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An evaluation of two drugs for treating a familial form of pulmonary arterial hypertension

Submission date 03/03/2023	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 22/09/2023	**Overall study status** Ongoing	
Last Edited 24/08/2026	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Pulmonary arterial hypertension (PAH) is a progressive respiratory condition that causes high blood pressure in the blood vessels that supply blood to the lungs. Current treatments help to manage the symptoms of the disease but do not treat the underlying cause. The condition can occur in families due to an alteration in a gene (a piece of inherited material) called the bone morphogenetic protein type 2 receptor (BMPR2). Currently, there are no therapies that target BMPR2 dysfunction. In a previous study, the study team identified a set of proteins or biological markers (biomarkers) in the blood that regulate BMPR2. In this study, the study team will be using two repurposed drug therapies, hydroxychloroquine and glycerol phenylbutyrate, both of which can change the way BMPR2 is expressed to see if changing the function of BMPR2 is a potential therapy area in PAH.

Who can participate?
Patients aged between 18-75 years old with PAH

What does the study involve?
Participants will be randomised to either active treatment arms:
(T1 = standard of care + hydroxychloroquine; T2 = standard of care + phenylbutyrate)
or control group either:
(C = standard of care + liquid or tablet placebo).

What are the possible benefits and risks of participating?
It is not known whether you will gain any personal benefit from this research. However, information from this study could improve our understanding of the treatment of PAH and help doctors treat patients better in the future.

There are possible risks associated with the following:
ECG:
The electrodes (small sticky sensors) may cause slight discomfort when being taken off the skin. Male participants may need to have small patches of hair on the chest shaved to properly

connect the electrodes. Some participants may be sensitive to the adhesive pads resulting in itchy red areas where the patches were placed. These will be performed by an experienced member of staff.

Blood sampling:
Minor discomfort, lightheadedness or irritation, such as redness, tenderness and bruising at the site used to obtain blood. These will be drawn by an experienced member of the research team.

Trial medication:
Both drug treatments (hydroxychloroquine and glycerol phenylbutyrate) used in this trial, are prescribed in the UK for licensed indications and are well tolerated. The doses used in this trial are normal treatment doses prescribed and the drug will be prescribed according to BMI. However, individual participants may react differently to the same drug which means that there is a possibility of experiencing some of the side effects of the drug. Details of drug treatment and side effects are provided in the participant information sheet so participants are fully informed. The trial doctor will monitor any side effects regularly and participants will be encouraged to contact sites if they experience any AEs and take appropriate actions where necessary, by ensuring that all SAEs are assessed for relatedness and expectedness and onward notification of all SARs to the Chief Investigator and Sponsor immediately but not more than 24 hours of first notification.

Where is the study run from?
Royal Papworth NHS Foundation (UK)

When is the study starting and how long is it expected to run for?
January 2020 to April 2027

Who is funding the study?
Medical Research Council (MRC)

Who is the main contact?
1. Dr Mark Toshner (CI), mrt34@medschl.cam.ac.uk
2. Ellen Temple-Jones (StratosPHere Trial Manager), ellen.temple4@nhs.net

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Dr Mark Toshner

ORCID ID
https://orcid.org/0000-0002-3969-6143

Contact details
Victor Phillip Dahdaleh Heart and Lung Research Institute
University of Cambridge
Papworth Rd
Cambridge
United Kingdom

CB2 0AY
+44 (0)1223 762007
mrt34@medschl.cam.ac.uk

Type(s)
Public

Contact name
Ms Ellen Temple-Jones

Contact details
Clinical Trial Manager
Papworth Trials Unit Collaboration (PTUC)
Royal Papworth Hospital
Papworth Road
Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0AY
+44 (0)1223 639809
ellen.temple4@nhs.net

Additional identifiers

Integrated Research Application System (IRAS)
1003631

Central Portfolio Management System (CPMS)
56619

Protocol serial number
STRATOSPHERE223

Study information

Scientific Title
StratosPHere 2: A response-adaptive randomised placebo-controlled Phase IIa trial to evaluate hydroxychloroquine and phenylbutyrate in pulmonary arterial hypertension caused by mutations in BMPR2

Acronym
StratosPHere 2

Study objectives
Pulmonary arterial hypertension (PAH) is a condition in which a narrowing of the blood vessels carrying blood through the lungs puts increased pressure on the heart resulting in it having to work harder to pump blood through the lungs. While current treatments relieve some of the symptoms, they do not stop or reverse the disease in the affected blood vessels. When the disease occurs in families it can be due to an alteration in a gene (a piece of inherited material) called the bone morphogenetic protein type 2 receptor (BMPR2).

The purpose of this study is to improve our understanding of increasing BMPR2 as a treatment for people with PAH by testing two drug therapies; hydroxychloroquine and glycerol phenylbutyrate. We know there are different types of BMPR2 and we want to investigate how these different drug work. In a recent trial, the study team identified biological markers 'biomarkers' in the blood that regulate BMPR2 and we aim to use these as potential targets for both of these drug therapies.

Evaluating the effectiveness of the two drug therapies in a sample of people with a BMPR2 mutation by measuring patient-related outcomes and function specific to this group.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/09/2023, London - Surrey Borders Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8057, (0)207 104 8104, (0)207 104 8199; surreyborders.rec@hra.nhs.uk), ref: 23/LO/0285

Primary study design
Interventional

Study design
Double-blind three-armed response-adaptive randomized controlled study

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Pulmonary arterial hypertension

Interventions
StratosPHere 2 is a double-blind, three-armed response-adaptive randomised controlled trial of two active arms (T1 = standard of care + hydroxychloroquine; T2 = standard of care + phenylbutyrate) and a control group (C = standard of care + placebo). The adaptation will be performed based on a Bayesian response-adaptive strategy, designed to dynamically allocate more patients in each subgroup to a promising arm if it is showing an earlier positive effect, making efficient use of a small population and giving patients a higher chance of being allocated to the current most efficacious arm of the trial.

Updated 24/08/2026:
Following interim analyses in December 2025, the T2 standard of care + phenylbutyrate arm and its corresponding placebo arm have been dropped from the study. Also, due to logistical reasons, the missense mutation stratum has been discontinued, reducing the target sample size from 40 to 20 participants.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Hydroxychloroquine, glycerol phenylbutyrate

Primary outcome(s)
Target engagement of the BMPR2 pathway determined by change in peripheral blood-based BMPR2 function is measured by changes in the expression of a panel of eight BMPR2-modulated genes (i.e., ID3, SMAD1, SMAD5, NOTCH1, NOTCH2, ID2, ARL4C, PTGS2) using quantitative PCR from baseline (study entry/randomisation) to 8 weeks follow-up (8 weeks from treatment initiation)

Key secondary outcome(s)
BMPR2 cell surface protein expression on peripheral blood white cells, measured using flow cytometry at baseline and 8, 16 and 20 weeks

Completion date
01/04/2027

Eligibility

Key inclusion criteria
Subjects eligible for enrolment in the study must meet all of the following criteria:
1. Aged between 18-75 years inclusive
2. Weight >40.0 kg at the Screening Visit
3. Having a diagnosis of group 1 PAH due to the following: Idiopathic or Heritable PAH with a known mutation in BMPR2
4. Being stable on an unchanged PAH therapeutic regime for at least 1 month prior to screening
5. Being competent to understand the information given in the approved Informed Consent Form and must sign the form prior to the initiation of any study procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
0

Key exclusion criteria

PAH treatments:
1. Patients on TNF antagonists or other biological treatments
2. Subject has a known hypersensitivity to the Investigational Products, metabolites, or formulation excipients
3. Subject has a severe renal impairment (creatinine clearance <30 mL/min) at the Screening Visit
4. Subject is currently on either the active treatment arm or trial medication drug class

Medical history/current medical conditions:
1. Subject with an active infection at the time of screening
2. Subjects with known Hepatitis B or Tuberculosis
3. Subject has a severe hepatic impairment (Child-Pugh class C with or without cirrhosis) at the screening Visit
4. Patient with ALT or AST >5 x upper limit of normal

Haematology and bleeding disorders:
1. Subject has clinically significant anaemia in the opinion of the investigator, in particular from pyruvate kinase and G6PD deficiencies
2. Subjects with bleeding disorders or significant active peptic ulceration in the opinion of the investigator
3. Subject has peripheral blood platelets <100x109/L
4. Subject has a neutrophil count <2x109/L

Cardiovascular:
1. Subject has had an acute myocardial infarction within the last 90 days prior to screening

General medical conditions:
1. Subject with cardiovascular, liver, renal, haematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or efficacy of the investigational product or severely limit the lifespan of the subject other than the condition being studied
2. Subject has a history of malignancies within the past 5 years, except for a subject with localized, non-metastatic basal cell carcinoma of the skin, in situ carcinoma of the cervix, or prostate cancer who is not currently or expected, during the study, to undergo radiation therapy, chemotherapy, and/or surgical intervention, or to initiate hormonal treatment
3. History of known retinal disease
4. Currently taking any of the following contraindicated medications:
4.1. Chloroquine
4.2. Halofantrine
4.3. Amiodarone
4.4. Moxifloxacin
4.5. Cyclosporin
4.6. Mefloquine
4.7. Praziquantel
4.8. Prochlorperazine
4.9. Fluconazole
4.10. Penicillamine
4.11. Ivabridine

General Criteria:
1. Female subject who is pregnant or breastfeeding
2. Subject has demonstrated noncompliance with previous medical regimens

3. Subject has a recent (within 1 year) history of abusing alcohol or illicit drugs
4. Subject has participated in a clinical study involving another investigational drug or device within 4 weeks before the Screening Visit

Date of first enrolment
11/12/2023

Date of final enrolment
01/12/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Papworth Hospital
Papworth Road
Cambridge Biomedical Campus
Cambridge
England
CB2 0AY

Study participating centre
Golden Jubilee National Hospital
Agamemnon Street
Clydebank
Scotland
G81 4DY

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
England
NW3 2QG

Study participating centre

Royal Hallamshire Hospital
Glossop Road
Sheffield
England
S10 2JF

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
England
NE7 7DN

Study participating centre
Royal Brompton Hospital
Sydney Street
London
England
SW3 6NP

Sponsor information

Organisation
Papworth Hospital NHS Foundation Trust

ROR
https://ror.org/01qbebb31

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/10/2024	17/10/2024	Yes	No
Statistical Analysis Plan		11/07/2025	14/07/2025	No	No