A Phase II randomized, placebo controlled, double-blind, multi-centre study to assess safety and efficacy of incremental doses of QGC001 in patients with NYHA class II/III chronic heart failure with left ventricular systolic dysfunction

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Objectives:Primary: Primary objective of the study is to investigate the safety (blood pressure changes until Day 28 and after discontinuation from Day 28 up to Day 35) and efficacy (rate of decrease in NT-proBNP of more then 30% from baseline to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46235

Source
ToetsingOnline

Brief title
QUantum genomics Incremental Dosing in Heart Failure
Acronym 'QUID-HF'

Condition

- Heart failures

Synonym
cardiac output, Heart Failure

Research involving
Human

Sponsors and support

Primary sponsor: European Drug Development Hub, Fondation Force
Source(s) of monetary or material Support: Quantum Genomics

Intervention

Keyword: Worsening Heart Failure

Outcome measures

Primary outcome

*The Efficacy Primary endpoint will be the percentage of subjects with a relative decrease in NT-proBNP (Central Lab) of more than 30% from baseline to Day 28. *The Safety Primary endpoint will be the blood pressure changes at each visit, compared to the baseline measure

Secondary outcome

*Blood biochemistry, electrolytes, urinary osmolarity at Day 7, Day 14, Day 21, Day 28, Day 35 *Change in central lab values of NT-proBNP and BNP, at Day 7, Day 14, Day 21, Day 28, Day 35 *Changes in central lab values from baseline in selected biomarker levels (copeptin, apelin, PRA and others biomarkers involved in the pathophysiology of the disease, which will be decided later) at Day 7, Day 14, Day 21, Day 28 *Death from any cause or readmission for worsening heart failure at Day 28 and Day 35 *Quality of life Minnesota Living with Heart Failure Score and D0 and Day 28.

Study description

Background summary

In heart failure, a variety of mechanisms contribute to progressive cardiac remodeling and dysfunction: progressive left ventricular dilation, fibrosis, and decrease in contractile performance. New therapeutic approaches, specifically preventing activation of the brain neuromodulatory pathway, may lead to more optimal and specific approaches to improve heart failure. Inhibition of brain aminopeptidase A (APA) which converts angiotensin II into angiotensin III has emerged as a novel antihypertensive treatment, as demonstrated in several experimental animal models. QGC001 is a prodrug of the specific and selective APA inhibitor, EC33, and as such it is the prototype of a new class of centrally-acting brain aminopeptidase A inhibitor (BAPAI). In animal models, QGC001 antihypertensive effect is in part due 1) to a decrease in arginine vasopressin release in the blood circulation, increasing diuresis, and 2) to a reduction in the sympathetic tone leading to subsequent decrease in vascular resistances. In heart failure, these targets of interest are the same. The novel brain aminopeptidase A inhibitor QGC001 would be a reasonable candidate to address the needs of heart failure patients.

Study objective

Objectives:
Primary:
Primary objective of the study is to investigate the safety (blood pressure changes until Day 28 and after discontinuation from Day 28 up to Day 35) and efficacy (rate of decrease in NT-proBNP of more then 30% from baseline to Day 28 of QGC001 up-titrated from 50 mg twice daily to a maximum of 500mg twice daily).

Secundary objectives:
Further exploratory objectives of the study are:
Blood biochemistry, electrolytes, urinary osmolarity at Day 7, 14, 21, 28, 35
Change in central lab values of NT-proBNP and BNP at Day 7, 14, 21, 28 35.
Death from any cause or readmission for worsening heart failure at day 28 and 35
Quality of Life Minnesota Living with Heart Failure Score at Day 0 and 35.

Study design

Study design:
The trial is a multinational (approximately 23 sites in several European countries), randomized, double blind, placebo controlled, parallel group trial.

Intervention

Interventions are blood samples taken at each visit.

Study burden and risks

Burden:

The time involved in this study, in the clinic is approximately 6 hours.

Risks:
No SAE and no important medical events were recorded after single oral administration of QGC001 up to 2000 mg and repeated oral administrations up to 1000mg b.i.d. for 7 consecutive days in healthy male subjects. No withdrawal due to AE occurred during these Phase I studies.

Potentially there are risks related to the insertion of a needle for the blood samples. Those are bruising, pain, dizziness, and bleeding.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

*A signed and dated informed consent form prior to any study procedure
*Adult male subjects and female subjects without childbearing potential.
*Clinical diagnosis of CHF with history of NYHA class II-III for at least 3 months before randomisation.
*Documented left ventricular ejection fraction (LVEF) < 40% measured by any modality within the previous 12 months in the subject*s medical history.
*Subjects must also have at least one local measurement of BNP level * 300 pg/mL or NT-proBNP level * 1200 pg/mL (preferred assay, local laboratory) at the screening visit (maximum 7 days before randomisation).
*eGFR * 30 mL/min/1.73 m2 (MDRD) at screening.
*Serum potassium < 5.0 mmol/L at screening.
*Systolic blood pressure *110 mmHg (average of 3 consecutive measurements) at screening.
*Prescribed to optimal pharmacologic therapy per *ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2016*, or based on the updated current clinical practice, unless contra-indicated or not-tolerated, and on a stable dose for at least 30 days prior to enrolment (the dosage of the drugs cannot be increased or decreased respectively by more than double or half of initial dosage).
*Taking oral loop diuretics at doses < 250 mg furosemide daily (or equivalent).

Exclusion criteria

*BMI > 45 kg.m-2.
*Patients who require the use of HF IV therapy or oral furosemide > 250 mg (or equivalent) at any time during the 48 hours immediately before randomisation.
*Patients with unstable angina, myocardial infarction, PTCA, coronary artery bypass graft, cerebral vascular accident, or transient ischemic attack within previous 3 months (90 days) before enrolment.
*Patients whose primary cause of heart failure is mitral or aortic valve disease or congenital heart disease or hypertrophic obstructive cardiomyopathy or infiltrative cardiomyopathy (e.g. amyloidosis, sarcoidosis) or myocarditis.
* Patients with *new* permanent atrial fibrillation (AF), discovered within 3 months prior to randomization.
* Heart rate > 110 beats/min at screening.
*Patients scheduled for Pacemaker (including ICD, CRT), Angioplasty, CABG or LVAD within the next 3 months.
*Patients with severe documented chronic obstructive lung disease (COPD), defined as chronic need for oxygen therapy
*eGFR < 30 mL/min/1.73 m2 (MDRD) at screening.
* Decrease in eGFR greater than 20% within 3 weeks prior to the screening visit.
*Serum potassium > 5.0 mmol/L at screening.
*Systolic blood pressure < 110 mmHg or with signs or symptoms of hypotension.

*Symptomatic hypotension or orthostatic hypotension defined by a decrease of systolic blood pressure of more than 30 mm Hg in the standing vs. sitting position at screening and at the basal SBP of the D0 (before having taken the study medication).
*A marked baseline prolongation of QT/QTc interval (e.g. repeated demonstrated of a QTc interval > 450 ms) AND QRS < 100 ms. In case of QRS enlargement > 100 ms (i-e bundle branch block, pacemakers) QT does not accurately reflect repolarization and may not be calculated.
* A history of additional risk factors for Torsade de Pointes (TdP) (e.g. hypokalemia, family history of long QT Syndrome).
*The use of concomitant medications that prolong the QT/QTc interval.
*Insulin-requiring diabetic patients (including type 1 Diabetes).
*History of angioneurotic edema.
Severe liver failure at screening defined by a value of ALAT and/or ASAT 5 from the normal value.
*Patients involved in any interventional clinical study, patients enrolled in Registries and/or in non-interventional studies may participate.
*Patients who take an investigational or non-approved treatment.
*Women of childbearing potential.
*Patients with a prior cardiac transplant or patients currently on the list for cardiac transplantation.
* Patient with hypersensitivity to the active substance or to one of the other components of the trial preparation.
* Patients in whom an allergy requiring chronic treatment is known or exists.
*Patients with a history of previous illnesses of neurological or psychiatric nature that affect the Central Nervous System.
*Patients with a life expectancy of less than 12 months per physician judgment.
*Frail patient who, in the opinion of the investigator will not be able to follow the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-11-2017
Enrollment:	13
Type:	Actual

Ethics review

Approved WMO Date:	03-03-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2018

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-005607-92-NL
CCMO	NL56815.042.16