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A study to evaluate the effect of Obeticholic Acid to treat patients with Primary Biliary Cholangitis (PBC) who also experience issues with cognitive function around memory and problem solving

Submission date	**Recruitment status**	[X] Prospectively registered
27/01/2021	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
08/04/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
15/04/2025	Digestive System	[X] Record updated in last year

Plain English Summary
Background and study aims
The aim of OACS-1 is to evaluate the effect of Obeticholic Acid (OCALIVA) in patients with a diagnosis of Primary Biliary Cholangitis (PBC) who also experience issues with cognitive function around memory and problem-solving.
The study is based on results of preclinical studies in mice where OCALIVA was shown to reverse both the liver disease and related cognitive impairment. OCALIVA is currently licensed for the treatment of PBC. It can be treated in combination with Ursodeoxycholic acid (UDCA) another drug used to treat with PBC or on its own. This study will treat patients who respond well to treatment with UDCA and also those who do not respond to UDCA. It has a well-known safety profile.
The aim of the study is to treat patients with OCALIVA at an earlier stage in the disease course to determine whether OCALIVA can improve cognitive function in patients with PBC.

Who can participate?
Patients between the ages of 18 and 65 years with established diagnosis of PBC.

What does the study involve?
Participants will be allocated at random to receive either Obeticholic acid or Placebo for approximately 26 weeks. Participant assessments will include MRI scans, blood tests, questionnaires, and a series of cognitive assessments on a validated research software tool.

What are the possible benefits and risks of participating?
It is hoped that study participants reciving Obeticholic Acid treatment will receive benefits to their cognitive symptoms. Additionally, feedback from patient groups, suggests that participation in the research programme, which is highly focused on the aspects of disease which matter most to patients is associated with a high degree of satisfaction. Fatigue with cognitive

symptoms, the target of the OACS-1 trial, is the number one patient priority for research because of the nature and scale of its impact. It is therefore believed that there will be indirect participant benefit from participating in the programme

Obeticholic acid is currently licensed for the treatment of PBC in the UK. The treating Clinicians in the study have clinical experience with Obeticholic acid 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 Obeticholic acid is not known. All participants will be asked to use effective contraception or to practice sexual abstinence for the entire duration of the treatment period. If a participant were to become pregnant during the course of study, the patient will be withdrawn from study treatment but will be followed up until the end of the pregnancy. The study team will also follow up any pregnancies of partners of participants who become pregnant while the participant is on the trial.

Where is the study run from?
The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
From April 2021 to December 2024

Who is funding the study?
Intercept Pharmaceuticals Inc (USA)

Who is the main contact?
Ms Ana Alvarez Franco, oacstrials@newcastle.ac.uk

Study website
http://research.ncl.ac.uk/oacs/

Contact information

Type(s)
Scientific

Contact name
Ms Ana Alvarez Franco

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Additional identifiers

EudraCT/CTIS number
2019-004776-19

IRAS number
270777

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 47265, IRAS 270777

Study information

Scientific Title
Obeticholic acid for the Amelioration of Cognitive Symptoms trial -1 (OACS-1)

Acronym
OACS-1

Study hypothesis
The aim of OACS-1 is to evaluate the effect of Obeticholic Acid (OCALIVA) in patients with a diagnosis of Primary Biliary Cholangitis (PBC) who also experience issues with cognitive function around memory and problem solving.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/12/2020, North East - Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ; +44 (0) 2071048285; tyneandwearsouth.rec@hra.nhs.uk), ref: 20/NE/0248

Study design
Single-centre double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Condition
Primary biliary cholangitis (PBC) leading to issues with cognitive function around memory and problem-solving.

Interventions
OACS-1 is looking at obeticholic acid (OCA) treatment in patients with stabilised Primary Biliary Cholangitis (PBC) (>2 years since diagnosis) and its effect on cognitive function. Participants will be randomised (1:1) to receive either obeticholic acid or matched placebo. A parallel trial (OACS-2) will be looking at OCA and early onset PBC. Neither the participant nor the study team will know what the treatment allocation. Rbadomisation will be carried out by designated and trained members of the research team using the Sealed Envelope system (a central, secure, 24 h web-based randomisation system with concealed allocation). The allocation sequence will be computer-generated, using a random permuted block design, with blocks of varying sizes. Block sizes will not be disclosed, to ensure concealment. Local research staff delegated this task via the delegation log, will be provided with a login and password for the randomisation system. Once consent has been obtained the research team will access the randomisation system, which will allocate the patient to receive OCALIVA or matched placebo. The randomisation system will generate a unique participant trial identifier and will allocate a kit number to be dispensed to the participant.

Potential participants will be identified through the Newcastle Specialist PBC clinics and the UK-PBC Cohort. Potential participants will be screened and if eligible, and happy to take part, they will be consented to the trial. As part of the trial, the participant will undertake a number of activities, questionnaires and imaging assessments. At the screening visit, following the participant giving consent to take part in the trial, demographic and medical history information will be taken, along with a clinical examination of the participant. Blood samples will be taken (for safety bloods) and female participants will undertake a pregnancy test. A fibroscan will also be undertaken as part of the screening activities. Consent will be sought from participants to use the MRI and CANTAB data for potential future PBC research. This will be optional. Consent will also be sought for optional additional blood samples to be used in future PBC research. These will be stored at a biobank facility.Participants will give consent to follow up any pregnancies which occur in the trial. This includes partners of participants who will complete a separate consent form.

Participants will also complete a series of CANTAB assessments as part of a familiarisation session. The aim of the familiarisation session is to allow participants to become familiar with the tests and testing environment. The results from the CANTAB tests in the familiarisation session will not be included in the analysis.

As part of the baseline visit, the participant will undertake the study questionnaires (EQ-5D-5L, PBC 40, COGFAIL, HADS, ESS, PSQI), complete the CANTAB assessments and have the MRI. Study

medication will be prescribed as part of the baseline visit. Participants will also be asked if they would like to give an optional additional blood sample to be analysed and stored in a biobank on top of their safety blood sample.

Visits will take place at 2 weeks (telephone call), 4 weeks, 12 weeks, 26 weeks and 30 weeks. At the 2 week telephone call, study treatment compliance, along with concomitant medications and adverse events will be checked.

Clinical examination will also be completed at 26 weeks. Vital signs will be assessed at 4, 12, 26, and 30 weeks. Blood samples will be taken at 4, 12, 26, and 30 weeks. The fibroscan will also be completed at 26 weeks. Questionnaires (EQ-5D-5L, PBC 40, COGFAIL, HADS, ESS, PSQI) will be completed 12, 26, and 30 weeks. An additional optional blood sample for the biobank will be taken at 26 weeks. The CANTAB assessments will also take place at 26 weeks. Participants will undergo another MRI at 26 weeks. Study therapy will be prescribed at the 4 and 12 week visits and study treatment compliance checked at 4, 12, and 26 week visits. Concomitant medication will be checked at visits 4, 12, and week 26. Adverse events will be checked at weeks 4, 12, 26, and 30.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Cognitive function measured using a composite score from the CANTAB cognitive testing platform, derived using individual scores from four core tests: One Touch Stockings of Cambridge (OTS), Paired Associates Learning (PAL), Rapid Visual Information Processing (RVP), and Spatial Working Memory (SWM) at baseline and 26 weeks

Secondary outcome measures
1. Cognitive function measured using the change in score for three additional CANTAB domains: Emotion Recognition Task (ERT), Multitasking Test (MTT), and Reaction Time (RTI) at baseline and 26 weeks
2. Cognitive symptoms measured using the patient-reported PBC-40 Cognitive Domain COGFAIL tool at baseline, 12, and 26 weeks
3. Primary biliary cholangitis (PBC) symptoms measured using the PBC-40 Cognitive Domain, Hospital Anxiety and Depression Scale (HADS), Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI) at baseline, 12, and 26 weeks
4. Global quality of life and health utility measured using the EuroQol 5-dimension 5-level quality of life questionnaire (EQ-5D-5L) at baseline, 12, and 26 weeks
5. Impact of Obeticholic Acid treatment on mechanistic brain changes in patients with PBC measured using Diffusion Tensor Imaging (DTI) (change in diffusion fractional anisotropy in the Bilateral Forceps Minor white matter tract) and T1 mapping MRI (change in frontal grey matter T1 relaxation time) at baseline and 26 weeks

Overall study start date
01/08/2019

Overall study end date
02/12/2024

Eligibility

Participant inclusion criteria
1. Established diagnosis of PBC based on the presence of ≥2 of the following key disease characteristics:
1.1. AMA or PBC-specific ANA at a titre of ≥1/40
1.2. Elevated alkaline phosphatase (above the upper limit of normal for the relevant laboratory)
1.3. Compatible or diagnostic liver biopsy
2. Diagnosed disease duration of ≥2 years
3. PBC-40 Cognitive Domain score of ≥12 at screening
4. Stable UDCA dose for 3 months, or not on UDCA if intolerant
5. Willing to complete the study assessment protocols
6. Willing to use highly effective contraception or to practice sexual abstinence to avoid pregnancy for the entire duration of the treatment period
7. Good command of the English language (to ensure that participants are able to comply with cognitive testing)
8. Able to consent, comply with the study protocol, and attend clinic visits
9. Aged between 18 and 75 years (updated 03/05/2023, previously 18 - 65 years)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

Total final enrolment
34

Participant exclusion criteria
1. Clinical suspicion of advanced disease evidenced by a history of ≥1 of the following:
1.1. Ascites requiring diuretic therapy or percutaneous drainage
1.2. Endoscopically confirmed varices
1.3. Liver biopsy suggesting cirrhosis
1.4. Platelet count <150
1.5. Bipolar spleen length >12 cm on ultrasound

1.6. Hepatocellular carcinoma confirmed by biopsy or 2 imaging modalities
1.7. Bilirubin >1.5 x ULN
1.8. Complete biliary obstruction
1.9 Fibroscan >17.6 kPa within the year prior to screening
2. Inter-current disease characterised by cognitive dysfunction (such as dementia or neurodegenerative disease) or clinical suspicion of age-related cognitive decline
3. Inter-current medication characterised by cognitive dysfunction (benzodiazepines, opiates other than codeine phosphate, sleeping pills, regular daily anti-histamine use in the last four weeks, anti-psychotic agents, or recreational drug use)
4. Anticipated change in PBC medication within the duration of the study
5. Contraindications to contrast free MRI assessment (active medical implants, such as cardiac pacemaker and metal implants)
6. Previous exposure to OCA (either in clinical trials or in clinical practice) or fibrate therapy for ≥3 months and within the last 3 months
7. Regular (more than one week per month) alcohol consumption in excess of recommended safe limits (14 units per week)
8. Active participation in another interventional trial or exposure to another experimental drug within 5 half-lives
9. Pregnancy or planning to get pregnant during the study period
10. Clinical diagnosis of Autoimmune Hepatitis (AIH)
11. Concurrent liver disease of another aetiology
12. Severe pruritus (>11 on PBC-40 pruritus domain)
13. Treating clinician deems the patient is not suitable to participate in the trial based on other criteria apparent during screening or from medical history

Recruitment start date
26/04/2021

Recruitment end date
13/09/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Newcastle Joint Research Office
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+44 (0)191 2824461
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Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Intercept Pharmaceuticals Inc

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/04/2026

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

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No