrawn from the study, the study monitor/sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned.

If the subject withdraws consent for disclosure of further information, the sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

At the time of premature study discontinuation, the investigator should make every effort to ensure the subject completes the assessments indicated at the EOT Visit; see [Table 1](#).

Subjects who prematurely discontinue from the study cannot subsequently rejoin the study.

For details on the discontinuation of study sites or the study as a whole, see [Section 17](#).

5.4.3 *Lost to Follow-up*

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator (or designee) must make every effort to regain contact with the subject (where possible, 2 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 eCRF.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

6 DESCRIPTION OF STUDY ASSESSMENTS

Refer to [Table 1](#) for the schedule of assessments.

Unless indicated otherwise, all laboratory samples will be processed and shipped to the central laboratory, as described in the central laboratory manual. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the manual. Refer to the central laboratory manual for the maximum total volume of blood to be collected per subject throughout the study.

6.1 Demographics and Other Screening Assessments

Safety assessments that are also part of the screening assessments are described in [Section 6.3](#).

6.1.1 Medical History

Medical history, including any ongoing illnesses, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition.

Any pre-study procedures will be recorded in the eCRF as part of the medical history assessment.

6.1.2 Demographics

Demographic data, including year of birth/age, sex, and ethnicity will be recorded in the eCRF.

6.2 Efficacy Assessments

6.2.1 Automated Office Blood Pressure, Heart Rate, and Orthostatic Blood Pressure

Office BP and HR measurements will be taken at the times detailed in [Table 1](#). Heart rate will be measured at the same time as AOBP.

The office blood pressure (OBP) device will be provided to all sites by the sponsor or its designee. The OBP device uses a BP cuff with an automated inflation and deflation mechanism and takes serial measurements of SBP, DBP, and HR. Blood pressure measurements must be taken prior to any blood being drawn or any IP being administered, specifically at Visit 2, Day 1. For all other visits after Visit 2, Day 1, it is recommended that BP measurements be taken before IP administration, but is not compulsory.

Orthostatic BP measurements should be performed on the same arm as OBP and ABP measurements and, if possible, by the same person.

At each visit, the following procedural order will be used to assess OBP (AOBP and orthostatic BP):

1. The upper arm circumference will be measured to ensure the subject's arm does not exceed the maximum allowable cuff size. Cuff placement instructions from the device instructions manual should be followed.
2. BP must be taken in the nondominant arm at the Screening Visit and for all BP measurements until study termination.
3. **Automated Office Blood Pressure:**
 - a. Prior to any BP measurement the subject must rest comfortably in the seated position with back support in a quiet room. There should be no talking. The subjects' legs should not be crossed and should be placed on the floor throughout the measurements.
 - b. After the cuff has been placed on the arm, the device will automatically launch the procedure when the start button is pressed.
 - c. The initial single reading will be taken while a physician or nurse is present. The first measurement will be reviewed to verify cuff position and the validity of the measurement and will then be automatically discarded.
 - d. The subject will then continue to rest quietly and will be left alone in the room.
 - e. Five additional BP and HR measurements will then be taken at 1-minute intervals while the subject is alone. The average of the last 5 readings will be automatically displayed by the device and collected in the electronic data capture (EDC) to the nearest 1 mmHg.
4. **Orthostatic Blood Pressure:**
 - a. The staff member will then come back into the room, and the subject will lie in a supine position for at least 5 minutes.
 - b. The subject's BP and HR measurements will be obtained while the subject is in the supine position, and will then be repeated in the same arm after the subject has been standing for 1 minute and 3 minutes (orthostatic BP).

6.2.2 *Ambulatory Blood Pressure Monitoring*

Ambulatory BP monitoring devices will be provided to all sites by the sponsor or its designee. Ambulatory BP monitoring will be performed at the times detailed in [Table 1](#) using the ABPM device provided.

Set up:

- The appropriately sized cuff should be applied to the nondominant arm.
- The device should be set to record for a duration of at least 24 hours, with the measurement frequency set at 30-minute intervals during the day (8:00 am to 10:00 pm [theoretically 28 readings, 2 per hour]) and 60-minute intervals at night (10:00 pm to 8:00 am [theoretically 10 readings, 1 per hour]).

A duration of less than 24 hours (eg, 23 hours and 30 minutes) would be acceptable for a successful ABPM recording as long as it successfully confirms 21 daytime and 6 nighttime readings.

ABPM review:

Subjects will return to the site the following day, when the ABPM device will be removed.

The ABPM report should include all of the individual BP readings (numerically and graphically), the percentage of successful readings, the averages for each time frame (daytime, nighttime, 24 hours), and the “dipping” percentage (the percentage the average BP changed from daytime to nighttime).

The 24-hour ABPM measurements will be read locally. A printed report will be filed in the subject’s record for source verification, and ABPM data will be reported in the eCRF.

A reconciliation with clinical data (from EDC system) will be performed to ensure the accuracy and consistency of every subject’s data.

6.2.2.1 *Criteria for a Successful ABPM Recording*

An ABPM recording is considered successful if at least 21 daytime and 6 nighttime readings are successful.

If an ABPM measurement is not successful, the subject should continue to take the treatment and the ABPM measurement should be repeated within 24 hours of the unsuccessful measurement, if possible.

If required, a third attempt at ABPM is allowed at Day 84.

A duration of less than 24 hours (eg, 23 hours and 30 minutes) would be acceptable for a successful ABPM recording as long as it successfully confirms 21 daytime and 6 nighttime readings.

6.2.3 *Biomarker NT-ProBNP*

Blood samples for the biomarker NT-ProBNP from plasma will be collected at Visit 2, Day 1, and the EOT Visit (Visit 5, Day 84), as detailed in [Table 1](#).

Analysis of NT-ProBNP in blood will be performed by the central laboratory. Refer to the central laboratory manual for details regarding the collection, processing, and shipping of the blood samples.

6.3 Safety Assessments

6.3.1 *Adverse Events*

Adverse events will be followed, recorded, and reported in line with the procedures described in [Section 9](#).

6.3.2 *Hypotensive Events*

Hypotensive events will be assessed at each visit and are defined by the following:

- Automated office SBP <90 mmHg; OR
- Automated office DBP <60 mmHg; AND/OR
- Any BP with symptoms of hypotension. (eg, lightheadedness, dizziness).

Reporting of hypotensive events is described in [Section 9.1.2](#).

6.3.3 *Adverse Events of Special Interest*

The events described in the following subsections are considered AESIs for this study, and should be reported as an AESI with immediate notification (within 24 hours of the investigator's first knowledge, see [Section 9.5](#)).

6.3.3.1 *Allergic Reaction*

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 can be described as itch, nasal itch, flushing, hives, swelling of lips, eyes, face, tongue, hands, or feet, lump in throat, difficulty

swallowing, hoarseness or change in pitch of voice, inability to speak, wheezing, chest tightness, stridor, cutaneous reaction, pruritus, etc.

Subjects will be instructed 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.

Any incipient allergic skin reaction must result in IP discontinuation as outlined in [Section 9.1.3](#). 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.

Any allergic skin reaction must be reported as an AESI and should be evaluated by a dermatologist as soon as possible and preferably within 7 days of the investigator's first knowledge.

The investigator should evaluate the subject for possible etiologies and extracutaneous symptoms and signs.

Additional blood tests will be performed, if necessary, according to the guidance of the dermatologist. Whenever possible, the site/dermatologist 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 and uploaded in the EDC portal for adjudication. 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.

The full report of the dermatologist should include, at a minimum, a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg, scattered, grouped, or linear], distribution, color, consistency, presence of pruritus or pain, and other clinical signs). A skin biopsy (including histopathology and immunofluorescence) will be performed if deemed necessary as per the specific procedure or dermatologist's medical judgment, and biopsy samples should be sent to the referent for central reading. **The full report should be sent by the dermatologist to the investigator and will be adjudicated by the independent Adjudication Committee for Allergic Skin Reactions ([Section 12.4.2](#)).**

In case of potential allergic reactions (including delayed hypersensitivity), whatever the intensity of the observed symptoms, 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 IV steroids, β_2 -agonists, or adrenaline if needed.

6.3.3.2 *Diabetes Insipidus*

One consequence of the inhibition of APA is the decrease in vasopressin levels. Although not observed in any animal or human subject during the study of fribastat (QGC001), the suppression of vasopressin's production 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.

6.3.4 *Clinical Laboratory Evaluations*

Laboratory assessments will be performed by a central laboratory.

Blood samples will be collected at the times indicated in [Table 1](#). On dosing day(s) sampling for the analysis of clinical laboratory parameters will be performed before the administration of IP.

The following parameters will be assessed:

Hematology: Blood samples for hematology assessment will be taken after a period of rest. Analysis will include:

- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count (RBC)
- White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils [manual microscopic review will be performed only if WBC and/or differential values are out of reference range])

Chemistry: Blood sample analysis for chemistry will include:

- Albumin
- ALP
- ALT
- AST

- Bicarbonate
- Blood urea nitrogen (BUN)
- Calcium
- Creatine kinase
- Creatinine
- Direct bilirubin
- eGFR (calculated using the CKD-EPI formula⁴¹)
- Glucose
- Potassium
- Serum triglycerides
- Sodium
- Total bilirubin
- Total cholesterol
- Uric acid

With the addition of:

- Prothrombin time at Screening
- HbA1c at Screening, and Visit 5, Day 84
- TSH only at Screening

Refer to the central laboratory manual for details regarding the collection, processing, and shipping of the blood samples.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during the subject's participation in the study should be repeated until the values return to normal, or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, then the etiology should be identified, and the sponsor notified.

6.3.5 Pregnancy

All subjects are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see [Section 5.1](#) and [Section 5.2](#), respectively).

Serum (beta human chorionic gonadotrophin [β -hCG]) or urine pregnancy tests will be performed for female subjects of childbearing potential at the timepoints indicated in [Table 1](#).

Women of childbearing potential must have a negative serum pregnancy test result at Screening (Visit 1, Day -28), and negative urine pregnancy test results at the Inclusion Visit (Day -1), and Visits 3, 4, and 5.

A urine pregnancy test must be performed prior to dosing on Visit 2, Day 1; the result must be negative for the subject to be eligible for dosing. If the test result is positive, the subject must be excluded from the study.

Serum pregnancy tests will be analyzed by the central laboratory; urine pregnancy tests will be analyzed locally.

Monitoring for pregnancies in female subjects and the partners of male subjects will continue from the subject's inclusion in the study until the Follow-up Visit at Day 112 (± 3 days). Male subjects will be required to inform the investigator if their partner becomes pregnant during the study. The investigator should inform the sponsor within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a pregnancy report form to the sponsor.

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing IP, the investigator should report the pregnancy to the PRA Drug Safety Center within 24 hours of being notified.

A subject becoming pregnant while on IP will immediately be withdrawn from the study and will not receive any further IP, and early termination study procedures should be performed.

The subject or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator

should notify the PRA Drug Safety Center. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

6.3.6 12-lead Electrocardiogram

A single 12-lead ECG will be performed as outlined in [Table 1](#), and must be done prior to blood sampling at each visit. The ECG will be recorded prior to any IP administration, and time since last IP dose will be recorded.

Subjects must rest in a supine position for at least 5 minutes before the ECG recording.

The investigator will measure the QT interval on a precordial or DII lead (the same lead must be used for the different visits) and report the results as normal or abnormal in EDC. In the case of left or right bundle branch block (QRS enlargement [>120 ms]), QT will not be calculated. Concomitant HR (as measured on the same ECG) will also be captured in EDC.

All ECGs will be collected for subsequent central reading of the QT/QTc interval.

The ECG tracing should include the date and time of the assessment and the signature of the person who made the interpretation; the tracing will be archived at the study site.

6.3.7 Clinical Examination

Subjects will undergo clinical examination as indicated in [Table 1](#).

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the subject's health.

Height, weight, and hip and waist circumference will be measured:

- Waist circumference will be measured to the nearest 0.5 cm at the level of the iliac crest while the subject is at minimal respiration.
- Hip circumference will be measured at the widest portion of the buttocks.

The subject should be dressed in light clothing, without shoes.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see [Section 9](#)).

7 COVID-19 MITIGATIONS

It may be that coronavirus disease 2019 (COVID-19) pandemic forces local/regional lockdown and/or travel restrictions that do not allow subjects to come to the site for some of the planned assessments. If necessary, site visits can take place ± 7 days after the scheduled date to avoid treatment interruption.

If the visit at the site cannot be set within the protocol timeframe, the site will attempt to delegate a staff member to visit the subject at home, wherever possible, to complete the study visit and related assessments (ie, BP measurement, safety assessment, drug dispensing, and laboratory sampling), when technically possible.

If a visit at the site or at the subject's home by a site-authorized member cannot take place within the protocol timeframe:

- The investigator should call the subject to evaluate safety (eg, AEs, SAEs, concomitant medications, IP compliance, etc.) and document the call in the subject's source records. Data will be entered in EDC at the corresponding visit.
- To ensure subject safety, if deemed relevant by the investigator, laboratory assessments may be done locally. Results provided will be kept in the subject's source record, and will be used to assess safety reporting (eg, AEs) but will not be reported in EDC (unless supporting SAE or AESI criteria). Similarly, whenever possible, and if it cannot be measured by the site, OBP will be controlled locally via the subject's general practitioner (GP), local physician, or via a self-measurement ensured by the subject. Results will be communicated to the investigator who will update the subject's source records, and report the data in a specific section/field of the EDC.
- For subjects who cannot attend site visits due to local/regional lockdowns or travel restrictions etc, if permitted by site policy and/or by the IEC/IRB/Regulatory authorities, where required, and if subject consents, all efforts will be made to allow the site to ship IP units directly to the subject, at subject's home or known/confirmed location. See [Section 8.4.1](#) for further details.
- If a subject is withdrawn because of COVID-19 (eg, inability to perform protocol assessments even partially, IP discontinued for more than 5 consecutive days, or 1 visit missed and no phone follow-up done), relation to COVID-19 as a reason for discontinuation should be clearly documented in the source records and entered in EDC.

In all cases, any protocol non-adherence will be recorded as a protocol deviation related to COVID-19.

8 TREATMENTS

8.1 Investigational Products

8.1.1 *Description of Investigational Products*

Test Product

IP/non-IP:	IP
Name:	Firibastat (QGC001)
Dose(s):	2 x 250 mg capsules bid
Mode of administration:	Oral capsules
Manufacturer:	Amatsi group - France

Placebo

Substance:	Matching placebo
Dose(s):	2 capsules bid
Mode of administration:	Oral capsules
Manufacturer:	Amatsi group - France

8.1.2 *Preparation, Handling, and Storage*

The IP supplied is to be used exclusively in the clinical study according to instructions of this study protocol. The investigator (or designee) is responsible for the safe and proper storage of IP at the site.

All IP supplied to the site will be stored at controlled room temperatures of 15°C to 25°C (59°F to 77°F) in a securely locked area, only accessible to authorized personnel. The study site will be responsible for the correct storage and handling of IP and for keeping the corresponding accountability forms up to date.

The investigator (or designee) will instruct the subjects to store the IP in accordance to the instructions on the label(s).

8.1.3 *Packaging, Labeling, and Shipment*

Investigational product will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Firibastat (QGC001) will be provided in 250 mg capsules. The packaging of the placebo will be the same as the firibastat packaging in order to maintain the blind.

Firibastat (QGC001) and placebo will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the Pharmacy Manual for full details for packaging, labeling, and shipment of the IP.

The sponsor (through Amatsi group) will supply the firibastat (QGC001) and placebo.

The subject's current antihypertensive medications (including diuretics, if applicable) will not be provided by the sponsor; they will be provided by the subject, as per the subject's usual standard of care.

8.2 Blinding

The study is double-blinded; therefore, the investigators, study personnel, and the study subjects will remain blinded to treatment allocation. All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations.

Randomization data will be kept strictly confidential, accessible only to authorized staff until the time of unblinding. Authorized staff includes the randomization statistician who will store the master randomization list in a secure system. All authorized unblinded staff must be documented.

Firibastat (QGC001) and placebo will be coded and labeled in a manner that protects blinding. The interactive web response system (IWRS) will permit rapid identification of the product in case of medical emergencies.

Breaking of the blind is only allowed in the case of an emergency, when knowledge of the IP is essential for the clinical management of the subject. If "emergency unblinding" becomes necessary, the decision whether or not to unblind is the sole responsibility of the investigator. In that case, the investigator should contact the sponsor only if this delay will not affect the subject's safety. Otherwise, the investigator should contact the sponsor as soon as possible after unblinding, without revealing to the sponsor (or contract research organization [CRO]) the results of the code break, except to the designated global patient safety representative. Subjects whose treatment assignments are unblinded will not receive any further IP. Subjects who have been unblinded will be followed for safety.

The investigator must record the date of unblinding and the reason. All breaks of the blind must be adequately documented.

If an SAE is reported, the designated global patient safety representative may unblind the treatment assignment for the individual subject through IWRS in order to meet regulatory reporting requirements.

The Adjudication Committee for Allergic Skin Reactions will use blinded data.

8.3 Method of Assigning Treatment

The randomization methodology used will be a fixed permuted-block randomization taking into account center as unique stratification factor.

Subjects will be randomly assigned in a balanced manner (ratio 1:1) to one of the 2 following treatment arms:

- Firibastat (QGC001)
- Placebo

Concretely, each subject will have a unique subject identification number obtained during subject creation into the EDC. This will be assigned at the Screening Visit. The investigator will keep a record (the subject screening log) of subjects who entered Screening.

Once the subject has been successfully screened and the investigator has determined that the subject is eligible (respect of inclusion/exclusion criteria), the investigator can randomize the subject through IWRS. Thus, on Visit 2, Day 1, the subject will be assigned a unique randomization number and allocated the corresponding treatment kit number according to the randomization schedule.

If a subject withdraws from study participation, his/her unique identification number(s) cannot be re-used for another subject.

8.4 Dose and Administration

At the completion of the Run-in Period, all eligible subjects who have successful ABPM measurements at Visit 2, Day 1 will be randomized to IP and will receive either 2 capsules of 250 mg firibastat (QGC001: 500 mg) bid or 2 capsules of matching placebo bid (ie, a total of 4 capsules of IP daily) for the 12-week Treatment Period. Subjects will take IP in addition to their current chronic antihypertensive treatment. The IP dose will remain unchanged at each visit.

Subjects will receive their first dose of IP on-site at Visit 2, Day 1, after which they will continue to take the IP at home and at the study visits.

At Visit 2, Day 1, Visit 3, Day 28 (± 3 d), and Visit 4, Day 56 (± 3 d), an approximate 4-week supply of IP will be dispensed to subjects, as required (see [Section 4.1.3](#)).

Subjects will be instructed by the site to follow dosing instructions on the drug packaging and to return the remaining IP at the next visit.

Subjects will continue treatment until the EOT Visit on Visit 5, Day 84 (± 3 d). The IP will be discontinued if ABPM measurements meet requirements as specified in [Section 6.2.2.1](#).

8.4.1 *Direct-to-Subject IP Delivery*

It may be that COVID-19 pandemic forces local/regional lockdown and/or travel restrictions that do not allow subjects to visit a site for the planned assessments. Unless the subject is withdrawn, whenever it is permitted by the site policy and/or by the IEC/IRB/Regulatory authorities, with the subject's consent, all efforts will be made to allow the site to deliver IP units directly to the subject, at the subject's home or known/confirmed location. Documentation will be kept at site.

Separate shipments of IP should be provided for each visit not performed on-site. If 2 or more consecutive visits cannot be performed at site and IP shipment is required, sponsor approval must be obtained first. Gaining sponsor approval will ensure any criteria for IP or study discontinuation are not met (as outlined in [Section 5.4](#) and [Section 7](#)).

Further instructions will be provided to the investigator to manage the shipment to the subject.

8.4.2 *Dose Interruption*

In the event of a subject missing a dose of IP, the subject should take the IP dose as soon as possible, allowing a minimum interval of 4 hours between doses.

If interruption of IP administration is ≤ 5 days, the subject may resume treatment with IP and remain on the study.

8.4.3 *Dose Reduction*

Dose reductions are not allowed.

8.5 Intervention After the End of the Study

There are no further planned interventions following the subject's participation in the study.

8.6 Precautions and/or Lifestyle Considerations

There are no lifestyle considerations (such as dietary or physical activity restrictions) for this study further to those listed in the inclusion/exclusion criteria ([Section 5.1](#) and [Section 5.2](#), respectively).

8.7 Prior and Concomitant Medication and Procedures

See [Section 5](#) for details of medications and procedures that are permitted or prohibited according to the study inclusion and exclusion criteria.

Prior medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken within 30 days of the Screening Visit will be recorded in the eCRF.

A medication will be considered as concomitant if it occurs the day of or after the first IP administration (firibastat [QGC001] or placebo).

All concomitant medications will be recorded in the eCRF. The following details must be recorded:

- Medication name, ideally the generic name
- Reason for use
- Start and end date of administration
- The dose and frequency of administration

The medical monitor should be contacted if there are any questions regarding prior or concomitant medications or procedures.

8.7.1 Permitted Medication

During the study, subjects will continue with their current antihypertensive treatment, ie 2 antihypertensive classes of drug, and if applicable, a diuretic, at the MTD.

For women of childbearing potential, permitted forms of hormonal contraception include hormonal intrauterine devices, hormonal contraceptives (oral birth control pills, depo, patch, or injectable).

The following medications are permitted for subjects with Type 2 diabetes **providing the dose has been stable for ≥ 12 weeks prior to Screening:**

- Glucagon-like peptide-1 analog
- Metformin
- Sulfonylurea
- Dipeptidyl peptidase-4 inhibitor
- Metformin plus sulfonylurea
- Metformin plus dipeptidyl peptidase-4 inhibitor
- Single basal insulin

- Pioglitazone
- SGLT2 inhibitor

8.7.2 *Prohibited and Restricted Medications*

The following are prohibited or restricted during the study:

- Routine or anticipated use of systemic corticosteroids is prohibited. Use of topical, inhaled, intra-articular, or nasal corticosteroids is permitted.
- For subjects with Type 2 diabetes mellitus, short-acting insulin (see [Section 8.7.1](#) for the permitted medications).
- For subjects taking thyroid hormone therapy at Screening, the therapy must have been stable for ≥ 4 weeks.

8.8 Overdose

At present there are no data available for overdosage in humans.

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported.

In the event of an overdose, administration of QGC001 should be discontinued and subjects should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved fribastat [QGC001]) must be communicated to the sponsor (or a specified designee) using the corresponding eCRF page(s) within 24 hours of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in [Section 9.4](#).

8.9 Compliance

The investigator (or designee) will explain the correct use of the IP to each subject and will check that each subject is following the instructions properly. Compliance will be assessed at each visit by direct questioning and counting returned capsules and will be documented in the source documents and eCRF. Any deviation from the correct use of the IP will be recorded in the eCRF.

A record of the number of IP capsules dispensed to and taken by each subject will be maintained and reconciled with IP and compliance records. The IP start and stop dates, including dates for IP delays will also be recorded in the eCRF.

Investigational product will be dispensed in excess of the amount required between study visits; an additional week's supply of IP will be provided.

Subjects will be considered compliant if they have taken between 80% and 120% of the intended regimen. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the subject will be counseled about the importance of compliance with the regimen and taking the IP as instructed.

8.10 Accountability

The IP must not be used for any purpose other than that defined in this protocol. All supplies of IP will be accounted for in accordance with Good Clinical Practice (GCP).

Subjects will be instructed to return all unused IP at the next visit.

The pharmacist or (designee) should maintain accurate records of all IP supplies received during the study. These records should include the dates and amounts of IP that were received at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the IP and study subjects. If errors or damage in the IP shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the IP accountability records will be provided by each investigator for inclusion in the trial master file (TMF). The study monitor will periodically check the supplies of IP held by the investigator or pharmacist to verify accountability of the IP used.

The investigator (or designee) will administer the IP only to the identified subjects in this study, according to the procedures described in this study protocol. Details of IP administered to subjects will be recorded in the eCRF. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IP received from the sponsor (or designee).

After the end of the study, all unused IP and all medication containers should be destroyed at the study center or returned to the sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the sponsor. The IP resupply will be managed by the IWRS.

9 ADVERSE EVENTS

9.1 Definitions

9.1.1 *Adverse Events*

An AE is any untoward medical occurrence in a subject or clinical study subject administered a pharmaceutical product and which 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), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: where a subject becomes diagnosed with COVID-19 infection, the local health authority recommendations regarding treatment should be followed, and the event should be reported as an AE/SAE, depending on the seriousness of infection.

9.1.2 *Hypotensive Events*

Hypotensive events are defined in [Section 6.3.2](#).

Any symptomatic hypotension or symptomatic orthostatic hypotension must lead to IP discontinuation. In case of any suspicion or symptoms related to hypotension, the subject will be advised to immediately contact the investigator or his/her GP.

9.1.3 *Incipient Allergic Skin Reactions*

Any incipient allergic skin reaction must result in IP discontinuation. In the case of any incipient allergic skin reaction, the subject will be advised to immediately contact the investigator or his/her GP. Allergic skin reactions are defined and the process for reporting is outlined in [Section 6.3.3.1](#).

9.1.4 *Serious Adverse Events*

An SAE is any event that meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event that may not result in death, be life-threatening, or require hospitalization. The event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Definition of Terms

Life-threatening: an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the subject providing informed consent, or routine clinical procedures that are not the result of an AE (eg, elective surgery for a preexisting condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

9.1.5 *Clinical Laboratory Abnormalities and Other Abnormal Assessments*

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IP interruption, modification, or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (eg, in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in [Section 9.1.1](#) and [Section 9.1.4](#). If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities, see [Section 6.3.4](#).

9.1.6 *Adverse Events of Special Interest*

Adverse events of special interest are AEs (serious or nonserious) that need to be monitored, documented, and managed in a prespecified manner.

For the tested drug, allergic reaction and DI are considered as AESIs with immediate notification (ie, within 24 hours of the investigator’s first knowledge, see [Section 9.5](#)).

- AEs that may constitute an allergic reaction are described in [Section 6.3.3.1](#).
- DI is described in [Section 6.3.3.2](#).

For AESIs with immediate notification, the sponsor is to be informed immediately. See [Section 9.5](#).

Subjects who report an AESI will be followed until the full disappearance of symptoms.

9.2 Assessment of Adverse Events

9.2.1 *Severity*

The terms serious and severe are not synonymous. The general term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a subject’s life or ability to function (see [Section 9.1.4](#)). A severe AE (classified as “severe”) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm³ to less than 2000/mm³ is considered severe but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

The investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to IP using the categories of yes or no.

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate: minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)

Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADL

9.2.2 Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the exposure to the IP using the following definitions:

Related:

- The AE follows a reasonable temporal sequence to IP administration, and it cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications).
- The AE follows a reasonable temporal sequence to IP administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology.

Not related:

- The AE does not follow a reasonable sequence from IP administration, or it can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.3 Documenting and Reporting Adverse Events

Reporting of AEs (serious or not) will begin when the subject has provided informed consent and will continue until study participation is complete. Adverse events will be recorded as occurring either pretreatment (during the Run-in Period) or during treatment (during the Treatment Period).

Occurrence of AEs may be volunteered spontaneously by the subject; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study.

For all AEs, the investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence [including whether the AE onset was before, during, or after the IP administration if the AE started on a dosing day], duration, and any action, eg, treatment/follow-up tests). The outcome of the event should be provided along with the investigator's assessment of the relationship to the IP. The investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at Screening should not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Investigators are not obligated to actively seek AEs or SAEs after the subject's conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the sponsor.

9.4 Reporting of Serious Adverse Events

Any SAEs occurring up to 30 days following the last administration of IP must immediately be reported by the investigator in the eCRF. In case of technical issues with the eCRF the investigator can report the SAE by utilizing the safety report form (refer to the SAE contact information at the beginning of this protocol). After the technical issue is resolved, the SAE must be reported in the eCRF.

The investigator is obliged to respond to any request for follow-up information (eg, additional information, event outcome, final evaluation, or other records where needed) or to any question the sponsor (or designee) may have concerning the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor (or designee) and, as applicable, to allow the sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

9.5 Reporting Adverse Events of Special Interest

For AESIs with immediate notification, the sponsor is to be informed immediately (ie, 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.

An AESI should be reported by the investigative site to the PRA Drug Safety Center within 24 hours of learning about the event by completing the relevant page of the eCRF. The documentation and processing of AESIs is further detailed in the investigator site file.

9.6 Adverse Event and Serious Adverse Event Follow-up

During the study (and after the EOT Visit), all AEs and SAEs should be followed proactively by the investigator until the event resolves or the condition stabilizes to a level acceptable to the investigator, until the event is otherwise explained, or until the subject is lost to follow-up. At the time the subject's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF and the investigator will submit any updated SAE information to the sponsor within 24 hours of receipt of the information.

9.7 Safety Reporting Oversight

In accordance with ICH GCP, the sponsor (or designee) will inform investigators of "findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the independent ethics committee's (IEC's)/institutional review board's (IRB's) approval/favorable opinion to continue the trial."

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. To support compliance with these requirements, the investigator must provide requested information in a timely manner.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

10 INDEPENDENT DATA MONITORING COMMITTEE

Safety oversight will be under the direction of an IDMC, composed of individuals with the appropriate expertise, including cardiology.

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. 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 first IDMC meeting for the study.

At that time, each data element that the IDMC needs to assess will be clearly defined.

The IDMC will submit its recommendations to the Steering Committee and Quantum Genomics. In case of significant safety concerns, the IDMC may recommend temporary interruption of subject recruitment as well as the termination of the study.

11 STATISTICS

11.1 General Procedures

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations. Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.4 by representatives of the sponsor.

The statistical analysis plan (SAP) will be approved prior to any lock of the study database and unblinding of the study data. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

All data will be presented by treatment group. Descriptive statistics (number of observations, number of missing data, mean, SD, median, minimum, and maximum) will be provided for continuous variables, and counts, percentages (excluding missing data) and number of missing data will be presented for categorical variables.

Baseline is defined as the last nonmissing measurement before or on the date of first IP administration (firibastat [QGC001] or placebo).

Inferential tests will be performed 2-sided, with an alpha risk at 5%. Confidence intervals (CIs) will be calculated at 95%. P-values will be displayed for all efficacy criteria. Efficacy analyses will be adjusted on baseline of parameter.

11.2 Analysis Populations

- The Enrolled Population Set will include all subjects entered in the database.
- The Randomized Set will include all subjects with a date and a number of randomization.
- The Full Analysis Set (FAS) will include all randomized subjects who received at least 1 dose of IP (firibastat [QGC001] or placebo). This analysis set will be the primary set used for analyses of the primary efficacy endpoint, as well as for all secondary efficacy endpoints. The FAS will be analyzed according to planned treatment.
- The Safety Set (SS) will include all subjects who receive at least 1 dose of IP (firibastat [QGC001] or placebo) and will be analyzed according to actual treatment. This analysis set will be used for summaries of safety data.
- The Per Protocol Set (PPS) will include all subjects in the FAS without any major deviation to the present protocol. Important protocol deviations that could affect the primary endpoint will be defined in the SAP and agreed upon before unblinding. This analysis set will be used for sensitivity analyses. The PPS will be analyzed according to planned treatment.

11.3 Sample Size

Based on a minimum difference between fribastat (QGC001) and placebo in change from baseline in systolic AOBP of 5 mmHg, as requested by HTN guidelines,³⁹ and Phase 2 hypotheses of SD of 14.3 mmHg, $\alpha=5\%$ and 95% power, 213 subjects per group are requested.

Considering the 15% drop-out rate observed in Phase 2, 251 subjects have to be enrolled in each group for a total of 502 subjects.

This sample size will provide enough power for subgroup analyses (difficult-to-treat subjects and resistant subjects).

11.4 Statistical Methods

11.4.1 Primary Endpoint

The main criterion is the change from baseline to Week 12 of systolic AOBP.

Descriptive statistics on baseline, value at Week 12, and change from baseline will be described in a table. In addition, a scatter plot with ellipse confidence will be drawn for each treatment group with value at baseline in abscissa and value at Week 12 in ordinate.

The main criterion will be analyzed with a mixed model with repeated measures (MMRM) at Weeks 4, 8, and 12, with an unstructured matrix of covariance.

A mixed model uses restricted maximum likelihood to estimate all unknown variance-covariance parameters⁴², whereas a linear model uses method of moments estimators on transformed data. The advantage of the likelihood-based approach of the mixed model is that it can accommodate data that are missing at random⁴³, in contrast with the linear model, which must ignore data from all subjects which have missing repeated measures. The other advantage of this approach is the ability to be robust to the normality, associated with the sample size of 500 subjects, and provide a contrast and estimates of difference versus placebo, suitable in treatment of BP.

The main analyses will be performed on the FAS, and on the PPS as a sensitivity analysis.

11.4.2 Secondary Endpoints

In order to check the homogeneity of the efficacy results, forest plots at Week 12 of the estimates will be provided for each modality of each subgroup (age, sex, BMI, ethnicity, eGFR, and treatment-resistant/difficult-to-treat) and for the global population in the same graph.

The change from baseline to Week 4 and 8 of systolic and diastolic AOBP will be analyzed from the same model as for the main criterion.

Descriptive statistics on 24-hour ABP mean value at baseline, 24-hour mean value at Week 12 and change from baseline to Week 12 will be described in a table, for SBP and DBP, for daytime, nighttime, and all along the 24 hours. These criteria will be analyzed through an analysis of covariance (ANCOVA) with baseline as covariate. Adjusted means (LS-Means) and difference of adjusted means between firibastat (QGC001) and placebo will be estimated with 95% CI.

These analyses will be performed on subgroup of FAS with successful ABPM data.

Controlled subjects (defined as systolic AOBP <140 mmHg and diastolic AOBP <90 mmHg as per 2018 ESC/ESH guidelines, and systolic AOBP <130 mmHg and diastolic AOBP <80 mmHg as per 2017 ACC/AHA guidelines) at Week 12 will be analyzed using a logistic regression with baseline of systolic AOBP and baseline of diastolic AOBP as covariates. Odds-ratio with 95% CI will be displayed.

The same analysis of controlled subjects at Week 12 will be repeated for each modality of each subgroup. Forest plots at Week 12 of the estimates (odds-ratios) will be provided for each subgroup and for the global population in the same graph.

The biomarker is planned to be NT-ProBNP. The change in NT-ProBNP in plasma concentration from baseline to the EOT Visit will be analyzed with the same strategy as for the ABP (ANCOVA).

11.4.3 Safety Endpoint(s)

Safety endpoints are all AEs, vital signs, ECG, laboratory parameters, and concomitant treatments.

11.4.4 Analysis of Safety

The SS will be used for the analysis of safety data.

Adverse events' reported terms will be coded with the Medical Dictionary for Regulatory Activities (MedDRA). The primary MedDRA system organ class (SOC) will be used to report results.

A summary table will be provided to have an overview of the incidence of all AEs in terms of the number of subjects (subjects with at least one AE) and events with:

- All AEs
- All SAEs
- All TEAEs
- TEAEs according to the intensity (mild, moderate, severe)

- All serious TEAEs
- All drug-related TEAEs
- Drug-related TEAE according to the intensity (mild, moderate, severe)
- All TEAEs leading to a discontinuation
- All TEAEs leading to death
- All AESIs

In addition, the number of subjects with at least one of the following types of AEs will be summarized according to SOC and preferred term (PT), sorted by descending order of frequency (number of events, then number of subjects):

- All AEs
- TEAEs
- TEAEs, according to the intensity of AE
- Drug-related TEAEs
- Drug-related TEAEs, according to the intensity of AE
- Serious TEAEs
- TEAEs leading to a discontinuation
- TEAEs leading to death
- AESI

An AE will be considered as treatment-emergent if it begins the day of, or after the first IP administration (firibastat [QGC001] or placebo). Using this definition, only AEs at Screening/Run-in Period and at Day -1 will theoretically be considered as not treatment-emergent.

The date of an AE may be imputed if necessary, in a way that the worst case (ie, considering AE as emergent) will be applied. The SAP will provide full details.

Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International (SI) units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively, as well as clinical significance. Laboratory data outside study-specific reference ranges will be listed.

Vital signs (including hypotensive events) and ECG parameters will be presented descriptively. Descriptive summaries at each relevant timepoint will be displayed for value at visit and change from baseline for each parameter of vital signs and ECG, as well as clinical significance.

Prior and concomitant medications reported names will be coded in Anatomic Therapeutic Chemical (ATC) codes with World Health Organization (WHO)-Drug.

A medication will be considered as concomitant if it occurred the day of or after the first IP administration (firibastat [QGC001] or placebo). Using this definition, only medication ended before the first IP administration will theoretically not be considered as concomitant but only prior. With this definition, a concomitant may also be a prior medication.

The number of subjects with at least 1 prior medication (ended before the first IP administration) will be summarized according to the Anatomical group (ATC1) and Therapeutic main group (ATC2). Date of medications may be imputed if necessary, in a way that the worst case (ie, considering medication as concomitant) will be applied. The SAP will provide full details.

11.4.5 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, and ethnicity) and baseline characteristics (including height, weight, BMI, hip and weight circumference, disease characteristics and comorbidities) will be presented descriptively, for subjects difficult-to-treat, resistant subjects, and all subjects. No inferential statistics is planned on baseline characteristics.

11.4.6 Subgroup Analyses

To explore the uniformity of the detected overall treatment effect on the primary, and when applicable, key secondary efficacy endpoints, subgroup analyses may be performed for the following factors:

- Resistance status (difficult-to-treat or resistant)
- Age (<65 years, ≥65 years)
- Ethnicity (Black, nonBlack)
- eGFR (<60 mL/min/1.73 m², ≥60 mL/min/1.73 m²)
- BMI (<25 kg/m², ≥25 kg/m²)
- Sex

Full details of the subgroup analyses will be prespecified in the SAP.

11.4.7 *Handling of Missing Values*

Missing data will be accommodated by the use of MMRM with restricted maximum likelihood.⁴³

11.4.8 *Interim Analysis*

No interim analysis is planned.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA Code of Federal Regulations (CFR) (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

12.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions (ADRs) that are both serious and unexpected, as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects

12.3 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary, and consent can be withdrawn at any point.
- Subjects will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements in the US, and the IRB/IEC or study site.
- Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained.
- The original copy of the signed ICF will be retained at the study site.
- A copy of the ICF and any other written information must be provided to the subject.
- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

12.4 Committees

12.4.1 Steering Committee

The sponsor will appoint a Steering Committee that will be comprised of approximately 5 clinical experts (eg, cardiologists, nephrologists, internists). All members of the Steering Committee will remain blinded during the course of the trial.

The Steering Committee will advise on the study protocol and study management (sites and study conduct) and will be responsible for the scientific integrity of the trial. The Steering Committee will undertake blinded safety reviews, and reviews of data and study results as described in the Steering Committee's Charter.

12.4.2 Adjudication Committee for Allergic Skin Reaction

The sponsor will appoint an Adjudication Committee for Allergic Skin Reaction, which will be comprised of at least 3 independent dermatologists.

The Adjudication Committee for Allergic Skin Reaction will be responsible for the review of all skin reaction events that present clinically with allergic signs and symptoms or when an allergic etiology cannot be ruled out. This committee will adjudicate skin reactions that may occur during the course of the study for diagnosis and imputation according to the procedures detailed in the Committee's Charter.

All cases of allergic skin reaction will be reported to the (blinded) Adjudication Committee for Allergic Skin Reaction, with details including the subject's clinical profile, date collected, dermatologist's report, pictures, and biopsy results (if any).

The Adjudication Committee for Allergic Skin Reaction's reports, safety conclusions, and recommendations will be transmitted to the Steering Committee who will take the appropriate measures for the study conduction.

12.5 Financing and Insurance

12.5.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

12.5.2 Insurance, Indemnity, and Compensation

Quantum Genomics will maintain an appropriate clinical study insurance policy.

12.5.3 *Financial Disclosure*

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

13 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit subject information. The eCRF must be reviewed and electronically signed and dated by the investigator. The investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is related to IP
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the investigator (or designee).

If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

13.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, laboratory reports, screening logs, subject medication diaries, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

13.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

13.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, eCRFs, and the IP inventory, must be kept on file.

Essential documents should be retained until at least 2 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 clinical development of firibastat (QGC001). However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the sponsor and is to provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

13.4 External Data

13.4.1 Laboratory Data

Laboratory assessments (hematology, chemistry, coagulation, and biomarker NT-ProBNP) will be performed by a central laboratory. External files will be transferred to the data management department in order to upload data in the clinical database.

A reconciliation with clinical data (from EDC system) will be performed to ensure the accuracy and consistency of every subject's data.

14 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the study monitoring plan (eg, the CRO Clinical Management Plan). All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

14.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study.

The sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report (CSR).

14.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the subject.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study subject, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor's medical monitor and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

Protocol deviations will be recorded in the monitoring visit report and/or in the clinical trial management tracking tool used by the sponsor or designee (eg, CRO Clinical Trial Management System).

14.3 Site Monitoring During COVID-19 Pandemic

Whenever possible, CRO monitors will continue to conduct on-site monitoring visits, per the current Clinical Management Plan. If a monitor is unable to travel for an on-site monitoring visit (local lockdown/travel restriction) or if an investigational study site is unable to accommodate a monitor for an on-site monitoring visit, then a remote monitoring visit will be conducted where approved by site policies and where it is regulatory permitted. An on-site monitoring visit will be performed at a later date, as soon as possible.

If a remote monitoring visit is not possible, an off-site monitoring visit can be conducted to ensure that rights and well-being of subjects are protected, reported data are collected and entered in timely manner, and site confirms the source documents meet ALCOA-C/CCEA requirements. Any monitoring mitigations implemented due to COVID-19 will be included in the Clinical Management Plan, revised accordingly.

15 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the subject and/or impact the subject's involvement as a study subject. In such cases, the ICF will be renewed for enrolled subjects before their continued participation in the study.

16 STUDY REPORT AND PUBLICATIONS

16.1 Clinical Study Report

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

16.2 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the sponsor or their designee, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

16.3 Publication Policy

The publication policy of the sponsor is discussed in the investigator's clinical research agreement.

17 STUDY START AND TERMINATION

The study start date is the date on which the first subject provides informed consent.

The end of the study is defined as the last subject's last assessment.

Both the sponsor and the investigator reserve the right to terminate the study or the participation in the study at an investigator's site at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

The IDMC may recommend termination of the study if it finds evidence of unacceptable risk to subjects.

If the study is prematurely terminated or suspended for any reason, the sponsor/investigator/site personnel should promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the site personnel. The investigator/site personnel should promptly inform the sponsor and the IRB/IEC. The investigator/site personnel should also provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

18 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, the sponsor and its authorized representatives are allowed full access to the records.

All study subjects must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs shall be by unique subject identification numbers only. All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at PRA.

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20 APPENDICES

20.1 APPENDIX I – Study Administrative Structure

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A log of the name and title of the investigators who are responsible for conducting the study, and the address and telephone numbers of the study sites will be maintained.

The names and addresses of laboratories involved in the study will be provided in the laboratory manual.