ISRCTN96750019 https://doi.org/10.1186/ISRCTN96750019

Testing new medicine for adults with Cystic Fibrosis who do not have access to the currently available CFTR-modulating drugs due to genetic mutations

Submission date
06/05/2024

Recruitment status
No longer recruiting

Registration date
23/05/2024

Overall study status
Completed

Last Edited
03/07/2025

Condition category
Genetic Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The CHOICES study is conducted within the Human Individualised Therapy of CF (HIT-CF) project. The aim of this project is to provide drugs to people with cystic fibrosis (CF) who have (extremely) rare mutations and therefore do not have access to the currently available 'Cystic Fibrosis Transmembrane Conductance Regulator' (CFTR)-modulating drugs. CFTR modulators are a relatively new group of treatments that target the defect in CF. In the HIT-CF project, intestinal organoids ('mini-intestines') that have been cultured from the patient's own tissue (from rectal biopsies) are being tested in the laboratory to predict the clinical drug response to the CFTR modulators tested in this study: the three-part combination of dirocaftor (DIR) /posenacaftor (POS)/nesolicaftor (NES). Dirocaftor is a CFTR potentiator, posenacaftor is a CFTR corrector, and nesolicaftor is a CFTR enhancer. Several proof-of-principle studies have shown that intestinal organoids can predict the clinical response to CFTR modulators in patients with rare mutations.

Who can participate?
The study population consists of subjects diagnosed with CF who are at least 18 years old (at the time of informed consent) and who have completed organoid screening (conducted by the HIT-CF consortium; HIT-CF organoid study [NTR7520]) before screening for this study.

What does the study involve?
Active and placebo study drugs are supplied as capsules for oral administration. The combination of dirocaftor, posenacaftor and nesolicaftor is given as a triple treatment in the following doses, respectively: 300 mg/day, 600 mg/day and 10 mg/day.
In both groups, suitable subjects will be randomised in a 1:1 ratio in one of 2 treatment series: either 8 weeks of DIR/POS/NES once a day, followed by 8 weeks of placebo once a day.

Subjects come to the study site several times during each treatment period and a total of 10 times:

- Screening
- Treatment period 1 and 2: D1, D29, D43, D57
- Follow-up visit at D71
Blood, sweat and urine samples are collected at screening, in treatment periods 1, 2 and during the follow-up visit. One 12-lead electrocardiogram (heart monitor) and lung tests are done before the collection of blood samples. The CFQ-R is completed at each study visit, before procedures related to the study are done and before the study drug is administered on the day of the visit.

What are the possible benefits and risks of participating?
Possible benefits are that the study drugs may provide relief of, or lessening of, the signs and symptoms of CF; however, such a benefit cannot be guaranteed. The possible benefit to other people with this condition includes learning more information about treatment in patients who are diagnosed with CF.
Possible discomforts of the tests and measurements in the study. For example, taking a blood sample can be a little painful. Or you could get a bruise as a result

Where is the study run from?
University Medical Center Utrecht (Netherlands)

When is the study starting and how long is it expected to run for?
February 2024 to June 2025

Who is funding the study?
Horizon 2020 (European Union)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2022-500410-26-01

Integrated Research Application System (IRAS)
1005882

ClinicalTrials.gov (NCT)
NCT06468527

Protocol serial number
HIT-CF-001, IRAS 1005882, CPMS 61067

Study information

Scientific Title
A phase IIb, multicentre, randomised, double-blind, placebo-controlled, crossover study to evaluate the efficacy and safety of dirocaftor/posenacaftor/nesolicaftor in subjects with cystic fibrosis aged 18 years or older

Acronym
CHOICES

Study objectives
1. To evaluate the efficacy of DIR/POS/NES after 8 weeks compared to placebo in:
1.1. CF patients with rare CFTR mutations and a high organoid response to DIR/POS/NES and
1.2. CF patients with rare CFTR mutations not pre-selected on organoid response.
2. To evaluate the safety and tolerability of efficacy of DIR/POS/NES in CF patients with rare CFTR mutations and to evaluate PK of DIR/POS/NES and their respective metabolites, when relevant.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/02/2024, East Midlands - Leicester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8066; leicestercentral.rec@hra.nhs.uk), ref: 22/EM/0192

Study design
Interventional double-blind randomized placebo cross over trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Treatment of Cystic Fibrosis (CF) in patients with CFTR mutations who are responders in the organoid assay

Interventions
CHOICES is a randomized, double-blind, placebo-controlled, cross-over trial. The study population will comprise of subjects with a diagnosis of CF who are ≥18 years of age (at the time of informed consent) and have completed organoid screening (conducted by the HIT-CF consortium; HIT-CF Organoid Study [NTR7520]) prior to screening for this study. The study will consist of two groups. The first group will consist of 26 subjects of the HIT-CF Organoid Study with the highest organoid response to the combination of DIR/POS/NES. For the second group, 26 subjects, no such pre-selection criteria and no such screening will be performed (i.e. a simple random sample will be drawn instead). This approach will allow unbiased evaluation of the treatment effect in both populations, as well as for exploratory assessment of a possible difference in treatment effects. An unblinded coordinating team will be responsible for subject selection based on a subject's organoid response and the detailed description will be captured in a separate sample and subject selection plan.
Subjects will participate in an 8-week, double blind, placebo controlled, cross-over study including an approximate 8 week washout period. In both groups, eligible subjects will be randomized at a 1:1 randomization ratio into one of 2 treatment sequences:
Either DIR/POS/NES once daily for 8 weeks followed by placebo once daily for 8 weeks, or placebo once daily for 8 weeks followed by DIR/POS/NES once daily for 8 weeks.

Intervention Type

Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Dirocaftor, posenacaftor, nesolicaftor

Primary outcome(s)
Mean percent predicted forced expiratory volume in 1 second (ppFEV1) of measurements taken after 4, 6 and 8 weeks of treatment. Period baseline values will be corrected for in the analysis

Key secondary outcome(s))
1. The average of the sweat chloride measurements taken after 4, 6 and 8 weeks of treatment
2. The average of the body weight measurements taken after 4, 6 and 8 weeks of treatment
3. The average of the Cystic Fibrosis Questionnaire Revised (CFQ R) respiratory domain measurements taken after 4, 6 and 8 weeks of treatment
For all outcomes above (including the primary endpoint), the separate (i.e. not averaged) week 4, 6 and 8 measurements will also be analysed individually. Period baseline values will be corrected for in the analysis.
4. Safety and tolerability assessments based on treatment-emergent Adverse Events (AEs) and Serious Adverse events (SAEs), clinical laboratory tests (ie, haematology, serum chemistry, coagulation studies, and urinalysis), physical examinations, electrocardiography (ECG), and vital signs
5. PK parameter estimates and metabolites of DIR/POS/NES derived from plasma after 4, 6 and 8 weeks of treatment

Completion date
20/06/2025

Eligibility

Key inclusion criteria
1. Male or female subjects who completed the HIT-CF Organoid Study and are 18 years of age or older on the date of informed consent
2. Confirmed diagnosis of CF as follows:
2.1. Sweat chloride value of ≥60 mmol/L based on quantitative pilocarpine iontophoresis (at screening) OR 2 CF-causing mutations
AND
2.2. chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities
3. Clinically stable CF disease in the opinion of the investigator with no significant changes in health status within 28 days prior to Day 1
4. Forced expiratory volume in one second (FEV1) ≥40% of predicted to ≤90% of predicted at the Screening Visit, based on the Global Lung Function Initiative (GLI) -2012 multi-ethnic all-age reference equations
5. Body mass index (BMI) ≥16 kg/m² and ≤30 kg/m²
6. Non-smoker and non-tobacco user (including all inhalational nicotine delivery systems) for a minimum of 30 days prior to screening, and subject agrees not to smoke or use tobacco for the duration of the study
7. Subjects of childbearing potential must meet contraception requirements
8. Willing to remain on a stable medication regimen for CF from 28 days before Day 1 through

the last study visit
9. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, and other study procedures
10. Selected by an unblinded coordinating team based on organoid response or random selection
11. Subject will sign and date an informed consent form (ICF)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
41

Key exclusion criteria
1. Subject has at least one of the following CFTR-mutations: F508del, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, A455E, 3849+10kbC>T OR A combination of any two of the following mutations: any nonsense mutation, 1717-1G>A, 621+1G>T, 3120+1G>A, 1898+1G->A, CFTRdele2,3, and 2183AA->G
2. History or current evidence of any clinically significant cardiac (eg, heart failure, left ventricular hypertrophy, myocardial infarction, and arrhythmia), endocrinologic, hematologic, hepatobiliary (eg, clinically significant cirrhosis with or without portal hypertension), immunologic, metabolic, urologic, pulmonary (besides CF), neurologic (eg, subarachnoid haemorrhage, intracranial haemorrhage, cerebrovascular accident, intracranial trauma, and autonomic neuropathy), dermatologic, psychiatric, renal, or other major disease, that is unstable or could interfere with the subject's participation in or completion of the study, in the opinion of the investigator
3. Clinically significant screening results that would exclude subject from the study (eg, medical history, physical examination, ECG, vital sign, pulse oximetry, and laboratory profiles) or any conditions that, would make the subject unsuitable for enrolment or could interfere with the subject's participation in or completion of the study, in the opinion of the investigator. The medical monitor must be contacted for review of any subjects with screening results or conditions that may make them unsuitable for enrolment or could interfere with participation in or completion of the study.
4. Prolonged QTcF >450 msec at screening
5. Abnormal liver function as defined by AST, ALT, gamma-glutamyl transferase (GGT), or alkaline phosphatase ≥3 times or total bilirubin ≥2 times upper limit of the normal range
6. Haemoglobin <10 g/dL
7. Platelet count <150,000 cells/mm^3
8. Abnormal renal function at screening defined as creatinine clearance <60 mL/min using the Modified Diet in Renal Disease (MDRD)

9. Hospitalisation, sinopulmonary infection, CF exacerbation, or other clinically significant infection or illness (in the opinion of the investigator) requiring an increase or addition of medication, such as antibiotics or corticosteroids, within 28 days of Day 1
10. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). Subjects who have a current or past history of a positive culture must be reviewed with the medical monitor to confirm clinical stability.
11. Subject is currently taking or has taken a CFTR modulator within 28 days prior to Day 1
12. Participation in another clinical trial or treatment with an investigational agent within 28 days or 5 half-lives, whichever is longer, prior to screening. The duration of the elapsed time may be longer if required by local regulations
13. History of cancer (excluding cervical carcinoma in situ and non-melanoma skin cancer with curative therapy for at least 5 years prior to screening)
14. History of organ or hematologic transplantation
15. History or current evidence of alcohol or drug abuse or dependence within 12 months of screening, in the opinion of the investigator
16. Initiation of any new chronic therapy (eg, ibuprofen, hypertonic saline, azithromycin, dornase alfa, aztreonam for inhalation solution, and tobramycin) or any change in chronic therapy (excluding pancreatic enzyme replacement therapy) within 28 days prior to Day 1
17. Known or suspected hypersensitivity or idiosyncratic reaction to the study drugs or any components thereof
18. Pregnant or nursing women
19. Special or vulnerable status (e.g. institutionalized, or person related to or an employee of the sponsor, FAIR Therapeutics, or investigator)

Date of first enrolment
01/05/2024

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
United Kingdom

England

Belgium

Czech Republic

France

Germany

Italy

Netherlands

Portugal

Spain

Sweden

Study participating centre
UZ Leuven
Leuven
Belgium
3000

Study participating centre
Motol University Hospital
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Study participating centre
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Sponsor information

Organisation
University Medical Center Utrecht

ROR
https://ror.org/0575yy874

Funder(s)

Funder type
Government

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes