CLINICAL STUDY PROTOCOL

A Study in Healthy Subjects Designed to Evaluate the Pharmacokinetic Profile of Firibastat (QGC001) and Metabolites EC33 and QGC515 Following Multiple Dose Administration of QGC001 Immediate Release and Modified Release Formulations

Quotient Study Number:	QSC202835
Sponsor Study Number:	1QG5
EudraCT Number:	2019-003748-55

Clinical Study Site:	Quotient Sciences Mere Way Ruddington Fields Ruddington Nottingham NG11 6JS, UK Tel: +44 (0)115 974 9000
Sponsor:	Quantum Genomics 33 Rue Marbeuf Paris 75008 France Tel: +33 (0)1 85 34 77 70
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Study Contacts

Principal Investigator: Sharan Sidhu MBChB, BAO, MRCS, MFPM
Quotient Sciences
Mere Way
Ruddington Fields
Ruddington
Nottingham NG11 6JS, UK
Tel: +44 (0)115 974 9000 (day)
Tel: +44 (0)7774 017236 (out of hours emergency)

Sub-Investigators: Philip Evans MBChB, MRCS (Ed)
Stuart Mair MBChB, DRCOG, DCPSA, FFPM
Nand Singh BSc, MD, DPM, MFPM
Litza McKenzie MBChB, BScMedSci
Martina Fieldingova MD
Dan Hamzea MD
Elizabeth Maria van Niekerk MBChB, DipPalMed
Somasekhara Menakuru MBBS, MS, MRCS,
Dip Pharm Med
Jonathan Whitton BMBS, BSc, MRCS, PGcert
David Everton BSc, MBBS
Jeyanthi Rangaraj MBBS, MRCPH, MRCP, DCH,
MRCGP
Quotient Sciences
Tel: +44 (0)115 974 9000 (day)
Tel: +44 (0)7774 017236 (out of hours emergency)

Scientific Lead: Vanessa Zann BSc (Hons), PhD
Quotient Sciences
Tel: +61 (0)412976741

Programme Manager: Sue Sweet-Smith BSc (Hons)
Quotient Sciences
Tel: +44 (0)115 931 5502

Project Manager: Richard Coxon BMedSci
Quotient Sciences
Tel: +44 (0)115 931 3211

Study Monitor: Jane Muir
Wirral Clinical Consultancy Ltd
Tel: +44 (0)151 342 8863

Medical Monitor: Bruno Besse MD
Chief Medical Officer, Quantum Genomics
Tel: +33 (0)1 85 34 77 73

Pharmacovigilance Provider:	Voisin Consulting Life Sciences 64 Avenue Pierre Grenier Boulogne (Paris) 92100 France Tel: +33 (0)1 41 31 83 00
Central Laboratory:	The Doctors Laboratory The Halo Building 1 Mabledon Place London WC1H 9AX
Bioanalytical Laboratory:	Jordan Gonçalves PK/PDesign (Oncodesign) Centre de Recherches François Hyafil 38 avenue de la Baltique ZAC Courtaboeuf 91140 Villebon sur Yvette France Tel : +33 (0)1 69 29 60 00 Tel : +33 (0)6 24 86 43 78 E-mail: jordan.goncalves@oncodesign.com www.oncodesign.com

Signatures for Quotient

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 16.4 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

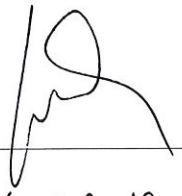
Sharan Sidhu MBChB, BAO, MRCS, MFPM
Principal Investigator
Senior Clinical Research Physician

Sharan
Signature

17 OCT 2019
Date

Signatures for Sponsor

Bruno Besse MD



Signature

18/10/2019

Date

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3 Synopsis

Sponsor:	Drug Substance:	EudraCT No.:
Quantum Genomics	QGC001	2019-003748-55

Title of Study:

A Study in Healthy Subjects Designed to Evaluate the Pharmacokinetic Profile of Firibastat (QGC001) and Metabolites EC33 and QGC515 Following Multiple Dose Administration of QGC001 Immediate Release and Modified Release Formulations

Principal Investigator:

Sharan Sidhu MBChB, BAO, MRCS, MFPM

Study Centre:

Quotient Sciences, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, UK

Objectives and Endpoints:

Objectives	Endpoints
Primary • To evaluate the pharmacokinetic (PK) profiles of QGC001, EC33 and QGC515 following multiple dose administration of QGC001 immediate release (IR) formulations and a modified release (MR) formulation in healthy subjects	• Evaluate the PK profiles of QGC001 IR and MR formulations by assessing the following primary PK parameters for QGC001, EC33 and QGC515: Tmax, Cmax, AUC,T1/2 and Ctau
Secondary • To provide additional safety and tolerability information for multiple doses of QGC001 in healthy subjects	• To provide additional safety and tolerability information for multiple doses of QGC001 by assessing: adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations and laboratory safety tests

Methodology:

This is a single centre, multiple dose, non-randomised, open-label study in healthy male subjects and healthy female subjects of non-childbearing potential designed to investigate the PK and safety of QGC001 IR and MR tablet formulations compared to an IR capsule. It is planned to enrol 3 cohorts of 10 subjects. Each cohort will receive one of the regimens in the table below.

Cohort	Regimen	IMP Dose	Route of Administration
1	A	500 mg (2 × 250 mg) QGC001 IR capsule BID on Days 1 to 6 and QD dosing on Day 7	Oral Administration, Fasted
2	B	1000 mg (2 × 500 mg) QGC001 MR tablet QD for 7 days	Oral Administration, Fasted
3	C	1000 mg (2 × 500 mg) QGC001 IR tablet QD for 7 days	Oral Administration, Fasted

BID: twice daily, IR: immediate release, MR: modified release, QD: once daily
The order in which regimens are dosed may be subject to change due to logistical reasons. The regimens may be dosed in parallel.

Study Design:

Each cohort will follow the same study design. Subjects will be screened to participate in the study up to 28 days prior to dosing and will be admitted to the clinical unit in the evening of the day before dosing (Day -1). Subjects will remain on site until 48 h post-final dose (Day 9).

In Regimen A, subjects will receive a single dose of 500 mg QGC001 as 2 × 250 mg IR capsules twice daily (BID) on Days 1 to 6 and a single 500 mg dose as 2 × 250 mg IR

capsules in the morning of Day 7. For BID dosing in Regimen A, subjects will receive the first daily dose following an overnight fast (minimum 10 h) and the second daily dose at approximately 12 h post-morning dose, which will be 2 h after the evening meal. For Regimens B and C, subjects will receive a single dose of 1000 mg as 2 ×500 mg MR or IR tablets once daily in the morning on Days 1 to 7 following an overnight fast (minimum 10 h). A follow-up phone call will take place 7 to 10 days post-final dose to ensure the ongoing wellbeing of the subjects.

The cohorts may be dosed in parallel. It is expected that the study will be executed in 3 cohorts, each requiring a single study period.

Number of Subjects Planned:

It is planned to enrol 10 healthy male and female subjects in each cohort to ensure data in 8 evaluable subjects per cohort. An evaluable subject is defined as a subject who has received investigational medicinal product (IMP) for 7 days and who has safety and PK assessments up to 48 h post-final dose. Subjects withdrawn due to an IMP-related AE will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator and the sponsor to ensure sufficient evaluable subjects. Up to 6 replacement subjects (2 per cohort) may be enrolled into the study. The maximum number of subjects that may be dosed is 36 (12 per cohort).

Duration of Study:

Multiple dose administration for 7 days. The estimated time from screening until the follow-up phone call for each cohort is approximately up to 7 weeks.

Main Inclusion Criteria:

Healthy males and females of non-childbearing potential aged 18 to 55 years.

Body mass index (BMI) 18.0 to 32.0 kg/m^2.

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMPs will be used in this clinical study.

IMP Name	Unit Dose	Route of Administration
Firibastat (QGC001) IR Capsule Formulation	250 mg	Oral Administration, Fasted
Firibastat (QGC001) MR Tablet Formulation	500 mg	Oral Administration, Fasted
Firibastat (QGC001) IR Tablet Formulation	500 mg	Oral Administration, Fasted

Subjects will be given 240 mL water immediately following IMP administration. Additional water may be given with the IMP if required.

Pharmacokinetic Assessments:

The plasma concentration data for QGC001, EC33 and QGC515 will be analysed by Quotient Sciences on Day 1 and Day 7, using appropriate non-compartmental techniques to obtain estimates of the following parameters where possible and appropriate.

Day 1

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration (first dose only)
AUC(0-4)	Area under the curve from 0 time to 4 h post-dose
AUC(0-12)	Area under the curve from 0 time to 12 h post-dose
AUC(0-24)	Area under the curve from 0 time to 24 h post dose (Regimens B and C only)
AUC(0-tau)	Area under the curve over the dosing interval from time 0 to tau (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)

C12	Concentration observed at 12 h post-dose
C24	Concentration observed at 24 h post-dose (Regimens B and C only)
MPR Cmax	Metabolite to parent ratio based on Cmax
MPR AUC(0-tau)	Metabolite to parent ratio based on AUC(0-tau) (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)

Day 7

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-4)	Area under the curve from 0 time to 4 h post dose
AUC(0-12)	Area under the curve from 0 time to 12 h post dose
AUC(0-24)	Area under the curve from 0 time to 24 h post dose (Regimens B and C only)
AUC(0-tau)	Area under the curve over the dosing interval from time 0 to tau (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)
AUC(0-24)p	Predicted area under the curve from 0 time to 24 h post dose following BID dosing, calculated as AUC(0-12) multiplied by 2 (Regimen A only)
Ctau	Concentration at the end of a dosing interval (12 h for Regimen A and 24 h for Regimens B and C)
C12	Concentration observed at 12 h post-dose
C24	Concentration observed at 24 h post-dose (Regimens B and C only)
Cavg	Average concentration at steady state (AUC(0-tau)/tau)
Fluctuation%	Peak to trough fluctuation (Cmax-Cmin)/Cavg × 100
T1/2	Apparent elimination half-life (last dose only)
Lambda-z	Slope of the apparent elimination phase
AR Cmax	Accumulation Ratio based on Cmax for Day 1 vs Day 7
AR AUC	Accumulation Ratio based on AUC(0-tau) for Day 1 vs Day 7
MPR Cmax	Metabolite to parent ratio based on Cmax
MPR AUC(0-tau)	Metabolite to parent ratio based on AUC(0-tau) (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)
CL_{ss}/F	Apparent total body clearance at steady state calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
Vz_{ss}/F	Apparent volume of distribution at steady state based on the terminal phase calculated after a single extravascular administration where F (fraction of dose absorbed) is unknown

Safety Assessments:

The safety assessments to be conducted are:

- Adverse events
- 12-lead ECGs
- Vital signs
- Clinical laboratory tests (clinical chemistry, haematology and urinalysis)
- Physical examinations

Statistical Methodology:

Descriptive summaries will be provided for all safety and PK data by treatment.

Formal statistical analysis will be performed on the log-transformed Cmax, AUC(0-4), AUC(0-12) and AUC(0-24) values for QGC001, EC33 and QGC515 on each of Days 1 and 7 where possible and appropriate. On Day 7, for comparisons versus the IR capsule, AUC(0-24) of Regimens B and C will be compared against AUC(0-24)p for Regimen A. The PK parameters will be analysed using a fixed effects model including treatment as a fixed effect.

Ratios of geometric means and 90% confidence intervals (CIs) will be provided where possible for the following comparisons:

- MR tablet vs IR capsule
- MR tablet vs IR tablet
- IR tablet vs IR capsule

In addition, in order to assess dose accumulation, log-transformed Cmax and AUC(0-tau) for QGC001, EC33 and QGC515 will be subjected to a mixed effects model with treatment, day (Day 1 or 7) and treatment by day as fixed effects and subject as a random effect. The adjusted means obtained from the model, including differences for each comparison of interest and the associated 90% CIs, will be back-transformed on the log scale to obtain adjusted geometric means, adjusted geometric mean ratios (GMRs) and 90% CIs of the ratio. The GMRs and 90% CIs will be provided for each treatment, ie Day 7/Day 1. If the interaction term is not significant at the 10% level, an estimation of the overall accumulation (ie accumulation across formulations) will be provided.

Sample Size and Power:

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 10 subjects per cohort is to be enrolled and a minimum of 8 evaluable subjects per cohort is considered sufficient.

4 List of Abbreviations

Abbreviation	Definition
ACE	angiotensin I converting enzyme
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APA	aminopeptidase A
AT1	angiotensin-II receptor type 1
BAPAI	brain aminopeptidase A inhibitor
BID	twice daily
BMI	body mass index
BP	blood pressure
DI	diabetes insipidus
DSP	diastolic blood pressure
DMP	data management plan
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
GCP	good clinical practice
GP	general practitioner
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HF	heart failure
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HTN	hypertension
ICF	informed consent form
IMP	investigational medicinal product
IR	immediate release
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
MR	modified release
NOAEL	no observable adverse effect level
PC	post-coitum

PD	pharmacodynamic
PI	Principal Investigator
PIS	Participant Information Sheet
PK	pharmacokinetic(s)
QA	quality assurance
QD	once daily
QTcF	Corrected QT interval by Fridericia's formula
RAAS	renin-angiotensin aldosterone system
RAP	Reporting and Analysis Plan
RAS	renin-angiotensin system
SAD	single ascending dose
SAE	serious adverse event
SBP	systolic blood pressure
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

5 Background Information

5.1 Introduction

Arterial hypertension (HTN) and heart failure (HF) are 2 major cardiovascular pathologies for which there are still unmet medical needs to develop new efficient and safe classes of drugs. Hypertension affects approximately 1 billion individuals worldwide. It is a leading risk factor for coronary heart disease, Heart failure, stroke and renal insufficiency. Despite the availability of effective and safe drugs, HTN and its concomitant risk factors remain uncontrolled in many patients. Heart failure is the leading cause of hospitalisation for patients over 65 years old in western countries. Heart failure affects 1 to 5 persons in 1000 in industrialised countries, all ages considered, with a prevalence of 3 to 20 in 1000. In the US, HF healthcare expenses represented $21 billion in 2012, with the majority of costs related to hospitalisations. Despite the large number of drugs available HF has a poor prognosis as the 1-year survival, all stages considered, is about 65% and HF remains one of the first causes of cardiovascular death.

The systemic renin-angiotensin system (RAS) is known to play a central role in blood pressure (BP) regulation and sodium metabolism and in the pathogenesis of chronic HF with a reduced ejection fraction. Systemic drugs targeting the RAS such as angiotensin I converting enzyme (ACE) inhibitors and angiotensin-II receptor type 1 (AT1) antagonists are clinically effective in lowering BP and in preventing cardiovascular and renal morbidity and mortality in patients. Activity of the renin-angiotensin aldosterone system (RAAS) is increased in patients with HF, and its maladaptive mechanisms may lead to adverse effects such as cardiac remodelling and sympathetic activation. Current evidence based guideline IA recommended medicines for HF with reduced ejection fraction are mainly RAAS-acting molecules such ACE inhibitors or AT1 receptor blockers and beta-adrenergic receptor blocking agents.

A functional RAS controlling cardiovascular functions and body fluid homeostasis is also present in the brain. Several studies suggest that increased activity of the brain RAS results in an increase in sympathetic neuron activity and vasopressin release and that hyperactivity of the brain RAS plays a critical role in mediating high BP in various animal models of HTN as well as cardiac remodelling and dysfunction in animals models of HF. Because recent evidences support that angiotensin III (Ang III) through its action on AT1 receptor may be the true peptide effector of the brain RAS for the central control of BP, the brain aminopeptidase A (APA), the enzyme generating Ang III from angiotensin II (Ang II) in the brain, constitutes a promising therapeutic target for treatment of HTN and for the treatment of HF.

Quantum Genomics is developing the molecule QGC001 recently denominated firibastat by the World Health Organisation, as the first drug-candidate of a new class of central anti-hypertensive agents, brain aminopeptidase A inhibitors (BAPAIs). QGC001 ((3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) previously named RB150) is a prodrug of the selective APA inhibitor, EC33 ((3S)-3-amino-4- sulfanylbutane-1-sulfonic acid). QGC001 effects on BP and HF observed in animals is in part due 1) to a decrease in arginine vasopressin release in the blood circulation, increasing diuresis which reduces the size of body fluid compartment, and 2) to a reduction in the sympathetic tone leading to subsequent decrease in vascular resistances.

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

5.2 Investigational Medicinal Product(s)

The following investigational medicinal products (IMPs) will be used in this clinical study (Table 1).

Table 1 Investigational Medicinal Products

IMP Name	Unit Dose	Route of Administration
Firibastat (QGC001) IR Capsule Formulation	250 mg	Oral Administration, Fasted
Firibastat (QGC001) MR Tablet Formulation	500 mg	Oral Administration, Fasted
Firibastat (QGC001) IR Tablet Formulation	500 mg	Oral Administration, Fasted

The QGC001 is an un-licensed medicinal product for use only in the proposed clinical trial.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments will be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

Where Quotient Sciences is manufacturing the IMPs, suitability of the manufacturing process will be documented in a Pharmaceutical Development and Control Strategy Report.

Investigational medicinal products will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

5.3 Previous Study Findings

Full details of the non-clinical and clinical trials conducted for Firibastat (QGC001) can be found in the Investigator's Brochure [1]; a summary is provided below.

5.3.1 Non-clinical Findings

Pharmacology

When administered intravenously (1 mg/kg) or orally (15 mg/kg) to conscious hypertensive deoxycortisterone acetate-salt rats, Firibastat (QGC001) enters the brain and is converted into EC33 by brain reductases, which in turn leads to the blockade of brain Ang III formation and normalisation of BP for several hours.

Pharmacokinetics

Following single or multiple oral administrations in rats and dogs, QGC001 is rapidly absorbed with Tmax values of 1 h to 2 h; however, oral absorption was highly variable between species. Oral bioavailability of QGC001 calculated from area under the curve (AUC) values, is below 1% in rats and around 30% in dogs with no noticeable difference between genders observed. The plasma concentration time profile studies in rats and dogs indicate a rapid decline with half-lives being shorter than 2 h in rats and dogs. Excretion after single oral dosing of QGC001 at 50 mg/kg in rats occurs predominantly via the faecal route. Excretion is rapid and essentially complete (99.56%) 48 h after QGC001 administration.

QGC001 was found to be metabolised in rat, dog, monkey and human into one common metabolite different from EC33 in in vitro assays performed with hepatocyte fractions of each species. This metabolite (QGC515) results from the conjugation of one molecule of EC33 with one molecule of L-cysteine through a disulfide bridge.

Risk of adverse side-effects 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 QGC001 or by EC33 or by QGC515 when tested in vitro at 100 µmol/L. Additionally, QGC001 was found not to inhibit activities of uridine glucuronyl transferases UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 as well as transport mediated via P-gp and BCRP, or via OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1 and MATE2-K.

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

Toxicity

In 28-day repeat oral administration toxicity studies, QGC001 was safe and well tolerated in both rats (no observable adverse effect level [NOAEL] of 550 mg/kg) and Beagle dogs (NOAEL of 1000 mg/kg) at doses significantly superior to the dose showing anti-hypertensive activity in rats. No relevant signs of toxicity were observed with the exception of diarrhoea at doses of 500 mg/kg and 1000 mg/kg in male and female dogs.

When oral QGC001 was administered daily in rats for 13-weeks at 125, 550 and 1000 mg/kg, no adverse test item related effect was observed on measurements obtained during the in-life period of the study. Treatment at a dose level of 1000 mg/kg induced significantly increased relative liver weight and hepatocellular hypertrophy in all males, indicating test item related metabolic enzyme induction. The intermediate dose level of 550 mg/kg is considered the NOAEL in rats treated by oral gavage for 13 weeks with QGC001.

Oral QGC001 was planned to be administered daily for 13-weeks at 30, 100 and 300 mg/kg doses in Beagle dogs. At 30 mg/kg, daily oral gavage treatment for at least 91 days was clinically well tolerated. Following treatment, a single animal inflammatory cell infiltration was observed in the pituitary gland; relationship to treatment could not be excluded. Treatment at dose levels of 100 and 300 mg/kg resulted in clinical signs of pallor skin, spots and redness/erythema at the abdomen, ears and mouth mucous membrane. Furthermore, observed decreases in haemoglobin concentration, red blood cell count, haematocrit and platelet count were considered treatment-related. Microscopic findings considered QGC001-related findings were also observed in several organs; notably, red foci in various tissues corresponding to widespread haemorrhages, increase in the number of megakaryocytes in bone marrow, and extramedullary haematopoiesis (megakaryocytic) in the spleen. Furthermore, infiltration of inflammatory cells, mainly characterised by mononuclear and/or mixed inflammatory cells was seen in various organs and overall this finding was reported with a higher incidence and/or severity in animals treated with QGC001 at dose levels of 100 and 300 mg/kg.

QGC001 was not found to be genotoxic in both in vitro and in vivo assays, and was not categorised as a phototoxic compound in in vitro assays.

Reprotoxicity

Effects on embryo-foetal development in rabbits

QGC001 was administered daily to time-mated female New Zealand White rabbits by the oral route at dose levels of 100, 200 or 400 mg/kg/day from Day 6 to Day 18 post-coitum (PC), inclusive. Based on the results obtained in this study:

- The NOAEL for maternal parameters was considered to be 400 mg/kg/day (corresponding for QGC001 and EC33 to mean Cmax values of 5631 ng/mL and 4756 ng/mL and to mean AUC(0-t) values of 44430 h.ng/mL and 45305 h.ng/mL on Day 18 PC)
- The No Observed Effect Level (NOEL) for embryo-foetal development was considered to be 400 mg/kg/day

Effects on embryo-foetal development in rats

QGC001 was administered to time-mated female Sprague Dawley rats, by gavage, once daily (QD), from Days 6 to 17 PC, at dose levels of 125, 550 or 1000 mg/kg/day. Under the experimental condition of this study, QGC001 did not elicit any teratogenic activity in the rat.

The NOAEL for maternal parameters and for embryo-foetal development was considered to be 1000 mg/kg/day (corresponding to mean Cmax of 8004 ng/mL and mean AUC(0-t) of 15547 h.ng/mL on Day 17 PC), based on the absence of adverse effects at this dose level.

Effects on fertility and early embryonic development to implementation in rats

The objective of this study was to evaluate the potential toxic effects of QGC001, following daily oral administration to male and female rats, from before mating, through mating and implantation. For males, this type of study permits the detection of functional effects (eg on libido or epididymal sperm maturation); for females, this type of study

permits the detection of effects on the oestrous cycle, tubal transport, implantation and the development of pre-implantation stages of the embryo.

QGC001 was administered daily by oral administration to male and female Sprague-Dawley rats, from before mating, during mating and until implantation, at dose levels of 125, 550 or 1000 mg/kg/day. Based on the results obtained in this study:

- The parental NOAEL was considered to be 1000 mg/kg/day based on absence of adverse findings at this dose level
- The no observed effect level for pairing, mating and fertility performances was considered to be 1000 mg/kg/day, based on absence of findings at this dose level

5.3.2 Clinical Findings

The clinical development of firibastat includes 6 completed clinical studies: 3 completed Phase I studies conducted in 137 healthy male volunteers, a completed Phase IIa study in 34 hypertensive patients, a completed Phase IIb study in 256 hypertensive patients, and a completed Phase II study in 23 patients with HF. One Phase II study in post myocardial infarction and 1 Phase I study are ongoing.

Completed Phase I studies

Study N°QGC001/1QG1:

A Phase I, double-blind, placebo-controlled, ascending single-dose, safety, tolerability and PK study of QGC001 was conducted between 14 Feb 2012 and 18 Jun 2012 in France with an objective to evaluate safety, tolerability, PK and pharmacodynamics (PD) of the single ascending dose (SAD) of QGC001 up to 1250 mg in 56 healthy volunteers. Following oral administration, QGC001 is absorbed via the gastrointestinal tract and converted partially into its active metabolite EC33 in plasma. Cmax increased with the dose, with a Tmax around 2 h for QGC001 and around 3 h for EC33. The median plasma half-life of QGC001 was around 2 h for QGC001 and consistent throughout doses. Less than 2% of the administered dose was recovered in urine as QGC001 or as its metabolite EC33, suggesting a minor urinary elimination pathway. In normotensive subjects, QGC001 had no effect on systolic blood pressure (SBP), on diastolic blood pressure (DBP) and on heart rate (HR). QGC001 had no effect on the systemic renin-angiotensin-aldosterone parameters and plasma copeptin concentrations, known as a biomarker of vasopressin release.

Study N°QGC001/1QG2:

A 2-part Phase I, single centre, randomised, double blind, placebo controlled study was conducted in healthy volunteers between 09 Dec 2012 and 15 March 2012 in France. The first part was to evaluate safety, tolerability, PK and PD when given as SAD (1000 mg, 1500 mg and 2000 mg, N = 24 male healthy volunteers) orally. This study also included an assessment of food effect (1000 mg SAD orally, N = 8 male healthy volunteers) in a cross over design. The second part was conducted to evaluate safety, tolerability, PK and PD when given in multiple ascending dose (MAD; 500 mg twice daily [BID], 750 mg BID and 1000 mg BID, N = 36 male healthy volunteers). Food intake had no influence on the safety and the tolerability of QGC001 after single oral administration at the dose of 1000 mg in healthy male normotensive subjects. Blood pressure and HR of healthy volunteers did not change following the administration of QGC001 1000 mg in fed as in fasted conditions. Food intake had no significant influence on the Tmax and the half-life of QGC001 which remained around 2.5 h and 2 h in fed as in fasted conditions.

A moderate decrease in QGC001 plasma peak (30%) and exposure (15%) was observed when the drug was taken with food, while food intake had no influence on the PK parameters of EC33.

The administration of a multiple oral dose of QGC001 (500 mg BID, 750 mg BID and 1000 mg BID) in healthy normotensive male subjects for 7 consecutive days was safe and well-tolerated up to 750 mg BID. All QGC001 doses were rapidly absorbed (Tmax between 3 h to 5 h) and converted to EC33 within 3.5 to 5 h. Peak plasma concentrations and exposure of QGC001 and EC33 increased with the dose. There was a mild accumulation of QGC001 and EC33 and increase in half-lives with time. 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. As shown in normotensive animals, QGC001 did not significantly change plasma renin concentrations, plasma aldosterone and plasma cortisol as well as plasma copeptin levels in any treatment group. QGC001 did not affect HR, SBP and DBP in any treatment group.

No treatment-emergent adverse event (TEAE) was reported in the QGC001 500 mg BID group. A total of 24 TEAEs were reported by 15 subjects. There was no severe TEAEs. Overall, 17 TEAEs were mild in intensity and 7 TEAEs were moderate in intensity. Among the 24 TEAEs reported, 19 TEAEs were considered possibly related to treatment. The most frequent TEAEs considered possibly related to treatment were pruritic rash and diarrhoea. At the 1000 mg BID dose, 4 subjects had liquid stools and 4 cases of probable skin allergy were observed (spreading erythema, pruritic or not, with an onset after the end of the treatment period, pointing to delayed reaction mechanisms). All cases remained of mild intensity and were regressed spontaneously. Following the observation of these allergic reactions, the French competent authority has asked Quantum Genomics to proactively collect and analyse similar adverse events (AEs) as adverse events of special interest (AESIs).

Study N°QGC001/1QG3:

A Phase I single-centre, open-label, non-randomised, 5-period fixed sequence study was conducted in healthy volunteers between 15 Mar 2019 and 15 May 2019 in the United Kingdom. This study aimed to investigate the PK and safety of Firibastat (QGC001) modified release (MR) prototype tablet formulations and compare them to a reference Firibastat (QGC001) immediate release (IR) capsule formulation in 12 healthy male subjects.

There were no serious adverse events (SAEs) or deaths reported during this study. No stopping criteria were met during this study. All subjects tolerated firibastat 500 mg QD and 1000 mg QD, and there were no clinically significant safety concerns related to the IMP. Last patient last visit occurred on 15 May 2019. Full efficacy results are not yet available and further details will be provided at the finalisation of the clinical study report.

Completed Phase II studies

Study N°QGC001/2QG1:

A single Phase II safety and efficacy study has been completed between 23 Feb 2015 and 13 Apr 2016 in France. This was a Phase IIa multicentre, randomised, double-blind, 2-period, placebo controlled, forced-titration proof of concept 2-period of 4 weeks crossover study to evaluate efficacy, safety, tolerability, PK and PD of QGC001 in patients with grade I or II essential HTN. In this study, QGC001 was given orally at the dose of 250 mg BID for 1 week followed by 500 mg BID during 3 weeks.

QGC001 decreased ambulatory daytime SBP by 2 to 3 mmHg compared to placebo, but the difference was not significant. QGC001 did not influence HR, or plasma and urine hormones including renin, aldosterone, copeptin, apelin and adrenocorticotrophic hormone. The non-significant BP lowering effect of QGC001 may be of multifactorial origin including the small sample size of the study, the short duration of exposure to QGC001, the short half-life of QGC001 in its present formulation, the low penetration of QGC001 at the level of blood brain barrier especially if converted to its metabolite EC33 in the systemic circulation, and the large between-patient variability in BP levels.

Overall QGC001 was well tolerated in the study. Three SAEs were reported in this study: a vestibular disorder, considered possibly related to QGC001; a probable allergic reaction (an AESI) to QGC001 presenting as a macular rash and periorbital oedema, treated with an antihistamine which resolved within 4 days. The case of macular rash was the only TEAE occurring during treatment with QGC001 considered probably related to study treatment. Other than the case of vestibular disorder, TEAEs occurring during treatment with QGC001 and considered possibly related to study treatment were arthralgia, blood creatinine increased, chest pain, headache and hyper-triglyceridemia, each only reported in one patient. Laboratory results showed no anomaly in this study.

Study N°QGC001/2QG2 – QUID-HF:

A randomised, double-blind, multi-centre Phase IIa study to assess safety and efficacy of incremental doses of QGC001 versus placebo was conducted in patients with NYHA class II/III chronic HF with left ventricular systolic dysfunction to investigate the safety (BP changes until Day 28) and efficacy (rate of decrease in NT-proBNP of more than 30% from baseline to Day 28) of QGC001 up-titrated orally from 50 mg BID to a maximum of 500 mg BID. The study was conducted in 23 sites in Europe (France, Germany, Netherlands, Norway, Poland, United Kingdom, Hungary, and Czech Republic). A total of 23 patients who satisfied the inclusion and exclusion criteria at the end of screening were randomised to 1 of the 2 treatment groups (ie QGC001 or placebo in a 2:1 ratio). 14 patients received QGC001 and 9 patients received matching placebo treatment. Subjects were up-titrated from 50 mg BID to 500 mg BID or matching placebo for a treatment period of 1 month.

Three SAEs (ventricular tachycardia, cardiac failure and pneumonia) occurred in the same subject and were assessed as “unrelated”. The study did not demonstrate any difference between QGC001 and placebo in the primary endpoint (relative decrease of more than 30% in NT-proBNP) between QGC001 and placebo in a small cohort of 23 patients (1 third of the planned enrolment). Nevertheless, in this cohort of patients in class II/III congestive HF with reduced left ventricular ejection fraction (29%), firibastat administered on top of standard of care treatment (including angiotensin I converting enzyme/angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and diuretics) was as safe as placebo and particularly did not decrease BP as compared to placebo.

Study N°QGC001/2QG3 – NEW-HOPE:

An open-label, dose-titrating, multi-centre Phase II study was conducted in the United States between 13 Oct 2017 and 17 Oct 2018 to assess the safety and the effects on BP of BID oral administration of QGC001 (250 mg BID, 500 mg BID, or 500 mg BID with hydrochlorothiazide 25 mg QD) over 8 weeks in 256 hypertensive overweight/obese American patients of multiple races/ethnicities.

Overall, firibastat was well-tolerated. 64 TEAEs (considered as related to treatment) were reported by 36 subjects. The most common side-effects were skin reactions and headaches, with occurrence frequencies of 4% and 3% respectively. No angioedema was reported. Among the 64 TEAEs reported, 10 were reported as AESIs. All the subjects recovered. There were 4 SAEs assessed as unrelated (1 case of squamous cell carcinoma, 1 case of umbilical hernia, 1 case of myocardial infarction, and 1 case of lung nodule) and 2 SAEs (erythema multiforme) considered as related to the investigational product and reported also as AESIs. Eight other non-serious AESI occurred in study and were considered as related to the study drug (3 cases of erythematous rash, 2 cases of eczema and 3 cases of drug hypersensitivity). All the patients recovered.

This study demonstrated improvement in the primary efficacy endpoint (the change in office SBP from baseline to Week 8 [Day 56 visit]), supported by statistically significant differences in all secondary efficacy endpoints and by pre-specified subgroup (by race and by body mass index [BMI]) analyses in a diverse population of overweight and obese patients with primary HTN including at least 50% black and Hispanic subjects:

- There was a statistically significant decrease in mean office SBP from 154.0 mmHg (±7.27 mmHg) at baseline to 144.4 mmHg (±14.14 mmHg) at Day 56 last observation carried forward, with a change from baseline of -9.5 mmHg (±14.31 mmHg). The predicted mean value (with 95% CI) of change from baseline to Day 56 last observation carried forward at the median baseline level was 9.0 (10.7, 7.3) mmHg, with a p value of <0.0001
- There was a statistically significant decrease in mean office DBP from 91.5 mmHg (±8.47 mmHg) at baseline to 87.3 mmHg (±10.59 mmHg) at Day 56 last observation carried forward, with a change from baseline of -4.2 mmHg (±9.39 mmHg). The predicted mean value (with 95% CI) of change from baseline to Day 56 last observation carried forward at the median baseline level was 4.4 (5.5, 3.3) mmHg, with a p value of <0.0001

6 Rationale

6.1 Study Rationale

Quantum Genomics is developing QGC001, a first in class BAPAI for the treatment of HTN. QGC001 has been evaluated in Phase I and Phase II studies in HTN and HF as IR oral suspension and capsule formulations. Due to the short T1/2 in humans, it is thought that the IR formulation requires BID dosing. Recent output from the NEW-HOPE patient efficacy study has provided steady state PK exposure targets for Cmax and AUC(0-4); however, these are from subjects receiving a combination of 250 mg IR capsule BID and 500 mg IR capsule BID. An MR formulation has recently been developed and tested in the clinic (Quotient Sciences study number QSC118052) to try and achieve a QD formulation. NPS modelling of the data from study QSC118052, in which the IR capsule formulation was also dosed, indicated that predictions for exposure from the 500 mg IR BID capsule are lower than measured at steady state (NEW-HOPE data). The NPS also suggests that the optimised MR formulation will be required to be dosed BID at 1000 mg to give equivalent steady state exposure to that seen with the NEW-HOPE data. The current study will explore the PK from multiple dosing of the IR capsule, the optimised MR formulation from QSC118052 and a new IR tablet formulation.

6.2 Dose Rationale

Firibastat (QGC001) has been shown to be safe and well tolerated following oral administration of single doses up to 2000 mg, and multiple doses up to 750 mg BID to healthy subjects for 7 consecutive days. Doses of 250 mg BID for 1 week followed by 500 mg BID for 3 weeks were also well tolerated in the Phase II clinical trial in HTN. Doses up to 500 mg BID up to 12 weeks were all well tolerated in the NEW-HOPE study (Phase II clinical trial in HTN) and QUID-HF (Phase II clinical trial in HF).

The maximum dose that will be administered will be predicted to not exceed individual exposure to that observed with the 1500 mg Firibastat (QGC001) mean Cmax 153.0 ng/mL and mean AUC(0-last) 741.2 ng.h/mL, and for the 2000 mg Firibastat IR formulation in the single ascending dose study for EC33 mean Cmax 208 ng/mL and mean AUC(0-last) 1352 ng.h/mL. The MR dose will be predicted not to exceed the IR single dose exposure limits, even if dose dumping occurs with the MR formulations. The IR tablet has previously been dosed as a capsule to doses up to 2000 mg and was safe and well tolerated.

6.3 Population Rationale

As this is a Phase I study assessing the PK and safety of QGC001, the most relevant population is healthy volunteers. Subjects who are non-smokers without a history of alcohol or drug abuse or regular co-medication (except hormone replacement therapy [HRT]) are proposed, to avoid interaction on drug metabolism and to avoid non-compliance.

Not all fertility and teratology pre-clinical studies with QGC001 (required per ICH R5(R2)) have been completed; therefore, females of childbearing potential are not permitted to participate in the study. Only females of non-childbearing potential will be allowed to participate in the study.

Based on the above considerations and target population, healthy female subjects of non-childbearing potential and healthy male subjects, aged 18 to 55 years are considered suitable for this study.

6.4 Risks and Benefits

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

Following this observation, the French competent authority, the ANSM, requested that all allergic reactions should be collected and analysed as AESIs by Quantum Genomics. Additionally, the sponsor has put in place in the clinical protocols a procedure to collect any suspected diabetes insipidus and report as an AESI with immediate notification.

Cumulatively, 12 SAEs, collected into 9 different reports, occurred during the clinical trials program:

- Three SAEs were reported from study QGC001/2QG1 among which 2 SAEs were experienced by the same subject, and during treatment with QGC001. There was 1 case of a vestibular disorder, considered possibly related to study medication, which led to treatment discontinuation and hospitalisation; the patient recovered within 48 h. The 2 other SAEs were experienced by the same subject and were a macular rash and a periorbital oedema, thought to be a drug-induced toxidermia and probably related to study medication. Treatment was discontinued and the patient was hospitalised and treated with an antihistamine. The patient recovered within 4 days. These 2 SAEs were also classified as AESIs. Two other AESIs of pruritic rash occurred in another patient during this study, but both events occurred whilst the patient was being treated with placebo.
- Three SAEs were experienced by the same subject from QUID-HF study (QGC001/2QG2): ventricular tachycardia, cardiac failure and pneumonia. These events were assessed as “unrelated” and were not unblended.
- Six SAEs occurred during NEW-HOPE (QGC001/2QG3) study and were all experienced by different patients. There were 4 cases assessed as “unrelated” (1 case of squamous cell carcinoma, 1 case of umbilical hernia, 1 case of myocardial infarction and 1 case of lung nodule) and 2 cases of erythema multiforme which were also reported as AESI. These cases were assessed as “related” to study medication to study medication. All the patients recovered.

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

- Four AESIs were collected from study QGC001/2QG1, among which 2 non-serious AESIs of pruritic rash occurred during the placebo treatment phase and 2 serious AESIs of rash macular and periorbital oedema occurred in the same patient during the study drug treatment phase and were also considered as suspected unexpected serious adverse reactions (SUSARs).
- Ten AESIs were collected from study QGC001/2QG3, among which 2 reports of erythema multiform were serious and considered as SUSARs. The 8 other non-serious AESI reports included 3 reports of rash, 2 reports of eczema and 3 reports of drug hypersensitivity, and were all experienced by different patients.

Data obtained from a non-clinical 13-week toxicity study conducted in dogs suggest that high dose of QGC001 (100 mg/kg or more) could affect haematological parameters, such as platelet counts. However, available clinical safety data from clinical trials (Phase I study N°QGC001/1QG2: exposure to QGC001 in human dosed at 500 mg BID for 7 consecutive days; Phase II study N°QGC001/2QG1: exposure to QGC001 in human dosed at 250 mg BID for 1 week then 500 mg BID for 3 weeks) did not put in evidence of any effect on haematological parameters in human. Based on PK analysis of the Phase I clinical study QGC001/1QG2, QGC001 exposure in human dosed for 7 consecutive days with QGC001 500 mg BID is below 200 ng.h/mL, which is more than 100 times lower than the exposure found in the 13-week non-clinical study in dogs, which were dosed at 100 mg/kg.

The data obtained so far imply a good safety profile of QGC001 for the treatment of HTN and HF. Allergic reactions have been identified as a potential risk for QGC001 but due to the low number of subjects treated so far in the development program, no frequency calculation has been established for allergic reactions. Yet, the sponsor has put in place relevant measures to closely monitor, collect and assess all allergic reactions occurring in the development program.

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

Collecting a blood sample from a vein may cause pain, swelling, bruising, light-headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

There is no benefit to the subjects from taking part in this study. The development of a product to treat HTN will be of benefit to patients with this condition.

The overall risk benefit balance is therefore considered to be acceptable.

7 Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the pharmacokinetic (PK) profiles of QGC001, EC33 and QGC515 following multiple dose administration of QGC001 immediate release (IR) formulations and a modified release (MR) formulation in healthy subjects	• Evaluate the PK profiles of QGC001 IR and MR formulations by assessing the following primary PK parameters for QGC001, EC33 and QGC515: Tmax, Cmax, AUC, T1/2 and Ctau
Secondary • To provide additional safety and tolerability information for multiple doses of QGC001 in healthy subjects	• To provide additional safety and tolerability information for multiple doses of QGC001 by assessing: AEs, vital signs, electrocardiograms (ECGs), physical examinations and laboratory safety tests

8 Study Design

8.1 Study Plan

This is a single centre, multiple dose, non-randomised, open-label study in healthy male subjects and healthy female subjects of non-childbearing potential designed to investigate the PK and safety of QGC001 IR and MR tablet formulations compared to an IR capsule. It is planned to enrol 3 cohorts of 10 subjects. Each cohort will receive one of the regimens in Table 2.

Table 2 Investigational Medicinal Product Administration

Cohort	Regimen	IMP Dose	Route of Administration
1	A	500 mg (2 × 250 mg) QGC001 IR capsule BID on Days 1 to 6 and QD dosing on Day 7	Oral Administration, Fasted
2	B	1000 mg (2 × 500 mg) QGC001 MR tablet QD for 7 days	Oral Administration, Fasted
3	C	1000 mg (2 × 500 mg) QGC001 IR tablet QD for 7 days	Oral Administration, Fasted

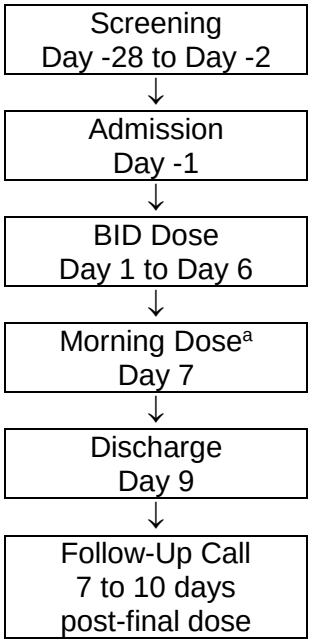
BID: twice daily, IR: immediate release, MR: modified release, QD: once daily
The order in which regimens are dosed may be subject to change due to logistical reasons. The regimens may be dosed in parallel.

Each cohort will follow the same study design for BID (Figure 1) or QD dosing (Figure 2). Subjects will be screened to participate in the study up to 28 days prior to dosing and will be admitted to the clinical unit in the evening of the day before dosing (Day -1). Subjects will remain on site until 48 h post final-dose (Day 9).

In Regimen A, subjects will receive a dose of 500 mg QGC001 as 2 × 250 mg IR capsules BID on Days 1 to 6 and a single dose of 500 mg QGC001 as 2 × 250 mg IR capsules in the morning of Day 7. For BID dosing in Regimen A, subjects will receive the first daily dose following an overnight fast (minimum 10 h) and the second daily dose at approximately 12 h post-morning dose, which will be 2 h after the evening meal. For Regimens B and C, subjects will receive a single dose of 1000 mg as 2 × 500 mg MR or IR tablets QD in the morning on Days 1 to 7 following an overnight fast (minimum 10 h). A follow-up phone call will take place 7 to 10 days post-final dose to ensure the ongoing wellbeing of the subjects.

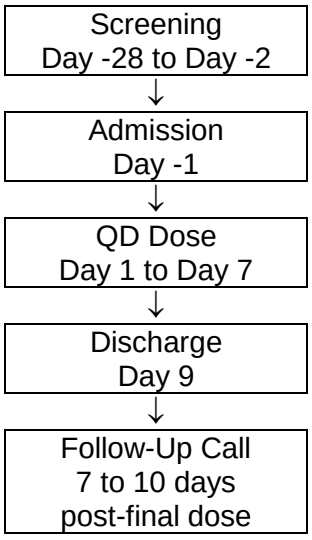
The cohorts may be dosed in parallel. It is expected that the study will be executed in 3 cohorts, each requiring 1 study period.

Figure 1 Study Sequence: Regimen A



[a] Subjects will receive a single dose in the morning of Day 7

Figure 2 Study Sequence: Regimens B and C



8.2 Criteria for In-Study Decisions

Not applicable for this study.

8.3 Subject Withdrawal

If a subject wishes to leave the study at any time, they will be permitted to do so. Every reasonable effort will be made by Quotient Sciences to complete a final assessment/discharge procedures. Quotient Sciences will advise the sponsor of the withdrawal of any subject from the study.

Early withdrawal is defined as the date of the decision to withdraw the subject from the study. Subject completion is defined as the date of the last procedure conducted or last contact (ie phone call) for that subject.

If a subject requests to leave the clinical unit earlier than the planned discharge time eg due to unforeseen personal circumstances, but aims to return to the clinical unit to complete the study, this will be documented as a subject self-discharge and a protocol deviation. The subject must complete the planned assessments/discharge procedures before discharge from the clinical unit and will return for the next study assessments, as planned.

Subjects will be withdrawn from the study drug(s) for the following reasons:

- Experiencing a serious or severe AE including but not limited to:
    - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)
    - alanine aminotransferase (ALT) concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Pregnancy
- Termination of the study
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness that would adversely affect subject safety or data integrity or requirement for prohibited medication
- At the discretion of the investigator

For the purpose of withdrawal criteria, baseline will be considered as the pre-dose Day 1 measurement.

For a subject who withdraws because of an IMP-related AE, every effort will be made to ensure the subject completes follow-up procedures.

Early termination of the study will be distinguished from withdrawal of consent by the subject to participate in any further activities.

8.4 Subject Replacement

Up to 2 replacement subjects per cohort may be enrolled into the study. The maximum number of subjects that may be dosed is 36 (12 per cohort).

Any subject withdrawn due to an IMP-related AE will not be replaced.

Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and the sponsor to ensure sufficient evaluable subjects.

An evaluable subject is defined as a subject who has received IMP for 7 days and who has safety and PK assessments up to 48 h post-final dose.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (ie a serious AE considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (ie severe non-serious AE considered as, at least possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system organ class.

Relatedness will be determined by the investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

8.6 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow-up measures taken for safety reasons if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the PI or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe adverse event(s), as defined in Section 8.5, if considered to be related to the IMP, as defined in Section 14.2.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section 6.4 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

8.7 Lost to Follow-up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and cannot be contacted by the clinical unit.

If a subject fails to return to the clinical unit for a required study visit:

- The clinical unit must attempt to contact the subject and reschedule the missed visit as soon as possible
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (eg 3 telephone calls on 3 separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented in the subject's source.
- If the subject cannot be contacted, they will be considered lost to follow-up.

8.8 Treatment Allocation

This is an open-label, non-randomised study, therefore a randomisation schedule will not be produced. A treatment allocation will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The treatment allocation will be retained in the Investigator Site File (ISF).

8.8.1 Subject Numbers

Subject numbers will be allocated on the morning of dosing according to the code 001 to 030 using the lowest number available. Replacement subjects will be allocated subject numbers 901 to 930, where the last 2 digits are the same as those of the original subject (eg if Subject 005 withdraws, the replacement will have Subject Number 905 and will receive the same regimen as Subject 005).

Subject numbering by cohort is provided in Table 3.

Table 3 Subject Numbers by Cohort

Cohort	Subject Numbers
1	001 to 010
2	011 to 020
3	021 to 030

8.8.2 Blinding

This is an open-label, non-randomised study and therefore blinding is not required.

9 Selection of Subjects

Quotient Sciences must have a full medical history from each subject's general practitioner (GP) within the last 12 months, prior to enrolment for the study.

Subjects will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 90 days of the dosing date.

9.1 Informed Consent

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an informed consent form (ICF). Until written consent has been obtained from the subject no study specific procedure or investigation will be performed. If an amendment is made to the participant information sheet (PIS), participants will be re-consented to the most current version of the ICF(s) where appropriate.

9.2 Inclusion Criteria

1. Healthy males or healthy females of non-childbearing potential
2. Age 18 to 55 years of age at the time of signing informed consent
3. Body mass index of 18.0 to 32.0 kg/m^2 as measured at screening
4. Must be willing and able to communicate and participate in the whole study
5. Must provide written informed consent
6. Must agree to adhere to the contraception requirements defined in Section 9.4

Inclusion criterion 6 from the list above will be re-assessed at admission/pre-dose.

9.3 Exclusion Criteria

1. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1
2. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
3. Subjects who have previously been enrolled in this study (subjects who participated in study QSC118052 are allowed)
4. History of any drug or alcohol abuse in the past 2 years
5. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type)
6. A confirmed positive alcohol breath test at screening or admission
7. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
8. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
9. Females of childbearing potential including those who are pregnant or lactating (all female subjects must have a negative urine pregnancy test). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle-stimulating hormone [FSH] concentration ≥40 IU/L)

10. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
11. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator (laboratory parameters are listed in Appendix 1)
12. Subjects with BP <90/40 mmHg at screening and pre-dose
13. Subjects with Gilbert's Syndrome
14. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)
15. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results
16. History of clinically significant cardiovascular, renal, hepatic, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
17. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients
18. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
19. Donation or loss of greater than 400 mL of blood within the previous 3 months
20. Subjects who are taking, or have taken, any prescribed or over-the-counter drugs or herbal remedies (other than 4 g of paracetamol per day and HRT) in the 14 days before IMP administration (see Section 11.4). Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as determined by the PI
21. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 6, 7, 12, 14, 16, 20 and 21 from the list above will be re-assessed at admission/pre-dose.

Healthy subjects who do not meet the inclusion/exclusion criteria for a study will not be enrolled.

9.4 Contraception

Male Subjects

Male subjects who are sexually active with a partner of child bearing potential must use, with their partner, a condom plus an approved method of effective contraception from the time of informed consent until 1 day after last IMP administration.

The following methods are acceptable:

- Partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Partner's use of progestogen-only hormonal contraception:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system
- Partner's use of intrauterine device
- Surgical sterilisation (for example, vasectomy or partner's bilateral tubal occlusion)
- Partner's use of female cap or diaphragm or sponge with spermicide (double barrier)

Alternatively, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

These contraception requirements are aligned with guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [1].

Female Subjects of Non-Child Bearing Potential

Female subjects who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential (WOCBP) unless post-menopausal or permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a FSH result of ≥40 IU/L.

9.4.1 Exposure to Sexual Partners During the Study

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to sexual partners (both male and female), including pregnant partners of male subjects. Therefore, a condom should be used by all male subjects throughout the study and for 1 day after last IMP administration.

9.4.2 Sperm Donation

Male subjects should not donate sperm for the duration of the study and for 1 day after last IMP administration.

9.4.3 Egg Donation

Female subjects should not participate in egg donation from dosing, for the duration of the study and for at least 1 day after last follow-up visit (to cover anticipated washout based on half-life).

9.5 Pregnancy

Subjects will be instructed that if they/their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject/subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery. Any subject reporting a pregnancy during the study will be discontinued from the study treatment and every reasonable effort will be made by Quotient Sciences to follow up the pregnancy until delivery.

A pregnancy notification form and follow-up will be completed.

9.6 Additional Study Restrictions

The following additional restrictions will be in place for the duration of the study:

1. Subjects must abstain from alcohol during the 24 h prior to screening and the 24 h prior to admission until discharge from the clinical unit

2. Subjects must not drink liquids or eat food containing grapefruit, cranberry, caffeine or other xanthines from 24 h prior to admission until discharge from the clinical unit
3. Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to admission until discharge from the clinical unit
4. Subjects must not take part in any unaccustomed strenuous exercise from the 72 h before the screening visit and then from 72 h prior to admission until discharge from the clinical unit

The additional restrictions above are not exclusion criteria; if non-compliance occurs, a protocol deviation will be completed.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments in Appendix 2, and in accordance with Quotient Sciences standard operating procedures (SOPs) unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose, all subjects will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the schedule of assessments in Appendix 2.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the investigator.

Subjects previously screened generically may participate in this study provided they meet the subject selection criteria. Procedures required by this protocol will only be done if they were not performed during generic screening. All screening data must be obtained within 28 days prior to administration of study medication, as stipulated above.

Screening safety procedures such as safety bloods, ECGs, vital signs, carbon monoxide breath tests, alcohol breath tests and urinalysis can be repeated as clinically indicated under the discretion of the investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the trial.

10.1.1 Subject Re-Screening

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (ie has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

10.2 Admission and Pre-dose Procedures

The identity of the subjects will be confirmed at admission and pre-dose.

In addition, the ongoing eligibility of subjects will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

Admission/pre-dose safety procedures such as safety bloods, ECGs, vital signs, urinalysis and drugs of abuse tests can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the clinical trial.

Reserve subjects for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days.

The subjects will be admitted to the clinical unit on the evening before (Day -1).

The admission and pre-dose procedures are presented in Appendix 2.

10.3 Study Day Procedures

10.3.1 Blood Volume

The total blood volume for each subject will not exceed 550 mL in a 4 week period.

The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances the following will apply to post-dose time points:

PK samples should take priority over other procedures scheduled at the same time point.

Electrocardiograms should be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, eg physical examinations, will be performed within the required time windows.

As guidance, the preferred order of assessments is:

ECGs → **Vitals** → **PK blood sampling** → **Other assessments eg physical examinations**

All safety assessments will be timed and performed relative to the start of dosing.

10.3.3 Discharge from the Clinical Unit

A subject will be allowed to leave the premises without additional investigator or delegate review, following completion of study-specific procedures at 48 h post-final dose, providing that:

- no AEs have been reported during the study visit
- the subject responds in the affirmative when asked if they are feeling well

If any of these conditions are not met, then the subject will only be allowed to leave the clinical unit with the authorisation of the investigator or appropriately qualified delegate.

There will be no continued provision of the study intervention or treatment for subjects as this study involves healthy volunteers only.

10.3.4 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines [3], each subject will receive a card stating the telephone number of the investigator and the 24/7 contact details of the Quotient on-call physician.

10.3.5 Follow-up

A follow-up phone call will take place 7 to 10 days after the final dose to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs which can present a cause for concern, they will be required to attend the clinical unit for a further follow-up assessment (as an unscheduled visit). Completion of the last follow-up call or unscheduled follow-up visit will be considered the end of the study.

11 Dosing of Subjects

11.1 Food and Fluid Intake

The calorie/fat content of meals is not required to be controlled during this study. Meals will be provided at nominal times.

Subjects will be allowed water up to 1 h before each scheduled dosing time and will be allowed water ad libitum from 1 h after each dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing (all doses) and until 1 h before and then from 1 h after the evening dose (Regimen A Days 1 to 6 only).

If, for technical reasons, dosing is delayed for more than 2 h beyond the expected dosing time, subjects will receive 200 mL of Lucozade Sport at the originally scheduled dosing time, or earlier if possible.

Regimen A

On Days 1 and 7, subjects will be provided with a light snack and then fast from all food and drink (except water) for a minimum of 10 h on the day prior to dosing until approximately 4 h post-morning dose, at which time lunch will be provided. On Days 1 and 7, an evening meal will be provided at approximately 10 h post-morning dose and an evening snack at approximately 14 h post-morning dose. On subsequent days, meals will be provided at appropriate times.

Regimens B and C

On Days 1 and 7, subjects will be provided with a light snack and then fast from all food and drink (except water) for a minimum of 10 h on the day prior to dosing until approximately 4 h post-dose, at which time lunch will be provided. On Days 1 and 7, an evening meal will be provided at approximately 10 h post-dose and an evening snack at approximately 14 h post-dose. On subsequent days, meals will be provided at appropriate times.

For all regimens, on intervening days when PK samples are not being collected, meals will be provided at appropriate times, ie a light breakfast at 2 h post-morning dose, lunch at approximately 4 h post-morning dose, dinner at approximately 10 h post-morning dose and an evening snack at approximately 14 h post-morning dose.

11.2 Administration of Test Preparations

Specific details of IMP(s) and doses to be administered are provided in Section 5.2 and Section 8.1, respectively.

For Regimen A, subjects will be dosed on the mornings and evenings (approximately 12 h apart) of Days 1 to 6 and on the morning of Day 7, ie subjects will receive single dose administrations of IMP on 13 separate occasions.

For Regimens B and C, subjects will be dosed on the mornings of Days 1 to 7, ie subjects will receive single dose administrations of IMP on 7 separate occasions.

The exact time of dosing will be decided based on logistics and will be documented in the source. The order in which regimens are dosed may be subject to change due to logistical reasons. Regimens may be dosed in parallel.

The acceptable deviation for dose administrations from the nominal time point is:

- Evening dose will be administered within ± 30 min of the nominal time point
- On Days 2 to 7*:* morning doses will be administered within ± 30 min of the Day 1 time

240 mL of water will be given immediately following oral administration. Additional water may be given with the IMP if required.

11.3 Dosing Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration.

Mouth and hand checks will be conducted after dosing to ensure the tablet/capsule has been swallowed.

The date and time that each subject is dosed will be recorded in the subject's source data. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject can continue in the study.

11.4 Prior and Concomitant Medications

No prescribed, over-the-counter medication or herbal remedies will be permitted from 14 days before IMP administration until the follow-up call except up to 4 g of paracetamol per day, HRT and those deemed necessary by the investigator to treat AEs (see also Section 9.3). Any medications used will be recorded in the source.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

12 Assessment of Efficacy

Not applicable for this Phase I study.

13 Assessment of Pharmacokinetics and Pharmacodynamics

13.1 Assessment of Pharmacokinetics

Venous blood samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study. Samples will be processed to isolate plasma and PK analysis will be carried out on plasma samples.

Plasma samples are sent for laboratory testing in linked anonymised form (subject number only). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor, however not by the laboratory staff or sponsor.

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture according to the time schedule presented in Appendix 2.

The acceptable deviations from the nominal blood sampling times are as follows:

- Day 1 only: The pre-dose samples will be taken ≤1 h before dosing
- On Days 2 to 7: Where the 12 h (Regimen A) or 24 h time point (Regimens B and C) coincides with the pre-dose sample, samples will be taken ≤10 min of the nominal time point
- 0 to 1 h post-dose samples will be taken within ± 2 min of the nominal post-dose sampling time
- >1 to 12 h post-dose samples will be taken within ± 10 min of the nominal post-dose sampling time
- >12 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time if subjects are resident in the clinical unit

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the Clinical Sample Processing Manual.

Samples will be shipped to Oncodesign for the analysis of QGC001, EC33 and QGC515.

13.2 Assessment of Pharmacodynamics

Not applicable for this Phase I study.

14 Assessment of Safety

14.1 Definition and Classification of Adverse Events

An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An adverse drug reaction is any AE where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related).

Adverse events will be monitored from the time the subject signs the ICF until after the final follow-up call. The severity of AEs should be assessed as follows:

Mild An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities

Moderate An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed

Severe An AE that prevents normal everyday activities; treatment or other intervention usually needed

14.2 Assessment of Causality

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the IMP. The temporal relationship of the event to IMP administration should be considered in the causality assessment (ie if the event starts soon after IMP administration and resolves when the IMP is stopped).

Causality should be assessed using the following categories:

Unrelated: Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP

Possibly related: Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals

Related: Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, eg natural history of the underlying disease, concomitant therapy) will be determined by how well the experience can be understood in terms of one or more of the following:

- known pharmacology of the IMP
- reactions of a similar nature have been previously observed with the IMP or this class of drug
- the experience being related by time to IMP administration, terminating with IMP withdrawal or recurring on re-challenge
- alternative cause

14.3 Recording Adverse Events

Adverse events will be recorded from the time of providing written informed consent until discharge from the study at the follow-up call/unscheduled follow-up visit. During each study visit the subject will be questioned directly regarding the occurrence of any adverse medical event according to the schedule in the source. All AEs, whether ascribed to study procedures or not, will be documented immediately in the source. This will include the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the investigator.

Any subject who withdraws from the study due to an AE will be followed up until the outcome is determined and written reports provided by the investigator.

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

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

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- an important medical event as recognised by the PI

Serious adverse events must be immediately reported to the sponsor.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions are AEs that are believed to be related to an IMP and are both unexpected (ie the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the MHRA, European Medicines Agency (EMA) and EC (see Section 16.4.2 for details on reporting SUSARs).

14.5 Laboratory Measurements

Venous blood and urine samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study.

Blood and urine samples are sent for laboratory testing in linked anonymised form (subject number, the subjects' gender and date of birth for analytical reasons). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor, however not by the laboratory staff or sponsor.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. The research will not involve analysis or use of human DNA.

Blood and urine samples results will be reviewed by a physician and acted upon before the subject is dosed or receives their next dose, or is released from the study, as is appropriate. A list of the laboratory parameters measured is presented in Appendix 1.

14.5.1 Haematology and Clinical Chemistry

Laboratory tests will be performed by The Doctors Laboratory according to the time schedule presented in Appendix 2. Blood samples will be collected and processed as detailed in the Clinical Sample Processing Manual. Scheduled blood samples will be taken following an 8 h fast.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- The pre-dose blood sample will be taken ≤2 h before dosing
- Post-dose blood samples will be taken ± 1 h from the nominal blood sampling time

14.5.2 Urinalysis

Urinalysis will be performed on-site using a dipstick according to the time schedule presented in Appendix 2. Urine samples will be collected and processed as detailed in the Clinical Sample Processing Manual. If microscopy is required, a urine sample will be sent to The Doctors Laboratory.

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- Day 1 only: The pre-dose urine sample will be taken ≤3 h before dosing or the first void of the day
- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time

14.5.3 Pregnancy Test

Urine pregnancy tests will be performed as detailed in Appendix 2. The samples will be collected and processed as detailed in the Clinical Sample Processing Manual.

14.5.4 Follicle-Stimulating Hormone Test

Serum FSH tests will be performed as detailed in Appendix 2. The samples will be collected and processed as detailed in the Clinical Sample Processing Manual.

14.5.5 Drug Screen

A urine drug screen will be performed on-site using a dipstick method according to the time schedule presented in Appendix 2. The sample will be collected and processed as detailed in the Clinical Sample Processing Manual. Subjects will be screened for the drugs of abuse listed in Appendix 1.

14.5.6 Alcohol Breath Test

An alcohol breath test will be performed according to the time schedule presented in Appendix 2. A positive result will exclude the subject from dosing during that admission.

14.5.7 Carbon Monoxide Breath Test

A carbon monoxide breath test will be performed according to the time schedule presented in Appendix 2. A result of greater than 10 ppm will exclude the subject from the study.

14.5.8 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken eg the subject will not be entered into the study or the subject may be withdrawn from the study. The subject will be referred to their GP or other appropriate provider for further care. The same will apply if the results of the HBsAg, HCV Ab or HIV test are positive and in addition the investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the investigator believes the results may be of clinical significance.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator or sub-investigator.

14.6 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the subject has been in a supine position for a minimum of 5 min according to the time schedule presented in Appendix 2. Oral temperature will also be measured. The acceptable deviations from the nominal vital signs measurement time points are:

- Day 1 only: The pre-dose vital signs measurements will be taken ≤2 h before dosing

- On Days 2 to 7*:* the pre-dose vital sign measurements will be taken ≤1 h before dosing. All vital sign measurements taken at 24 h post-dose will be classed as pre-dose for the next dose where applicable
- Post-dose vital signs measurements will be taken ± 15 min from the nominal post-dose time points
- Discharge vital signs measurements will be taken ± 1 h from the nominal time point

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator or sub-investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

14.7 Electrocardiogram Measurements

Single 12-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min according to the time schedule presented in Appendix 2. The acceptable deviations from the nominal ECG measurement time points are:

- Day 1 only: The pre-dose ECG measurements will be taken ≤2 h before dosing
- On Days 2 to 7*:* the pre-dose ECG measurements will be taken ≤1 h before dosing. All ECGs measurements taken at 24 h post-dose will be classed as pre-dose for the next dose where applicable
- Post-dose ECG measurements will be taken ± 15 min from the nominal post-dose time point
- Discharge ECG measurements will be taken ± 1 h from the nominal time point

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator or sub-investigator.

Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

14.8 Body Weight and Height

The subject's body weight and height will be measured as detailed in Appendix 2.

14.9 Physical Examination

Subjects will undergo a physical examination as detailed in Appendix 2.

14.10 Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed, if it is believed that an important effect of the IMP(s) is occurring or may occur at a time when no measurements are scheduled, or if extra procedures are needed in the interests of safety.

Additional blood samples for safety assessments may be taken if required by the investigator or sub-investigator at any point.

15 Statistics and Data Analysis

15.1 Sample Size Justification

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 10 subjects per cohort is to be enrolled and a minimum of 8 evaluable subjects per cohort is considered sufficient.

15.2 Data Management

Data management will be performed by Quotient Sciences.

Study data will be managed using a validated electronic case report form (eCRF) database system and subjected to data consistency and validation checks. Data queries will be raised within the study eCRF database by data management staff and resolved with the assistance of clinical staff.

Adverse events and medications will be coded using the Medical Dictionary for Regulatory Activities (v23.0) and the World Health Organisation Drug Dictionary Global Drug Reference (2020), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and haematology data (and other safety laboratory data) will be collected by a central laboratory (The Doctors Laboratory) and stored electronically in their clinical pathology system. The data will be transferred electronically to Quotient Sciences and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the Data Management Plan (DMP) are met.

Further details are addressed in the DMP.

15.3 Pharmacokinetic Data Analysis

The plasma concentration data for QGC001, EC33 and QGC515 provided by Oncodesign will be analysed by Quotient Sciences on Day 1 and Day 7 using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA).

Pharmacokinetic analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters:

Day 1

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration (first dose only)
AUC(0-4)	Area under the curve from 0 time to 4 h post-dose
AUC(0-12)	Area under the curve from 0 time to 12 h post-dose
AUC(0-24)	Area under the curve from 0 time to 24 h post dose (Regimens B and C only)
AUC(0-tau)	Area under the curve over the dosing interval from time 0 to tau (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)

Parameter	Definition
C12	Concentration observed at 12 h post-dose
C24	Concentration observed at 24 h post-dose (Regimens B and C only)
MPR Cmax	Metabolite to parent ratio based on Cmax
MPR AUC(0-tau)	Metabolite to parent ratio based on AUC(0-tau) (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)

Day 7

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-4)	Area under the curve from 0 time to 4 h post dose
AUC(0-12)	Area under the curve from 0 time to 12 h post dose
AUC(0-24)	Area under the curve from 0 time to 24 h post dose (Regimens B and C only)
AUC(0-tau)	Area under the curve over the dosing interval from time 0 to tau (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)
AUC(0-24)p	Predicted area under the curve from 0 time to 24 h post dose following BID dosing, calculated as AUC(0-12) multiplied by 2 (Regimen A only)
Ctau	Concentration at the end of a dosing interval (12 h for Regimen A and 24 h for Regimens B and C)
C12	Concentration observed at 12 h post-dose
C24	Concentration observed at 24 h post-dose (Regimens B and C only)
Cavg	Average concentration at steady state (AUC(0-tau)/tau)
Fluctuation%	Peak to trough fluctuation (Cmax-Cmin)/Cavg × 100
T1/2	Apparent elimination half-life (last dose only)
Lambda-z	Slope of the apparent elimination phase
AR Cmax	Accumulation Ratio based on Cmax for Day 1 vs Day 7
AR AUC	Accumulation Ratio based on AUC(0-tau) for Day 1 vs Day 7
MPR Cmax	Metabolite to parent ratio based on Cmax
MPR AUC(0-tau)	Metabolite to parent ratio based on AUC(0-tau) (0 to 12 h for Regimen A and 0 to 24 h for Regimens B and C)
CL_{ss}/F	Apparent total body clearance at steady state calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
Vz_{ss}/F	Apparent volume of distribution at steady state based on the terminal phase calculated after a single extravascular administration where F (fraction of dose absorbed) is unknown

Further details of the PK data analysis will be included in the reporting and analysis plan (RAP).

15.4 Statistical Data Analysis

Statistical analysis and production of summary tables, figures and listings for this study will be performed by Quotient Sciences using the statistical package SAS (v9.4 or more recent version).

In general terms, categorical data (including treatment-emergent AEs) will be presented using counts and percentages, while continuous variables will be presented using the mean, median, standard deviation, minimum and maximum. Additional statistics will be provided for PK-related data including coefficient of variation (CV%), geometric mean, geometric CV% and geometric n (ie the number of subjects with an observation that were included in the natural logarithmic transformation).

Descriptive summaries for all safety data (AEs, vital signs, ECGs and safety laboratory assessments) by treatment will be provided (including changes from baseline as required).

Descriptive summaries for all PK data by treatment will be provided.

Formal statistical analysis will be performed on the log-transformed Cmax, AUC(0-4), AUC(0-12) and AUC(0-24) values for QGC001, EC33 and QGC515 on each of Days 1 and 7 where possible and appropriate. On Day 7, for comparisons versus the IR capsule, AUC(0-24) of Regimens B and C will be compared against AUC(0-24)p for Regimen A. The PK parameters will be analysed using a fixed effects model including treatment as a fixed effect. Ratios of geometric means and 90% confidence intervals (CIs) will be provided where possible for the following comparisons:

- MR tablet vs IR capsule
- MR tablet vs IR tablet
- IR tablet vs IR capsule

In addition, in order to assess dose accumulation, log-transformed AUC(0-tau) and Cmax for QGC001, EC33 and QGC515 will be subjected to a mixed effects model with treatment, day (Day 1 or 7) and treatment by day as fixed effects and subject as a random effect. The adjusted means obtained from the model, including differences for each comparison of interest and the associated 90% CIs, will be back-transformed on the log scale to obtain adjusted geometric means, adjusted geometric mean ratios (GMRs) and 90% CIs of the ratio. The GMRs and 90% CIs will be provided for each treatment, ie Day 7/Day 1. If the interaction term is not significant at the 10% level, an estimation of the overall accumulation (ie accumulation across formulations) will be provided.

Populations and analysis sets will be determined for safety and PK data after database lock using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

All populations and analysis sets will be defined after database lock when the relevant data are available.

Further details relating to the statistical analysis will be included in the RAP including the following:

- Criteria to be used to define each of the populations and analysis sets
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn subjects

All safety and PK data will be listed.

15.5 Interim Analysis

No formal interim analyses are planned for this study.

16 Safety Reporting to Ethics Committees and Regulatory Authorities

16.1 Events Requiring Expedited Reporting

SUSARs (Section 14.4.2) are subject to expedited reporting to the MHRA, EMA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the subject has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects, such as:
    - an SAE which could be associated with the study procedures and which could modify the conduct of the study
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
    - any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same sponsor

16.2 Adverse Events of Special Interest

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

16.2.1 Allergic Reactions

Drug reactions deemed to be allergic or have an allergic component that require consultation with another physician for further evaluation of hypersensitivity/allergy, as per the investigator's medical judgment, should be reported as an AESI with immediate notification (within 24 h).

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

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

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

Adverse events with cutaneous involvement that are obviously of allergic origin should be evaluated by a dermatologist as soon as possible and preferably within 7 days of the investigator's first knowledge. The full report of the dermatologist should include at least a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg scattered, grouped or linear], distribution, colour, consistency, presence of pruritus or pain, and other clinical signs), and, if a skin biopsy (including histopathology and immunofluorescence) is performed (if deemed necessary as per the dermatologist's or investigator's medical judgment), the results of this investigation with, if applicable, a specific diagnosis for the biopsy. The full report should be sent by the dermatologist to the investigator. Skin biopsy samples should be sent to the referent for central reading.

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

16.2.2 Diabetes Insipidus

One consequence of the inhibition of APA is the decrease of vasopressin. Although not observed in any animal or human subject during the study of firibastat, the suppression of vasopressin holds a theoretical risk for the development of central diabetes insipidus (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 (within 24 h).

16.3 Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

16.4 Reporting

16.4.1 Reporting Serious Adverse Events

The investigator is required to notify the study sponsor and pharmacovigilance provider within 24 h of becoming aware of the occurrence of an SAE or serious adverse reaction. A copy of the written report of the event should promptly be sent to the study sponsor for information purposes, in accordance with International Council for Harmonisation guidelines for GCP.

16.4.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

16.4.3 Expedited Reporting of Events

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

<u>Fatal or life-threatening SUSARs</u>

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

16.4.4 Reporting of Urgent Safety Issues

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

16.5 Serious Breaches

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

17 Protocol Amendments and Deviations

17.1 Amendments

After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

If the PIS and ICF are updated as a result of the substantial amendment, the new approved versions will be used to re-consent currently enrolled subjects and must be provided to additional/replacement subjects prior to their entry into the study.

17.2 Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8.3 have been met.

18 Regulatory

18.1 Compliance

This study will be conducted in accordance with the protocol and with the following legislation:

- International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 [4]
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [5]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [6]
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [7]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [8]

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [9].

18.2 Ethical Approval

Prior to the initiation of the study, the protocol and associated documentation must be given a favourable opinion by an EC. A copy of this written approval and any correspondence with the EC will be provided to the sponsor.

18.3 MHRA Approval

Prior to the initiation of the study, the Clinical Trial Authorisation application must be approved by the MHRA. A copy of this approval and any correspondence with the MHRA will be available at the clinical and sponsor sites. A copy of the MHRA approval will be provided to the EC.

18.4 Source Data

A study-specific source document identification list will be finalised with the sponsor prior to the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

For this study, electronic data capture will be used where possible and data will be automatically recorded into an electronic case report form. In instances where paper source documents are used, data to be transcribed into the eCRF will be identified using a Source Document Identification List, as governed by Quotient Sciences SOPs.

18.5 Declaration of the End of the Study

The end of the study is defined as the last visit of the last subject (eg follow-up assessment or phone call). Any changes to this definition will be notified as a substantial amendment (see Section 17.1).

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

18.6 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters etc) will be kept in accordance with the ICH guidelines for Good Clinical Practice 1996, updated 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 (ICH GCP Section 4.9.5) [4], The Medicines for Human Use (Clinical Trials) Regulations 2004 [5] and The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [6],[7].

All study related documents will be retained for a minimum period of 5 years. After this time, the sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

18.7 Protection of Personal Data and Confidentiality

Personal data are securely stored to prevent unauthorised access, disclosure, dissemination, alteration or loss of information and unauthorised personal data processing. Access to personal information is restricted so that only personnel who are required to access personal data as part of their job role can do so. All personnel who access personal information are bound by a duty of confidentiality.

Technical arrangements surrounding the electronic storage and use of data are as follows:

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls
- Off-site personnel can only access networked computers through a virtual private network
- Electronic access of data is limited according to user roles
- All data are stored on password protected computers

Organisational arrangements are as follows:

- All buildings are secured by key-card access
- Manual files of personal data are stored within locked cabinets that can only be accessed by authorised personnel
- Data security and/or confidentiality provisions are utilised in agreements with third parties
- Documented Back-up and disaster recovery procedures are in place
- Internal audit and compliance functions provide regulatory oversight

The personal data of volunteers will be pseudonymised in that they will only include health, initials, date of birth and demographics (gender and ethnicity) and cannot be linked back to the individual by the recipient. The Sponsor shall be the data controller in respect of the personal data of the study subjects collected in connection with the study, and shall act in accordance with the relevant data protection laws in relation to the collection and processing of those personal data. The study subjects' pseudonymised personal data shall be collected and processed for the purposes of the study and may also be added to research databases and used in the future by the Sponsor and its affiliates for certain additional clinical research, for product regulation and safety reporting purposes and for ensuring compliance with legal requirements. The study subjects' pseudonymised personal data may be processed for such purposes by other parties including: the Sponsor's affiliates and licensing partners, its business partners, regulatory agencies and other health authorities, and ECs. The study subjects' authorisation for such use and disclosure shall be obtained by the study subjects signing the ICF for the study.

Additionally, Quotient personnel are contractually bound by a duty of confidentiality and receive training in this matter.

18.8 Data Security Breach

Quotient has a comprehensive process in place for identifying, assessing, resolving and reporting any potential data security breach. All staff are trained in the identification of potential data security breaches. Potential breaches are managed by appropriately trained quality (QA) assurance personnel in accordance with Quotient Sciences SOPs. After robust assessment of data breaches, those deemed serious will be reported to the sponsor and Information Commissioner's Office, as applicable.

19 Quality Control and Quality Assurance

Quality control of all data collected from this study will be performed in accordance with Quotient SOPs. This study (or elements thereof) may be subject to Quotient QA audit, in line with current internal auditing procedures. Similarly, the study (or elements thereof) may be subject to sponsor QA audit.

19.1 Monitoring

GCP requires that studies are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. A study monitor, independent of Quotient Sciences, will be appointed to verify that the study is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The investigator agrees to receive visits from a study monitor and provide assistance to verify protocol implementation, source completion and transcription of data into the electronic case report form, document storage and AE reporting.

Quotient Sciences will extend the professional privilege of access to the subjects' clinical source documents to the study monitor, EC, regulatory bodies or other authorised personnel (eg auditor) for the purposes of source data verification.

Following completion of the study both study related documents and subject data may be sent to the sponsor at a location outside of the UK where data protection laws differ. In the interests of confidentiality, subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained.

20 Finance and Insurance

The sponsor (Quantum Genomics) has funded this study. A no-fault clinical trials insurance has been obtained by the sponsor. The sponsor insurance will compensate subjects in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2018 edition [3].

21 Publication

Please refer to the Master Services Agreement for information on publication.

Quotient Sciences shall have the right to publish the results of the research, subject to the sponsor's prior written consent, which shall not be unreasonably withheld or delayed. Following the receipt of such consent, Quotient Sciences shall submit a copy of the proposed publication to the sponsor who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, Quotient shall be obliged to incorporate prior to such publication.

The sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning the research, it will submit a copy of such publication to Quotient Sciences who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendment are reasonable, the sponsor shall be obliged to incorporate prior to such publication.

22 References

[1] Quantum Genomics Investigator's Brochure for Firibastat (QGC001). Edition Number: QGC001IBPIIA7. 20 Sep 2019.

[2] Heads of Medicines Agency: Clinical Trials Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. 15 Sep 2014 http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

[3] Guidelines for Phase I Clinical Trials. Association of the British Pharmaceutical Industry Guidelines. London, UK; 2018 Edition (publication date 29 May 2018).

[4] International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016.

[5] The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031.

[6] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928.

[7] The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984.

[8] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941.

[9] World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (and all subsequent amendments).

Appendix 1 Clinical Laboratory Parameters

Haematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Basophils Eosinophils Haematocrit (Packed Cell Volume- PCV) Haemoglobin Lymphocytes Mean Cell Haemoglobin (MCH) Mean Cell Haemoglobin Concentration (MCHC) Mean Cell Volume (MCV) Monocytes Neutrophils Platelet Count Red Blood Cell (RBC) Count White Blood Cell (WBC) Count	Alanine Aminotransferase Albumin Alkaline Phosphatase Aspartate Aminotransferase Bicarbonate Bilirubin (Total) Bilirubin (Direct) (only if Total is elevated) Calcium Chloride Creatine Kinase Creatinine Follicle Stimulating Hormone (FSH; post-menopausal female subjects only) Gamma Glutamyl Transferase Glucose Glucose (Fasting) Potassium Phosphate (Inorganic) Protein (Total) Sodium Urea	Hepatitis B Surface Antigen Hepatitis C Antibody HIV Antibody	Bilirubin Blood Glucose hCG (all female subjects) Ketones Leukocytes Nitrites pH Protein Specific gravity Urobilinogen **At discretion of investigator based on urinalysis results** Microbiology Urine Microscopy	Amphetamines Barbiturates Benzodiazepines Cocaine Marijuana/Cannabis Methadone Methamphetamine/ Ecstasy Morphine/Opiates Phencyclidine Tricyclic Antidepressants

Appendix 2 Schedule of Assessments

Study Day	-28 to -2	-1	1													2 to 6				
				Times After Morning Dosing (h)																
	S	A	P	0	0.5	1	2	3	4	6	8	10	12	16	20	P	0	3	6	12
General Assessments																				
Informed Consent	X																			
Medical History	X	X[b]																		
Weight and Height	X																			
Vein Assessment	X																			
Carbon Monoxide Breath Test	X	X																		
Drug Screen	X	X																		
Alcohol Breath Test	X	X																		
IMP Administration[c]				X									X[d]				X			X[d]
Safety Assessments																				
Physical Examination	X		X[e]																	
Safety Labs[f]	X		X																	
Urinalysis	X		X																	
Urine Pregnancy Test[g]	X	X																		
Electrocardiograms	X		X					X								X				
Vital Signs[h]	X		X					X		X						X		X	X	
Adverse Events	←																			→
Prior and Concomitant Medication	←																			→
PK Assessments																				
Plasma Samples for QGC001, EC33 and QGC515			X		X	X	X	X	X	X	X	X	X	X[i]	X[i]	X				

A: admission, P: pre-dose, S: Screening
Footnotes follow the table

Appendix 2 Schedule of Assessments (continued)

Study Day	7													8		9	14 to 17
		Times After Morning Dosing (h)															Follow-up call
	P	0	0.5	1	2	3	4	6	8	10	12	16	20	24	36	48[a]	
General Assessments																	
IMP Administration[c]		X															
Safety Assessments																	
Physical Examination																X[e]	
Safety Labs[f]																X	
Urinalysis																X	
ECG	X															X	
Vital Signs[h]	X					X		X								X	
Adverse Events	◄																►
Prior and Concomitant Medication	◄																►
PK Assessments																	
Plasma Samples for QGC001, EC33 and QGC515	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

A: admission, P: pre-dose, S: Screening
[a] Discharge from clinical unit
[b] Update
[c] Subjects will be dosed BID in Regimen A and QD in Regimens B and C. For BID dosing, subjects will receive the IMP on Days 1 to 6 in the morning and evening approximately 12 h apart and on Day 7 as one morning dose (QD). For QD dosing, subjects will receive the IMP in the morning of Days 1 to 7
[d] Regimen A only
[e] Targeted (symptom driven) physical examination
[f] Haematology and clinical chemistry at each time point including virology and FSH (post-menopausal female subjects only) at screening
[g] All female subjects
[h] Blood pressure and heart rate. Oral temperature will be measured at screening and pre-dose (Day 1) only
[i] Regimens B and C only