BMJ Open Gastroenterology

Assessing brodalumab in the treatment of primary sclerosing cholangitis (SABR-PSC pilot study): protocol for a single-arm, multicentre, pilot study

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To cite: Elzubeir A, High J, Hammond M, *et al*. Assessing brodalumab in the treatment of primary sclerosing cholangitis (SABR-PSC pilot study): protocol for a single-arm, multicentre, pilot study. *BMJ Open Gastroenterol* 2025;**12**:e001596. doi:10.1136/bmjgast-2024-001596

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjgast-2024-001596).

Received 16 September 2024
Accepted 13 January 2025

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ABSTRACT

Introduction Primary sclerosing cholangitis (PSC) is a rare immune-mediated hepatobiliary disease, characterised by progressive biliary fibrosis, cirrhosis, and end-stage liver disease. As yet, no licensed pharmacological therapy exists. While significant advancements have been made in our understanding of the pathophysiology, the exact aetiology remains poorly defined. Compelling evidence from basic science and translational studies implicates the role of T helper 17 cells (Th17) and the interleukin 17 (IL-17) pro-inflammatory signalling pathway in the pathogenesis of PSC. However, exploration of the safety and efficacy of inhibiting the IL-17 pathway in PSC is lacking.

Methods and analysis This is a phase 2a, open-label, multicentre pilot study, testing the safety of brodalumab, a recombinant human monoclonal antibody that binds with high affinity to interleukin-17RA, in adults with PSC. This study will enrol 20 PSC patients across five large National Health Service tertiary centres in the UK. The primary outcome of the study relates to determining the safety and feasibility of administering brodalumab in early, non-cirrhotic PSC patients. Secondary efficacy outcomes include non-invasive assessment of liver fibrosis, changes in alkaline phosphatase values and other liver biochemical readouts, assessment of biliary metrics through quantitative MR cholangiography+, and quality of life evaluation on completion of follow-up (using the 5D-itch tool, the PSC-patient-reported outcome and PSC-specific Chronic Liver Disease Questionnaire).

Ethics and dissemination Ethical approval for this study has been obtained from the London Bridge Research Ethics Committee (REC23/LO/0718). Written informed consent will be obtained from all trial participants prior to undertaking any trial-specific examinations or investigations. On completion of the study, results will be submitted for publication in peer-reviewed journals and presented at national and international hepatology meetings. A summary of the findings will also be shared with participants and PSC communities.

Trial registration number ISRCTN15271834.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Over the past decade, there has been a surge in emerging evidence from basic science and translational studies implicating the IL-17 pathway in the pathogenesis of primary sclerosing cholangitis (PSC). Nonetheless, a trial of pharmacological IL-17 inhibition in PSC patients has not been undertaken to date. Evaluation of IL-17 inhibition in PSC patients to determine its safety and potential efficacy is a priority.

WHAT THIS STUDY ADDS

⇒ This is the first novel clinical trial of a repurposed anti-IL-17 drug in PSC.

⇒ The unique application of novel non-invasive MRI quantitative metrics using MR cholangiography (MRCP+) and Liver MultiScan (Perspectum) to chart pretreatment and post-treatment biliary changes is a significant strength of the study. As is the unique opportunity to conduct exploratory translational research from samples collected during the study—most notably IL-17 cytokine profiling pretreatment and post-treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will significantly improve our understanding of the safety and potential efficacy of IL-17 inhibition in early-stage PSC. If the results are positive, it would provide compelling grounds to carry out a phase 3 randomised controlled trial.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare immune-mediated chronic cholestatic disease. It is characterised by chronic biliary inflammation, stricturing and concentric fibrosis of the intra and/or extrahepatic bile ducts ultimately leading to cholestasis, recurrent bacterial cholangitis, biliary cirrhosis and end-stage liver disease for a proportion

of patients.[1–4] The exact aetiology of PSC remains elusive; nonetheless, it is widely regarded as a composite interaction between genetics and environment, leading to a dysregulated immune system.[5 6] Regrettably, despite recent advancements in our understanding of the disease, no licensed pharmacological treatment exists that alters the natural history of the disease, and for many, liver transplantation is the only life-extending intervention.[7]

PSC is a male predominant disease (2:1), with a median age of onset of 41 years.[8 9] An indisputable hallmark of the disease is the concomitant diagnosis of inflammatory bowel disease (PSC-IBD)—typically colitis, which is a clinically, phenotypically and genetically distinct entity from classical IBD without PSC and occurs in approximately 70%–80% of those with PSC.[10 11]

The PSC phenotype is largely characterised based on the site of biliary injury, that is, small duct or large duct disease, with large duct disease ('classic PSC') being the predominant phenotype (90%), and small duct disease representing a more indolent form.[12 13]

Reported mean incidence and prevalence rates range from 0 to 1.58 per 100 000 and 0–31.7 per 100 000, respectively.[14 15] While a progressive disease, the natural history of PSC is heterogeneous and often unpredictable. At a population level, the estimated median transplant-free survival is 21 years, with shorter time to events reported in cohorts diagnosed in tertiary referral transplant centres.[16]

While alkaline phosphatase (ALP) remains the conventional non-invasive marker of prognosis and treatment response in PSC (used as an endpoint in phase 2 clinical trials), its natural fluctuation during the disease course renders it an imperfect primary endpoint[17 18] in phase 3 studies. Additionally, the low event rate of hard clinical endpoints such as liver transplantation renders it an impractical trial endpoint.[19 20] The enhanced liver fibrosis score (ELF score) and liver stiffness measurements (LSM) (using transient elastography) are both reliable predictors of advanced fibrosis and adverse long-term clinical outcomes in PSC.[21–23] Given the ccorrelation of liver fibrosis with clinical outcomes, the ELF score and LSM have emerged as non-invasive proxy markers for long-term clinical outcomes in PSC, potentially avoiding the need for invasive liver biopsies.

Several pharmacological approaches have been trialled in PSC including antifibrotics, antibiotics, bile acid regulators and immunomodulators, although results to date have been disappointing.[24] Over recent years, biological agents have revolutionised the management and outcomes of numerous chronic immune-mediated and inflammatory conditions, including IBD. To date, five broad classes of biologics have been evaluated in PSC and/or PSC-IBD.

Th17 and IL-17 signalling pathways

The family of interleukin-17 (IL-17) cytokines consists of six structurally analogous cytokines—IL-17A to F.[25] IL-17A, the archetypal cytokine was discovered in 1993,[26] with its associated binding receptor- IL-17RA discovered later in 1995.[25 27] The main effector of IL-17 activity is a unique lineage of T cells known as T helper 17 cells (Th17), a subset distinct from traditionally regarded T helper 1 and 2 cells.[28 29] Th17 cells differentiate from naïve T cells in the presence of transforming growth factor β (TGF-β), IL-1β, IL-6, IL-23 and STAT signalling.[30–33] Although knowledge with regard to the regulation and function of the full composition of IL-17 cytokines is in its infancy, its role as a potent pro-inflammatory cytokine is well established.[26 27 33] Amplified Th17 and IL-17 activity has been implicated in numerous chronic inflammatory conditions. IL-17 inhibitors, such as brodalumab, have transformed the therapeutic landscape of IL-17 predominant inflammatory conditions such as psoriasis, offering a safe and highly effective alternative agent particularly in patients with a lack of response to biologics previously.[34–36]

Proof of concept

There is compelling evidence from basic science and translational studies of Th17 cells and the IL-17 pathway being critical to the pathogenesis of PSC. Human PSC studies have described increased IL-17+secreting cellular aggregates in periductal areas around damaged bile ducts.[37] Garcia Moreno *et al*[38] demonstrated the expression of IL-17 receptors A, C and E on human disease-derived extrahepatic cholangiocyte organoids originating from patients with and without PSC. Furthermore, peripheral blood mononuclear cells appear to exhibit increased Th17 cell responses to pathogenic stimulation in vitro.[37 39] Meng *et al*[40] demonstrated that IL17A and its associated receptor upregulate in response to liver injury, and abrogation of IL17 receptor A subunit in Mdr2 knockout (−/−) mice (a murine model of biliary fibrosis) inhibits hepatic fibrogenesis. Complementary studies report a reduction in hepatic injury and fibrosis when blocking IL-17 activity either through inhibition of the IL-17A cytokine or in IL-17A−/− or IL-17RA−/− knockout mice.[40–44] Jiang *et al*[45] more recently demonstrated that pathological biliary resident CD4 T cells are enriched with Th17 cell aggregates in PSC.

Brodalumab

Brodalumab is a fully humanised anti-IL-17RA monoclonal antibody that binds to IL-17RA with high affinity (figure 1), inhibiting the downstream pro-inflammatory cytokine storm.[46 47] In addition, brodalumab concurrently nullifies IL-17A, IL-17F, IL-17A/F heterodimer, IL-25 and IL-17C signalling.[47] Brodalumab is a systemic biologic, administered subcutaneously. In 2017, brodalumab was licensed for the treatment of moderate to severe chronic plaque psoriasis in adults. We postulate that treatment of PSC patients with brodalumab will inhibit the destructive inflammatory IL-17 cytokine storm and potentially suppress periductal fibrosis.

As a result of recent research implicating the IL-17 pathway in PSC, we are undertaking the first clinical trial, to the best of our knowledge, of an IL-17 receptor

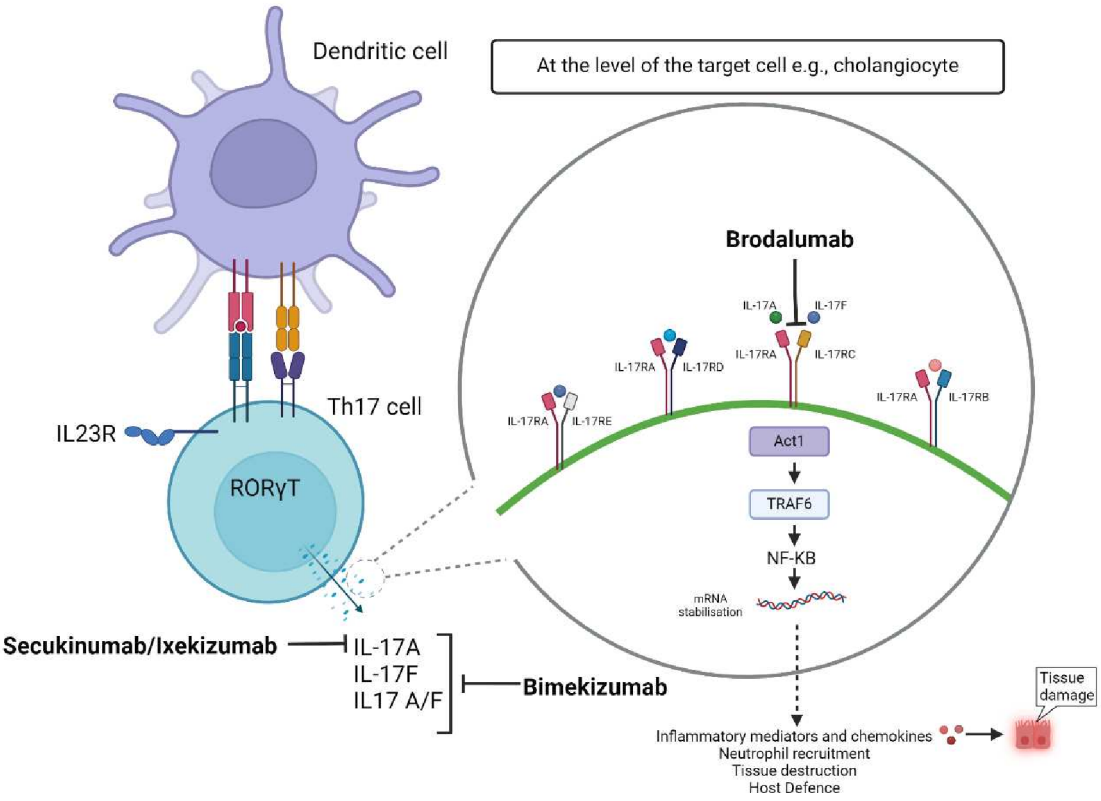

Figure 1 Mechanism and site of action of pharmacological agents targeting the IL-17 signalling pathway (figure created in BioRender.com). SABR, single-arm pilot study of brodalumab.

inhibitor (brodalumab) in patients with PSC. This decisive pilot study will help to inform the design and conduct of a future phase 3 randomised controlled trial (RCT). Principally, determining the safety of brodalumab in PSC in addition to feasibility standpoints (recruitment, retention, sample size calculations). We will also non-invasively assess preliminary signs of efficacy with regard to periductal disease stability or change (improvement or deterioration). Here, we describe the protocol for the SABR-PSC pilot study.

METHODS AND ANALYSIS

Study design overview

SABR-PSC (single-arm pilot study of brodalumab in the treatment of primary sclerosing cholangitis) is a phase 2a, multicentre, single-arm, open-label pilot study to assess the safety and feasibility of using anti-IL-17RA antibody, brodalumab, as a treatment in adults with PSC. 20 patients with a confirmed diagnosis of early-stage (non-cirrhotic) large-duct PSC will be enrolled. Participants will be recruited from five UK hospitals (Norfolk and Norwich University Hospital; Queen Elizabeth Hospital, Birmingham; John Radcliffe Hospital, Oxford; Addenbrookes Hospital, Cambridge; Nottingham University Hospital National Health Service (NHS) Trust). Additional sites will be added where necessary to achieve the target sample size.

Eligible participants having provided prior written informed consent and completed screening will commence study visits occurring at week 0 (baseline), 2, 4, 8, 12, 16 and 6 months. During which, all will receive a total of eight subcutaneous injections of brodalumab over 13 weeks (weeks 0, 1, 2, 4, 6, 8, 10 and 12) (figure 2), before returning to their standard of care. Treatment is initiated weekly for the opening 3 weeks and on alternative weeks thereafter. All participants will receive the standard dosing of 210 mg/1.5 mL of brodalumab, as is currently licensed for use in moderate to severe chronic plaque psoriasis[48] and repurposed for use in this study. Training on subcutaneous drug administration will be provided to participants at their baseline study visit. Participants will attend six face-to-face study visits and one remote consultation at 6 months.

In addition to exploring the safety and feasibility of brodalumab in PSC, this study will facilitate opportunities for future exploratory research. At predefined time points throughout the study, research serum samples will be collected to allow for future analysis of cytokine profiles including IL-17 levels, in addition to optional DNA and urine analysis for future translational research.

The study protocol was reviewed by an internal review board and adopted by the National Institute for Health and Care Research (NIHR) as part of a Doctoral Research Fellowship (Award ID: NIHR302616) and will be conducted in accordance with the Good Clinical Practice (GCP) guidelines. The study has received appropriate external Research Ethics Committee (REC) and

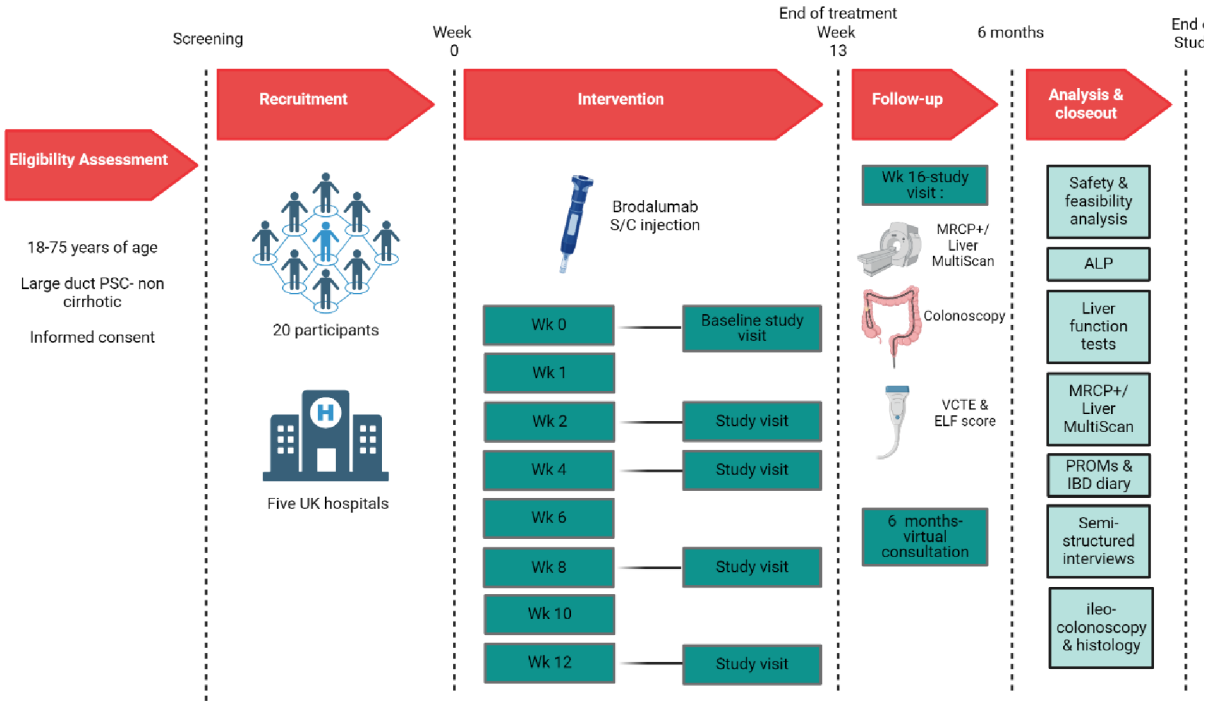

Figure 2 SABR-PSC trial schema. ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; MRCP, MR cholangiography; PROM, patient reported outcome measure; PSC, primary sclerosing cholangitis; SABR, single-arm pilot study of brodalumab; VCTE, vibration-controlled transient elastography (figure created in BioRender.com).

Medicine and Healthcare products Regulatory Agency (MHRA) approval (CTA ref: 13630/0015/001-0001).

The protocol manuscript was developed and written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines (see online supplemental file 1 for checklist).[49]

Study design rationale

A single-arm pilot study was chosen primarily to ensure adequate enrolment of participants in an orphan disease. There were concerns that allocation of participants to a placebo arm, in a study of intensive nature, may significantly impede enrolment, an apprehension that was corroborated by participants during a patient forum coordinated by PSC Support. Additionally, the side effect and adverse event profile for brodalumab have been well documented from previous clinical trials and pharmacovigilance analysis. Thus, the side effect profile was felt to be suitably specific and unlikely to occur within the natural history of PSC to make it sufficiently measurable without the requirement of a control group. Moreover, the primary interest of this study is to establish safety and feasibility, outcomes that can be suitably assessed without a control arm.

Sample size

As this is a pilot study in a complex orphan disease, a total recruitment target of 20 participants is pragmatic and considerate of this point, acknowledging that recruitment may be challenging. No formal sample size calculation was undertaken for this study as it is not powered or designed to detect a statistically significant difference in clinical efficacy outcomes. Rather, collected quantitative data will monitor for deterioration in these outcomes.

Aims and objectives

To ascertain if a future full-scale phase 3 RCT is feasible, the following objectives must be established:

1. Primary objectives: to determine the safety and feasibility of brodalumab administration in early-stage PSC (non-cirrhotic) with respect to patient acceptance, adherence, practicality, tolerability, recruitment and retention across five large PSC treatment centres.
2. Secondary exploratory objectives: evaluation of potential biochemical and histological signals of drug efficacy and disease stability or progression using a combination of liver biochemistry, non-invasive surrogate markers of liver fibrosis and MRI quantitative metrics of liver fibro-inflammation and biliary volume.

Study participants

The main inclusion criteria are adults aged 18–75 with an established clinical diagnosis of large duct PSC, as defined by the British Society of Gastroenterology and UK-PSC guidelines.[2] Participants may be recruited with or without a confirmed diagnosis of colonic IBD. For those with a history of confirmed IBD, they must have quiescent-mild disease prior to enrolment. Determination of quiescent or mild disease will be established through clinical determinants (history, IBD diary and disease activity index scoring), biochemical (C reactive protein) and endoscopic activity corroborated with a histopathology report. All participants with IBD must have undertaken their annual surveillance

colonoscopy in keeping with national guidelines,[2] within the 12 months prior to enrolment, which will be reviewed to assess eligibility. Participants meeting all the inclusion criteria and none of the exclusion criteria will be enrolled.

Recruitment of participants with a confirmed diagnosis of IBD and quiescent-mild disease will be undertaken in a 2-step process. The initial 10 PSC-IBD patients recruited into the SABR-PSC study will have quiescent disease (defined as a Crohn's Disease Activity Index, CDAI score <150; partial Mayo score, pMayo score <2, corroborated by ileocolonoscopy report and histology). An interim safety committee meeting will convene to review any adverse colonic safety signals ahead of the subsequent 10 participants with mild disease being recruited (CDAI score 150-219, pMayo 2-4 and substantiated by ileocolonoscopy report and histology). The rationale for this two-step process is as follows:

1. To safeguard prompt recognition and management of any adverse IBD events: While it is widely accepted that PSC-IBD is a clinically and phenotypically distinct disease entity to IBD without PSC,[7 10 50 51] a 2016 phase 2 RCT of brodalumab in Crohn's disease[52] was terminated early due to worsening of symptoms in a proportion of patients with active disease and failure to meet its primary efficacy outcome. Several studies have cited an association between IL-17 inhibitors and new onset or exacerbations of IBD de novo.[53–55] Three recent systematic reviews with meta-analyses have concluded that there is no apparent statistically significant difference in developing new-onset IBD with IL-17 inhibitors compared with placebo (MH RD 0.00062, 95% CI −0.00072 to 0.0021, p=0.35).[56–58] New-onset IBD event rates with IL-17 inhibitors appear to be rare, although clinical caution is advised prior to treatment initiation.[59 60]
2. To include disease states representative of the general PSC-IBD population: The long-held notion that PSC-IBD is quiescent is being disproved. Studies highlight that PSC-IBD demonstrates mild histological activity, despite patients being clinically asymptomatic and, therefore, appearing to be quiescent.[61 62] Recruiting participants with both quiescent and mild disease improves the generalisability of the study. Main inclusion and exclusion criteria for the study are outlined in box 1.

Outcome measures

Throughout the study, composite qualitative and quantitative data will be collated relating to the outlined primary and secondary outcomes.

Primary and secondary outcome measures are detailed in box 2.

Qualitative data

Participant perceptions on acceptability and tolerability will be extracted from semistructured interviews and exit/withdrawal questionnaires. During the week

Box 1 Main eligibility criteria for SABR-primary sclerosing cholangitis (PSC) pilot study

Main inclusion criteria (all must be satisfied to be considered eligible):

1. Male or female aged ≥18–75.
2. Written informed consent received.
3. Established clinical diagnosis of large duct PSC.
4. Participants may be recruited with or without an established diagnosis of concomitant colonic inflammatory bowel disease (IBD). For those recruited with an established diagnosis of concomitant colonic IBD, there must be a confirmed diagnosis of quiescent-mild disease established at screening—with a corroboratory colonoscopy completed within 12 months of the screening visit (quiescent/mild—depending on trial phase).
5. Participants with a diagnosis of IBD on maintenance therapy with 5-aminosalicylic acid or thiopurine therapy must be taking a stable dose for at least 12 weeks prior to screening, with no dose changes and expected to remain on the same dose and medication for the duration of the trial.
6. If pretreated 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 a colorectal cancer screen within 12 months of the screening visit with no signs of malignancy or 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.

Main exclusion criteria

1. Gallbladder lesion or polyp (>5 mm diameter), cholangiocarcinoma mass lesion or high suspicion of cholangiocarcinoma, as indicated on imaging.
2. Evidence of any other concomitant liver disease including but not limited to overlap syndromes with autoimmune hepatitis, IgG_4-related cholangitis, primary biliary cholangitis, alcohol-related liver disease, hepatitis B or C, or clinically significant metabolic-associated fatty liver disease.
3. Has received a liver transplant, is listed for a liver transplant or has an anticipated need for liver transplantation within the next 12 months.
4. Had a total or subtotal colectomy or presence of an ileostomy or colostomy.
5. Has current or recent history of Crohn's abscess, stricturing or fistulating disease.
6. Has had one 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 (ie, stenting or dilatation). The definition of a 'dominant stricture' for the purposes of this trial is a clinically significant biliary stricture exhibiting functional consequences as established by clinical, biochemical and radiological features.
7. 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 prophylaxis).
8. Has evidence of liver cirrhosis based on liver histology, ultrasound or vibration-controlled transient elastography (KPa >14.4) or

Continued

Box 1 Continued

history of presence of decompensated liver disease, for example, ascites, variceal bleed, hepatic encephalopathy, portal hypertension or hepatic hydrothorax.
9. Acceptable references for portal hypertension meeting study exclusion include a recent gastroscopy with evidence of varices, platelets <150 and/or splenomegaly on recent imaging measuring >12 cm.
10. Any active malignant disease or history of malignancy within the past 5 years.
11. Existing or intended pregnancy or breastfeeding during study period.
12. 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.
13. Positive stool culture for *Clostridioides difficile* or enteric pathogens within 12 weeks prior to study visit.
14. 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.
15. Has proven a history of systemic fungal sepsis (note: the presence of mucocutaneous involvement is not included in this definition).
16. Has any identified congenital or acquired immunodeficiency (eg common variable immunodeficiency, HIV infection, organ transplantation).
17. Has active tuberculosis (TB). Anti-TB therapy should be considered for all participants with latent TB prior to initiation with brodalumab or proven prior therapy provided.
18. Currently receiving treatment with any of the following: biological therapy (eg, anti-tumour necrosis factor α drugs, anti-integrins, anti IL12/23 agents), Janus-associated kinase inhibitors, ciclosporin, tacrolimus, methotrexate. Antimetabolite therapy, such as azathioprine, mercaptopurine and mycophenolate, would be allowed provided it has been established at a steady state for ≥12 weeks.
19. 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.
20. 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 the study drug.
21. Current or previous exposure to any IL-17 inhibitor.

16 study visit, an extended semistructured interview of participants' lived experience and perceptions of the trial including the intervention, side effects, study investigations/assessments, and frequency of study visits will be explored in depth. The interview will be audio recorded where participants have provided expressed written informed consent and transcribed verbatim. This will ensure that the answers captured are full, accurate and faithfully represent those given by participants.

Participant recruitment and screening

Potentially eligible participants will be identified at the five participating UK centres by their usual gastroenterology/hepatology healthcare team. Individuals who express an interest in the study will be provided with a patient information sheet (PIS) and invitation letter and introduced to the clinical trial team (if different from their usual healthcare team). Following written informed consent patients will be screened to establish study eligibility.

Screening investigations include full medical and medication history, physical examination, stool (enteric PCR, *Clostridioides difficile* and faecal calprotectin) and urine samples (for evidence of infection). Basic baseline physiological tests will be performed including height, weight, blood pressure, heart rate, pulse and temperature. Safety bloods undertaken at baseline will include carbohydrate antigen 19-9 (CA19-9), ELF score, bloodborne virus screening and QuantiFERON testing. Furthermore, a baseline MR cholangiopancreatography (MRCP) to include MRCP+ and Liver MultiScan, and vibration-controlled transient elastography (VCTE) will be undertaken. For females of childbearing age, a urine pregnancy test will be undertaken. While there are reports of brodalumab being associated with suicidal

Box 2 Primary and secondary outcome measures of the SABR-primary sclerosing cholangitis (PSC) pilot study

Primary outcome measures

To evaluate:
1. The safety profile of brodalumab in patients with PSC: assessed through monitoring of adverse events (AE) and serious AE rates; monitoring changes from baseline in serum haematological and biochemical blood parameters including liver function tests and surrogate markers of liver fibroinflammation; quantitative and qualitative assessment of inflammatory bowel disease (IBD) activity from serial measurements of faecal calprotectin, IBD diaries, disease-specific activity indexes (pMayo and Crohn's Disease Activity Index) and a single ileocolonoscopy with biopsies at week 16.
2. Acceptability, as determined by participants, of self-administering brodalumab, frequency of study visits, completion of assessments and patient perception of taking part in a study of a novel repurposed drug.
3. Adherence to the treatment schedule.
4. Tolerability, as determined by participants, of subcutaneous administration of brodalumab.
5. Practicality (administratively and logistically) of administering the study as per protocol across five sites.
6. Recruitment and retention rates.

Secondary outcome measures

To monitor:
1. Mean changes in serum alkaline phosphatase and other liver biochemical parameters, alongside surrogate markers of liver fibrosis (vibration-controlled transient elastography; Enhanced Liver Fibrosis score) from baseline.
2. Any change from baseline (worsening or improvement) in liver fibroinflammation and biliary volume from baseline to week 16, according to MR cholangiography+ and Liver MultiScan (Perspectum; Oxford, UK).
3. Subject reported quality of life outcomes using the 5-D itch tool, the PSC-specific Chronic Liver Disease Questionnaire and PSC patient-reported outcomes health questionnaires.

ideation and behaviour, no causal link has been established. To safeguard participants, all will be screened at baseline for depression as part of medical history taking and consolidated using the Patient Health Questionnaire 9 (PHQ-9) depression tool.

Participants will be provided IBD diaries to record bowel symptoms (allowing for calculation of the CDAI and pMAYO score as part of safety metrics) and quality of life questionnaires (table 1).

Intervention

The investigational medicinal product is brodalumab (Kyntheum) 210 mg/1.5 mL prefilled injection syringe. Each prefilled pen is for single use only. Brodalumab is currently licensed for moderate to severe chronic plaque psoriasis and is being repurposed for this study (table 2). Brodalumab will be supplied by Leo Pharma to local hospital pharmacy sites participating in the study.

Brodalumab is administered subcutaneously into the tissues of the thigh, upper outer arm or abdomen. All participants will undertake formal training by the clinical research nurse on subcutaneous injection administration at their baseline study visit. Thereafter, participants will be able to self-inject at home, at study visits if this coincides with their scheduled day of administration (which has potential to improve treatment adherence), or they may elect for injections to be administered by the research team.

Concomitant medication

Participants are permitted to continue treatment with ursodeoxycholic acid provided it has remained at a stable dose for 12 weeks prior to screening, does not exceed 20 mg/kg/day and there is no anticipated dose change during the trial period. Treatment with 5-aminosalicylic acid, antimetabolite therapy (azathioprine, mercaptopurine) and licensed/guideline-supported anti-pruritic agents (including rifampicin, cholestyramine, bezafibrate and naltrexone) is permissible, provided participants have been established on a stable dose for 12 weeks prior to screening, and no dose changes or treatment escalation are anticipated.

Concomitant treatment with biologics, small molecule inhibitors or immunomodulators, for example, infliximab, tofacitinib or methotrexate is contraindicated.

Participants are ineligible for the study if they have received colonic topical or systemic corticosteroids (including budesonide) within the last 3 months prior to screening.

Study visits

During each prescribed study visit, participants will undertake basic physiological testing, physical examination, medication review, semistructured interview, safety bloods, research serum sample collection, and urine dipstick (for occult infection), PROMs (patient reported outcome measure) including Chronic Liver Disease Questionnaire-PSC, PSC-patient-reported outcome (PRO), 5-D itch, and IBD diaries as per protocol. PROMs and IBD questionnaires will be sent and expectedly completed by participants ahead of each requisite study visit. Pregnancy testing will take place at screening and thereafter every 4 weeks throughout the trial for women of childbearing age.

A single ileocolonoscopy (including biopsies) will take place at week 16 of the study as part of colonic safety metrics. A single ileocolonoscopy contributing towards participants' standard of care surveillance programme was felt acceptable by members of the PSC patient and public involvement (PPI) group. Faecal calprotectin testing will take place at screening, weeks 0, 4 and 16 of the study to augment IBD diaries and assessment of IBD activity.

PHQ-9 depression screening, CA19-9, ELF score, VCTE, MRCP including MRCP+ and Liver MultiScan will be undertaken at screening and week 16 only. Additionally, clinical questioning regarding participants' mental health while taking brodalumab will be sought at each study visit during semistructured interviews.

Trial withdrawal criteria

To ensure patient safety, the following withdrawal criteria are explicit:

- ALP above 10-fold compared with baseline value will result in the withdrawal of the respective patient; an increase of bilirubin above 3-fold compared with baseline values or alanine transaminase >5 folds compared with baseline values may be considered as a reason for withdrawal based on medical judgement.

Trial conduct

The trial is conducted in adherence with the Declaration of Helsinki (2024), principles of GCP, Medicine of Human Use Clinical Trials 2004, Human Tissues Regulations (2007) and UK Data Protection Act.

Adverse event reporting

A trial safety committee has been convened and is responsible for providing independent oversight of the trial. The trial management group (TMG) will periodically review serious adverse event (SAE) rates. Any emerging concerns of potential toxicity will be escalated to the safety committee. Safety data of reported non-SAEs and suspected unexpected serious adverse reactions (SUSARs) will additionally be reviewed by the safety committee.

Adverse events and/or reaction severity will be reported and graded in accordance with Common Terminology Criteria for Adverse Events V.5.0 criteria. SAEs will be recorded and promptly reported to the Norwich Clinical Trials Unit within 24 hours. SUSARs will be promptly reported to the sponsor, regulatory authorities MHRA and REC as per current guidelines.

Acute flares of cholangitis will be exempt from being reported as a SAE, due to the natural history

Table 1 Summary SABR-PSC study visit schedule

	Study period										
	Screening	Treatment								Close out week 16	6-month follow-up (teleclinic or video conference)
Time point	–2 weeks Up to 14days prior to week 0 visit)	Week 0 (±3 days)	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	Week 16	6 months
Screening:											
Eligibility screen	X										
Informed consent	X										
Physical examination*	X	X		X	X		X		X	X	
Medical history	X										
Medication's review	X	X		X	X		X		X		
Intervention: Brodalumab 210 mg S/C		X	X	X	X	X	X	X	X		
Study visits		X		X	X		X		X	X	X
Assessments:											
Safety bloods	X	X		X	X		X		X	X	X
Research serum sample	X	X		X	X		X		X	X	X
CA19-9	X									X	
blood borne virus and QuantiFERON†	X										
Pregnancy test (urine)‡	X	X			X		X		X	X	
Urine sample	X	X		X	X		X		X	X	
Fibroscan and ELF score	X									X	
Faecal calprotectin§	X	X			X					X	
Stool culture¶	X										
MRCP/MRCP	X									X	

Continued

Table 1 Continued

	Study period										
	Screening	Treatment								Close out week 16	6-month follow-up (teleclinic or video conference)
Time point	–2 weeks Up to 14days prior to week 0 visit)	Week 0 (±3 days)	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	Week 16	6 months
Colonoscopy and biopsy**										X	
Questionnaires											
PSC-PRO	X			X		X			X	X	
CLDQ-PSC	X			X		X			X	X	
5D-Itch	X	X		X	X	X	X	X	X	X	
Depression Tool (PHQ-9)	X									X	
IBD diary review††	X	X		X	X		X		X	X	
Exit interview‡‡										X	

*Physical examination is to include weight measurement.
†Bloodborne virus and Quantiferon test to be collected for all participants at screening, irrespective of previous test results. Test results from screening visit will be used as valid result for entry or exclusion from study.†
‡Positive urine pregnancy test at any point in the study will result in the participant being withdrawn from treatment.‡
§A known faecal calprotectin result from screening visit is required prior to enrolment in the study. Participant to return stool sample for testing within 5 days of screening visit.§
¶Stool microbiology for enteric pathogens and *Clostridium difficile*. Participant to return stool sample for testing within 5 days of screening visit.¶
Baseline colonoscopy will be part of patients' standard of care surveillance colonoscopy and providing it has been undertaken with biopsies within 12 months of the screening tests—will be eligible to be included in the study. An ileocolonoscopy will be required for end of study of participant has a diagnosis of CD, in all other cases a full colonoscopy is accepted.
††Only for those with a confirmed prior diagnosis of concomitant inflammatory bowel disease.††
‡‡All participants that withdraw early (due to participant choice or PI decision) from the study will be offered the opportunity to complete a withdrawal questionnaire.‡‡
CA19-9, carbohydrate antigen 19-9; CLDQ, Chronic Liver Disease Questionnaire; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; MRCP, MR cholangiography; PHQ-9, Patient Health Questionnaire 9; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; SABR, Single-arm pilot study of brodalumab.

Table 2 Summary characteristics of currently licensed IL-17 inhibitors

	Secukinumab (Cosentyx)	Ixekizumab (Taltz)	Brodalumab (Kyntheum)	Bimekizumab (Bimzelx)
Manufacturer	Novartis Pharma	Eli Lily & Company	Leo Pharma	UCB Pharma
Mechanism of action	Humanised IgG_1 Mab	Humanised IgG_4 Mab	Humanised IgG_2 Mab	Humanised IgG_1 Mab
Selective target	IL-17A cytokine	Il-17A cytokine	IL-17 Receptor A	IL17, IL17 F & IL17 AF cytokines
Approved indications	► Moderate to severe PsO ► PsA ► AS ► axSpA	► Moderate to severe PsO ► PsA ► AS ► axSpA	► Moderate to severe PsO	► Moderate- severe PsO ► PsA ► AS ► axSpA
First approval	2015	2016	2017	2021
Route of administration	subcutaneous injection			
Device	75 mg/0.5 mL prefilled syringe	80 mg/1 mL prefilled syringe	210 mg/1.5 mL prefilled syringe	160 mg/1 mL prefilled syringe
Induction dose	► PsO—300 mg weekly for 5 doses ► PsA/axSpA/AS—150mg weekly for 5 doses	160 mg for 1 dose	210 mg weekly for 3 doses	► PsO—320 mg every 4 weeks for 0–16 weeks
Maintenance dose	► PsO—300 mg monthly ► PsA/axSpA/AS—150 mg monthly	► PsO—80 mg alternate weeks for 5 doses, then 80 mg every 4 weeks ► PsA/axSpA/AS 80 mg every 4 weeks	210 mg alternate weeks	► PsO—320 mg 8 weekly ► PsA/axSpA/AS—160 mg every 4 weeks
Drug Half life	Approx.27 days	13 days	10.9 days	23 days
Peak concentration (post first dose)	2–14 days post dose	4–7 days	3 days	3–4 days
Specific cautions	–	–	Depressive disorders, SIB*	–
Class side effects	Increased risk of infections including oral candidiasis, fatigue, injection site reactions, skin reactions, reported cases of new or exacerbations of IBD, headache.			

*A causal link between brodalumab and SIB has not been established, caution is nevertheless advised by the manufacturer in those with a history of depressive disorders or SIB.
AS, ankylosing spondylitis; axSpA, axial spondylarthritis; IBD, inflammatory bowel disease; IL-17RA, interleukin 17 receptor A; Mab, monoclonal antibody; PsA, psoriatic arthritis; PsO, plaque psoriasis; SIB, suicidal ideation and behaviour.

of the disease, but will be routinely recorded as trial outcome data.

In the event of a female participant becoming pregnant, the trial medication will be discontinued immediately, an SAE form will be completed, and where possible, the pregnancy will be followed up to completion for the outcome of the mother and child.

Trial monitoring

A combination of central and onsite monitoring will be used across the hospital sites. Local on-site monitoring will occur at least once during the trial. Additional site visits may be triggered in relation to reported SAE's, poor recruitment rates, high rates of participant withdrawal or poor data reporting quality.

Trial status

SABR-PSC participant recruitment commenced on 1 February 2024. Recruitment will desist in March 2025, unless amended to ensure the sample size is reached. 5/20 participants have been enrolled to date. Participant follow-up will be completed by September 2025.

Current protocol version 1.4 (20 June 2024).

Data analysis

The primary outcomes of the study are to determine safety and feasibility and will largely form that of descriptive statistics. The prevalence of adverse events will be calculated together with a 95% CI, using the Clopper-Pearson exact approach. This will be done for all major categories of adverse events.

At this preliminary stage, the investigators do not aim to make inferences regarding efficacy with any degree of confidence but rather monitor for deterioration in requisite outcomes. Changes in efficacy outcomes will be expressed as a mean change from baseline with a 95% CI, assuming the change follows a normal distribution. If not, a transformation will be applied.

Brodalumab's effect on participants' PROMs assessed at each time point will be monitored and the absolute change from baseline to week 16 will be analysed using descriptive statistics.

Patient and public involvement

PSC Support has been instrumental in the design of the study and preparing patient-facing documentation through consultation with a PSC PPI group. A patient forum of 10 PSC patients convened to discuss key aspects of the trial, including views on a single-arm open-label design, use of a novel repurposed subcutaneous drug and attitudes towards invasive histological assessments such as colonoscopy and liver biopsy. Their views were incorporated into the design of this study to help meet its primary and secondary objectives. Participants suggested that this was a timely, relevant and important study to undertake. The head of research strategy at PSC Support is a key member of the TMG and two individuals living with PSC will sit on the trial steering committee. The SABR-PSC trial has been shared by PSC Support with the wider PSC community and will additionally disseminate the trial findings at the end of the study.

CONSENT AND DISSEMINATION

Potential participants will be provided a PIS and invitation letter and given time to read them fully and an opportunity to ask questions. Written informed consent will be obtained in person at the screening visit by a trained member of the research team (informed consent form available in online supplemental file 2. Both the patient and the primary investigator will sign the informed consent form with a wet signature, named and dated.

Patient confidentiality and data handling standard regulations are being adhered to in accordance with the UK Data Protection Act. Participant confidentiality will be maintained by allocating a unique trial participant identification number to consented participants. Participants have the right to refuse to take part in or to withdraw at any time from the study, without providing a reason or explanation, and without this prejudicing their future care or treatment.

Trial-related documents have been submitted to the local research and development departments at the respective NHS recruitment sites in order to gain confirmation of capacity and capability prior to screening.

Trial results will be disseminated through publication in peer-reviewed journals and national and international conference presentations. A lay summary of trial results will be provided to participants and to members of the PSC community with support from PSC Support.

DISCUSSION

PSC is a complex orphan disease, to date, no effective medical therapy has been shown to alter the natural progression of the disease or confer a survival benefit. With its expanding incidence, substantial cost for liver transplantation and significant morbidity and mortality, there exists an irrefutable need for an efficacious pharmacological agent in PSC. Therapeutic advancements have been limited by an incomplete understanding of the pathophysiology of the disease. Nonetheless, emerging research from human and murine PSC models provides compelling evidence of an upregulated pro-inflammatory IL-17 pathway being potentially critical to its underlying pathogenesis. While this is a small pilot study, with a short duration of treatment, this study is the critical first step in investigating the safety and efficacy of brodalumab treatment in PSC patients with and without IBD. Assessment of efficacy will still need to be assessed in a future large-scale RCT.

The SABR-PSC study adopts novel emerging MRI-based assessments of hepatic fibroinflammation and strictures as part of its exploratory assessment of therapeutic response, alongside LSM (FibroScan), ELF score and ALP. Additionally, this study uses the unique position of drug repurposing to bridge the gap between proof-of-concept basic science and translational research implicating the IL-17 pathway in the first clinical trial of an IL-17 inhibitor in patients with PSC. SABR-PSC is the first open-label, multicentre clinical trial to investigate the safety and feasibility of brodalumab in adults with PSC. The results from this pilot study will help to inform the design and conduct of a future full-scale phase 3 RCT.

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Funding This study is funded by the National Institute for Health and Care Research (NIHR) as part of the NIHR Doctoral Research Fellowship (DRF)

programme awarded to Dr Amera Elzubeir (award ID. NIHR302616). EC is supported by NIHR Oxford BRC.

Disclaimer The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by London Bridge Research Ethics Committee (REC23/LO/0718). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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