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Study of BROdalumab in Primary Sclerosing Cholangitis

Submission date 01/08/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 27/10/2023	**Overall study status** Ongoing	
Last Edited 28/01/2025	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims:
Primary sclerosing cholangitis (PSC) is a rare liver disease where the body attacks itself, causing inflammation and scarring of the bile ducts and liver. This in turn leads to repeated infections, liver failure, and in some cases cancer. There is no recognised PSC medication that improves survival. For some, liver transplantation is the only lifesaving option.

Recent research shows that the immune system (T cells and B cells) is responsible for bile duct damage in PSC. Research has shown us that in people with PSC, these T cells release a chemical called Interleukin 17 (IL-17). Importantly, powerful drugs called biologics that target the specific parts of the immune system have already been developed to treat these diseases. One such biologic is brodalumab. It is used for psoriasis (a skin condition) and reduces the effects of IL-17.

Therefore, given the potential importance of IL-17 in PSC, we will study the effect of brodalumab in people with PSC. Before brodalumab can be recommended as a treatment for PSC, larger studies are required to prove its effect.

Before a clinical trial we need to understand how to design a larger study; recruitment and retention rates; whether participants will be willing to take the medication; side effects experienced; quality of life and the impact of Brodalumab on the liver and bowel pf those with PSC.

Who can participate? Patients aged 18-75 years with PSC from four large PSC centres (Norwich, Oxford, Cambridge and Birmingham)

What does the study involve? Participants will all be given brodalumab for 12 weeks (once a week for 3 weeks, then every other week). Brodalumab will be given using an injection pen and participants will be able to do this themselves at home after training. The researchers will monitor participants with blood tests, liver scans, a colonoscopy and questionnaires. A group of PSC patients from across the UK helped us improve the design of our study and highlight patients' needs and concerns.

What are the possible benefits and risks of participating?
Brodalumab is a safe and effective treatment for psoriasis. Currently we do not know if brodalumab is of any benefit to people with PSC. We need to do this study to find out if it is safe and could be effective in patients with PSC. The main benefit will be that information gained from the study will help doctors in the treatment of patients with PSC and inflammatory bowel disease in the future.

The medication is generally well tolerated, but side effects may occur. Side effects are typically mild and rarely require the treatment to be stopped. All patients are closely monitored throughout the study. The frequency of study visits ensures that any side effects are reported early and treated promptly.

Patients will be made fully aware of the risks and benefits of taking part in the study during the consent process. Written information and further explanation of the study and what is involved is available in the patient information sheet.

Where is the study run from?
Norwich Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
July 2023 to September 2025

Who is funding the study?
National Institute for Health and Care Research (UK)

Who is the main contact?
Dr Amera Elzubeir, A.elzubeir@uea.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Dr Amera Elzubeir

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006951

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1006951, CPMS 57248

Study information

Scientific Title
A Single Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis

Acronym
SABR-PSC Pilot Study

Study objectives
The main objective of the study is to understand if this study could be done on a larger scale in the future and if so how to do it. Therefore, the research questions are as follows:
1. What is the recruitment and retention rate of this study?
2. What is the safety profile of brodalumab in this cohort of patients?
3. Will participants be willing to take brodalumab as subcutaneous injection according to the treatment schedule for the duration of the study?
4. Will participants be willing to take part in the frequency of study visits, have blood tests, fill in questionnaires and undergo investigations for the duration of treatment with brodalumab?
5. Will we practically be able to administer a trial across 4 sites in the time frame specified?
6. Is patients' health related quality of life affected by taking brodalumab?

The secondary research objectives are to examine if there are any signals that brodalumab has an impact on (in a positive or negative fashion) the liver blood test results, and liver scarring.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 26/10/2023, London - London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)2071048387, +44 (0)207 104 8140, +44 (0) 207 104 8016; londonbridge.rec@hra.nhs.uk), ref: 23/LO/0718

Study design
Interventional non-randomized single-arm pilot study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)

Hospital

Study type(s)
Safety

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

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

Interventions
Single Arm Study.
Patient with Primary Sclerosing Cholangitis- Brodalumab 210mg will be administered subcutaneously at weeks 0,1,2,4,6,8,10,12.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase II

Drug/device/biological/vaccine name(s)
Brodalumab

Primary outcome measure
1. The recruitment rate of eligible participants and their subsequent retention during follow-up, measured at baseline, weeks 0, 2, 4, 8, 12, 16 and 6 months by reviewing associated dropout rates, and time to recruitment of all 20 participants.
2. The proportions of participants who adhere to trial medication, measured by empty packet counts and unused injection counts at weeks 2, 4, 8, and 12
3. Adverse events detected through safety reporting procedures and at follow-up visits, recorded according to common terminology criteria for adverse events version 5.0. Detected: continually throughout study period to end of study at 6 months.
4. Acceptability, as determined by eligible participants, of self-administering brodalumab as a subcutaneous injection, its associated number and frequency of study/follow-up visits, assessments, PROM’s and investigations. To be evaluated at end of study by way of exit interview and semi structured interview.
5. Acceptability, and patient perception of taking part in a pilot study of a novel repurposed drug. To be evaluated at the end of the study by way of semi-structured interview at 16 weeks study visit and exit interview.
6. Practicality of administering the study visits and follow up period within the specified time frame across the 4 sites. Review of adherence to study protocol, recruitment and completion of study within the allocated time frame- evaluated at closure of study.
7. Tolerability: participants tolerance of self-administering subcutaneous (S/C) brodalumab injections evaluated by way of reported side effects and establishing if the IMP side effect led to discontinuation of study by participants

Secondary outcome measures
1. ALP levels measured at baseline and weeks 0, 2, 4, 8, 12, 16 and 6 months
2. Surrogate markers of liver fibrosis: vibration controlled transient elastography (VCTE) e.g., Fibroscan measures and enhanced liver fibrosis (ELF) scores: measured at baseline and 16 weeks.
3. Liver function tests (bilirubin, alanine transaminase, aspartate transaminase, gamma glutamyl transferase, albumin) and INR measured at baseline, weeks 0, 2, 4 , 8, 12, 16, and 6 months
4. Biliary volume measured using MRCP+ scan and fibro-inflammation measured using the Liver MultiScan at baseline and week 16
5. Quality of life measured using PSC-PRO, CLDQ-PSC and 5D- Itch questionnaire at baseline and weeks 0, 2, 4, 6, 8, 10, 12, 16

Overall study start date
28/07/2023

Completion date
30/09/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 08/05/2024:
1. Age 18-75 years
2. Written informed consent
3. Established clinical diagnosis of large duct PSC-based on a standard disease definition (adopted from the British Society of Gastroenterology guidelines): i) cholestatic blood tests, ii) typical cholangiographic findings on endoscopic retrograde cholangiography (ERCP) or magnetic resonance cholangiography (MRCP), and absence of Anti-mitochondrial antibodies and causes of secondary cholangitis.
4. Participants may be recruited with OR without a confirmed diagnosis of inflammatory bowel disease (IBD). For those recruited with an established diagnosis of concomitant colonic inflammatory bowel disease (IBD), there must be a confirmed diagnosis of quiescent-mild disease established prior to enrolment (with endoscopy performed within 12 months of screening visit) by clinical, biochemical, AND endoscopic evidence corroborated by a histopathology report. Where there is a disparity in disease activity between the endoscopic and histological report- histology should be taken as the gold standard of actual disease activity.
Note: enrolment of participants into the SABR-PSC study with mild disease, will be a phased 2 step process:
Phase 1: The initial 10 patients enrolled in the study will have QUIESCENT disease (UC or CD) clinically, biochemically and histologically. There will be a review by the safety committee after enrolment and treatment commencement of the 9th patient with regards to any IBD safety signals or adverse events. The safety committee will then advise the trial steering committee and CI of their views.
Phase 2: If the safety committee are satisfied that there are no significant safety concerns, the final 10 patients recruited may be recruited with either quiescent or mild disease.
Quiescent Crohns Disease (CD) is clinically defined by a Crohns Disease Activity Index (CDAI) of <150
Mild CD is clinically defined by a Crohns Disease Activity Index (CDAI) of 15-219
Quiescent Ulcerative Colitis (UC) is clinically defined by a partial Mayo score of <2
Mild Ulcerative Colitis (UC) is clinically defined by a partial Mayo score of 2-5
5. Participants with a diagnosis of IBD on maintenance therapy with 5-aminosalicylic acid (5-ASA)

or thiopurine therapy must be taking a stable dose for at least 12 weeks prior to screening, with no dose changes and be expected to remain on the same dose and medication for the duration of the trial.
6. If pre-treated with ursodeoxycholic acid (UDCA)- UDCA therapy should remain at a stable dose for 12 weeks prior to screening, and not exceeding 20 mg/kg/day.
7. All patients with IBD must have had colorectal cancer screen within 12 months of the screening visit with no signs of malignancy or dysplasia- evidenced by a colonoscopy with segmental biopsies and histological confirmation of absence of dysplasia.
8. Female subjects of childbearing age must be on a highly effective contraceptive method from screening to at least 12 weeks after the last dose of the drug. All hormonal contraceptive methods must be supplemented by use of a male condom.

Previous inclusion criteria:
1. Age 18-75 years
2. Written informed consent
3. Established clinical diagnosis of large duct PSC-based on a standard disease definition (adopted from the British Society of Gastroenterology guidelines): i) cholestatic blood tests, ii) typical cholangiographic findings on endoscopic retrograde cholangiography (ERCP) or magnetic resonance cholangiography (MRCP), and absence of Anti-mitochondrial antibodies and causes of secondary cholangitis.
4. An established diagnosis of concomitant colonic inflammatory bowel disease (IBD) with a confirmed diagnosis of quiescent-mild disease established prior to enrolment (with endoscopy performed within 12 months of screening visit) by clinical, biochemical, AND endoscopic evidence corroborated by a histopathology report. Note: enrolment of participants into the SABR-PSC study with mild disease, will be a phased 2 step process:
Phase 1: The initial 10 patients enrolled in the study will have QUIESCENT disease (UC or CD) clinically, biochemically and histologically. There will be a review by the safety committee after enrolment and treatment commencement of the 9th patient with regards to any IBD safety signals or adverse events. The safety committee will then advise the trial steering committee and CI of their views.
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Mild CD is clinically defined by a Crohns Disease Activity Index (CDAI) of 15-219
Quiescent Ulcerative Colitis (UC) is clinically defined by a partial Mayo score of <2
Mild Ulcerative Colitis (UC) is clinically defined by a partial Mayo score of 2-5
5. Participants with a diagnosis of IBD on maintenance therapy with 5-aminosalicylic acid (5-ASA) or thiopurine therapy must be taking a stable dose for at least 12 weeks prior to screening, with no dose changes and be expected to remain on the same dose and medication for the duration of the trial.
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Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
20

Key exclusion criteria
Current exclusion criteria as of 08/05/2024:
1. Gallbladder lesion or polyp (>5 mm diameter), cholangiocarcinoma mass lesion, or high suspicion of cholangiocarcinoma, as indicated on imaging such as ultrasound, computer tomography (CT), dynamic magnetic resonance imaging (MRI) or MRCP.
2. Evidence of any other concomitant liver disease including but not limited to overlap syndromes with autoimmune hepatitis, primary biliary cholangitis, alcohol-related liver disease, or clinically significant metabolic-associated fatty liver disease (at investigator's discretion).
3. Primary biliary cholangitis, or IgG4-Related cholangitis as judged by the investigator.
4. Has received a liver transplant, is listed for a liver transplant or in the opinion of the investigator, the participant has an anticipated need for liver transplantation within the next 12 months.
5. Had a total or subtotal colectomy or presence of an ileostomy or colostomy.
6. Has current or recent history of Crohn’s abscess, stricturing or fistulating disease.
7. Has had 1 or more interventional treatments for dominant biliary stricture (including stent placement/replacement) within 6 months prior to the screening visit, or a dominant bile duct stricture thought to need intervention in the next 6 months (i.e., stenting or dilatation).
8. Has evidence of cholangitis, requiring antibiotics or hospitalisation, within 3 months prior to the screening visit [short courses of antibiotics for no more than 5 days are allowed for stent placement or endoscopic retrograde cholangiopancreatography (ERCP) prophylaxis].
9. Has evidence of liver cirrhosis based on liver histology, ultrasound, or vibration-controlled transient elastography (VCTE) (KPa >14.4) or history of the presence of decompensated liver disease e.g., ascites, variceal bleed, hepatic encephalopathy, portal hypertension or hepatic hydrothorax.
10. Acceptable references for portal hypertension meeting study exclusion include: a recent gastroscopy with evidence or varices, platelets <150, and/or splenomegaly on recent imaging measuring >12 cm
11. Chronic alcohol consumption or participants consuming more than the recommended allowance of 14 units of alcohol per week (as set out by the Department of Health).
12. Any active malignant disease or history of malignancy within the past 5 years including high risk basal cell carcinoma.
13. Existing or intended pregnancy or breastfeeding during the study period.
14. Current or recent participation in any other clinical trial involving a CTIMP within the last 6 weeks prior to the screening period (to be reviewed on a case-by-case basis).

15. Have received any systemic corticosteroid or topical colonic corticosteroid including budesonide, or any disease-specific IBD treatment (outside of normal maintenance therapy) within the last 3 months prior to the screening visit.
16. Positive stool culture for Clostridium difficile or enteric pathogens within 12 weeks prior to the study visit.

Infectious disease exclusion criteria:
1. Has chronic hepatitis B virus (HBV), hepatitis C virus (HCV) or positive hepatitis B core antibody (anti-HBc) at screening.
2. Has evidence of an active infection (defined as infection of any organ or where antibiotics are required except minor skin infections not requiring antibiotics) within 28 days, or within 8 weeks if serious infection, of screening visit or known long term (chronic) infection.
3. Has proven previous history of systemic fungal sepsis- as defined by invasive organ infiltration and positive blood cultures (note: presence of mucocutaneous involvement is not included in this definition).
4. Has any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
5. Has active tuberculosis (TB). Anti-TB therapy should be considered for all participants with latent TB prior to initiation with IMP or proven prior therapy provided.

General/drug-related exclusion criteria:
1. Current or previous exposure to any IL-17 Inhibitor.
2. Currently receiving treatment with any of the following: biologic therapy (anti-Tumour Necrosis Factor, anti-integrin inhibitors), Janus-associated Kinase inhibitor (JAK), ciclosporin, tacrolimus, methotrexate. Antimetabolite therapy would be allowed provided they have been established at a steady state for ≥12 weeks.
3. Has a diagnosis of active depression or currently receiving any form of treatment for depression (including psychotherapies), or suicidal ideation or behaviour in the previous 12 months.
4. Known hypersensitivity reaction to any of the list of excipients of Brodalumab.
5. Recently received or scheduled to receive a live vaccine within 4 weeks prior to the screening visit or for 6 months after the last dose of IMP.

Previous exclusion criteria:
1. Gallbladder lesion or polyp (>5 mm diameter), cholangiocarcinoma mass lesion, or high suspicion of cholangiocarcinoma, as indicated on imaging such as ultrasound, computer tomography (CT), dynamic magnetic resonance imaging (MRI) or MRCP.
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3. Has a diagnosis of active depression or currently receiving any form of treatment for depression (including psychotherapies), or suicidal ideation or behaviour in the previous 12 months.
4. Known hypersensitivity reaction to any of the list of excipients of Brodalumab.
5. Recently received or scheduled to receive a live vaccine within 4 weeks prior to the screening visit or for 6 months after the last dose of IMP.

Date of first enrolment
02/02/2024

Date of final enrolment

30/03/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Queen Elizabeth Hospital
University Hospital Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

Sponsor information

Organisation
Norfolk and Norwich University Hospitals NHS Foundation Trust

Sponsor details
Colney Lane
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England
United Kingdom
NR4 7TJ
-
Julie.dawson@nnuh.nhs.uk

Sponsor type
University/education

Website
http://www.nnuh.nhs.uk/

ROR
https://ror.org/01wspv808

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG. Considerations for approving access are documented in the TMG Terms of Reference. Where data is shared with other researchers data will be anonymised. Generic consent will be obtained for this purpose.

Intention to publish date
30/09/2026

Individual participant data (IPD) sharing plan
Requests for access to datasets generated and/and or analysed during the current study will be considered, and approved in writing where appropriate, upon formal request to the trial management group.
SABR.PSC@uea.ac.uk

IPD sharing plan summary
Available on request