A Phase 3, Double-blind, Placebo-controlled and Open-label Efficacy and Long-term Safety Study of Firibastat (QGC001) Administered Orally, Once Daily, for Up to 48 Weeks in Patients with Difficult-to-treat/Resistant Hypertension

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Primary objective:To assess the effects of firibastat (QGC001) administered at 1000 mg orally (po) once daily (QD) on blood pressure (BP) over 12 weeksSecondary objectives:• To assess the safety of firibastat (QGC001) administered at 1000 mg po QD...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52137

Source
ToetsingOnline

Brief title
REFRESH

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Difficult to treat and Treatment-resistant high blood pressure

Research involving

Human

Sponsors and support

Primary sponsor: Quantum Genomics
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Difficult-to-treat hypertension, Phase 3, Treatment-resistant hypertension

Outcome measures

Primary outcome

The primary efficacy endpoint is the change from baseline in systolic AOBP at

Week 12.

Secondary outcome

Secondary efficacy endpoints: AOBP at every visit. 24-hour ambulatory BP after

12 weeks (end of double-blind period [Period 1]). Biomarker NT-ProBNP,

fibrinogen and hsCRP at Visit 2B, Day 1, and Visit 4B, Day 85 (±3 d).

Proportion of subjects requiring an increase in the dose of current

antihypertensive drugs or addition of another hypertensive drug during the

open-label treatment periods (Periods 2 and 3) of the study.

Study description

Background summary

So far, Firibastat has been proposed to approximately 670 healthy subjects and patients as a study drug during medical studies.
Previous studies demonstrated that Firibastat is in general safe and well-tolerated in healthy subjects and efficient to lower the blood pressure in hypertensive patients when given as monotherapy (treatment of a disease with a single drug) compared to currently available treatments.

See protocol section 1.1 for more details.

Study objective

Primary objective:
To assess the effects of firibastat (QGC001) administered at 1000 mg orally (po) once daily (QD) on blood pressure (BP) over 12 weeks

Secondary objectives:
• To assess the safety of firibastat (QGC001) administered at 1000 mg po QD over 24 weeks and 48 weeks
• To assess change in BP over time

in subjects with uncontrolled primary HTN who have been treated with at least 2 classes of antihypertensive therapies at the maximum tolerated doses (MTDs) (ie, difficult-to-treat or treatment resistant patients)

Study design

This is a double-blind, placebo-controlled and open-label, multicenter efficacy and long-term safety study of firibastat (QGC001) 1000 mg (2×500 mg tablets) administered po, QD, for up to 48 weeks in patients with difficult-to-treat/treatment-resistant HTN. Subjects will continue to take their chronic antihypertensive therapies (at least 2 classes of antihypertensive therapies) at the MTDs during the Run in Period and for the duration of the study. For treatment-resistant subjects, one of the antihypertensive therapies must be a diuretic; for difficult-to-treat subjects, the antihypertensive therapies do not have to include a diuretic. Subjects will complete subject medication diaries during the Run-in Period. If systolic automated office BP (AOBP) is >=180 mmHg or diastolic BP (DBP) >=110 mmHg (and repeated and confirmed within 30 min) at any visit after randomization (ie, after Visit 2B, Day 1), the subject will be withdrawn from the study and will receive appropriate treatment.
For each subject, the study will include a Screening Visit, a Run-in Period, an Inclusion Visit (Visit 2A, Day 0, and Visit 2B, Day 1), and up to 3 study treatment periods with clinic visits and safety phone calls.
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 medication diary. The duration of the Run in Period will be no less than 28 days and no more than 33 days; this time period allows for 2 repeat ambulatory BP monitoring (ABPM) recordings at Visit 2A, if required. Subjects who meet the inclusion/exclusion criteria at the end of the Run in Period will be randomly assigned to either Group A or Group B. A total of 200 subjects (100 in Group A and 100 in Group B) will be randomized to continue treatment with firibastat (QGC001) during Period 3. Subjects will receive either double-blind firibastat (QGC001) or placebo for the first 12-week study

treatment period (Period 1), followed by open label treatment with firibastat for 24 weeks (Period 2), or 36-weeks (Period 2 plus an additional 12-weeks of open-label treatment in Period 3).
At Visit 2A, Day 0, an ABPM device will be installed for each subject who has successfully completed the Run-in Period with a medication adherence >=80%, and remains eligible to participate in the study. The ABPM device 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 investigational product (IP) at Visit 2B, 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 (e.g., 23 hours and 30 minutes) would be acceptable for a successful ABPM recording providing it successfully confirms 21 daytime readings and 6 nighttime readings. If the ABPM recording is not successful, 2 further attempts are permitted.
Following a successful ABPM recording (assessed at Visit 2B, Day 1), subjects who still meet the inclusion/exclusion criteria and who have a mean daytime systolic ambulatory blood pressure (ABP) >135 mmHg, will undergo visit-specific assessments and will be randomized to Group A or Group B, and receive either firibastat (QGC001) or placebo for the 12-week double-blind treatment period (Period 1), followed by open label firibastat (QGC001) for 24 weeks (Period 2), or 36 weeks (Period 2 plus Period 3 [200 subjects]), in addition to their current chronic antihypertensive treatments. During Period 1, the investigator (or designee) will call subjects by telephone on Day 14 (±3 d) to collect any potential adverse events (AEs), check IP compliance, and record any concomitant medications. Subjects will receive a second safety phone call during Period 2, at Day 98 (±3 d).
Subjects will attend the study site for the following study visits:
Period 1: Visit 2A, Day 0; Visit 2B, Day 1; Visit 3, Day 42 (±3 d); Visit 4A, Day 84 (±3 d); and Visit 4B, Day 85 (±3 d).
For Visit 4B, Day 85, the subject will attend the site without having taken any IP tablets. Subjects will only move to open-label firibastat (QGC001) if the ABPM recording is successful, otherwise they will continue to take double-blind IP and repeat the ABPM measurement within 24 hours of the first measurement. Open-label firibastat (QGC001) will be administered at the study site after the predose time point.
Period 2: Visit 5, Day 126 (±3 d); Visit 6, Day 168 (±3 d); Visit 7, Day 252 (±3 d); and Visit 8, Day 280 (±3 d).
Period 3:Visit 9, Day 336 (±3 d), and Visit 10, Day 364 (±3 d).
On completion of their final study treatment period, subjects will attend an End of Treatment (EOT) Visit. A safety follow-up will be performed at the End of Study (EOS) Visit.
For subjects who stop study treatment at the end of Period 2, the EOT Visit will be at Visit 7, Day 252 (±3 d), and the EOS Visit will be Visit 8, Day 280 (±3 d).

Subjects who continue study treatment into Period 3 will not attend Visit 8, Day 280 (±3 d). Subjects who stop treatment with firibastat (QGC001) after Period 3 will attend an EOT Visit at Visit 9, Day 336 (±3 d), and an EOS Visit at Visit 10, Day 364 (±3 d).
Subjects who discontinue the study early should undergo an Early Termination Visit, and an EOS Visit 28 days (±3 d) after the last dose of IP (except in the case of consent withdrawal).
Pharmacokinetic (PK) sampling will be conducted at sites selected for PK sampling; where the option to participate in PK sampling will be offered to all subjects. The total number of subjects who participate in PK sampling will be determined by the number of subjects who consent to PK sampling. Subjects who provide informed consent for PK sampling will be randomized to 1 of 5 PK subgroups. PK Subgroups 1, 2, 3, and 4 will comprise subjects who will be stopping treatment with firibastat (QGC001) at the end of Period 2. PK Subgroup 5 will comprise subjects who will continue to take firibastat (QGC001) in Period 3. A subset of 50 subjects will undergo the Enhanced PK Sampling Schedule via randomization into one of the PK Subgroups 1, 2 or 3; 6 PK samples will be collected from each subject according to their PK subgroup sampling schedule. For subjects undergoing the Standard PK Sampling Schedule, 2 PK samples will be collected according to the sampling schedule for PK Subgroups 4 and 5. The total number of subjects participating in the Standard PK Sampling Schedule will be based on the number of subjects who consent to PK sampling, and is therefore not predetermined; however, these subjects will be equally randomized to PK Subgroup 4 and PK Subgroup 5.
At each study visit, AOBP, orthostatic BP, and heart rate (HR) will be measured, and other visit-specific procedures will be performed, including electrocardiograms (ECGs), clinical laboratory evaluations, clinical examinations, collection of blood for PK samples and the biomarker N terminal pro-B-type natriuretic peptide (NT-ProBNP), fibrinogen and highly sensitive C-reactive protein (hsCRP), and monitoring of AEs and concomitant medications.
At the EOS Visit (safety follow-up) assessments will include clinical examination, AOBP, orthostatic BP, ECG, HR, and clinical laboratory assessments, AE monitoring, and concomitant medications.
Allergic skin reactions and/or diabetes insipidus (DI) are considered adverse events of special interest (AESIs) with immediate notification during the study treatment period.

Intervention

This trial will evaluate the firibastat (QGC001) for the treatment of Hypertension. The trial will be divided into Period 1, 2 and 3. The trial will have 2 groups of patients. Patients will be randomly assigned to Group A (who will receive firibastat during period 1) or Group B (who will receive placebo during period 1). During period 1, patients will have a 50% chance of receiving firibastat and a 50% chance of receiving placebo. During period 2 and 3 both groups will receive Firibastat. A total of 200 patients (100 in Group A and 100

in Group B) will be randomized to continue the trial during Period 3.

Study burden and risks

Please see protocol section 6.0 for a description of study assessments.
Please see section 6.0 in the MainICF for possible side effects and complications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Able to understand and willing to provide written informed consent, and able to comply with the study procedures and restrictions.

2. Adult men and women (at Screening). For all countries, age criteria must be as per local regulations; eg, subjects in Canada must be aged >= 18 years or >=19 years of age at Screening, as per the applicable.
Canadian provincial criteria
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 179 mmHg (inclusive) at Screening (visit 1) 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 post dose. Approved forms of contraception include intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, or hormonal intrauterine devices, hormonal contraceptives (oral birth control pills, depo, patch, or injectable) together with supplementary barrier methods 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 2B, Day 1).

Exclusion criteria

1. Known or suspected secondary HTN (eg, hyperaldosteronism, renovascular HTN, pheochromocytoma, Cushing*s disease).
2. Systolic AOBP >=180 mmHg or DBP >=110 mmHg at the Screening or Inclusion Visit (Visit 2B, 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 any drug-related allergy or hypersensitivity to any components of the IP (firibastat [QGC001] or placebo).
7.Known severe aortic stenosis (symptomatic or asymptomatic with valvular

indexed surface <0.5 cm^2/m^2).
8.Subjects with severe symptomatic heart failure (New York Heart Association [NYHA] Class III or Class IV).
9.History of acute coronary syndrome (non-ST elevation myocardial infarction [MI], ST elevation MI, and unstable angina pectoris), stroke, or transient ischemic attack within 6 months prior to Visit 2A, Day 0.
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×upper limit of normal (ULN), or a total bilirubin >=1.5×ULN (unless secondary to Gilbert*s syndrome), or direct bilirubin >ULN in subjects with Gilbert*s syndrome at Screening.
16.Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 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, (or any combination of the following medications) is permitted: glucagon like peptide 1 analog, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, and 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×lower limit of normal or >1.5×ULN at Screening.
23.History of alcohol or drug abuse (including opioid overuse/misuse) within the 3 months prior to Screening that would interfere with study participation or lead to decreased compliance to study procedures or IP intake in the investigator*s opinion.

24.Participation in another clinical study involving an investigational drug within 30 days prior to Screening or plans to participate in another clinical study within 30 days of discontinuation of IP.
25.Any other condition that precludes adequate understanding, cooperation, and compliance with study procedures or any condition that could pose a risk to the subject*s safety, as per the investigator*s judgment.
26.Subjects with a life expectancy of less than 1 year per investigator*s discretion.
27.Legal incapacity or limited legal capacity.
28.Previous participation in any clinical study with firibastat (QGC001).
29.Subjects with any history of documented allergic reactions or allergic diseases, with the exception of documented seasonal allergies (per the investigator*s decision).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-07-2022
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	QGC001
Generic name:	firibastat

Ethics review

Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-001404-14-NL
ClinicalTrials.gov	NCT04857840
CCMO	NL78941.100.21