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Optimising primary therapy in primary biliary cholangitis

Submission date 08/11/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 10/07/2023	**Overall study status** Ongoing	
Last Edited 12/03/2026	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Primary biliary cholangitis (PBC) is a rare liver disease. A number of treatments exist, which slow the rate that liver disease gets worse. However, at the moment, doctors have to wait for one treatment to fail before adding in a second. As a result, many people with PBC develop symptoms and some go on to need a liver transplant. The aim of the OPERA trial is to see if people who are newly/recently diagnosed with PBC have a better outcome if they receive two medicines from the start rather than one. Importantly, this trial will recruit people who are at risk of not responding to the one therapy alone (ursodeoxycholic acid, UDCA or “urso”). The second, additional medicine offered as part of this study is called obeticholic acid (OCA). OCA is already licenced for the treatment of PBC in people who have not responded to urso, and it has a well-known safety profile.

Who can participate?
Adults with a recent diagnosis of PBC

What does the study involve?
People who meet trial criteria and want to take part will be treated with either OCA or placebo ("dummy drug"), in addition to urso (the current standard care) for up to 6 months. After this time point, people will be followed up as part of the trial for an additional 6 months thereafter. The trial will recruit at hospitals across the UK, and aims to recruit 106 people with PBC.

What are the possible benefits and risks of participating?
We cannot promise the trial will help you directly. We hope the information we get from this trial will help to improve the treatment for PBC patients in the future who are at high risk of progression of their disease to cirrhosis. By being part of this trial you will also be more closely monitored and have follow up visits and calls which would not happen as part of your normal care.

OCA is currently licensed for the treatment of PBC in the UK. The treating clinicians in the study have clinical experience with OCA and there is no reason to suspect a different safety profile in treating patients with PBC at an earlier stage of their disease course. However as with any medication there is potential for side effects to occur. Patients will be advised of the known side

effects and will be provided with contact details of their local study team should they have any safety concerns. If side effects are reported, participant dosage may be reduced or withheld or they may treated with additional medication until side effects have resolved. Clinicians will refer to the British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis Treatment and Management Guidelines.

The safety profile of pregnant women taking OCA is not known. All participants will be asked to use acceptable contraception (e.g. barrier/ hormonal/ sterilisation) or to practice sexual abstinence for the entire duration of the treatment period. If a participant were to become pregnant during the course of the study, the patient will be withdrawn from study treatment but will be followed up until completion of pregnancy (i.e. termination, miscarriage, stillbirth or live birth) and for a year after birth. We will also follow up on any pregnancies of partners of participants who become pregnant while the participant is on the trial.

Where is the study run from?
Newcastle University (UK) and trial sites across the UK

When is the study starting and how long is it expected to run for?
November 2022 to March 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK). This project (NIHR131359) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000050-28

Integrated Research Application System (IRAS)
1006087

Central Portfolio Management System (CPMS)
54589

National Institute for Health and Care Research (NIHR)
131359

Other
10077

Study information

Scientific Title
Optimising primary therapy in primary biliary cholangitis

Acronym
OPERA

Study objectives
To assess the impact of first-line obeticholic acid therapy combined with ursodeoxycholic acid (UDCA) standard of care therapy compared to placebo in achieving biochemical remission of disease in new-onset PBC patients with enhanced disease risk.

1. To assess whether biochemical remission is sustained following discontinuation of experimental therapy and reversion to UDCA standard of care therapy
2. To assess the degree of biochemical improvement with obeticholic acid therapy combined with UDCA (or urso) standard of care therapy compared to placebo
3. To assess the impact of obeticholic acid therapy combined with UDCA standard of care therapy compared to placebo using conventional therapy response criteria (as used in current clinical practice)
4. To assess the safety and tolerability of obeticholic acid as first-line therapy in PBC
5. To assess the impact of the intervention compared to placebo on symptom severity and participant quality of life

Experimental:
1. To assess whether biochemical remission is sustained following discontinuation of experimental therapy and reversion to UDCA standard of care therapy in those participants who are in remission at 26 weeks
2. To assess changes in chemokine levels in the blood potentially associated with bile duct senescence
3. To assess the impact of intervention compared to placebo on the degree of liver inflammation and bile duct senescence

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 31/05/2023, London - Riverside Research Ethics Committee (Ground Floor Temple Quay House, 2 The Square, Bristol, BS1 6PN, United Kingdom; None available; riverside.rec@hra.nhs.uk), ref: 22/LO/0878

Primary study design
Interventional

Study design
Randomized placebo-controlled double-blind parallel-group superiority study

Study type(s)
Efficacy, Safety, Treatment

Health condition(s) or problem(s) studied
Primary biliary cholangitis

Interventions
The trial is a double-blinded, superiority, placebo-controlled, randomised, multi-centre trial of an investigational medicinal product (CTIMP). Participants will be randomised using a Sealed Envelope online tool.
The trial comprises a 26-week treatment phase in a cohort of 106 participants (Obeticholic Acid n=53; Placebo n=53), followed by a 26-week follow-up period. The study drug is taken orally at a dose of 5mg per day and titrated up to a maximum of 10mg/day after 12 weeks according to tolerability. All participants will continue to receive standard-of-care background treatment with UDCA throughout the trial.
The study population will be newly diagnosed, non-cirrhotic patients, with less than 3 months of treatment with UDCA at the time of consent and at an enhanced risk of not achieving biochemical disease remission with UDCA 1st-line therapy alone.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Obeticholic acid, ursodeoxycholic acid

Primary outcome(s)
Percentage of participants showing normalisation of serum alkaline phosphatase and total bilirubin levels, measured using blood samples at 26 weeks (visit 5)

Key secondary outcome(s)
1. Percentage of participants in each study group showing sustained normalisation of serum alkaline phosphatase and total bilirubin levels, measured using blood samples at 52 weeks (visit 6)
2. Magnitude of alkaline phosphatase and bilirubin reduction, measured using blood samples, from baseline to 26 weeks (visit 5), assessed as a continuous variable
3. Percentage of participants attaining serum alkaline phosphatase values lower than 1.67x the upper limit of normal and a bilirubin <1x the upper limit of normal, measured using blood samples at 26 weeks (visit 5). These are termed the POISE criteria, and are widely applied as outcome measures in conventional clinical trials of 2nd-line PBC therapy
4. Change in liver stiffness assessed by Transient Elastography (FibroScan) from screening to week 26
5. Safety and tolerability assessed by AE and SAE Reporting up to 26 weeks (visit 5)
6. Symptom severity and participant quality of life measured using the Quality of Life for Primary Biliary Cirrhosis (PBC-40) questionnaire (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6))
7. Symptom severity and participant quality of life measured using EQ-5D-5L questionnaire (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6))
8. Symptom severity and participant quality of life measured using Patient Health Questionnaire (26 and 52 weeks)

Experimental outcome measures
1. Percentage of participants in each study group who remain in remission at 52 weeks (visit 6) as a proportion of those who showed normalisation of serum alkaline phosphatase and total bilirubin levels, measured using blood samples at primary end-point assessment at 26 weeks (visit 5)
2. Serum levels of putative senescence-associated chemokines, demonstrated to be elevated in high-risk disease and UDCA non-responders in underpinning UK-PBC studies as outlined earlier, will be quantified using a bespoke multiplex assay and evaluated as dynamic risk and response markers. The combination of CCL20 and CXCL11 will be specifically explored as a baseline and early response predictive biomarker and validated against liver biopsy findings. Assessment of the capacity for ongoing elevation of chemokine biomarkers at 26 weeks to predict biochemical relapse at 52 weeks.
3. Change in liver fibrosis stage on liver histology and the degree of bile duct senescence assessed using p16 and p21 immunohistochemistry in a biopsy sub-study (n approx. 15 in each group). p16 and p21 are established and well-validated cellular markers of senescence. Biopsies will be centrally read by two pathologists blinded to treatment allocation and findings correlated with serum chemokine marker values.

Completion date
31/03/2027

Eligibility

Key inclusion criteria

1. Established diagnosis of PBC based on the presence of at least 2 out of the 3 key disease characteristics, specifically:
1.1. AMA or PBC-specific ANA at a clinically diagnostic level
1.2. Elevated alkaline phosphatase (above the upper limit of normal (ULN) for the relevant laboratory)
1.3. Compatible or diagnostic liver biopsy
2. Ongoing elevation of alkaline phosphatase (≥15% above ULN) at screening
3. Disease duration of <6 months from date of diagnosis at the time of consent
4. Use of UDCA for <3 months at the time of consent
5. Pre-treatment Ursodeoxycholic Acid Response Score with a predicted risk of future non-remission of liver biochemistry (ie ALP>ULN) with UDCA alone of >20%
6. For people of childbearing potential: an agreement to use at least an acceptable effective method contraception or to practise sexual abstinence to avoid pregnancy for entire duration of the study period.
7. Willing to complete the study assessment protocols
8. Ability to consent, able to comply with study protocol and attend clinic visits
9. Age ≥ 18 years at the time of consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Clinical contraindication to obeticholic acid use
2. Untreated, clinically significant pruritus (patients with effectively treated pruritus are eligible for inclusion)
3. Concomitant use of fibric acid derivatives (e.g. bezafibrate or fenofibrate) within 14 days prior to screening
4. Clinical suspicion of cirrhosis evidenced by a history of one or more of the following:
4.1. ascites requiring diuretic therapy or percutaneous drainage
4.2. endoscopically-confirmed varices
4.3. liver biopsy suggesting cirrhosis
4.4. platelet count <150 x109/L

4.5. transient elastography score >16.9 kPa within 3 months prior to or at screening
4.6. hepatocellular carcinoma confirmed by biopsy or 2 imaging modalities
4.7. hepatic encephalopathy
5. Bilirubin >twice the upper limit of normal
6. Evidence of complete biliary obstruction
7. Previous exposure to obeticholic acid (either in clinical trials or in clinical practice) or other potential PBC-modifying therapy
8. Regular (more than one week per month) alcohol consumption in excess of recommended safe limits (14 units per week)
9. Active participation in another interventional trial or exposure to another experimental drug within 5 half-lives
10. Pregnancy or planning to get pregnant within duration of participation in the trial
11. Currently breastfeeding
12. Overlapping features of an additional liver disease, including autoimmune hepatitis (using the Paris criteria for autoimmune hepatitis overlap)
13. Hypersensitivity to the active substance or to any of the excipients
14. If the participant's treating clinician deems the patient is not suitable to participate in the trial based on other criteria apparent during screening or from medical history
15. Previous liver transplantation

Date of first enrolment
30/09/2023

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust

Hills Road
Cambridge
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CB2 0QQ

Study participating centre
NHS Greater Glasgow and Clyde
Glasgow Royal Infirmary
91 Wishart Street
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G31 2HT

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
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England
NE7 7DN

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham Digestive Diseases Centre
E Floor, West Block
Derby Road
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England
NG7 2UH

Study participating centre
Portsmouth Hospitals University National Health Service Trust
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Study participating centre

Royal Free London NHS Foundation Trust
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		11/03/2026	12/03/2026	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes