Clinical Trial Protocol

Full Title:	Optimising Primary Therapy in Primary Biliary Cholangitis
Short Title/Acronym:	**OPERA**
Protocol Version Number & Date:	**V3.0 dated 17 Nov 2023**

Previous Versions: N/A

Statement: This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

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RESEARCH SPONSOR

Sponsor Name:	**The Newcastle upon Tyne Hospitals NHS Foundation Trust**
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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

The undersigned also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Representative of the Research Sponsor

Name: Laura Frisby

Position:

Signature: Date:

Chief Investigator

Name: Professor David Jones

Position:

Signature: Date:

Senior Statistician

Name: Professor James Wason/ Dr Holly Fisher

Position:

Signature: Date:

Newcastle Clinical Trials Unit (NCTU)

Name: Professor Helen Hancock/ Professor Dawn Teare

Position: Director/ Deputy Director, NCTU

Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: **OPERA**

Principal Investigator

I have carefully read and understood protocol version 2.0 dated, 15 May 2023. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

Name:

Position:

Signature: Date:

KEY TRIAL CONTACTS

Chief Investigator	**Prof. David Jones** Professor of Liver Immunology, Newcastle University Translational and Clinical Research Institute, 4th Floor William Leech Building, Framlington Place, Newcastle-upon-Tyne NE2 4HH Tel: 0191 208 7572; Email: david.jones@ncl.ac.uk
Trial Manager(s)	**Dr Ciara Kennedy** Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne NE2 4AE Email: ciara.kennedy1@ncl.ac.uk **Ms Lysbeth Evans** Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne NE2 4AE Email: lys.evans@ncl.ac.uk
Data Manager	**Mr Christopher Weetman** **Ms Rebecca Summerly-Wafer** Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne NE2 4AE Email: christopher.weetman@ncl.ac.uk or rebecca.summerly-wafer@ncl.ac.uk
Senior Trial Manager	**Ms Sarah Dunn** Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne NE2 4AE Email: sarah.dunn2@ncl.ac.uk
Senior Project Manager	**Dr Emma Burton** Faculty of Medical Sciences, Newcastle University Wolfson Building Framlington Place, Newcastle-upon-Tyne NE2 4HH Tel 0191 208 7744; Emma.Burton@ncl.ac.uk
Senior Statistician	**Dr Holly Fisher** Population Health Sciences Institute, Newcastle University 4th Floor Ridley Building 1, Queen Victoria Road, Newcastle-upon-Tyne NE1 7RU Tel: 0191 208 7976; Email: holly.fisher@ncl.ac.uk
Clinical Trial Administrator	**Ms Alison Liddle** Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne, NE2 4AE Email: alison.liddle@ncl.ac.uk

Sponsor	**The Newcastle upon Tyne Hospitals NHS Foundation Trust** Level 1, Regent Point, Regent Farm Road Newcastle-upon-Tyne NE3 3HD Tel: 0191 2825959; Email: tnu-tr.sponsormanagement@nhs.net
Funder(s)	**MRC/NIHR EME** Email: netsmonitoring@nihr.ac.uk
Collaborators/Co-Investigators	**Prof. Helen Hancock** Director, Newcastle Clinical Trials Unit, 1-4 Claremont Terrace, Newcastle University, Newcastle-upon-Tyne, NE1 3BZ Tel: 0191 208 2516; Email: helen.hancock@ncl.ac.uk **Prof. James Wason** Professor of Biostatistics, Biostatistics Research Group Population Health Sciences Institute, Newcastle University 4th Floor Ridley Building 1, Queen Victoria Road, Newcastle upon Tyne NE1 7RU Tel: 0191 208 5590; Email: james.wason@ncl.ac.uk **Prof. Alastair Burt** Prof of Precision & Molecular Pathology Translational and Clinical Research Institute, Newcastle University 4th Floor William Leech Building, Framlington Place, Newcastle-upon-Tyne NE2 4HH Email: alastair.burt@ncl.ac.uk **Dr George Mells** Consultant Hepatologist Cambridge Liver Unit Cambridge University Hospitals NHS Foundation Trust Cambridge CB2 0QQ Email: gfm26@medschl.cam.ac.uk **Dr Palak Trivedi** Associate Prof. of Cholestatic Diseases and Honorary Cons. Hepatologist NIHR Birmingham BRC, Centre of Liver and Gastrointestinal Research Institute of Translational Medicine Building University of Birmingham Birmingham, B15 2GW Email: P.J.Trivedi@bham.ac.uk **Penny Bradley** Senior Lead Clinical Trial Pharmacist

	Freeman Hospital, Newcastle upon Tyne, NE7 7DN Email: nuth.pharmacyrandd@nhs.net **Robert Mitchell-Thain** Chief Executive Officer, PBC Foundation Email: robert@pbcfoundation.org.uk **Dr Jessica Dyson** Consultant Hepatologist & Hon Senior Lecturer in Hepatology Translational and Clinical Research Institute, 3rd Floor William Leech Building, Framlington Place, Newcastle-upon-Tyne, NE2 4HH Email: Jessie.Dyson@newcastle.ac.uk **Dr Geraldine Carroll** Clinical Research Fellow Translational and Clinical Research Institute, 4th Floor William Leech Building, Framlington Place, Newcastle-upon-Tyne, NE2 4HH Email: geraldine.carroll@nhs.net **Dr Jem Palmer** Team Scientist Translational and Clinical Research Institute, 3rd Floor William Leech Building, Framlington Place, Newcastle-upon-Tyne, NE2 4HH Email: jeremy.palmer@ncl.ac.uk
Committees	**Trial Steering Committee (TSC), Chair** Prof Salim Khakoo Professor of Hepatology Head of The School of Clinical and Experimental Sciences University of Southampton Email: S.I.Khakoo@soton.ac.uk **Independent Data Monitoring Committee (IDMC), Chair** Prof Cynthia Levy Professor of Medicine Division of Hepatology University of Miami Miller School of Medicine Email: CLevy@med.miami.edu
NCTU Trial Management Team	opera@newcastle.ac.uk For all day to day queries
Secure email for NCTU trial team	nctu.opera.conf@nhs.net To securely send confidential consent forms
Secure email for SAE reporting	nctu.opera.sae@nhs.net This is a distribution list to inform Sponsor, NCTU and CI simultanenously

Contents

TRIAL SUMMARY

Trial Title	**O**ptimising **P**rimary Th**e**rapy in P**r**im**a**ry Biliary Cholangitis	
Acronym	OPERA	
Clinical Phase	Phase 2b	
Summary of Trial Design	Randomised, double blind, placebo-controlled trial of the FXR agonist Obeticholic Acid in combination with ursodeoxycholic acid (UDCA), as first-line treatment of high risk primary biliary cholangitis (PBC)	
Summary of Participant Population	Adults with recent onset Primary Biliary Cholangitis (PBC) who are at an enhanced risk of non-response to standard first-line therapy	
Planned Sample Size	Total n =106 (Obeticholic Acid n=53; Placebo n=53)	
Treatment Duration	26 weeks	
Follow Up Duration	26 weeks post treatment	
Endpoints	**Objective**	**Outcome measure/endpoint**
Primary	To assess the impact of first line obeticholic acid therapy combined with UDCA standard of care therapy compared to placebo in achieving biochemical remission of disease in new onset PBC patients with an enhanced disease risk.	Percentage of participants showing normalisation of serum alkaline phosphatase and total bilirubin levels at 26 weeks (visit 5).
Secondary	a) To assess whether biochemical remission is sustained following discontinuation of experimental therapy and reversion to UDCA standard of care therapy. b) To assess the degree of biochemical improvement with obeticholic acid therapy combined with UDCA standard of care therapy compared to placebo. c) To assess 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).	Percentage of participants in each study group showing sustained normalisation of serum alkaline phosphatase and total bilirubin levels at 52 weeks (visit 6). Magnitude of alkaline phosphatase and bilirubin reduction from baseline to 26 weeks (visit 5), assessed as a continuous variable. 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 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.

		Change in liver stiffness assessed by Transient Elastography (FibroScan) from screening to week 26.
	d) To assess the safety and tolerability of obeticholic acid as first line therapy in PBC.	AE and SAE Reporting up to 26 weeks (visit 5).
	e) To assess the impact of the intervention compared to placebo on symptom severity and participant quality of life.	PBC-40 (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6)). EQ-5D-5L (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6)). Patient Health Questionnaire (26 and 52 weeks).
Experimental	a) 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 in remission at 26 weeks.	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 at primary end-point assessment at 26 weeks (visit 5).
	b) To assess changes in chemokine levels in the blood potentially associated with bile duct senescence.	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
	c)To assess impact of intervention compared to placebo on degree of	Change in liver fibrosis stage on liver histology and the degree of bile duct

	liver inflammation and bile duct senescence.	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 [1]. Biopsies will be centrally read by two pathologists blinded to treatment allocation and findings correlated with serum chemokine marker values.
Investigational Medicinal Product(s)	Obeticholic acid and matched placebo	
Formulation, Dose & Route of Administration	Obeticholic Acid oral tablets at a dose of 5mg per day, titrated up to a maximum of 10mg/day after 12 weeks according to tolerability; or identical placebo.	

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-Mitochondrial Antibody
ANA	Anti-Nuclear Antibody
AR	Adverse Reaction
AST	Aspartate aminotransferase
BEC	Biliary epithelial cells
BSG	British Society of Gastroenterology
CESP	Common European Submission Portal system
CDMS	Clinical data management system
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DM	Data Manager
DPA	Data protection act
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EoT	End of trial
EudraCT	European Clinical Trials Database
FBC	Full blood count
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
GP	General Practitioner
HCRW	Health and Care Research Wales
HRA	Health Research Authority
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICO	Information Commissioner's Office
IDMC	Independent Data Monitoring Committee
IMP	Imvestigational Medicinal Product
INR	International normalised ratio
ISF	Investigator Site File
ITT	Intention to treat
LFT	Liver function test
LPLV	Last Patient Last Visit
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
OCA	Obeticholic acid
PBC	Primary Biliary Cholangitis (formerly Primary Biliary Cirrhosis)
PI	Principal Investigator
POCBP	People of Childbearing Potential

PP	Per-protocol
QA	Quality Assurance
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SE	Sealed Envelope
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TS	Trial Statistician
TSC	Trial Steering Committee
TMF	Trial Master File
U&Es	Urea and electrolytes
ULN	Upper limit of normal
UDCA	Ursodeoxycholic acid
UK-PBC	United Kingdom PBC (research consortium)
URS	UDCA Response Score
USM	Urgent Safety Measure

1. BACKGROUND & RATIONALE

Our systematic review of the literature, patient consultation and research programme carried out under the auspices of the UK-PBC research consortium (www.UK-PBC.com) have identified significant risks to life, and impairment of life quality, as important ongoing issues in the autoimmune liver disease primary biliary cholangitis (PBC) despite current treatments [2, 3]. PBC affects c18,000 UK patients (prevalence is 40/100,000 in the UK with an estimated incidence of 1-2/100,000 per year) [4]. Clinical impact in PBC comes from the risk of progression to cirrhosis with the associated complications of variceal bleeding, hepatocellular carcinoma and, eventually, liver failure and death [5-8]. Impact also comes from difficult-to-treat symptoms, specifically pruritus, fatigue and cognitive dysfunction, that can occur at any point in the disease course, and which result in significant impact on health utility [9-16].

Therapy is available for PBC, and used widely, but its effectiveness is limited. First-line treatment is with ursodeoxycholic acid (UDCA), which improves liver biochemistry, reduces liver cancer risk, delays liver transplantation, and increases life-expectancy in a proportion of individuals [8, 9, 17-19]. However, c40% of UDCA-treated patients still go on to develop cirrhosis (40% in a multicentre study of >1000 patients over 10 years [20]; 46% of patients in contemporary USA 'real world data' report of 15,875 patients [21]), c60% display persistently abnormal liver blood tests despite UDCA (59% in a UK-PBC nested cohort of 408 patients) and >80% continue to experience symptoms, especially fatigue and cognitive symptoms that are seemingly not modified by any current intervention [9, 10, 16, 22].

Current treatment paradigms grant access to the licensed 2nd-line therapy obeticholic acid (OCA; a first in class farnesoid X receptor (FXR) agonist) given in addition to UDCA**, only after patients are deemed to be 'non-responders' to UDCA**. This 'step-up' approach means that the most effective agent is only used after 1st-line therapy has been tested (and failed) for at least a year. We believe that this approach is inherently flawed, as it does not take into account the progressive nature of PBC and the importance of modifying the pivotal disease process leading to liver injury, **biliary epithelial cell (BEC) senescence** [1, 23-26]. Addressing this flaw lies at the heart of this trial.

An additional limitation in current PBC management is the acceptance of 'improving' liver biochemistry as a surrogate for disease activity and long-term outcomes, rather than complete normalisation ("biochemical remission). Recent data from the large, retrospective Global PBC Study (the other major source of large cohort clinical data in PBC after UK-PBC) has shown that anything other than normalisation of both alkaline phosphatase and bilirubin with UDCA therapy is associated with significantly increased risk of death or need for transplant [19, 27]. Recent UK-PBC data have shown that any degree of abnormality in liver function tests (LFT), even if they are within the rage of UDCA "response" is associated with ongoing disease inflammatory activity[28]. There is a growing consensus in the PBC field, therefore, that normalisation of liver serum biochemistry should be the goal for disease therapy.

In PBC, UDCA treatment failure does not occur at random; rather, it is predictable. Studies from UK-PBC have clearly shown that UDCA treatment failure can be accurately predicted by pre-treatment clinical parameters including the patient's age and serum biochemistry [17]. Furthermore, these parameters can be developed into a highly reproducible and accurate predictive score (the **UDCA Response Score, URS**) that has been validated in Italian and Japanese populations [29]. An accompanying editorial highlighted the potential utility of the UDCA Response Score in supporting a

changed model for PBC therapy in which, rather than waiting to 'step-up' to more effective therapy after proven UDCA failure, treatment may be 'stratified' at baseline, with primary combination therapy offered at diagnosis in patients unlikely to achieve remission on UDCA alone [30]. Once biochemical remission is achieved the potential for 'step down' to UDCA monotherapy can be explored in the future.

The impact of waiting to institute more effective therapy in UDCA non-responders goes beyond simply delaying clinical benefit. UK-PBC studies have demonstrated that delay in therapy in PBC leads to a significantly reduced likelihood that the therapy will work when eventually used [17]. The importance of BEC senescence in disease pathogenesis, its contribution to the high-risk phenotype (including progression to irreversible bile duct loss), and the fact that it begins early in the disease process in high-risk patients (and is progressive thereafter) affords explanation as to why treatment delay results in reduced treatment efficacy. This emphasises the need for earlier, better and more efficient treatment models – a concept that underpins the study proposed herein.

In this trial, we will evaluate a novel treatment strategy in newly presenting PBC patients. We will use the validated UDCA Response Score to identify, **at the point of disease diagnosis**, patients who are at reduced likelihood of going on to achieve biochemical remission in response to UDCA monotherapy, and implement a risk-determined stratified approach whereby the licensed 2nd-line therapy (OCA) is used from the outset in combination with existing first-line therapy [17]. This strategy will allow us to optimise treatment delivery in the higher risk group early on, without over-treating the lower risk patients. We will also adopt an emerging, evidence-based stringent primary outcome of complete disease control (normalisation of liver biochemistry). In a mouse model of cholestasis (bile duct ligation), there is a high degree of senescence within the liver (including the BEC) and associated ductular proliferation. **OCA, when given early in the disease, reverses senescence**, as well as reversing ductular proliferation and reducing the burden of liver fibrosis[31].

This trial will adopt a dosing regime optimal for reaching effective doses of obeticholic acid whilst avoiding pruritus in a trial design setting where liver function test levels aren't appropriate for use in assessing efficacy and guiding dose escalation.

As noted in section 4.4 of the NICE guideline for OCA in PBC [32] and based on the findings of the POISE Trial, clinical effectiveness would be better measured at 10mg. The OPERA trial will close this gap in the literature by measuring an observable disease modifying effect within the trial timeframe of 26 weeks. 26 weeks is long enough to see a disease modifying effect and yet short enough to allow us to discontinue therapy. If relapse is experienced by the participant after 26 weeks, participants will be assessed for suitability for introduction of OCA at one year post-UDCA start, according to the current NHS standard of care protocol.

The OPERA dosing regime and visit model will ensure safety and monitoring of participant above that currently in use in the PBC clinical environment. The safety profile of OCA in PBC is well understood (SmPC for OCALIVA 5mg film-coated tablets) and occurrence of pruritius, the most commonly reported side effect, is managed in standard care by a phone-call with the patient in between clinic visits.

In parallel, we will further validate, and explore the clinical utility of, a mechanistic composite biomarker linked to BEC senescence, based around circulating levels of the chemokines CCL20 and CXCL11 [33]. These parameters will be used to predict and quantify the response to 2nd-line therapy instituted early, comparing it to clinical outcomes, and to the gold standard of liver biopsy assessment of BEC senescence. This marker, developed in UK-PBC pilot studies, has a positive predictive value (PPV) of 94%, a negative predictive value (NPV) of 78%, and an area under the receiver operator curve (AUROC) of 0.91 for the identification of UDCA non-responding patients stratified using the current clinical criteria [33].

1.1. Risk Assessment

This trial is categorised as:

- **Type B = somewhat higher than the risk of standard clinical care**

2. OBJECTIVES AND OUTCOME MEASURES

a) Show that treatment with OCA and UDCA from diagnosis improves rates of biochemical remission in higher risk patients, and that biochemical remission is associated with reduction in histological activity. This will establish the concept of full disease remission and validate a disease modifying treatment model.

b) Establish the impact of that treatment model on PBC symptoms.

c) Assess whether remission is sustained over a further six months following reversion to standard of care with UDCA alone (indicating a possible disease trajectory modifying effect). This will guide future investigation of the need for, and optimal duration of, remission-maintaining therapy. Study of any such maintenance approach would lie outside the scope of the current study and would be the subject of a future research.

The **mechanistic objectives** of the study are to:

d) Assess the value of **UK-PBC Risk Marker** chemokine panel based on the peripheral blood markers CXCL11 and CCL20 for predicting response to therapy.

e) Assess the extent to which baseline and early therapy (at three months of trial medication) biomarker levels predict biochemical remission at six months. This is a key question as early response/non-response prediction has been a transformative step in other areas of liver therapeutics.

f) Determine the proportion of patients who enter biochemical remission at six months yet exhibit ongoing disease activity according to circulating biomarkers; and whether the latter can be used to predict future disease relapse at 12 months (i.e., six months after the end of the trial therapy period).

	OBJECTIVES	**OUTCOME MEASURES/ENDPOINTS**

Primary	To assess the impact of first line obeticholic acid therapy combined with UDCA standard of care therapy compared to placebo in achieving biochemical remission of disease in new onset PBC patients with an enhanced disease risk.	Percentage of participants showing normalisation of serum alkaline phosphatase and total bilirubin levels at 26 weeks (visit 5).
Secondary	a) To assess whether biochemical remission is sustained following discontinuation of experimental therapy and reversion to UDCA standard of care therapy. b) To assess the degree of biochemical improvement with obeticholic acid therapy combined with UDCA standard of care therapy compared to placebo. c) To assess 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). d) To assess the safety and tolerability of obeticholic acid as first line therapy in PBC. e) To assess the impact of the intervention compared to placebo on symptom severity and participant quality of life.	Percentage of participants in each study group showing sustained normalisation of serum alkaline phosphatase and total bilirubin levels at 52 weeks (visit 6). Magnitude of alkaline phosphatase and bilirubin reduction from baseline to 26 weeks (visit 5), assessed as a continuous variable. 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 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. Change in liver stiffness assessed by Transient Elastography (FibroScan) from screening to week 26. AE and SAE Reporting up to 26 weeks (visit 5). PBC-40 (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6)). EQ-5D-5L (change from baseline to 26 weeks (visit 5) and 52 weeks (visit 6)).

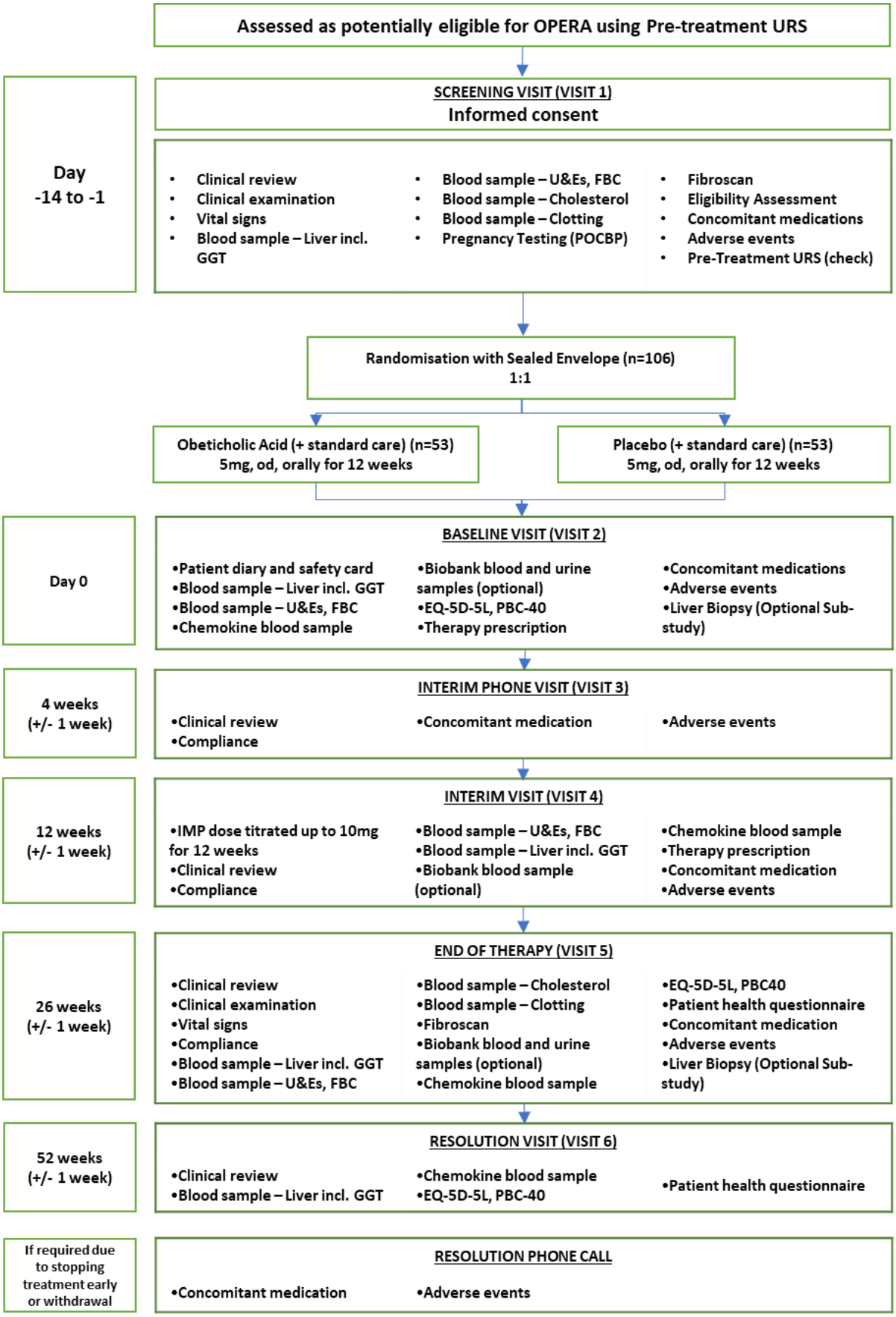
		Patient Health Questionnaire (26 and 52 weeks).
Experimental	a) To assess whether biochemical remission is sustained following discontinuation of experimental therapy and reversion to UDCA standard of care therapy in those participants who are in in remission at 26 weeks. b) To assess changes in chemokine levels in the blood potentially associated with bile duct senescence. c)To assess impact of intervention compared to placebo on degree of liver inflammation and bile duct senescence.	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 at primary end-point assessment at 26 weeks (visit 5). 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. 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 [1]. Biopsies will be centrally read by two pathologists blinded to treatment allocation and findings correlated with serum chemokine marker values.

3. TRIAL DESIGN

The trial is a double-blinded, superiority placebo-controlled randomised multi-centre trial of an investigational medicinal product (CTIMP). To improve trial efficiency, a key issue in a rare disease such as PBC, we will also use an innovative augmented binary analysis method to improve the precision of a trial where a dichotomous endpoint is derived from continuous data [34]. Using this method substantially reduces the sample size needed for a power of 90%.

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. 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 treatment with UDCA at the time of consent and at an enhanced risk of not achieving biochemical disease remission (based on URS) with UDCA 1st-line therapy alone.


Assessed as potentially eligible for OPERA using Pre-treatment URS
Day -14 to -1
SCREENING VISIT (VISIT 1)
Informed consent
• Clinical review
• Clinical examination
• Vital signs
• Blood sample – Liver incl. GGT
• Blood sample – U&Es, FBC
• Blood sample – Cholesterol
• Blood sample – Clotting
• Pregnancy Testing (POCBP)
• Fibroscan
• Eligibility Assessment
• Concomitant medications
• Adverse events
• Pre-Treatment URS (check)
Randomisation with Sealed Envelope (n=106)
1:1
Obeticholic Acid (+ standard care) (n=53)
5mg, od, orally for 12 weeks
Placebo (+ standard care) (n=53)
5mg, od, orally for 12 weeks
Day 0
BASELINE VISIT (VISIT 2)
•Patient diary and safety card
•Blood sample – Liver incl. GGT
•Blood sample – U&Es, FBC
•Chemokine blood sample
•Biobank blood and urine samples (optional)
•EQ-5D-5L, PBC-40
•Therapy prescription
•Concomitant medications
•Adverse events
•Liver Biopsy (Optional Sub-study)
4 weeks (+/- 1 week)
INTERIM PHONE VISIT (VISIT 3)
•Clinical review
•Compliance
•Concomitant medication
•Adverse events
12 weeks (+/- 1 week)
INTERIM VISIT (VISIT 4)
•IMP dose titrated up to 10mg for 12 weeks
•Clinical review
•Compliance
•Blood sample – U&Es, FBC
•Blood sample – Liver incl. GGT
•Biobank blood sample (optional)
•Chemokine blood sample
•Therapy prescription
•Concomitant medication
•Adverse events
26 weeks (+/- 1 week)
END OF THERAPY (VISIT 5)
•Clinical review
•Clinical examination
•Vital signs
•Compliance
•Blood sample – Liver incl. GGT
•Blood sample – U&Es, FBC
•Blood sample – Cholesterol
•Blood sample – Clotting
•Fibroscan
•Biobank blood and urine samples (optional)
•Chemokine blood sample
•EQ-5D-5L, PBC40
•Patient health questionnaire
•Concomitant medication
•Adverse events
•Liver Biopsy (Optional Sub-study)
52 weeks (+/- 1 week)
RESOLUTION VISIT (VISIT 6)
•Clinical review
•Blood sample – Liver incl. GGT
•Chemokine blood sample
•EQ-5D-5L, PBC-40
•Patient health questionnaire
If required due to stopping treatment early or withdrawal
RESOLUTION PHONE CALL
•Concomitant medication
•Adverse events

4. TRIAL SETTING

This is a multicentre study in England which will be undertaken in specialist clinics in secondary/tertiary referral centres (or as per local set up). These centres will be specialists in the area of PBC management and will manage patients from across their local region.

5. ELIGIBILITY CRITERIA

We will use the following approaches to participant identification/definition:

a) PBC Diagnosis: We will use the standard diagnostic approach used in the UK treatment guidelines for PBC i.e., the presence of at least two out of three key diagnostic criteria [35, 36].

b) Enhanced Risk of Future Non-Response to UDCA: The UK-PBC consortium developed and validated a predictive score (the UDCA Response Score (URS): http://www.uk-pbc.com/resources/tools/udca-treatment-response-score-urs/) that shows a high level of accuracy at predicting future UDCA non-response (reduction in biochemistry using historic criteria; AUROC 0.86) and non-remission (failure to normalise biochemistry), when used prior to UDCA therapy (at the point of disease diagnosis) [17]. The use of this tool to predict high-risk patients early in the disease in order to target more effective primary therapy has been advocated by experts in the field [30]. For the purposes of this study, we will use of criterion of a predicted risk of non-remission of >20% as the basis for stratification into the trial.

c) Non-cirrhotic disease: The study will be restricted to non-cirrhotic patients for reasons of safety and likely efficacy. Given that over 90% of PBC patients are not cirrhotic at presentation this will not materially impact upon recruitment.

Eligibility must be assessed by a medically qualified doctor and this assessment documented in the participant's medical notes using an eligibility checklist. Only personnel formally delegated by the Principal Investigator to assess eligibility may perform this task.

5.1. Inclusion Criteria

1. Established diagnosis of PBC based on the presence of at least 2 out of the 3 key disease characteristics, specifically:
    a. AMA or PBC-specific ANA at a clinically diagnostic level
    b. Elevated alkaline phosphatase (above the upper limit of normal (ULN) for the relevant laboratory)
    c. 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 [17] with a predicted risk of future non-remission of liver biochemistry (i.e., ALP>ULN) with UDCA alone of >20%.

6. For people of childbearing potential (POCBP): an agreement to use at least an acceptable effective method of contraception or to practise sexual abstinence* to avoid pregnancy for the 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

* Abstinence is defined as refraining from heterosexual intercourse during the entire study period Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. See section 8.6 for acceptable highly effective contraceptive methods.

5.2. 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:
    a. ascites requiring diuretic therapy or percutaneous drainage
    b. endoscopically-confirmed varices
    c. liver biopsy suggesting cirrhosis
    d. platelet count <150 $x10^9$/L
    e. transient elastography score >16.9 kPa within 3 months prior to or at screening
    f. hepatocellular carcinoma confirmed by biopsy or 2 imaging modalities
    g. 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.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. Protocol waivers are not permitted.

6. TRIAL PROCEDURES

6.1. Recruitment

6.1.1. Patient Identification

This is a multi-centre study recruiting from at least 10 centres giving broad geographical coverage and facilitating widespread patient access. Participants will be identified through attendance at routine clinics or by database search. Sites will use a standard letter of invitation and Participant Information Sheet (PIS) to approach patients who are potentially eligible for the trial. This may be in person at a routine clinic appointment, or by post, phone or email as appropriate. The patient's regular clinical care team will ask potentially eligible patients for their permission to be contacted by a member of the research team (where the regular clinical care team is not the same as the research team).

It is also expected that the clinical care team at nearby secondary centres will identify newly diagnosed PBC patients who are potentially eligible for the trial through routine clinics and refer to their local participating site. The patient's clinical care team will hand out a PIS to potentially eligible patients and request permission from the patient to refer him or her to the research team in the local trial centre.

If a patient agrees to be contacted by the research team, the referring clinical care team will directly contact the local trial centre research team by email. This e-mail will include the patient contact details, date of diagnosis, PBC medication details, age, sex and relevant blood biochemical tests to allow eligibility to be assessed in terms of the URS cut-off and URS (if calculated).

The main route for direct patient awareness raising will be through regional (e.g., LIVErNORTH) and national (PBC Foundation) patient groups. Interested patients can ask their doctor to be referred to the trial or contact the trial team directly. We will write articles for the newsletters, websites and social media for both organisations and will highlight the trial at local and national speaker meetings. We will also produce and display posters in the waiting areas alerting patients to the trial and invite them to discuss the opportunity further with members of the clinical team.

6.1.2. Pre-screening

When a referral is received, the URS will be calculated by a member of the trial team using the diagnostic blood test results available through standard care. The referring centres/clinicians will also have the option to assess URS to determine potential eligibility prior to referral, should they wish to.

The trial centre research team will then contact potentially eligible invited patients, usually by telephone to discuss the trial in more detail and arrange a formal screening visit where appropriate, or alternatively write to the referrer with a copy to the patient, to let them know that they are not eligible for the trial. If patients have not been given a PIS, this will be sent by post/email prior to the screening visit.

For patients deemed not eligible following pre-screening, only non-identifiable information will be retained (incl. sex and URS). The trial screening log will include all patients pre-screened for the trial (regardless of outcome).

6.1.3. Consent

Potentially eligible participants will be invited for a screening visit where informed consent will be taken. Screening will take place in a dedicated session held at the clinic facility in which normal care is offered, or at a research specific visit. Patients will be encouraged to ask questions about the trial and consider whether they wish to participate. The patient will be informed of his/her right to withdraw from the trial at any time without being subject to any resulting detriment, by revoking his/her informed consent. Consent discussions, including contraception if applicable, must be documented in the participant's medical records (see section 8.6 for definition of people of child-bearing potential and appropriate methods of contraception).

Informed consent will only be sought by a member of the trial team who is medically qualified, appropriately trained and delegated to do so. Potential participants will have sufficient time to review the trial documentation prior to this screening visit (this will likely be at least 24 hours but may be less depending on circumstances) as well as an opportunity to have a conversation with a member of the trial team. Consent will be obtained prior to any activities undertaken as part of the screening visit (Visit 1).

The original signed consent form will be retained in the Investigator Site File (ISF), with additional copies provided to the patient and filed (or scanned) into the patient's medical notes. Participants will specifically consent to their GP (and referring clinician where applicable) being informed of their participation in the trial.

A copy of the patient's consent form will be sent to NCTU via secure email (e.g., nhs.net to nhs.net or encrypted) to allow for monitoring of the consent process, and the copy then destroyed.

In the case of protocol amendments or information becoming available which may affect the participant's willingness to continue in the trial, it may be necessary to re-consent the participant on an updated consent form (after necessary regulatory approvals are obtained).

Consent for the optional biopsy sub-study will be through an optional clause on the main trial informed consent form.

Consent for the storage and use in future PBC research of remaining chemokine blood samples and associated sample information in Newcastle Biobank, following analysis for the purposes of the trial, will be through an optional clause on the main trial informed consent form. Participants can also optionally consent to provide additional blood and urine samples during the trial, and for these samples and associated sample information to be stored in Newcastle Biobank and used for future PBC research.

6.1.4. Screening & Eligibility Assessment

Following consent and prior to trial entry, all subjects will be screened to assess eligibility, ensuring compliance with trial inclusion and exclusion criteria (sections 5.1 and 5.2). Eligibility must be assessed by a medically qualified doctor and this assessment must be documented in the participant's medical

notes by completion of an eligibility checklist. The eligibility checklist must also be completed in the trial Clinical Data Management System (CDMS) for all patients screened for the trial. Only medically qualified personnel formally delegated by the site PI to assess eligibility may perform this task. For central monitoring purposes a copy of the eligibility checklist will be sent to NCTU via secure email.

6.1.5. Payment

Participants will be offered reasonable travel expense reimbursement for trial visits.

6.2. Randomisation

Patients who provide informed consent to participate and fulfil the eligibility criteria will be randomly allocated to receive either obeticholic acid or matched placebo by designated and trained members of the research team using the Sealed Envelope (SE) system (a central, secure, 24-hour web-based randomisation system with concealed allocation). Patients will be randomised in a ratio of 1:1 (placebo: intervention), with stratification according to consent to the biopsy sub-study (to ensure equal allocation between arms in the sub-study). 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 trial centre research staff delegated the randomisation task on the delegation log, will be provided with a login and password for SE.

Once consent is obtained and eligibility confirmed the research team will access SE, which will allocate the patient to receive obeticholic acid or matched placebo. SE will allocate a kit code to be dispensed to the participant.

Participants can be randomised ahead of their baseline visit, as long as all screening activity has been completed and the participant deemed eligible to participate in the trial by the PI or other medically qualified personnel at site and in line with local site policies and practices.

6.3. Blinding

The OPERA trial will be double-blinded. Participants, the clinical and research team will be unaware of each participant's allocated treatment group.

The TMG will be blind to the treatment allocation excluding the NCTU Data Manager (DM) and Trial Statistician (TS)/ Senior Statistician. In emergency situations, some clinical members of the TMG may be unblinded to individuals under their care. A contracted vendor is responsible for the labelling of the IMP and matched placebo and will therefore be unblinded from the start of the trial. The NCTU Blinding log is kept in the TMF and provides a list of all blinded and unblinded trial staff.

6.4. Unblinding

Unblinding should only occur for valid medical or safety reasons where it is necessary for the treating clinician to know which treatment the participant has been receiving. When treating a participant, and to avoid any unnecessary unblinding, it should be assumed that the patient is on

active treatment within the trial. In-line with current standard of care for PBC patients receiving OCA, there is no trial specific out of hours service for OPERA. The risk that participants may have an emergency due to their treatment is not deemed to be out with the standard of care model. Participants will be issued with a trial safety card which they are asked to carry at all times. The card states the name of the trial drug and instructs the holder to show it to any medical personnel involved in their care. The card will also state the local PI name and contact details should the participant or clinical staff have any questions. Participants who have undergone biopsy will be given local contact details at discharge as per standard care.

It is likely that if unblinding occurs it will be for one of the following reasons:

- In the event of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR)
    - see section 9 for reporting details
    - This will be undertaken in accordance with the regulatory requirements for safety reporting in CTIMPs
- At the request of a senior clinician responsible for the care of the trial participant
    - Such requests are likely to occur only in the case of an SAE and are expected to be rare

Unblinding will only be performed by the PI or another medically qualified trial member designated this task on the delegation log. Details provided in the unblinding notification will only be communicated to the individual performing the unblinding and must not be shared unless required in an emergency setting or for patient care. If the unblinding is performed by a delegated member of the team, they should inform the site PI immediately of any unblinding, but the PI should not be told what arm the participant had been allocated to The details of the unblinding will be documented in the ISF, TMF and participant's medical notes and include the following details:

- Participant ID
- Who broke the code
- When the code was broken
- Reason for unblinding

The NCTU will inform the Sponsor and the CI of all instances of unblinding but each of these parties will remain blind to treatment allocations themselves wherever possible.

A full audit trail of any unblinding performed on SE is recorded, this includes:

- Participant ID
- Date and time of unblinding
- Name of person performing unblinding
- Reason for unblinding

Where a trial participant's treatment allocation has been unblinded, the participant will be withdrawn from treatment in the trial. They may remain in the trial to be followed up as per protocol (see section 6.6 for withdrawal information).

All participants will be offered the opportunity to be unblinded following data download at the end of the trial (all patients completed).

Code break envelopes will not be utilised for this trial. In the event of an emergency, participants will be treated as if they are on trial treatment until they are unblinded using SE.

6.5. Trial Assessments

6.5.1. Clinical Review

Clinical history taking as relevant to PBC and this trial, adapted according to the type of visit. At screening this will include demographics, a detailed clinical review of PBC and its symptoms as well as medication history. At subsequent review the focus will be on the nature of any changes in the history since screening, including any symptom changes or de novo symptom development and/or difficulties with taking medication.

6.5.2. Clinical Examination

A full physical examination will be conducted, including examination of skin; lymph nodes; eyes; ears; nose; throat; respiratory; cardiovascular; abdomen; musculoskeletal; neurological assessment; mental status assessment. Bodyweight will also be measured.

6.5.3. Vital Signs

Heart rate, blood pressure and temperature will be recorded.

6.5.4. Blood Sampling

A blood sample will be taken (maximum 50 ml) at times specified in the schedule of events (Table 6.5.10) for the following assessments:

- Renal function: urea, creatinine and serum electrolytes (U&E's)
- Liver biochemistry: ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, albumin
- Cholesterol (total cholesterol, LDL, HDL, total:HDL ratio and triglycerides)
- Full blood count (haemoglobin, platelets & white cells – neutrophils & lymphocytes)
- Clotting: Prothrombin Time (PT) and activated partial thromboplastin time (APTT)
- Experimental chemokine blood marker
- Optional biobank blood sample

Clinical samples will be analysed in the routine clinical laboratories of the study site, following standard local laboratory procedures.

The samples for the experimental chemokine marker will be separated by centrifugation (following the trial SOP) and will be stored locally at -80°C before being transferred on dry ice to Newcastle Biobank for storage prior to analysis. All chemokine samples will be analysed simultaneously at the end of the trial. Following analysis, samples will be retained in Newcastle Biobank for use in future PBC research or destroyed depending on the consent of the participant. All chemokine assessments will be performed in a fully blinded manner, with regard to treatment group and pre and post-therapy timing.

Participants will be asked if they are willing to provide consent to give three optional additional blood samples (baseline, visits 4 and 5). One tube (4mL) will be taken at each of these visits and processed by site staff and stored locally at -80°C before being transferred on dry ice to Newcastle Biobank for storage and use in future PBC research. At visits 4 and 5, data associated with the samples (timing of last meal, and time IMP last taken) will also be collected.

Further details regarding the processing, transfer, analysis and storage of these samples can be found in the OPERA Lab Manual. Please refer to this document for more information.

6.5.5. Urine Sampling

Participants will be asked if they are willing to provide consent to give two optional urine samples (baseline and visit 5). Aliquots will be stored locally at -80°C before being transferred on dry ice to Newcastle Biobank for storage and use in future PBC research.

6.5.6. Ursodeoxycholic Response Score (URS)

The URS predicts the likelihood of someone responding to UDCA [17]. URS must be calculated using the OPERA URS calculator that is provided as part of this clinical trial.

The URS calculator considers three different “cut-offs” to define UDCA response, in this trial we use the version that considers the outcome of interest to be biochemical remission (that is ALP < 1 x ULN). Based on the URS value, a predicted probability of biochemical remission can be calculated. For the purposes of trial eligibility, URS will be calculated using blood results prior to treatment with UDCA.

6.5.7. Pregnancy testing

For people of childbearing potential, a urine sample based pregnancy test will be carried out during the trial screening visit (or serum as per local site policy).

6.5.8. Questionnaire based symptom assessment tool package

If site staff feel that it would be appropriate for more of the questionnaires to be completed by participants at home due to extenuating circumstances, then they can also be sent to participant’s homes for completion in advance of a visit if felt it would be of a benefit to the participant.

6.5.8.1. EQ-5D-5L

EQ-5D-5L is a 5 item, validated general quality of life measure form which health utility can be calculated [37]. This is a score within the range 0-1.0 for quality of life, where 0 is equivalent to death and 1 represents perfect health. EQ-5D-5L is optimised for patient self-completion and will be undertaken on paper in this trial.

6.5.8.2. PBC-40

PBC-40 is a disease specific, patient derived multi-domain quality of life measure. It has 6 domains relating to fatigue, cognitive symptoms, social function, emotional status and general symptoms. Each domain is calculated individually with each of the 40 items scored from 1-5 with higher scores denoting worse symptoms. PBC-40 is optimised for patient self-completion and will be undertaken on paper in this trial [12].

6.5.8.3. Patient Health Questionnaire

The post-trial questionnaire is a non-validated 5-point scale to assess health status perceived by participants in response to the trial medication at 26 and 52 weeks.

6.5.9. Transient Elastography (Fibroscan)

Fibroscan is clinically validated non-invasive tool used to assess liver stiffness; a surrogate marker of liver fibrosis (scarring which can eventually develop into cirrhosis). The assessment is painless and, to patients, is just like having a routine ultrasound scan. The assessments will be undertaken by appropriately trained members of staff within the setting for all trial assessments. If a fibroscan has been performed as part of standard care up to 3 months prior to screening, this data can be used to inform the eligibility criteria at the screening visit, and as the baseline result.

6.5.10. Liver Biopsy

Liver biopsy pre and post therapy will be undertaken in a subgroup of participants (n=30 in total) as part of an optional sub-study. Participants in the sub-study will be allocated in a ratio of 1:1 placebo:intervention via stratified randomisation. While the overall study participants will not be replaced (e.g., in the case of IMP discontinuation or trial withdrawal), biopsy substudy participants will be replaced until a target of 30 is reached. The procedure will be performed as for a normal clinical biopsy according to local centre practice. The research tissue will be formalin fixed and paraffin embedded at site. The local centre will section the blocks for analysis as per local standard of care. The remaining block will then be sent to NovoPath. NovoPath will cut research sections for immuno-histochemistry analysis for senescence markers (p16 and p21). If serious disease markers are identified during this analysis, NovoPath will inform NCTU who will then report the results to the Trial Centre. Sections will be retained in Newcastle until the end of the study to allow any additional staining and/or analysis directly related to the study that may emerge as relevant during the lifetime of the study. Unused FFPE blocks will be returned to the trial centre at the end of the trial. All histology assessment will be performed in a fully blinded manner with regard to treatment group and pre and post-therapy timing.

6.5.11. Schedule of Events

Assessment	Pre-screening	Screening (Visit 1)[i]	Baseline (Visit 2)	Interim Phone Call[a] (Visit 3)	Interim Visit (Visit 4)	End of therapy (Visit 5)	Resolution visit (Visit 6)	Resolution phone call[a,b]
		Day -14 to 0	Day 0	4 weeks (+/- 1 Week)	12 weeks (+/- 1 Week)	26 weeks (+/- 1 Week)	52 weeks (+/- 2 Wks)	If required
Pre-treatment URS	X	X[c]						
Informed Consent		X						
Clinical Review		X		X	X	X	X	
Clinical Examination		X				X		
Vital signs		X				X		
Blood sample – Liver incl. GGT		X[h]	X[j]		X	X	X	
Blood sampling – U&Es, FBC		X[h]	X[j]		X	X		
Blood sampling - Cholesterol		X[h]				X		
Blood sampling Clotting		X[h]				X		
Pregnancy testing (POCBP)		X						
Fibroscan[d]		X				X		
Eligibility assessment		X						
Randomisation[e]		X						
Liver biopsy (subset)[f]			X			X		
Chemokine blood sample			X		X	X	X	
Biobank blood sample (optional)			X		X	X		
Urine sample (optional)			X			X		
QoL Assessment **EQ-5D-5L** **PBC-40**			X			X	X	
Patient health questionnaire						X	X	
Issue patient diary and safety card			X					
Therapy prescription			X		X			
Compliance				X	X	X		

Assessment	Pre-screening	Screening (Visit 1)[i]	Baseline (Visit 2)	Interim Phone Call[a] (Visit 3)	Interim Visit (Visit 4)	End of therapy (Visit 5)	Resolution visit (Visit 6)	Resolution phone call[a,b]
		Day -14 to 0	Day 0	4 weeks (+/- 1 Week)	12 weeks (+/- 1 Week)	26 weeks (+/- 1 Week)	52 weeks (+/- 2 Wks)	If required
Concomitant medication[g]		**X**	**X**	**X**	**X**	**X**		**X**
Adverse event reporting[g]		**X**	**X**	**X**	**X**	**X**		**X**

a) Communication with participants may take the format preferred by the participants. Telephone, email and video call may be used depending on the participant preference.

b) This additional phone call is only for participants who have stopped taking their study medication and have either withdrawn completely or over 4 weeks from their next study visit to check on any safety issues/adverse events they may experience in the wash out period. Participants will be asked if they consent to this as part of the Withdrawal/discontinuation of treatment process.

c) URS to be confirmed at screening visit based on pre-treatment values where the URS wasn't calculated by the research team at pre-screening.

d) If a fibroscan has been performed as part of standard care up to 3 months prior to screening, this data can be used to inform the eligibility criteria at the screening visit, and as the baseline result. If a fibroscan is performed at screening, this will also be used as the baseline result.

e) Participant can be randomised prior to baseline visit, once all screening activity has been completed and participant has been deemed eligible by the PI or other medically qualified delegated person at site.

f) A window of +/- two weeks at Baseline (visit 2) and 26 weeks (visit 5) is permissible for liver biopsy (as long as patient has been confirmed as eligible and randomised).

g) Adverse events and concomitant medications will be collected from day of consent.

h) The bloods results used for the screening visit can be taken from the participant medical record, but must be within three months of randomisation.

i) Screening (Visit 1) and Baseline (Visit 2) can be combined, as long as eligibility is confirmed prior to randomisation, baseline bloods can be obtained and IMP can be dispensed.

j) If Screening (visit 1) and Baseline (Visit 2) are combined then blood tests for Liver incl. GGT & U&Es & FBC should not be duplicated.

6.6. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without giving a reason. Investigator sites can try to ascertain the reason for withdrawal and document this reason within the withdrawal form, CDMS and participant's medical notes in the event a participant is comfortable disclosing this. NB: there is no requirement to withdraw from the trial due to discontinuation of treatment, see section 6.7.

The Investigator may discontinue a participant from the trial at any time if necessary, including (but not limited to) the following reasons:

- Pregnancy
- Symptomatic deterioration
- Unacceptable toxicity
- Participant withdrawal of consent
- Significant protocol deviation or non-compliance
- Investigator's discretion that it is in the best interest of the participant to withdraw
- Sustained and significant issues with UDCA intolerance.
- A trial adverse event that requires discontinuation of the trial medication or renders the participant unable to continue in the trial
- Notification of an adverse event using the CTIMP in another trial; or with OCA use in routine clinical practice, which in the interpretation of the investigators, may potentially put trial participants at risk.
- Evidence of significant progression in underlying liver disease, as defined by the development of cirrhosis, hepato-cellular carcinoma, or clinically significant portal hypertension
- Termination of the clinical trial by the sponsor

If a trial participant withdraws from the trial, all data and samples collected to the point of withdrawal will be retained and if they have received one or more doses of IMP, routine NHS data will be collected for the trial up to the 52 week visit timepoint, unless a participant asks for this to stop. Consent will have been sought to allow this. Participants who withdraw from the trial after randomisation will not be replaced.

6.7. Discontinuation of treatment

Participants may stop taking the trial medication and remain on the trial. These participants will continue to take part in trial assessments as per the schedule of events.

A discontinuation of treatment form will be completed for participants who discontinue treatment and documented within the CDMS and the participant's medical notes.

6.8. Follow up for participants who withdraw/discontinue treatment

Participants who fully withdraw from the trial will be asked if they agree to an additional phone call 4 weeks after they stop their study medication to follow up regarding any adverse events experienced in the wash out period.

Participants who discontinue treatment who are more than 4 weeks away from their next trial visit will be asked if they agree to an additional phone call 4 weeks after they stop their study medication to follow up regarding any adverse events experienced in the wash out period.

6.9. End of Trial

The end of the trial is defined as last patient last sample analysis (LPLA). This analysis is expected to be within 2 months of the last patient's last follow up last visit (LPLV). Following data download, the treatment allocation of individual participants will be made available to site clinicians, and participants will be able to find out their allocation on request.

7. TRIAL MEDICATION

7.1. Name and Description of IMP

For the purposes of this trial, obeticholic acid 5mg tablets and matched placebo tablets will be classed as IMP. Obeticholic acid is currently licenced for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis).

7.2. Name and Description of NIMP

Ursodeoxycholic acid (UDCA) is the current standard of care first-line treatment of PBC in the NHS [https://bnf.nice.org.uk/drugs/ursodeoxycholic-acid/]. The participants in this clinical trial will receive UDCA in combination with the trial IMP (obeticholic acid/placebo). UDCA will be prescribed in line with NHS Standard of Care (usually 13–15 mg/kg daily) and will be prescribed, dispensed and received by the participant, outside of the parameters of this trial. Intolerability to UDCA will be managed as per standard of care. Treatment with UDCA will be recorded as a concomitant medicine.

7.3. Reference Safety Information

Section 4.8 of the approved SmPC for OCALIVA 5mg film-coated tablets will be used as the RSI for this trial. The version of the SmPC which contains the current, approved version of RSI can be found on the trial RSI log. Please note this may not always be the most recently released version of the SmPC.

Serious Adverse Reactions (SARs) that are thought to have a causal relationship with the IMP must be assessed for expectedness against the current, approved version of the RSI.

The marketing authorisation holders may update the SmPC over the duration of the clinical trial. The CI/Sponsor/NCTU will monitor and review any changes to the SmPC, considering the impact on the trial and will revise relevant documentation as required.

7.4. Drug Storage and Supply

IMP will be supplied as 5mg of obeticholic acid/placebo tablets. Accountability will be required to track receipt, supply, return and disposal of IMP. Further information regarding management of IMP is available in the pharmacy manual.

Returned and unused IMP will be disposed of at site in accordance with local pharmacy requirements following approval by Sponsor. Records of IMP disposal must be kept in line with GCP requirements.

At each visit requiring medication allocation, a kit code for each bottle will be generated by SE. Prescriptions should be sent to site Pharmacy as soon as possible following generation.

7.5. Preparation and Labelling of IMP

Obeticholic acid and placebo tablets will be UK QP certified and supplied to sites fully labelled to comply with Annex 13 Good Manufacturing Practice (GMP) regulations.

7.6. Dosage Schedule & Modifications

For all participants, initiation of trial treatment will commence once screening tests are complete and participant attends baseline visit. From baseline, participants will receive 5mg once a day of obeticholic acid or placebo to be taken orally for 12 weeks. Obeticholic acid or placebo will then be titrated up to 10mg once a day from visit 4 (week 12 +/- 1 week) until EoT (at 26 weeks) according to tolerability. Participants will be asked to record medication taken in the patient diary.

If issues with tolerability are encountered participants will be offered dose reduction using a predefined schedule:

5mg daily: Where patients are taking 5mg obeticholic acid /placebo daily (one tablet of the study medication) dose reduction should be to 5mg/placebo (i.e., one tablet) on alternate days. If tolerability is still an issue patients should reduce to 5mg/placebo (i.e., one tablet) once per week. At least a week should be allowed to elapse between dose reductions

10mg daily: Where participants have previously titrated up to 10mg obeticholic acid /placebo (i.e., two tablets per day) initial dose reduction should be 5mg/placebo (i.e., one tablet per day). Thereafter the 5mg dose reduction schedule should be followed

If a participant's dose is reduced, they are subsequently permitted to up-titrate to a maximum of 10 mg daily. Participants may experience side effects that mean that they wish to stop taking the study medication. Participants can have up to fourteen day's break in total from the medication while taking the trial IMP. However, if the participant takes a break for longer than 7 days in a row, please refer to the trial team to discuss re-introduction of IMP and the subsequent up-titration timetable. If a participant discontinues UDCA while receiving trial medication, they may continue on the trial taking IMP alone. Treatment dose, changes to treatment dose and any missed doses will all be reported in the participant medical records and in the CDMS.

7.7. Known Drug Reactions and Interactions

7.7.1. Medicinal products that are affected by obeticholic acid

7.7.1.1. Warfarin

International normalised ratio (INR) is decreased following co-administration of warfarin and obeticholic acid. INR should be monitored, and the dose of warfarin adjusted, if needed, to maintain the target INR range when co-administering obeticholic acid and warfarin.

7.7.1.2. Interaction with CYP1A2 substrates with narrow therapeutic index

Obeticholic acid may increase the exposure to concomitant medicinal products that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with narrow therapeutic index (e.g., theophylline and tizanidine) is recommended

7.7.2. Medicinal products that affect obeticholic acid

7.7.2.1. Bile acid binding resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce efficacy of obeticholic acid. When concomitant bile acid binding resins are administered, IMP should be taken at least 4-6 hours before or 4-6 hours after taking a bile acid binding resin, or at as great an interval as possible.

7.8. Pruritus treatment

As per standard clinical practice, if required, management for pruritus in study participants will be managed by dose reduction (as per section 7.6) in the first instance, before treatment with therapy according to the BSG PBC clinical practice guidelines and standard local practice.

Please refer to section 8.2.1.1 regarding reporting of pruritus as an adverse event/adverse reaction.

Any drug therapy for pruritus will be prescribed independently from the IMP and obtained via standard pharmacy routes.

7.9. Concomitant Medications

A complete listing of all concomitant medication received during the trial from consent through to last visit will be recorded in the CDMS and participant clinical notes.

7.10. Assessment of Compliance

Participants will be taking the trial IMP or placebo as part of the trial for 26 weeks. Compliance regarding IMP will be checked at the interim telephone visit (4 weeks after taking IMP at day 0) and followed up at a clinic visit at week 12 and week 26. IMP compliance will be recorded in the CDMS.

Participants will return all unused IMPs and all IMP packaging to the study team at each site at week 12 and week 26. The returned IMPs and packaging will be held in the Pharmacy Department at site. Pharmacy will count and record all returns received from each participant on the study accountability log. An accountability check will also be performed as part of on-site monitoring visits.

8. PHARMACOVIGILANCE

8.1. Definitions

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious, and in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

8.2. Recording AEs

All AEs occurring from consent onto the trial to the end of trial participation must be recorded in the CDMS as well as the participant's medical notes. The documentation of each AE should include an event term, event duration (start and stop dates), details of any action taken or treatment in response

to the event, and results of any assessments conducted in relation to the event. Each AE must be assessed by a delegated investigator for **severity (8.2.1), seriousness (8.2.2)** and after administration of IMP for **causality (8.2.3)**.

Out of range laboratory results that are deemed to be clinically significant should be reported as AEs.

8.2.1. Protocol Specific Reporting Exclusions

Any pre-planned hospital stay due to surgical intervention not involving the liver and/or biliary tree (bile duct, gallbladder or pancreas) will be excluded from AE reporting.

8.2.1.1. Pruritus (itch)

Trial participants may experience pruritus (itch) prior to starting on the trial as part of their symptoms of PBC. For these participants, pruritus does not need to be reported as an AE/AR unless the level of itch has worsened. For participants who do not experience pruritus prior to trial participation, any pruritus experienced will need to be reported as an AE/AR as normal.

8.2.1.2. Fatigue

Trial participants may experience fatigue prior to starting on the trial as part of their symptoms of PBC. For these participants, fatigue does not need to be reported as an AE/AR unless the level of fatigue has worsened. For participants who do not experience fatigue prior to trial participation, any fatigue experienced will need to be reported as an AE/AR as normal.

8.2.1.3. Biopsy Sub-Study

For trial participants who consent to the Biopsy Sub-study and who are hospitalised overnight or who have a prolonged hospital stay as a result of the biopsy procedure; this routine hospital stay does not need to be reported as an SAE. AEs that occur during/ as a result of the procedure will need to be reported as an AE/AR as normal.

8.2.2. Assessment of Severity

The PI, or delegated clinician, should make an assessment of severity for each AE according to the following criteria:

Severity of each AE will be graded as mild/moderate/severe.

8.2.3. Assessment of Seriousness

The PI, or delegated clinician, should make an assessment of seriousness against the standard definition in the Safety Reporting Definitions section 8.1.

8.2.4. Assessment of Causality

The relationship between the use of IMP/NIMP and the occurrence of each AE must be assessed and categorised by the PI or delegated clinician using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy and any other relevant risk factors should be considered. The PI should also consult the current version of the RSI.

Definitely	The event is considered related to the IMP/NIMP
Probable	It is probable that the event is related to the IMP/NIMP

Possible	It is possible that the event is related to the IMP/NIMP
Unlikely	It is unlikely that the event is related to the IMP/NIMP
Unrelated	The event is not considered related to the IMP/NIMP
Not assessable	After review of the information the PI/delegated clinician is unable to determine if the event is related to the IMP/NIMP or not

8.3. Recording and Reporting SAEs/SARs

Where an AE is assessed as serious, as well as recording in the participant's medical notes and the CDMA as described above, it must also be reported as an SAE as soon as possible (at least within 24 hours of awareness of a member of the study team).

All SAEs occurring from consent onto the trial to end of trial participation must be reported to NCTU on the OPERA SAE form as well as recorded as per AEs.

All SARs occurring from first participant's dose of IMP to the last participant's end of follow-up must be reported to NCTU on the OPERA SAE form as well as recorded as per AEs.

All SAEs/SARs must be reported to NCTU using the OPERA SAE Form via secure email to the OPERA circulation list: nctu.opera.sae@nhs.net within 24 hours of research staff becoming aware of the event. This is a distribution list to ensure that all relevant individuals (CI, NCTU trial management and QA management personnel and Sponsor) are informed of the event in a timely manner. All confirmed SAEs will be allocated a unique SAE number and a confirmation of receipt returned to the sender. SAEs will be recorded by trial management personnel on the CDMS.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24 hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Severity
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

Any change of condition or other follow-up information should be submitted to the NCTU via secure email to nctu.opera.sae@nhs.net as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Any SAR or pregnancy exposure will be reported to Intercept Pharmaceuticals, Inc. within the contractually agreed timescales. Quarterly reconciliation reports will be sent to Intercept Pharmaceuticals, Inc., which will include cumulative SARs and pregnancies reported as part of the

trial. The funder (Intercept) will also be provided a copy of all serious and non-serious AEs at the end of the study.

8.3.1. CI Assessment of SAEs/SARs

All reported SAEs will undergo documented review of assessment of causality by the CI or a delegate. All SARs will also be assessed for expectedness by the CI on behalf of Sponsor, using the current MHRA approved RSI.

8.4. Reporting SUSARs

All SARs assessed as unexpected, in accordance with the approved RSI, occurring from first administration of IMP up to the end of trial must be reported to the MHRA and REC as SUSARs. Reporting will be performed by the trial Sponsor. A copy of the electronic form and the CTIMP safety report form will be sent to the REC in line with current HRA guidance.

Fatal and life-threatening SUSARS must be reported to MHRA no later than 7 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported to the MHRA no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

For SARs that are assessed by the CI as unexpected, the reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Participant ID and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

The site should report the event as soon as possible and at least within 24 hours of awareness using the SAE reporting procedures in section 8.3 . The site is expected to fully cooperate with the NCTU and Sponsor in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

SARs thought to be related to the NIMP must be expedited if:

- The event might be linked to either the NIMP or IMP but it is not possible to attribute causality
- The event may be linked to an interaction between the NIMP and the IMP

- The reaction due to the NIMP is likely to affect the safety of the trial subjects

In addition, suspected adverse reactions of the NIMP will be reported via the Yellow Card Scheme where this is required.

The Trial Manager will ensure all trial PIs will be informed of any SUSARs that occur in relation to the trial IMP.

8.5. Notification of Deaths

AEs that result in death will meet the criteria for seriousness as defined in section 8.1 and be reported accordingly as SAEs.

8.6. Contraception and Pregnancy

For the purposes of this trial a woman is considered a person of child-bearing potential (POCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Sexually active POCBP are required to practice true abstinence* in line with their preferred and usual lifestyle or use an acceptable method of contraception. This should be in the form of any of the following methods:

- combined hormonal contraception (oral, intravaginal, transdermal)
- progestogen only contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

* Abstinence is defined as refraining from heterosexual intercourse during the entire study period. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8.6.1. Pregnancy Reporting

In the event of a trial participant or their partner becoming pregnant on study the site must notify NCTU, the Chief Investigator and the Sponsor representative within 24 hours of becoming aware of the pregnancy. Pregnancy reporting must be documented in the participant's medical notes, on a pregnancy report form and in the CDMS.

Site must approach the study participant or the partner of a trial participant to obtain consent to follow the pregnancy to completion and for 12 months following a live birth.

8.6.2. Procedure for notification of pregnancy

The trial participant or partner (if pregnant) will be asked to sign a consent form allowing the trial team to follow their pregnancy. The site will need to submit a completed pregnancy notification form to NCTU via secure e-mail to nctu.opera.sae@nhs.net or using appropriate secure transfer methods.

8.6.3. Procedure for following pregnancy

The pregnancy should be followed until completion (i.e., termination, miscarriage, stillbirth or live birth). This will comprise regular telephone calls to the participant and documentation of the outcome of the pregnancy, and any adverse events, in the ISF and patient medical notes.

If the pregnancy results in a live birth, then the child will need to be followed up for 12 months to ensure there is no congenital abnormality. If a congenital abnormality is detected for either a live or stillbirth child, then this will need to be reported as an SAE.

8.7. Overdose

Overdoses may be identified during trial calls or visits. Overdoses will be recorded in the CDMS and patient medical notes. Overdoses must be notified to the Sponsor as a deviation (or potentially violation). If an SAE is associated with the overdose, the event must also be reported using the SAE reporting procedures detailed in section 8.3.

8.8. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the Sponsor, CI and NCTU must be notified immediately and details of the USM given. The NCTU must inform the MHRA and the NHS REC within 3 days of the USM taking place in accordance with the Sponsor' standard operating procedures.

8.9. Development Safety Update Reports

A Development Safety Update Report (DSUR) will be submitted to the MHRA and NHS REC once a year on the anniversary of the date of the Sponsor's first authorisation to conduct a clinical trial with this IMP. The Trial Manager must ensure that the report is submitted within 60 days of the end of the reporting period. The Trial Management Group must contribute to the compilation of the DSUR, and the CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and sponsor Representative prior to submission via the Common European Submission Portal (CESP) system. NCTU staff will prepare and submit Development Safety Update Reports (DSURs) for the trial, in accordance with NCTU SOPs.

8.10. Responsibilities

8.10.1. Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness, severity and causality of AEs
- Ensuring that all SAEs and SARs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.
- Ensuring all AEs are recorded in the CDMS

8.10.2. Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness and causality of SAEs where it has not been possible to obtain local medical assessment.
- Provide review of assessment of causality of all SAEs on behalf of Sponsor (where the assessment was not originally performed by the CI).
- Undertake expectedness review of all SARs on behalf of Sponsor.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all AES, SAEs and SARs.
- Preparing the clinical sections and final sign off of the DSUR.
- Reviewing RSI at least annually and notifying PIs of any required updates (may be delegated to NCTU)

8.10.3. Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a CDMS (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the CA and REC within required timelines
- Reviewing RSI at least annually and notifying PIs of any required updates (may be delegated to NCTU and CI).
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to all appropriate CAs (including MHRA) and RECs, as required (may be delegated to NCTU)

8.10.4. IDMC

- Review of safety data collected at regular intervals throughout the trial to identify any trends.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Calculation

The proposed sample size is 106 (powered at 48 per group for two groups with a 10% increase for drop out (the experience of clinical trials in PBC is of a drop-out rate considerably below 10%). This sample size has been derived based on an analysis of the extensive UK-PBC dataset undertaken as part of the design of this trial, as well as published Dutch and Global PBC analyses [19, 38, 39]. Based on the UK-PBC patients who would fulfil the eligibility requirements of this trial, the normalisation rate (both serum alkaline phosphatase and total bilirubin below the upper limit of normal) at 12 months post-UDCA was 17%. To account for placebo effect, we assume the six-month control arm normalisation rate will be 20%.

We power the trial to detect a significant difference when the experimental arm has a 45% normalisation rate. If the normalisation rate were analysed as binary, then 144 patients would be required to attain 90% power (5% two-sided error) with a 2-arm design, not allowing for dropout (Pearson chi squared test). As the normalisation rate is defined in terms of alkaline phosphatase and bilirubin values (continuous variables) being below an upper limit, we will utilise an innovative statistical analysis called the augmented binary method [34]. This method also makes inference on the normalisation rate (specifically the odds-ratios between the experimental and control arm) but uses the continuous data on alkaline phosphatase and bilirubin to improve the precision. We have conducted simulation studies that resample data from the UK-PBC data to simulate trials under the null and alternative hypotheses. With the augmented binary analysis, the power is 90% when the number of patients per arm is 48 (which we increase by 10% to 53 to account for 10% dropout). Thus, the sample size required is 106.

The statistical code used to reproduce this analysis is stored within the statistical trial master file and is available on request.

9.2. Analysis Populations

- Intention-to-treat (ITT): participants are included as per their randomised group, regardless of whether they received or adhered to the allocated treatment.
- Per-protocol (PP): participants are included if they did not withdraw and received at least 80% of the planned IMP.
- Safety Population (SP): participants are included if they received at least one dose of IMP.

9.3. Statistical Analysis

The primary analysis will be in the ITT population and repeated in the PP population. All analyses will be described in a Statistical Analysis Plan (SAP), to be finalised prior to trial statisticians receiving any unblinded data.

For the analysis of the primary outcome, we will use the augmented binary method [34]. This will consist of fitting a bivariate normal regression model to the alkaline phosphatase and bilirubin values

(expressed as a percentage of the upper limit of normal). The model will include parameters representing the treatment effect and the effect of baseline measurements of the respective component. This model will be used to estimate the odds ratio of the normalisation rate between arms. The delta method is used to estimate the standard error and form a 95% confidence interval. A Wald test is used to provide a P-value for testing the null hypothesis of no difference between arms. As a secondary analysis we will also analyse the normalisation rate as a binary outcome using a logistic regression with the same parameters.

Continuous secondary outcomes will be analysed with linear mixed effects models, adjusting for baseline. Binary outcomes will be analysed with a logistic regression model (and, where the outcome is defined by a dichotomised continuous variable, with the augmented binary method).

Should there be a non-negligible level of missing data in the primary outcome (>5% loss to follow-up), we will consider performing a sensitivity analysis using multiple imputation techniques. The linear mixed effects model accounts for missing outcome data under a missing at random assumption.

9.4. Stopping Criteria

There are no formal stopping criteria for the trial, however the IDMC will have the option to recommend stopping early for futility, considering recruitment and/or ongoing outcome and safety data.

10. DATA HANDLING

The Clinical Data Management System (CDMS) used for the OPERA trial is Sealed Envelope (SE) which is fully compliant with all regulatory frameworks for research of this nature. SE in summary:

- Registered as a data controller with the Information Commissioner's Office (ICO) and has been inspected by the MHRA, the UK clinical trials regulator
- Certified as meeting Cyber Essential requirements (a UK Government led and industry – backed scheme) by a CREST accredited security company
- It has an inbuilt daily back-up facility, stored redundantly at two sites, which is encrypted
- It uses a secure web-based interface for data entry, no data is stored on computers at site
- Users are assigned role based permissions specific to their site and study role

Trial data for an individual participant will be collected by the PI or their delegated nominees and recorded in the relevant eCRFs within SE for the trial. Patient identification in SE will be through a unique participant ID, allocated screening. A Patient Identification Log linking the patient's name to the participant ID will be held within the ISF stored in a locked room at site and is the responsibility of the PI. As such, patients cannot be identified from SE.

The CI or nominated designee will continually monitor completeness and quality of data recording in SE and will correspond regularly with site staff with the aim of capturing any missing data where possible and ensuring continuous high quality of data.

Participants will complete paper assessment tool(s) (i.e., questionnaires) as required. The tools will also only be identified using the participant ID. Data will be entered at sites onto corresponding eCRF in SE, with the paper originals remaining at site.

10.1. Data Collection Tools and Source Document Identification

Clinical and safety data for all trial participants will be collected by the PI or their delegated nominees and recorded in the eCRF of the CDMS (Sealed Envelope) and on relevant trial specific worksheets. Participant identification in SE and paper documentation will be through a participant ID. A record linking the patient's name to the participant ID will be held within the ISF and is the responsibility of the PI. As such, patients cannot be identified from SE.

The CI or nominated delegate will continually monitor completeness and quality of data in SE and will correspond regularly with site staff with the aim of capturing all data and ensuring continuous high quality of data.

The CDMS will collate data from multiple sources, paper questionnaires for patient completion are:

- PBC-40, EQ-5D-5L, patient questionnaire

10.2. Data Handling and Record Keeping

Overall responsibility for data collection lies with the CI. Data will be handled, computerised and stored in accordance with the General Data Protection Regulations 2018. Paper copies of trial-related documentation will be annotated, signed and dated, and filed in the medical notes.

The overall quality and retention of trial data is the responsibility of the CI. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

The trial specific Data Management Plan will include details of how the validity and quality of data will be monitored and managed. As far as possible, validations will be built into SE and additional manual validations will be detailed in the Data Validation Plan.

10.3. Access to Data during trial

Staff involved in the conduct of the trial, including the PIs, trial management team and NHS staff involved in screening and intervention will have access to the ISF.

The trial data and patient medical records may be looked at during monitoring by NCTU or auditing personnel from a Research Ethics Committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA), the Newcastle upon Tyne Hospitals NHS Foundation Trust or NCTU.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the TSC/IDMC or the REC. Secure electronic data will be released to the Trial Statistician for analysis. The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Non-identifiable safety information will be released to Intercept Pharmaceuticals, Inc. for the purpose of meeting their global safety reporting obligations.

Password limited access to Sealed Envelope will be granted to site PIs and delegated data entry personnel, access is restricted to the individuals study role and site. NCTU trial management team will have access to SE for monitoring purposes and the Sponsor will have read only access for oversight.

10.4. Archiving

Trial data will be archived for a minimum of 5 years in accordance with Sponsor and NCTU SOPs. Archiving will be authorised by the Sponsor following submission of the end of trial report.

NCTU does not have its own archiving facility, therefore the archiving facility designated by the Sponsor will be used for storage of the Trial Master File (TMF), which contains the essential documents that individually and collectively permit the evaluation of the data produced.

Electronic data from SE will be provided for the sponsor TMF and to sites in an appropriate format (to be determined at the time in accordance with latest guidance and SOPs).

Each individual trial site is responsible for archiving their trial Investigator Site File (ISF).

Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

11. MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the Trial Management Group, NCTU QA representative and the Sponsor.

All monitoring activity will be detailed in the monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review and off- and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and appropriate regulations. Trial site monitoring will be undertaken by NCTU trial personnel as indicated in the monitoring plan.

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. Sites will be expected to assist the Sponsor in monitoring the trial e.g., hosting monitoring visits, providing information for on- and off-site monitoring and responding to monitoring findings within the timeframes requested, wherever possible.

The trial may be subject to audit by representatives of the Sponsor or inspection by MHRA. Each investigator site will be required to permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

12. TRIAL OVERSIGHT

12.1. Independent Data Monitoring Committee (IDMC)

The IDMC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The IDMC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial, including stopping early for futility as per section 9.4. The IDMC will meet at the start of the trial, regularly throughout the recruitment and follow-up period of the trial, and on an ad hoc basis if required.

12.2. Trial Steering Committee (TSC)

The TSC will consist of at least three independent members including an Independent Chair, and Independent Statistician, Independent Clinician and lay members. The TSC will oversee and supervise the progress of the trial and ensure that it is being conducted in accordance with applicable guidance and regulations. It will provide advice on the trial design and discuss proposals for substantial protocol amendments, endorsing these as appropriate. The TSC will review recommendations from the IDMC and provide advice regarding trial progress, to maximise the chances of completion within the proposed time scale. The TSC will meet following IDMC meetings.

12.3. Trial Management Group (TMG)

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the day-to-day progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit (NCTU). The Trial Management Group will include the CI, Senior Trial Manager, Trial Manager, Statisticians, Sponsor Representative, Data Manager, Senior Project Manager, Co-Investigator(s) and Pharmacist, as appropriate.

Quality control will be maintained through adherence to NCTU and Sponsor Standard Operating Procedures (SOPs), the trial protocol, the principles of GCP, research governance framework and applicable clinical trial regulations.

The following functions falling under the responsibility of the Sponsor will be delegated to the Chief Investigator and supported by NCTU:

- Medicines and Healthcare products Regulatory Agency (including obtaining clinical trial authorisation, notification of protocol amendments, submission of Development Safety Update Report (DSUR), notification of end of trial and submission of final trial report)
- Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- HRA and Health and Care Research Wales (HCRW) Approval and Application for Pharmacy Assurance.
- Good Clinical Practice and Trial Conduct (including Good Clinical Practice (GCP) arrangements, data monitoring, emergency & safety procedures).

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g., protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

13.2. Peer Review

The trial was independently reviewed as part of application for funding. The protocol will be reviewed by the IDMC and TSC as part of the peer review process.

The trial protocol has been reviewed and authorised by the Sponsor, Chief Investigator, Senior Statistician and NCTU Director/Deputy-Director.

13.3. Public and Patient Involvement

The trial team have, for over 20 years, worked closely with the PBC Foundation (a national PBC patient group with over 10,000 PBC patient members) and LIVErNORTH a regional liver patient support group with over 2000 patients. Amongst the PBC patient community effective treatment of symptoms is seen as a key research priority. Patient representatives from these 2 groups have been actively involved in priority setting which led to the trial, and in the development of both the concept and the detailed proposal for this trial. PPI representatives will join the Trial Steering Committee.

13.4. Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

The NCTU will obtain a Clinical Trial Authorisation from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial.

The Sponsor will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

13.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. Study tasks may be delegated to a suitably qualified or experienced member of the research team, but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations. Site staff are responsible for compliance with the protocol in their everyday trial activities and must report anything that they feel constitutes an SAE, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.

Protocol deviations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the protocol deviation log, including the relevant Corrective and Preventive Actions (CAPA) required.

Protocol violations are a consistent variation in practice from the study protocol that could potentially impact on study participant's rights/safety or affect the scientific value or outcome of a study. The PI will sign off each deviation and decide whether this is a deviation or violation. Violation documentation must be completed within 3 days of the violation being discovered using the violation reporting form.

Deviations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach. Notification of Serious Breaches to GCP and/or the Protocol
A serious breach is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial;
b) or the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach. The Sponsor will notify the MHRA and the NCTU will notify the NHS REC within the required timelines in accordance with the NCTU SOP.

13.6. Data Protection and Patient Confidentiality

The trial will be run in accordance with the Data Protection Act 2018, to maintain the confidentially of trial participants and trial data integrity.

All investigators and trial site staff must comply with the requirements of the applicable legislation (e.g., GDPR, DPA) with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation.

In line with the General Data Protection Regulations 2018 (GDPR) explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur.

Personal data will be regarded as strictly confidential. All trial files will be securely stored and access restricted to staff involved in the trial. Research staff at sites will enter data into a secure web-based CDMS (SE) maintained by the NCTU. Data will be entered using unique participant ID. Access to SE will be password protected and limited to staff at research sites or those employed by Newcastle University who are involved in the trial.

13.7. Indemnity

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g., General Practitioners or Dentists will provide their own professional indemnity.

13.8. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not. Study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group. The independent Trial Steering Committee will be made aware of all significant protocol amendments.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of the NCTU on behalf of the Sponsor to submit substantial amendments.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the capacity and capability assessment for that site. Amendment documentation will provided to sites by NCTU.

13.9. Post-Trial Care

Participants will be unblinded on request at the end of the study (following data download for analysis). At the end of the study participants will return to standard care. Obeticholic acid is available on the NHS subject to utilisation criteria set by NHS England based on NICE assessment. Participants meeting these criteria will be able to continue on Obeticholic acid, if this is in line with local prescribing procedures and at the discretion of the local team and treating clinician.

13.10. Access to the Final Trial Dataset

Until publication of the trial results, access to the full dataset will be restricted to the Trial Management Group and to authors of the publication.

Anonymised/Pseudonymised data from this trial/study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the lead author/Chief Investigator and NCTU in line with any applicable data sharing policies.

14. DISSEMINATION POLICY

The results of the trial will be communicated to the scientific community through meeting presentations and peer reviewed scientific publications. It is also our policy to publish the trial protocol itself. Communication to the patient community will be through the partner patient groups with articles written for their member newsletters and presentations at patient education events. Given the nature of the symptom and the novelty of the trial it is possible that there may be media interest in the trial and its findings. We are happy to undertake responsible media engagement to increase awareness of PBC, of fatigue and its impact and of the importance of high quality CTIMPs.

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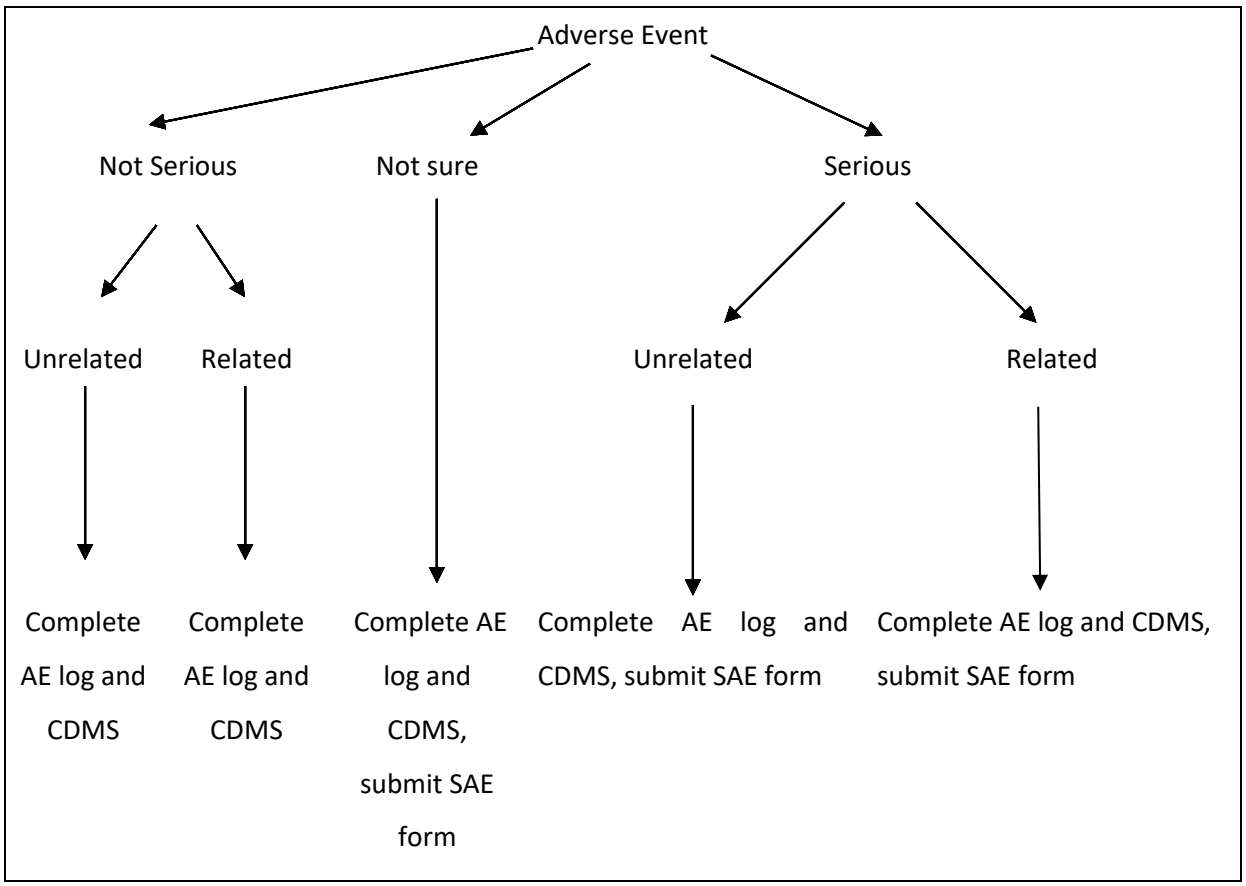
17. APPENDICES

17.1 Appendix 1 - Safety Reporting Diagram

Figure 1 Safety Reporting Diagram



Contact details for reporting SAEs

Please send SAE form(s) via secure email to **nctu.opera.sae@nhs.net**

17.2 Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA02	3.0	XX MMM YYYY		Section 6.1.2 - Clarification of the source of the screening bloods data Section 6.5.6 - Clarification of the URS calculator to be used for OPERA Section 6.5.10 - Clarification of participant replacement in the biopsy substudy Section 7.6 - Clarification of the IMP: • Titration may be up and down • IMP break may be for 14 days in total • Participant may remain on IMP and complete the trial if they stop taking NIMP UDCA.