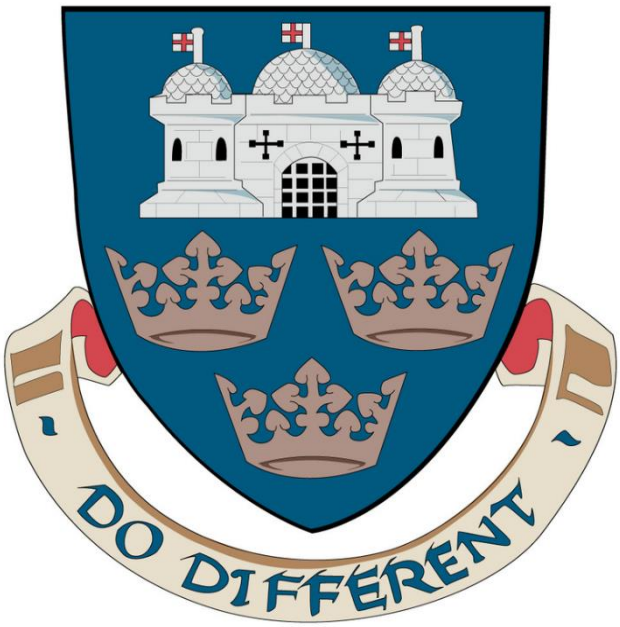
# A Single-Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis (SABR-PSC)

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2025

Thesis submitted for the degree of Doctor of Philosophy

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## Declaration

This dissertation and the work presented within it are my own, unless otherwise acknowledged in relevant sections of this thesis, and has been generated as the result of my own original research. I confirm that the work within this thesis has not been submitted in an application for another degree or qualification in this or any other institution.

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## Thesis abstract

# Single-Arm pilot study of Brodalumab in the treatment of Primary Sclerosing Cholangitis (SABR-PSC)

Primary sclerosing cholangitis (PSC) is a rare, chronic, progressive fibroinflammatory cholangiopathy of unknown aetiology, frequently associated with inflammatory bowel disease (IBD). Licensed medical therapies are lacking, rendering liver transplantation as the only life-extending option and underscoring the significant unmet need for safe, effective and acceptable disease-modifying interventions. Recent basic science and translational research implicates the interleukin 17 (IL-17) pathway and T-helper 17 cells (Th-17) in PSC pathogenesis.

This thesis aimed to evaluate the safety and feasibility of brodalumab, an IL-17 receptor-targeting monoclonal antibody licensed for psoriasis, in PSC, in order to inform the design and conduct of a future adequately powered study. A single-arm, open-label pilot study (*SABR-PSC*) was conducted at large UK tertiary NHS centres. Secondary exploratory efficacy outcomes included change from baseline in liver biochemistry, surrogate markers of liver fibrosis, quantitative multi-parametric magnetic resonance imaging (MRI) and patient reported outcome measures (5-D Itch, CLDQ-PSC, PSC-PRO). Semi-structured interviews explored participant experiences. In parallel a systematic review and meta-analysis evaluated the safety and efficacy of advanced therapies in PSC-IBD to inform safety monitoring. Pre-trial feasibility work confirmed a limited pool of eligible PSC patients at a single centre.

Recruitment was lower than expected for *SABR-PSC*. A total of six participants were enrolled and received treatment with brodalumab over 13 weeks. Retention and treatment adherence were

excellent (100%). Brodalumab was safe and well-tolerated in this small cohort with and without concomitant IBD, with no gastrointestinal safety signals observed.

These findings demonstrate the feasibility of delivering a trial of brodalumab in PSC and supports the rationale for a future phase 2 study. However, they also highlight the need for multicentre collaboration, careful dose selection, robust surrogate endpoints and optimised recruitment strategies to ensure success.

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## Abbreviations

| | |
|---|---|
| **AE** | Adverse event |
| **AR** | Adverse reaction |
| **Anti-TNF** | Anti-Tumour Necrosis Factor |
| **APC** | Antigen presenting cell |
| **ALP** | Alkaline phosphatase |
| **ALT** | Alanine transaminase |
| **AIH** | Autoimmune Hepatitis |
| **ASC** | Autoimmune sclerosing cholangitis |
| **AST** | Aspartate aminotransferase |
| **5-ASA** | 5-aminosalicylic acid |
| **BEC** | Biliary epithelial cell |
| **BDL** | Bile duct ligation |
| **BMI** | Body mass index |
| **BI** | Business Intelligence |
| **BSG** | British Society of Gastroenterology |
| **CA** | Cholic acid |
| **CCA** | Cholangiocarcinoma |
| **CDCA** | Chenodeoxycholic acid |
| **CRC** | Colorectal cancer |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CI** | Confidence interval |
| **CT** | Computer Tomography |
| **CD** | Crohn's disease |
| **CDAI** | Crohn's Disease Activity Index |
| **DCA** | Deoxycholic acid |
| **DSS** | Dextran sulphate sodium |
| **ECO** | Extrahepatic cholangiocyte organoids |
| **FC** | Faecal calprotectin |
| **FDA** | Food and Drug Administration |
| **GGT** | Gamma-glutamyl transferase |
| **GI** | Gastrointestinal |
| **GIT** | Gastrointestinal tract |
| **GWAS** | Genome Wide Association Studies |
| **ELF** | Enhanced liver fibrosis |
| **EH** | Extrahepatic |
| **ERCP** | Endoscopic Retrograde Cholangiopancreatography |
| **HR** | Hazard Ratio |
| **HRA** | Health regulatory agency |
| **HRQoL** | Health-related quality of life |
| **HSC** | Hepatic stellate cells |
| **HCC** | Hepatocellular carcinoma |
| **HRQoL** | Health-Related Quality of Life |
| **HGD** | High grade dysplasia |
| **HPB** | Hepatopancreatobiliary |
| **HIV** | Human immunodeficiency virus |

| | |
|---|---|
| **IBD** | Inflammatory bowel disease |
| **IBD-U** | Inflammatory bowel Disease-unclassified |
| **ICF** | Informed consent form |
| **IH** | Intrahepatic |
| **IFN** | Interferon |
| **IL** | Interleukin |
| **IL-17RA** | Interleukin 17 receptor A subunit |
| **INR** | International normalised ratio |
| **IMP** | Investigational medicinal products |
| **IQR** | Interquartile range |
| **KC** | Kupffer cell |
| **LdPSC** | Large-duct primary sclerosing cholangitis |
| **LCA** | Lithocholic Acid |
| **LFT** | Liver function test |
| **LMS** | LiverMultiScan |
| **LSM** | Liver stiffness measurement |
| **LT** | Liver transplant |
| **LGD** | Low grade dysplasia |
| **LLN** | Lower limit of normal |
| **LOXL2** | Lysyl oxidase-like 2 |
| **MASLD** | Metabolic dysfunction-Associated Steatotic Liver Disease |
| **MAIT** | Mucosal Associated Invariant T cells |
| **MHC** | Major Histocompatibility Complex |
| **MRCP** | Magnetic Resonance Cholangiopancreatography |
| **MRE** | Magnetic resonance elastography |
| **MRI** | Magnetic Resonance Imaging |
| **MHRA** | Medicine and Healthcare products Regulatory Agency |
| **mAb** | Monoclonal antibody |
| **MELD** | Model for End Stage Liver Disease |
| **NIHR** | National Institute for Health and care Research |
| **NK** | Natural killer |
| **NILS** | Non-invasive liver screen |
| **NNUH** | Norfolk and Norwich University Hospital NHS foundation trust |
| **NCTU** | Norwich clinical trials unit |
| **NCA** | Norucholic acid |
| **OR** | Odds Ratio |
| **OLT** | Orthotopic liver transplant |
| **PPI** | Patient and public involvement |
| **PROM** | Patient reported outcome measure |
| **PBMCs** | Peripheral Blood mononuclear cells |
| **p-ANCA** | Perinuclear anti neutrophil cytoplasmic antibody |
| **PBC** | Primary biliary cholangitis |
| **PBA** | Primary bile acid |
| **PBC** | Primary biliary cholangitis |
| **PI** | Primary investigator |
| **PSC** | Primary sclerosing cholangitis |
| **PSC-IBD** | Primary sclerosing cholangitis- inflammatory bowel disease |

| | |
|---|---|
| **PDFF** | Proton density fat fraction |
| **QoL** | Quality of life |
| **ROI** | Region of interest |
| **rTh-17** | Regulatory T helper 17 |
| **RORyT** | Retinoic acid receptor-related Orphan Receptor γT |
| **RCT** | Randomised controlled trial |
| **rPSC** | Recurrent primary sclerosing cholangitis |
| **STAT** | Signal transducer and activator of transcription |
| **SC** | Safety committee |
| **SBA** | Secondary bile acid |
| **SAE** | Serious adverse event |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **SdPSC** | Small-duct primary sclerosing cholangitis |
| **SD** | Standard deviation |
| **S/C** | Subcutaneous |
| **SIB** | Suicidal ideation or behaviour |
| **Th** | T helper |
| **TCR** | T cell receptor |
| **TMG** | Trial management group |
| **TSC** | Trial safety committee |
| **UC** | Ulcerative Colitis |
| **UDCA** | Ursodeoxycholic acid |
| **ULN** | Upper limit of normal |
| **USS** | Ultrasound |
| **VTCE** | Vibration controlled transient elastography |
| **VC** | Vidofludimus Calcium |

**Dedications**

*This thesis is dedicated to my husband Lee, and my sons Adnan and Idris, without whose patience, support and understanding this work would not have been possible.*

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I am most grateful to my parents Margaret and Zubeir, and to my sister Sarah, for their unwavering love, support and encouragement.

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## Acknowledgements of specific contributions

| Name | Position | Contributions |
|---|---|---|
| Juliet High | Research Lead, Norwich Clinical Trials Unit (NCTU) | Advice and development of trial specific working practice documents for *SABR-PSC* including protocol development, quality management, safety practices and monitoring. Review of trial specific case report forms. Auditing of trial master file and leading monitoring visit for *SABR-PSC* . NCTU representative on *SABR-PSC* trial management group. Co-author of *SABR-PSC* protocol paper. |
| Maria Leathersich | Database Programmer, NCTU | Development of *SABR-PSC* REDCap online interactive database to schedule study visits and send electronic questionnaires. Lead author of *SABR-PSC* data management plan. |
| Matthew Hammond | Deputy Director, NCTU | Adoption of *SABR-PSC* pilot study. Assistance with *SABR-PSC* trial design. Oversight of alignment of *SABR-PSC* with NCTU clinical trial working practices. Co-author of *SABR-PSC* protocol paper. |
| Michael Sheridan | Research Grants Coordinator, Norfolk and Norwich University Hospital (NNUH) | Sponsor representative on the *SABR-PSC* trial management group. Co-author of *SABR-PSC* protocol paper. |
| Julie Dawson | Research services manager, NNUH | Sponsor representative on the *SABR-PSC* trial management group. |
| Martin Pond | Head of data management, NCTU | Development of *SABR-PSC* REDCap database. Co-author of *SABR-PSC* protocol paper. |
| Professor Lee Shepstone | Professor of Medical Statistics, Norwich Medical School | Input into the statistical design of *SABR-PSC* (Chapter 4). Co-author of statistical analysis plan for *SABR-PSC*. Representative on *SABR-PSC* trial management group and safety committee. Co-author of *SABR-PSC* protocol paper. |
| Dr Allan Clark | Senior Lecturer in Medical Statistics | Critical review of Chapter 4. |
| Gail Healey | Specialist Clinical Trials Pharmacist, NNUH | Monitoring of pharmacy practises, critical review of pharmacy assurance documents, drug supply monitoring, assistance with trial prescription and drug label design. |
| Vanessa Martin | Clinical Research Nurse, NNUH | Assistance with patient study visits. |
| Kirsty Robinson | Research Administrator, Quadram Institute, NNUH | Assistance with coordinating patient study visits and patient correspondence. |

| | | |
|---|---|---|
| Martine Walmsley | Head of Research Strategy, PSC Support | Refinement of protocol and patient facing documents. Chair of *SABR-PSC* PPI patient forum. Independent representative of *SABR-PSC* trial management group. Co-author of *SABR-PSC* protocol paper. |
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| Dr Kate Lynch | Consultant Gastroenterologist and | Critical review of draft manuscript on the safety and efficacy of advanced therapies |

| | | |
|---|---|---|
| | Hepatologist, Royal Adelaide Hospital | in PSC-IBD, which was derived from Chapter 3 of this thesis. |
| Dr Simon Rushbrook | Consultant Hepatologist, NNUH | Primary Supervisor. Contribution to the overall design and clinical aspects of *SABR-PSC*. Sub-PI at NNUH for the *SABR-PSC* study. Critical review of all thesis chapters and manuscripts. Representative of the *SABR-PSC* trial management group. Co-author of *SABR-PSC* protocol paper. |
| Dr Leo Alexandre | Consultant Gastroenterologist, NNUH | Secondary Supervisor. Contribution to the overall design of *SABR-PSC*. Critical review of all thesis chapters and systematic review manuscript. Co-author of *SABR-PSC* protocol paper. |
| Dr Emily Holder | Resident Doctor, NNUH | PSC-IBD systematic review: screening of titles and abstracts and full text review (Chapter 3) |
| Dr Anjana Kumar | Resident Doctor, NNUH | PSC-IBD systematic review: data extraction. Critical review of draft manuscript (Chapter 3). |
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| Dr Jess Dyson | Consultant Hepatologist, The Freeman Hospital, Newcastle | Review of *SABR-PSC* protocol manuscript. Co-author of *SABR-PSC* protocol paper. |
| Dr Meha Patel | Doctoral Research Fellow, Norwich Medical School | Critical review of the manuscript on interleukin 17/ T-helper 17 axis, submitted for publication which was derived from Chapter 1 of this thesis. |

## Publications and statement of authorship

### List of publications arising from this work

1. **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 Gastroenterology* 2025;12:e001596. doi: 10.1136/bmjgast-2024-001596. **(Chapter 4).**

### Under peer-review

1. **Elzubeir A**, Patel M, Rushbrook S. The Interleukin-17-T helper 17 axis in primary sclerosing cholangitis: A narrative review of an emerging pathogenic frontier. Manuscript submitted and under review in: *Autoimmunity Reviews.* Manuscript Number: *AUTREV-D-25-00388.* **(Chapter 1).**

### In preparation

1. **Elzubeir A,** Kumar A, McArdle A, et al. Safety and efficacy of advanced therapies in inflammatory bowel disease patients with concomitant primary sclerosing cholangitis: a systematic review and meta-analysis **(Chapter 3).**

### List of conference abstracts arising from this work

1. **Elzubeir A,** Patel M, Patel J, Wong J, Rushbrook S, De Silva A. Characterisation, Surveillance and Outcomes of PSC-IBD: Insights from a Tertiary Care Cohort in the East of England.
   *British Society of Gastroenterology (BSG) Annual Meeting, 2025- poster presentation*

2. Al-Shakhshir S, Morris S, Kaur S, Culver E, **Elzubeir A**, Rushbrook S, Nayagam J S, Joshi D, Hernandez-Evole H, Schregel I, Schramm C, Rodriguez S, Leibovitzh H, Shibolet O, Cristoferi L, Vigano C, Carbone M, Invernizzi P, Trivedi P. An Evaluation of Anti-IL23 Therapy in Primary Sclerosing Cholangitis Associated Inflammatory Bowel Disease.

   *European Crohn's and Colitis Organisation 2025- poster presentation*

## List of oral presentations and invited speaker presentations arising from this work

1. Single-Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis:
   - *UK Primary Sclerosing Cholangitis stakeholder meeting 2023- oral presentation*
   - *British Association for the Study of the Liver (BASL) immune-mediated specialist interest group (SIG) 2023- oral presentation*
   - *International Primary Sclerosing Cholangitis Study Group (IPSCSG) Young Investigators workshop 2024- oral presentation*
   - *Annual Research Showcase, Norwich Research Park 2025- oral presentation*
   - *Clinical Academic Trainee Conference 2025, Norwich Medical School- oral presentation- 2nd prize*

2. Primary Sclerosing Cholangitis and abnormal liver blood tests in the rheumatology clinic
   - *British Society of Rheumatology (BSR) Annual meeting 2024- invited speaker*

### Statement of jointly authored publications

The research reported within this thesis is my own. Where collaborations were undertaken resulting in publication, these are reported as follows:

**Chapter 4:** published as ***Elzubeir A****, High J, Hammond M, Shepstone L, Pond M, Walmsley 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 Gastroenterology. 2025;12:e001596. https://doi.org/10.1136/bmjgast-2024-001596.*

Amera Elzubeir (AE) was the lead author of this work. AE designed and conducted this study. The initial study protocol and associated patient facing documents (patient information sheet, consent forms, invitations letters, GP letters, non-validated questionnaires, case report forms) were designed by AE with guidance from SMR, LA, JH and ML. AE gained REC, HRA and MHRA approvals and responded to oral or written questions and submitted subsequent amendments. AE drafted the protocol manuscript and responded to peer review questions. The statistical analysis plan was drafted by AE with contributions and final approval from LS and SMR. LA, SMR, JH, MH, LS, MP, MW, PT, ELC, JKD, DT, GPA reviewed the first draft and edited the protocol manuscript through to final draft.

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# Chapter 1: Introduction and background to Primary Sclerosing Cholangitis

## 1.1 Overview of chapter

Primary Sclerosing Cholangitis (PSC) is a rare and complex immune-mediated cholestatic liver disease, bearing significant morbidity and mortality to a young cohort of patients typically between the ages of 30-40. The complications of this rare disease include end stage liver disease and a significantly increased risk of colorectal and hepatopancreatobiliary malignancies. Up to 80% of patients have concomitant inflammatory bowel disease. The aetiopathogenesis of PSC remains elusive. To date there are no licensed treatments for PSC and the only life extending option is liver transplantation. Over recent decades several immune-mediated pathways have been implicated in the potential pathogenesis of PSC, with the hope that at least one may lead to therapeutic advancements, however none to date have provided a proven treatment pathway. Interleukin 17A (IL-17A) and its associated receptor (IL-17RA) were first discovered in 1993 and 1995 respectively. There has been significant interest in this immune-mediated pathway in dermatological and rheumatological conditions, with anti-interleukin 17 (anti-IL-17) agents successfully implemented and licensed for psoriasis and ankylosing spondylitis amongst others. However, of late there has been newfound interest in the IL-17 pathway with regards to other immune-mediated conditions such as PSC, with a growing body of evidence from both human and murine models suggesting significantly elevated and unopposed IL-17 activity may play a role in PSC pathogenesis. This thesis seeks to explore the potential role of an IL-17 inhibitor (brodalumab) in PSC as a safe and effective treatment, by way of a small multicentre pilot study.

This opening chapter begins with a comprehensive literature review on PSC and presents the current understanding on epidemiology, aetiology, clinical presentation, diagnosis, natural history and

medical management in addition to challenges and unmet need. The focus of the thesis then moves onto PSC-associated inflammatory bowel disease (PSC-IBD) followed by the T-helper 17 and IL-17 pathway, its role in the pathogenesis of PSC and the effect of abrogation of this pathway with an IL-17 blocking agent.

## 1.2 Primary Sclerosing Cholangitis (PSC)

Primary sclerosing cholangitis (PSC) is a rare immune-mediated chronic cholestatic liver disease characterised by intrahepatic and/or extrahepatic bile duct inflammation, fibrosis and multi-focal stricturing (1-4). This results in progressive cholestasis, recurrent cholangitis, cirrhosis, and portal hypertension leading to end stage liver disease for a subset of patients (3). Chronic inflammation and stricturing fibrosis seen in the biliary tree is thought to be driven by oligoclonal autoreactive B and T cells (5-7), with periductal fibrosis occurring as the end result of chronic inflammation and epithelial injury (8).

Secondary sclerosing cholangitis is a frequent mimic of PSC and its exclusion is essential in reaching a definitive diagnosis of PSC. Despite its overlapping mechanistic, clinical and/or pathological presentation of fibrosis and strictures of the intra and extrahepatic bile ducts and resultant biliary obstruction similar to that of PSC, the two conditions are distinct. Secondary sclerosing cholangitis is diagnosed when an identifiable, occasionally reversible biliary insult is uncovered (9-11). Several aetiologies have been identified to date, of which the most notorious is that of IgG4 autoimmune sclerosing cholangitis. Table 1-1 summarises known causes of secondary sclerosing cholangitis.

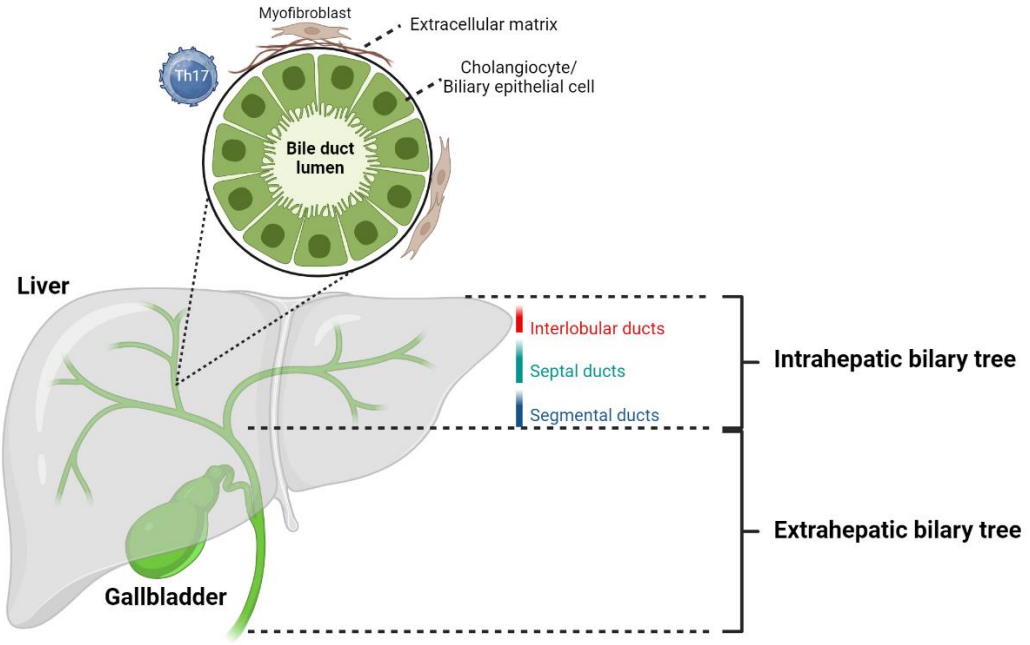
Several distinct clinical phenotypes of PSC exist, of which large-duct PSC (LdPSC) is the most common, affecting the intra and/or extrahepatic bile ducts and comprises up to 90% of cases (Figure 1-1A). LdPSC is characterised by cholestatic liver biochemistry and the presence of a "beaded appearance" on cholangiography (12, 13) (Figure 1-1B).

Histologically the hallmark of PSC is concentric fibro-obliteration of the bile ducts, referred to as an "onion skin" appearance (Figure 1-1C), however this is neither common nor unique to PSC (14, 15). Other histological findings described as the disease progresses include:

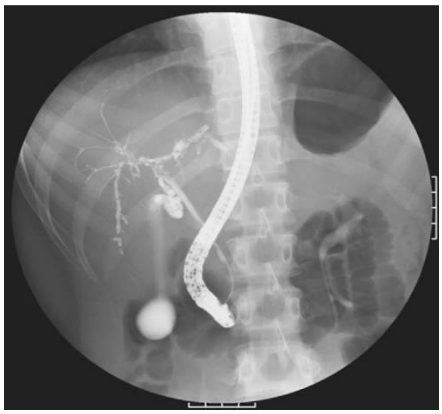
(i) **Early changes in PSC pathogenesis**: include diffuse portal tract inflammatory infiltrate. Typical portal cellular infiltrates include lymphocytes, neutrophils and plasma cells primarily centered around bile ducts, and confined to the boundaries of the portal tracts. Although, there may be evidence of interface hepatitis, mimicking autoimmune hepatitis.

(ii) **Later changes in PSC pathogenesis**: include evidence of bile duct loss (ductopenia), fibrous expansion of portal tracts, ductular fibro-obliteration, increased portal tract and biliary epithelial inflammatory infiltrate, ductular proliferation and portal oedema.

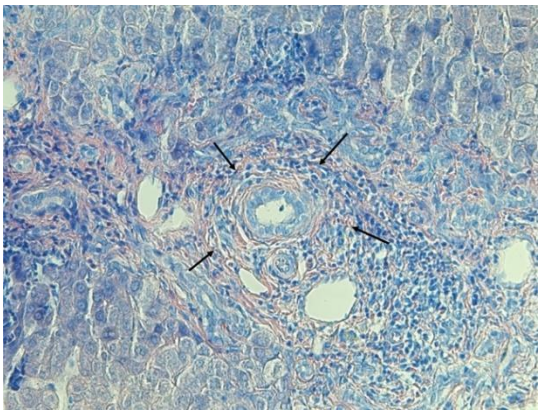
(iii) **Cholestasis**: may be seen in the later stages of the disease due to chronic biliary obstruction and cholestasis, evidenced by ductular proliferation, periportal hepatocyte copper deposition, cholestatic rosetting (glandular arrangement of hepatocytes around bile ducts), and hepatocytic cholestasis (cytoplasmic infiltration of bile into hepatocytes). Progressively, chronic injury results in architectural distortion, bridging fibrosis and development of biliary and hepatic cirrhosis (11, 15-18).




**1-1A.**



**1-1B.**



**1-1C.**

**Figure 1-1A.** Graphical representation of biliary tree anatomy. A complex network of bile ducts, which begin with small intrahepatic bile ducts within the hepatic lobes, merging progressively to become larger in diameter as they join the confluence of the right and left hepatic ducts, thereafter, becoming extrahepatic (Created with BioRender.com). **Figure 1-1B.** Cholangiogram demonstrating classic beading and stenoses of the biliary tree. Adapted from Higuchi et al. (19). **Figure 1-1C.** Histological slide demonstrating key features of PSC (Giemsa stain): hallmark concentric "onion skin" periductal fibrosis indicated by arrows. Adapted from Prokopič et al. (20).

In addition to LdPSC, other established sub-types of PSC include:

(i) **Small-duct PSC (SdPSC)** – a less common phenotype, affecting the intrahepatic ducts only (second and third-order branches). SdPSC is characterised by the presence of typical cholestatic liver biochemistry, however classic cholangiographic findings are absent and liver biopsy is essential to confirm the histological diagnosis (3). SdPSC appears to have a more favourable prognosis, with a more benign course and lower cholangiocarcinoma (CCA) rate (12, 21). Approximately 30% of patients with SdPSC will progress to LdPSC (22), however whether thereafter it inherits its associated increased risk of malignancy and poorer outcomes is controversial.

(ii) **PSC with elevated IgG4 levels**- occurring in up to 10% of patients with PSC, is a distinct clinical entity separate to that of IgG4 secondary sclerosing cholangitis (4). Typical IgG4 titres may be up to 1.5x the upper limit of normal (ULN) in PSC cohorts, emphasising the difficulty in clinically distinguishing PSC from IgG4 cholangiopathy (23).

(iii) **PSC/autoimmune hepatitis overlap syndrome (PSC/AIH-overlap)-** has clinical features of PSC in addition to autoimmune hepatitis (AIH) (3, 12). Overlap syndrome appear to form a continuous spectrum rather than distinct disease entity according to current understanding, with up to 14% of patients with PSC found to have biochemical and histological evidence of AIH (3). PSC/AIH-overlap presents with the classic cholangiographic findings of PSC, however, is associated with younger age and is combined with typical liver biochemistry elevations seen in AIH (elevated transaminases, positive immunoglobulins and anti-nuclear antibodies). Histologically there are mixed features of periductal fibro-obliteration and interface hepatitis (3).

(iv) **Autoimmune sclerosing cholangitis (ASC)**- is often seen in the paediatric setting, possibly representing an earlier more inflammatory phase of PSC (24).

**Table 1-1.** Secondary sclerosing cholangitis causes.

| Mechanism | Example |
|---|---|
| **Infectious** | Recurrent pyogenic cholangitis<br>Cytomegalovirus<br>HIV |
| **Obstructive** | Choledocholithiasis<br>Cholangiocarcinoma<br>Chronic Pancreatitis |
| **Immunological** | IgG4 disease<br>Eosinophilic cholangitis |
| **Infiltrative** | Sarcoidosis<br>Amyloidosis<br>Histiocytosis X |
| **Ischaemic** | Ischaemic cholangiopathy<br>Hepatic artery thrombosis<br>Critical care illness<br>Trauma-surgical biliary injury |
| **Toxins** | Ketamine |
| **Congenital** | ABCB4 disease<br>Caroli's disease<br>Cystic fibrosis |

### 1.2.1 Epidemiology & demographics

PSC affects approximately 10 per 100,000 in the most prevalent parts of the northern hemisphere (25). However, until recently its diagnosis has been hampered by the lack of an International Classification of Diseases code (ICD-10) (26), and thus historic epidemiological studies may underestimate the true incidence and prevalence. PSC typically affects young adults with a mean age at diagnosis between 40 to 59 years of age, with concomitant inflammatory bowel disease (IBD) in up to 80% (either ulcerative colitis, Crohn's disease or unclassified) and exhibits a slight male preponderance (2:1) (4, 25, 27) (28).

Global and regional variation in PSC epidemiology is well recognised, with a clear north south hemispheric divide. The most prevalent regions are that of Northern Europe (i.e., Scandinavia), and North America (28). Population based studies estimate the incidence of PSC ranging from 0-1.58 per 100,000 person years (mean 0.7), and a prevalence ranging from 0 to 31.7 per 100, 000 person years

(mean 10.0), with a mean estimated prevalence in the UK of 3.85 (28, 29). Figure 1-2A and 1-2B depict the global incidence and prevalence respectively (per 100,000) in PSC for men and women (30).

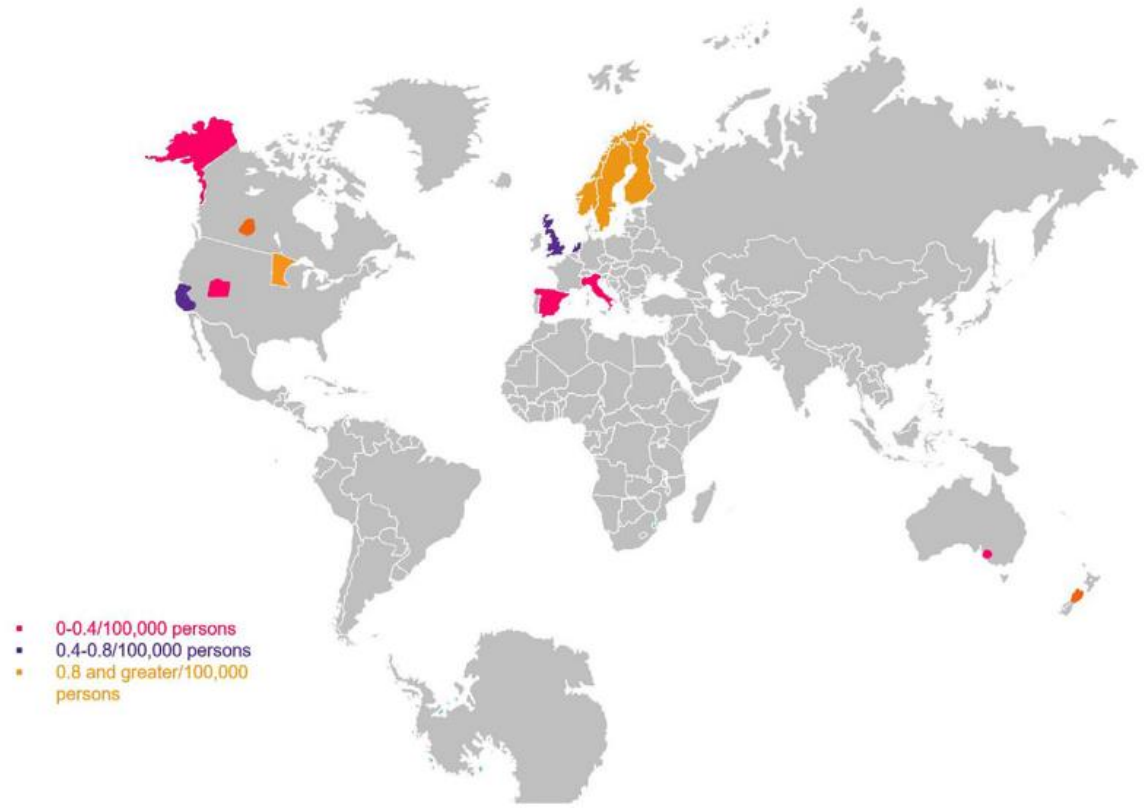



**Figure 1-2A.** Graphical representation of the global incidence of PSC (per 100,000) in men and women. Demonstrating higher rates in the northern hemisphere. Where one specific region has multiple reported studies of incidence, the highest reported incidence for that region is designated. Adapted from Sohal et al. (30) (approval for reuse granted from Elsevier order license ID:1510204-1).

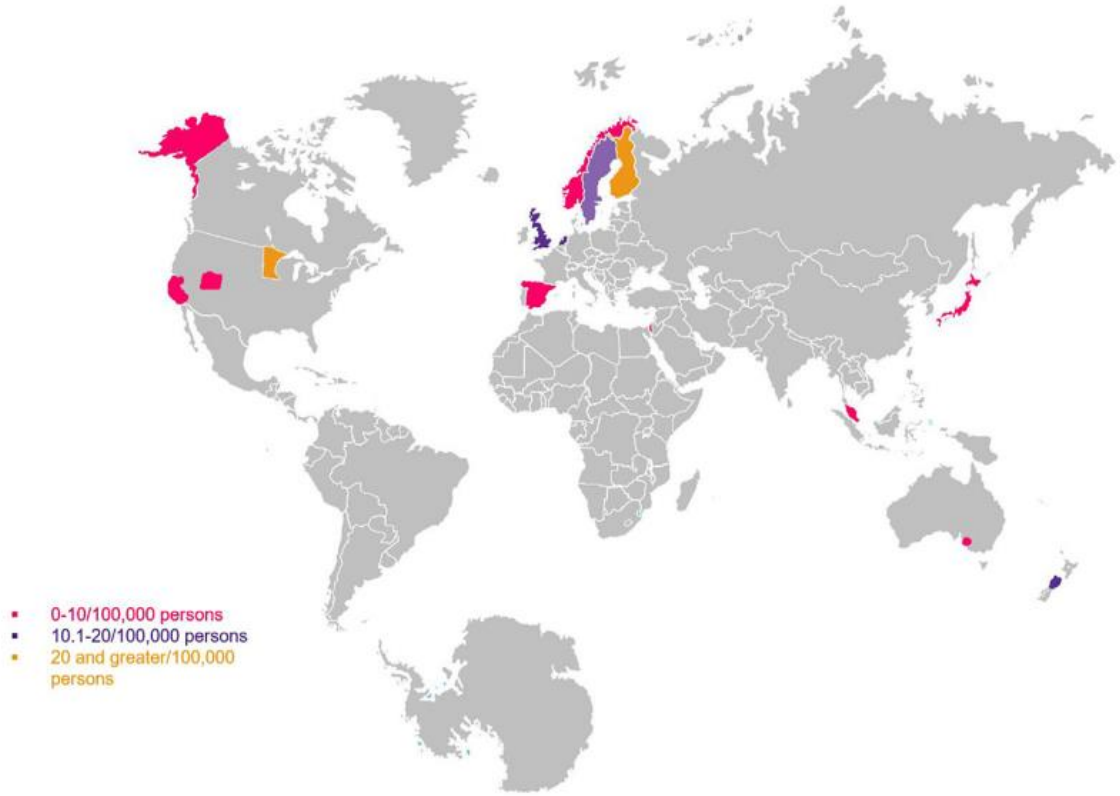



**Figure 1-2B.** Graphical representation of the global prevalence of PSC (per 100,000) in men and women. Where one specific region has multiple reported studies of prevalence, the highest reported incidence for that region is designated. Adapted from Sohal et al. (30) (approval for reuse granted from Elsevier order license ID:1510204-1).

Whilst asserting a geographical predilection, its incidence and prevalence in other ethnic groups is less well defined but appears to be lowest across the Mediterranean basin and Far East, with the lowest rates of PSC and PSC-IBD reported in Asian cohorts (28, 31). The variation in global prevalence of PSC is likely contributed to by different ethnic HLA susceptibility in addition to its regionally variable association with IBD particularly in the Far East (32), where the reported prevalence of IBD in PSC patients is as low as 20% - much lower than the reported prevalence in Iceland (88%) (28), as well as regional underreporting or lack of disease awareness.

There is an observed temporal increase in the incidence of PSC and its associated disease burden (23, 28, 29, 32, 33). Potential explanations of these observed trends are likely to be multifactorial and may include better radiographic, endoscopic and diagnostic tools, presence of digital patient registries and databases that can be interrogated, and greater disease awareness amongst physicians. These exact factors may also play a direct role in the disparity we see globally, particularly in less well-developed countries.

### 1.2.2 PSC Genetics and risk associations

PSC is widely regarded as an immune-mediated cholangiopathy, rather than a classical autoimmune disease. This distinction is supported by its male preponderance, lack of a disease-specific or diagnostic autoantigens and autoantibodies and limited or non-response to conventional immunosuppressive therapies. Nonetheless, PSC is associated with several classical autoimmune diseases (reported in up to 25% of patients) (4), including type 1 diabetes mellitus, Graves' disease, and coeliac disease. Moreover, its strong Human Leucocyte Antigen (HLA) class II association, provides a strong counter argument against its classification as a purely non-autoimmune pathology.

Our improved understanding of the fundamental genetic foundations of the pathophysiology of PSC is largely owed to the advancements in genome sequencing and Genome Wide Association Studies (GWAS). It is exceptional to have more than one family member affected with PSC despite its strong genetic association (34, 35), reflecting its rarity. The risk of developing PSC in a sibling of a patient with PSC and IBD, is estimated to be 11-fold and 8-fold respectively, making evident the association with genetic factors (4), at least in part.

The most significant PSC genetic susceptibility is associated within the HLA region, found on the short arm of chromosome 6. This region is intensely involved in modifying and refining the adaptive and innate immune systems and subsequent T and B cell responses (36, 37). To date there have been 23 genetic risk loci and 6 key haplotypes identified (8, 38, 39). The strongest genetic link to PSC identified to date is the presence of specific HLA class I alleles. HLA class I is normally expressed on the cell membrane of most cells including biliary epithelium. In health HLA class II expression is restricted to B cells and antigen-presenting cells.

Antigens (potentially derived from the gut) presented to T-cell receptors on CD4 and CD8 T cells by PSC-associated HLA likely evoke an adaptive immune response through molecular mimicry resulting in cellular injury (4, 40). In PSC there is a notable upregulation of aberrant HLA class I & II expression, with particular association observed for haplotypes DR6 and DR3 (i.e., HLA DRB1*0301), as well as B*08:01. These haplotypes are significantly more prevalent in patients with PSC compared to healthy controls (60% vs 25% respectively) (8, 41, 42). The HLA haplotypes B*08:01, DRB1*03, DQA1*0501, DQB1*02 (Table 1-2) confer the greatest relative risk for PSC susceptibility, with the strongest association observed within HLA class I, specifically B*08:01 (43). These findings implicate the adaptive immune system in disease pathogenesis. However, the development of PSC is more likely driven by a complex interplay between multiple genetic polymorphisms and exposure to specific environmental factors or other external insults.

Whilst HLA-DR3 demonstrates a strong association with PSC in European populations, this haplotype however is rare and seemingly non-contributory in African Americans with PSC listed for liver transplantation (44). This discovery further supports the established position that PSC risk is multifactorial and cannot wholly be explained by genetic risk loci alone. Irrespective, HLA-B8 appears to be shared between the two divergent populations (44).

Genes outside the HLA haplotypes have also been implicated in PSC pathogenic susceptibility, further implicating the role of the adaptive immune system. However, implicating both HLA and non-HLA loci in specific biological mechanisms remains complex. Current GWAS methods may neglect rare and private variants. Consequently, modelling and mapping of the effect of these rare variants remains challenging.

**Table 1-2:** Key HLA haplotypes and their significance in PSC. Adapted from Chapman et al. (1).

| Significance | Haplotype |
|---|---|
| **Associated with increased risk-strong association** | A1B8-TNF*2-DR3*0101-DRB1*0301-DQ*0501-DQB1*0201<br>DRB3*0101-DRB1*1301-DQA1*0103-DQB1*0603 |
| **Associated with increased risk-weak association** | DRB5*0101-DRB1*1501-DQA1*0102-DQB1*0602 |
| **Associated with reduced/protective risk** | DRB4*0103-DRB1*0401-DQA1*03-DQB1*0302 |

### 1.2.3 Current hypotheses of PSC aetiopathogenesis

The aetiology of PSC has yet to be fully elucidated, however several mechanistic theories have been proposed. PSC is thought to arise due to a complex interplay between genetics, environment, and a dysregulated immune system (45). Genetic susceptibility alone accounts for less than 10% of the attributable risk fraction, with environmental factors likely to account for the vast majority of risk association (4).

Our understanding of the key genetic components of PSC pathogenesis have been discussed above (Chapter 1.2.2), however our understanding of the complex immunological processes that underpin

PSC pathogenesis continues to evolve and will be discussed within this section. The proposed hypotheses, outlined below, are likely to overlap to varying degrees in their activity and predominance, with it being improbable that any one of the mechanisms are at play in isolation at any one time (46).

There are currently four widely accepted PSC pathogenic hypotheses, of which the majority implicate the colon, highlighting its integral link with a concomitant diagnosis of IBD as providing the appropriate immunological conditions and initial insult for hepatobiliary inflammation. Never has the understanding of the gut-liver axis in liver disease become more important than in the context of PSC and PSC-IBD. The four hypotheses are outlined below and summarised in Figure 1-3.

**Bacterial translocation, gut dysbiosis, and the "leaky gut" hypothesis**

The physiological protective barriers of the gut and liver are essential to divide their respective microbial environments, abrogate over-stimulation of the immune system and prevent immunogenic pathological bidirectional cross talk. Under physiological conditions the gut-barrier, comprising tightly opposed enterocytes and apical junction proteins, restrains the translocation of bacterial components from the gut lumen into the portal circulation (47). However, the integrity of the gut barrier system becomes compromised during colonic inflammation (IBD), rendering it permeable or 'leaky', leading to gut pathobiont exposure to the liver via the portal circulation and local immune activation, resulting in autoimmune-like molecular mimicry.

Typically, when small numbers of pathogen associated molecular patterns (PAMPs) (e.g., lipopolysaccharides, peptidoglycans and lipoteichoic acid) evade the gut barrier system and reach the liver they are swiftly detected and destroyed by hepatic Kupffer cells before reaching the systemic

circulation. Hepatic Kupffer cells (anchored onto the hepatic sinusoidal spaces) have a strategic role in maintaining immune tolerance and down regulating T cell recruitment to the vast quantities of antigens received by the liver in the portal circulation (48). The biliary system has an equivalent barrier function- Mucosal Associated Invariant T (MAIT) cells situated in the portal tracts around the bile ducts and interact with the biliary epithelial cells (BEC) protecting the biliary mucosa (49). MAIT cells are a unique subset of T cells, referred to as innate-like or "unconventional" T cells, recognising nonpeptidic antigens on their semi-variant T cell receptor (50, 51). MAIT cells are abundant in peripheral blood and represent up to 45% of hepatic T cells; principally found around bile ducts and hepatic sinusoids (50, 52). Their memory effector phenotype permits rapid response to antigen presenting molecules stimulation and upon activation secrete cytokines: IL-17, IL-22, TNF and IFN-γ. MAIT cells have been implicated in the development of hepatic fibrosis due to activation of myofibroblasts and hepatic stellate cells (HSC) through IL-17 production (53, 54). The extent and role of MAIT cells in PSC whilst remaining ill defined, is gathering scientific interest.

The liver, the largest organ in the body has a dual blood supply; the hepatic artery from which it receives oxygenated blood; however, 70% of the blood supply to the liver is derived from the portal vein which is formed by the union of the superior mesenteric vein and splenic vein carrying venous blood from the gastrointestinal tract (GIT) and spleen. It is therefore theorised that large swathes of gastrointestinal (GI) bacteria enter the portal system and biliary tree due to a breach of the normal physiological intestinal barrier as a result of colonic inflammation and disruption of the colonic tight junctions.

A study by Sabino et al., concluded that not only is there a diminution in colonic microbiota diversity in PSC but also the presence of a unique and altered intestinal microbial flora in patients with PSC with and without IBD compared to healthy controls and those with IBD alone, with *Enterococcus,*

*Fusobacterium* and *Lactobacillus* genera being disproportionately represented (55). Interestingly, one taxonomic unit belonging to the *Enterococcus* genus has been associated with elevated levels of alkaline phosphatase (ALP) (55), with *Enterococcus faecium* and *faecalis* being identified as the most frequently isolated from bile of those with PSC and dominant strictures (56, 57). It is therefore conjectured that intestinal dysbiosis triggers intestinal barrier dysfunction, increases lymphocyte homing and perpetuates the 'leaky gut' syndrome. Bacterial translocation via the portal circulation creates and propagates a proinflammatory hepatic and biliary response with Th17 activity being upregulated to specific bacteria (e.g., *Klebsiella pneumonia*) (58, 59). This breach of the liver by gut-derived bacteria stimulates cytokines and chemokines released by macrophages, dendritic cells, and natural killer (NK) cells, triggering a proinflammatory, profibrogenic cholangiocyte and hepatobiliary response resulting in progressive fibrosis and disease progression (43). Activated inflammatory cells induce Toll like receptors (TLRs) (a family of receptors that are stimulated by specific PAMPs) and CD14 resulting in the secretion of cytokines and activation of NK cells (IL-12) and lymphocytes (TNFα, IL-1β, CXCL8) perpetuating the inflammatory cycle and recruitment of lymphocytes (6).

Given the relationship of PSC with IBD Vierling et al, proposed that the initial insult seen in PSC originates as a result of bacteria or PAMPs entering the portal circulation through an inflamed and semi-permeable intestinal mucosa, allowing unfettered access to the biliary tree, with a resultant inflammatory reaction seen aggregated around the portal tracts due to biliary microbial infection. (60). The ensuing chronic inflammatory cascade initiates fibrosis as a result of stellate cell and portal fibroblast activity, leading to concentric fibrosis around the bile ducts. It is proposed that biliary fibrosis leads to biliary ischaemia and atrophy with biliary loss leading to cholestasis and eventually biliary cirrhosis (7). Vierling's hypothesis is substantially based on the initial insult in PSC being derived from colonic inflammation in the context of IBD and the associated colonic permeability as a result. There are several supporting observations of this hypothesis- (i) translocated bacterial products are

more frequently found in explanted livers of PSC patients compared to those with primary biliary cholangitis (PBC) (61); (ii) faecal transplant of *Klebsiella pneumonia* isolated from PSC patients microbiota into experimental murine models resulted in intestinal barrier dysfunction and induced an inflammatory hepatobiliary response resembling PSC (59); (iii) recent PSC studies trialling antimicrobials such as metronidazole and vancomycin have shown a transient improvement in liver biochemistry- supporting its role in altering bacterial microbial composition (62, 63); (iv) recurrent PSC (rPSC- recurrence of PSC in the new liver graft post liver transplantation) rates have been found to decrease in those who have undergone a pre-transplant colectomy (64), however a recent retrospective cohort study failed to corroborate these later findings (65). Whilst there is compelling evidence for Vierling's hypothesis there is similarly alternative evidence that contradicts the potential of this theory: firstly, PSC can occur following colectomy (66). Secondly, despite concomitant IBD occurring in the majority of PSC patients, there is a smaller but not insignificant group who have PSC without evidence of concomitant IBD and intestinal inflammation. Thirdly PSC can occur prior to active colonic inflammation and diagnosis of IBD (67). Finally, IBD activity in PSC-IBD is suggested to be milder than IBD only, although other studies do not support this observation (67-69); one would have thought that the colonic disease activity would need to be more severe to play any significant role in colonic permeability and the "leaky gut" hypothesis.

**Gut Homing- T cells return home**

A further postulation implicating the gut as central to the pathogenesis of PSC is the 'aberrant gut-homing lymphocyte' hypothesis (70, 71). PSC often runs an independent and non-correlated clinical course from that of IBD (72). However, an enterohepatic immune system that surveys and is capable of homing to both territories by memory T cells is central to this hypothesis and seeks to explain the disease activity that occurs in PSC despite typically mild-quiescent IBD. The aberrant dysregulation of the enterohepatic homing mechanism is theorised as being the catalyst of the destruction and

inflammation seen in the liver, having occurred much later following active inflammation in the GIT (73).

Under normal physiological conditions naïve T cells develop in and are then released from the thymus and circulate between the vascular system and lymphoid tissue. Within the lymphoid tissues the naïve T cells become primed on encountering dendritic cells which serve to present antigen epitopes on major histocompatibility complex (MHC) to T cells. Alongside this presentation there is an imprinting of intestinal lymphocytes with gut-homing adhesion receptors CCR9 and integrin $\alpha_4\beta_7$. These gut-homing lymphocytes that express integrin $\alpha_4\beta_7$ and CCR9 enhance recruitment of T cells to an inflamed GIT and are gut specific. These receptors facilitate signalling and direction of the intestinal lymphocytes back to the gut where they can bind to their specific ligands mucosal addressin cellular adhesion molecule 1 (MAdCAM-1) and CCL25 (74). T cells then go on to differentiate into effector T cells and persist long after active enteric inflammation has been resolved, as long-living memory T cells characterised by the expression of CD69 (47, 74). Thereby allowing them to rapidly, effectively, and preferentially expand if exposed to a further antigenic stimulus.

Endothelial adhesion molecules expressed at liver and colonic sites are phenotypically discrete. MAdCAM-1 and CCL25 being highly expressed and restricted to gut-associated lymphoid tissue, and VAP-1 being highly expressed on liver mucosa. However, it has been observed that in PSC there is an aberrant upregulated expression of MAdCAM-1 and CCL25 on portal vein endothelium and hepatic sinusoidal endothelium respectively (due to the combined effect of TNFα release due to hepatic inflammation and circulating bacteria in the portal circulation), and corresponding upregulation of VAP-1 on gut mucosa seen in IBD, allowing reciprocal transporting of activated memory lymphocytes between the two sites, using VAP-1, MAdCAM-1 or both (11, 37, 73). Leading to activation and

translocation of misdirected gut derived lymphocytes to the liver where they become aberrantly stimulated to antigens promoting a fibroinflammatory response (58). Grant et al. (71), further postulated that the $\alpha_4\beta_7$ + CCR9 memory T cells may use other proinflammatory chemokines such as CXCR6 to target biliary epithelium and initiate BEC inflammation. However, although the principle of the gut homing hypothesis is one of the most widely accepted theories in PSC pathogenesis it remains unfounded in its explanation as to why PSC can occur (i) in the absence of gut inflammation/IBD, (ii) has the propensity to occur post colectomy, and finally (iii) why only a small proportion of those with IBD go on to develop PSC.

Interestingly, inhibition of the gut specific $\alpha_4\beta_7$ integrin and cell trafficking subunit with vedolizumab is an effective treatment for IBD. Nonetheless, vedolizumab studies to date have been disappointing in PSC. A large retrospective analysis of PSC-IBD patients treated with vedolizumab (n = 102) in 20 centres across Europe and Northern America as part of the International PSC Study Group (iPSCSG), found there was a small increase in liver biochemistry at the end of the study period, with only 20% of the cohort experiencing a modest reduction in ALP of up to 20% (75, 76). A phase 3 randomised controlled trial (RCT) of vedolizumab in patient with PSC and concomitant IBD was withdrawn (no report) in 2017 (NCT03035058).

**Toxic bile acids**

Chronic cholestasis and biliary inflammation are the hallmark of PSC and are believed to arise as a result of impaired bile acid homeostasis, characterised by an altered bile acid composition and/or reduced bile acid flow (77).

Evidence points to a distinct, potentially pathological bile acid profile in PSC (78, 79). The 'toxic bile' hypothesis is based on PSC-like changes identified in the Multi-drug resistant knockout mice (Mdr2; Mdr2 -/-); which lacks the phospholipid biliary canalicular transporter (akin to the MDR3-ABCB4 in humans) (80). Phospholipids, bile acids and cholesterol combine to form mixed micelles, which protect the biliary epithelium against the cytotoxic properties of bile acids in normal physiological state. The canalicular phospholipid flippase Mdr2 transporter mediates phospholipid excretion in bile, however the Mdr2 -/- mice are devoid of this transporter resulting in retention of 'toxic' hydrophobic bile acids (non-micellar-bound), with consequent cholangiocyte injury closely resembling PSC in humans microscopically and macroscopically (81). Furthermore, an apparent reduction in bicarbonate ($HCO_3$), the so-called 'biliary bicarbonate umbrella' which may inherently serve as a compensatory or protective mechanism for cholangiocytes against toxic bile acid induced injury and apoptosis, has been implicated in PSC pathogenesis (82, 83).

Theories elucidating bile salts as potentially implicatory in PSC pathogenesis have given way to several clinical trials, and the controversial use of ursodeoxycholic acid (UDCA) following mixed results. UDCA, a naturally occurring hydrophilic dihydroxy bile acid, demonstrated some improvement in serum liver biochemistry in clinical trials without improvement in more tangible end points such as symptoms, decompensatory events or mortality, and as such is not licensed for PSC in the UK (80). It is however a licensed and effective treatment for PBC- its 'sister' cholestatic autoimmune liver disease, where its efficacy is apparent (46). Several other bile acid modulators have been investigated. Such agents will be discussed in more detail in Chapter 1.2.7.

However, the role of toxic bile acids as either the primary trigger of biliary injury or critical mediators that perpetuate ongoing damage in cholestatic liver disease remains to be fully elucidated.

**Cholangiocyte injury and 'onion skin fibrosis' model**

Cholangiocyte injury occurs in conjunction with, and is likely driven by, dynamic crosstalk involving activated immune pathways resulting in phenotypic alterations of cholangiocytes (46). The pathognomonic "onion skin" concentric obliterative periductal fibrosis and biliary strictures seen in PSC are the end-product of a progressive and prolonged inflammatory insult of the bile ducts (11, 42). Associated histological changes were described in Chapter 1.2.

Cholangiocytes are increasingly recognised as active participants in PSC pathogenesis, rather than passive bystanders. Cholangiocyte injury and senescence induction appear to have crucial roles in perpetuating the biliary destruction seen in PSC. Initial cholangiocyte insult activates pro-inflammatory and fibrogenic cytokines and chemokines perpetuating a chronic inflammatory and fibrotic process, with further stem cell activation and epithelial regeneration attempts (evidenced histologically by a ductular reaction) (11, 84). There is a predominant T-cell infiltration (including CCR6 expressing T cells) round the portal tracts, with some studies showing greater accumulation of CD4 to CD8 ratio, with reversal of this ratio in advanced disease, however the consistency of these finding has been variable, and the aetiological significance of this remains uncertain (37, 42, 85, 86).

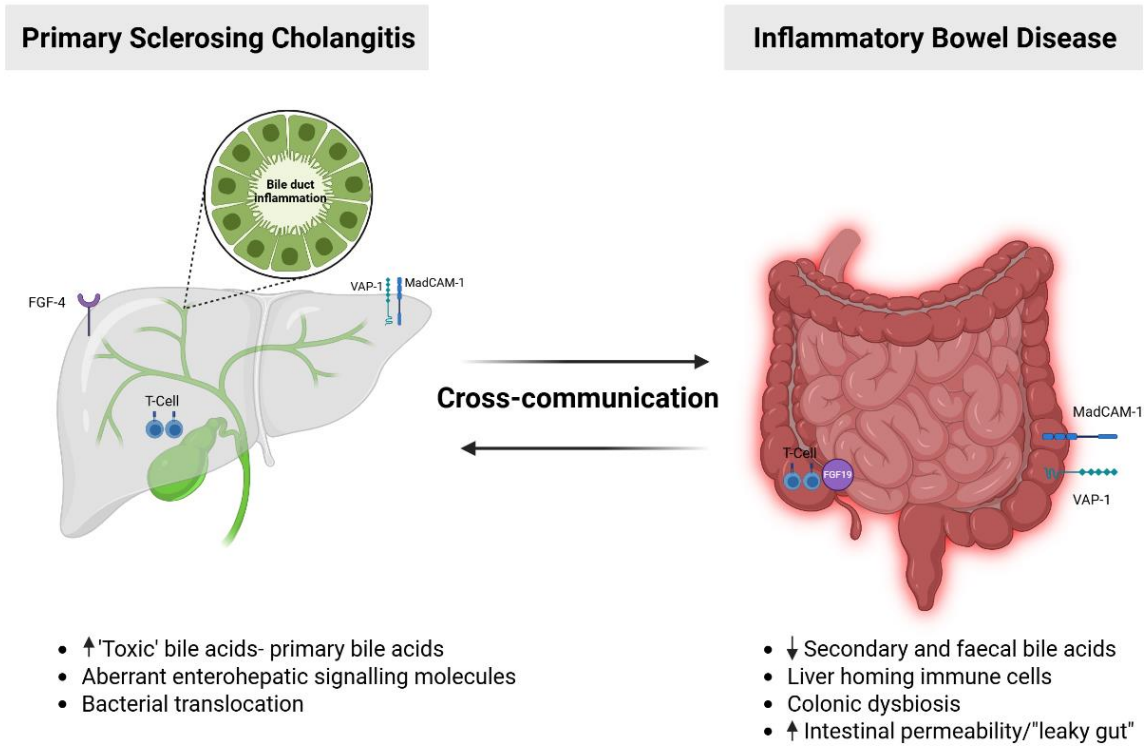



**Figure 1-3.** Graphical representation of the gut-liver axis bidirectional cross talk in PSC.

**Immunological landscape in PSC- the key players**

Although the immunological landscape of PSC is incompletely defined, emerging evidence implicates complementary roles for the innate and adaptive immune system, whose cross-talk appear critical to both disease onset and progression (87). Advances in single-cell RNA sequencing and spatial transcriptomics have substantially improved our understanding of the hepatic and biliary immune milieu in PSC- particularly in late-stage disease (87-89). However, insights into early-stage PSC remains limited due to the scarcity of suitable human liver specimens from this cohort. In this section, the broader immunological landscape in PSC is summarised before focusing on the IL-17 pathway and Th-17 cells in Chapter 1.5.

A mixed cellular infiltrate comprising neutrophils, macrophages and CD4+ T-cells is implicated in the development of PSC peribiliary fibroinflammation (43, 87, 90). Neutrophils are among the most abundant cells in peribiliary regions and are associated with disease progression in murine PSC models (91). Neutrophils mediate both acute and chronic inflammatory responses, sustain cross-talk with the adaptive immune system via chemokine/cytokine release, propagate biliary oxidative stress and form neutrophil extracellular traps (87). In the Mdr2 -/- mouse, neutrophil recruitment to inflamed bile ducts is driven by C-C motif chemokine ligand (CCL24) expressed by cholangiocytes and hepatic macrophages; importantly, CCL24 is elevated in PSC liver biopsy specimens (92). Cholangiocytes also secrete IL-8 (CXCL8), a potent neutrophil chemoattractant; biliary IL-8 is increased in PSC and correlates with peribiliary neutrophil counts (93). Together, these findings suggest that peribiliary inflammation in PSC is, at least in part, propagated by neutrophil recruitment triggered by cholangiocyte-derived cytokines and chemokines. Notably, neutrophils also express IL-17 (87), linking them to pathways discussed in Chapter 1.5.4.

Monocytes (circulating) and macrophages/Kupffer cells (tissue-resident) contribute to tissue repair and homeostasis but can adopt pathogenic phenotypes that propagate inflammation (87). Distinct inflammatory hepatic macrophages accumulate in periportal regions and within PSC scar lesions (89). These cells promote liver injury and fibrosis, drive disease progression, and recruit proinflammatory cells and secretion of mediators such as TGF-β, IL-6, IL-1β and TNF-α (89, 94). IL-6 and IL-1β are also crucial for Th17 differentiation (95), thereby linking macrophage-derived inflammation to fibrogenesis via activation of portal fibroblast and hepatic stellate cells and subsequent collagen deposition (96)

On the adaptive arm, strong HLA associations and additional genetic susceptibility loci point towards pathogenic T-cell infiltration. Multi-omics analyses reveal enrichment of Th1, Th2 and Th17 signalling, with variable regulatory T cell (Treg) dysregulation (87, 97). Peripheral Tregs are essential for tissue

repair and immune homeostasis, acting in a reciprocal relationship with Th17 cells to maintain equilibrium; notably, Tregs appear reduced in PSC compared with healthy controls (98), thereby allowing unchecked propagation of fibroinflammatory pathways. By contrast, compared to T-cell biology there is a relative dearth of literature on B-cell phenomena in PSC and on the pathological relevance of autoantibodies; antibodies are frequently observed but generally considered epiphenomenal rather than causative, as discussed in Chapter 1.2.5.

Against this background, the Th17/IL-17 axis represents a critical pathway linking the innate and adaptive immune systems, cholangiocyte activation, neutrophil chemotaxis, macrophage cross-talk and pro-fibrotic signalling.

### 1.2.4 Clinical presentation & natural history

The natural history of PSC is complex (Figure 1-4). Patients with PSC are often diagnosed incidentally and early in the disease course with approximately 50% asymptomatic at diagnosis (9, 99). Diagnosis is often bought about due to incidental findings of cholangiopathy seen on cross-sectional imaging, or elevated cholestatic liver biochemistry ALP and gamma-glutamyl transferase (GGT) during routine investigation or follow-up for other autoimmune diseases, principally IBD. Clinical presentation largely reflects the disease sequence of cholestasis, recurrent cholangitis, cirrhosis and for some resulting in end stage liver disease. More than three quarters of patients eventually develop either symptoms, biochemical, or radiological evidence of disease progression on average six years after initial diagnosis of asymptomatic PSC (99). The development of symptoms can be a critical turning point in the disease trajectory with a deleterious effect on the median time of survival to death or liver transplant (99).

The most common symptoms are often constitutional and nonspecific. Symptoms such as puritis, right upper quadrant pain, jaundice, fever, weight loss and fatigue become typical as the disease progresses. Fatigue is often worst in those with concomitant IBD and tends to be intractable, significantly impacting sleep and burdening ones health-related quality of life (HRQoL) (35). Advanced stages of the disease may become complicated by portal hypertensive gastrointestinal bleeding, hepatic encephalopathy and/or ascites, with ascites and encephalopathy being less prominent than seen in other non-cholestatic liver diseases until later in the disease course. Hepatomegaly or splenomegaly may be found on examination and suggest advanced disease (15).

Fever, rigors and right upper quadrant abdominal pain either with or without evidence of jaundice may represent bacterial cholangitis, and may be recurrent due to biliary strictures, cholestasis and bacterial invasion. Repeated courses of antibiotics may be required, with some patients eventually requiring cyclical prophylactic antibiotics.

There is currently no recognised or effective medical therapy available for PSC, necessitating liver transplantation in a subset of patients, and representing the only curative option. However, rPSC occurs in up to 25-30% of patients post liver transplantation and confers a greater incidence of graft loss post-transplantation as compared to all other liver disease aetiologies collectively (2, 28, 35, 65, 100). The natural course of PSC is unpredictable and highly variable, with a median time from diagnosis to death or transplantation of 10-22 years (3, 14, 28, 101). The lower estimates may however be less representative of the general PSC population due to tertiary referral bias and the rarity of the disease. PSC is among the leading indications for liver transplant (after alcohol and cancer) representing approximately 18% of all UK indications for transplantation (102).

In the pre-liver transplant era, the most common outcome was that of liver failure or a PSC-related complication (103). Since the 1990s liver transplantation is now the most common outcome, however death rates from cholangiocarcinoma, have only changed fractionally in this time (103). A large Dutch study of PSC patients found a fourfold increase in mortality compared to the general population with the top four causes of death relating to cholangiocarcinoma (accounting for 1/3$^{rd}$), liver failure, liver transplant-related complications and colorectal cancer (33).

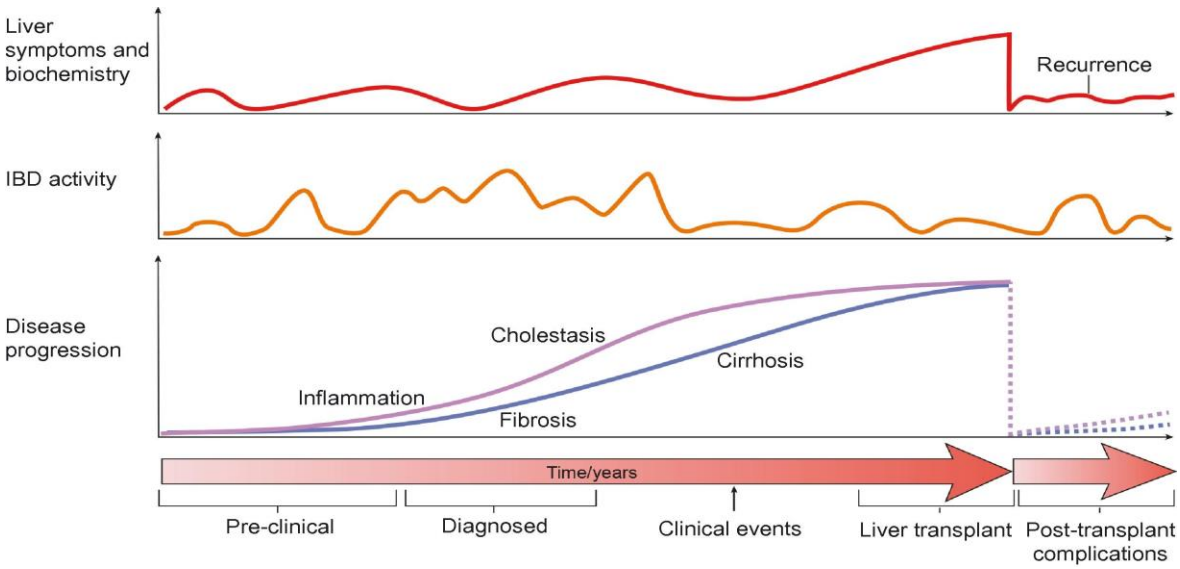



**Figure 1-4.** The natural history of PSC: there is often a prolonged PSC pre-clinical phase, with IBD typically diagnosed prior to that of PSC. Whilst progressive liver disease is inevitable for most, the rate of disease progression is highly variable. There are inter and intra-individual fluctuations in both symptomatology and liver biochemistry. Adapted from Karlsen et al. (4).

PSC related poor prognostic factors include: extensive IH and EH duct strictures, dominant strictures/clinically relevant strictures (i.e., stenosis ≤1.5mm diameter in the common bile duct or <1mm in the hepatic duct), recurrent cholangitis, coexisting UC, older age at diagnosis, male gender, large-duct PSC and end stage liver disease (78).

It is clear there is a subset of patients who will have a favourable more indolent course and others that will have a more aggressive and rapidly progressive phenotype. Technology or biomarkers to be able to accurately predict which patients will have a more progressive disease course still remains elusive.

**PSC-associated malignancies**

PSC is associated with significant morbidity and mortality, not only pertaining to the comorbid diagnosis of IBD but also due to its inherent increased risk of malignancy. This disease burden is associated with a significant impact on NHS resources.

CCA is a commonly fatal cancer arising from the bile ducts (104). PSC confers a 400-fold increased risk of CCA compared to the general population (33). The estimated annual incidence of CCA is between 0.5 to 1.5%, with a lifetime risk of 20% for patients with PSC, and is the most common PSC-associated malignancy (33) (104). A significant proportion of cases are diagnosed concurrently at PSC diagnosis or within the first year after diagnosis, with the highest risk seen in those with dominant strictures (103, 105, 106). Eighty percent of patients diagnosed with CCA die within a year owing to its aggressive nature, advanced stage at diagnosis and lack of effective management options (103). Curative resection is rarely an option, and biliary drainage and palliative chemotherapy remains the mainstay of treatment for those eligible (3), with liver transplantation becoming an option for a small minority (107).

PSC also confers an additional increased risk of other hepatopancreatobiliary (HPB) malignancies such as pancreatic, hepatocellular and gallbladder carcinoma, as illustrated in Figure 1-5 (108). Nearly 50% of all PSC related deaths are thought to be attributable to cancer (109, 110). Gallbladder abnormalities are not uncommon in PSC patients, with gallbladder polyps in this cohort frequently harbouring

malignancy. PSC confers a 10x greater risk of gallbladder cancer compared to the general population, and a 1-3.5% lifetime incidence (105). PSC-colorectal cancer risk will be addressed in detail in Chapter 1.4.4.

Cancer preventative strategies are lacking and national surveillance recommendations outside of colorectal cancer screening in PSC are ambiguous and non-uniform in the UK.

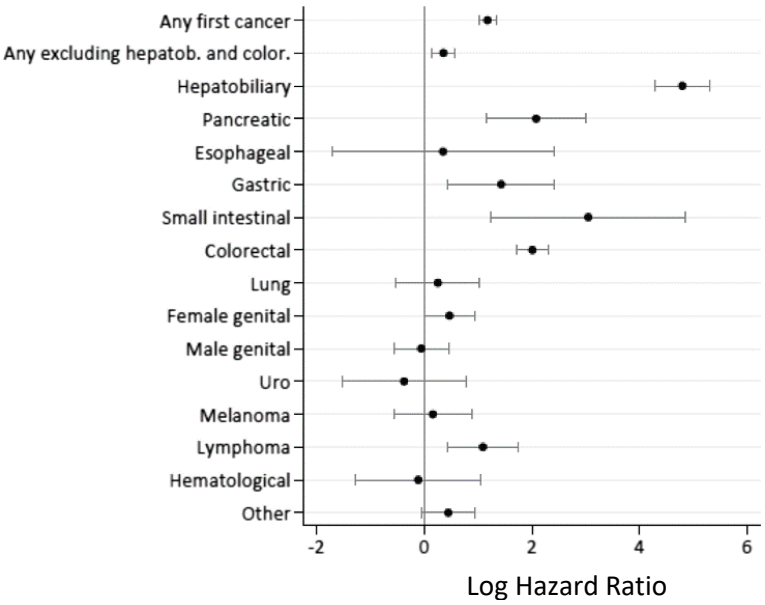



**Figure 1-5.** Forest plot of log hazard ratios (95% CI) for risk of site-specific cancers in PSC patients. Adapted from Lundberg Bave et al. (111). Abbreviation: CI, confidence interval.

### 1.2.5 PSC diagnosis

Suspicion of PSC due to cholestatic liver function derangement, warrants radiological investigation and exclusion of potential secondary causes of sclerosing cholangitis (Table 1-1). In practice the presence of IBD alongside this helps to strengthen the confidence in the diagnosis. It is important to note that ALP has a naturally fluctuant and unpredictable course in PSC and may be normal at diagnosis, which may limit its utility as a single measurement in the context of clinical trials and its

initial diagnosis (4, 78, 112). However, an ALP measurement less than 1.5x the upper limit of normal (ULN), has been associated with a better prognosis regardless of treatment (113). Bilirubin is typically normal especially early on in the disease course; however, elevations may suggest advanced liver disease or presence of a dominant stricture potentially heralding a poorer prognosis (1, 78). Elevation in aminotransferases (alanine aminotransferase-ALT; aspartate aminotransferase-AST) are commonplace but minor and may represent a more inflammatory phase. Elevations in transaminases greater than 5x the upper limit of normal should raise suspicion for PSC/AIH overlap, an episode of acute cholangitis or impending biliary obstruction (15, 78).

The first definitive case report of PSC was published by a Parisian vascular Surgeon Paul Delbert in 1924, however descriptions of what we now appreciate as a sclerosing cholangitis were made as far back as 1867 by C.E.E Hoffmann (1). It was the advent of ERCP in the 1970's that perhaps transformed the diagnostic passage (1), a modality that has largely become obsolete in the diagnosis now with the advent of Magnetic Resonance Cholangiopancreatography (MRCP). With ERCP now being predominantly used only in a therapeutic capacity.

The established gold standard diagnostic test is now high-quality MRCP (114), due to its high sensitivity and specificity, lack of ionising radiation, minimally invasive nature and cost-effectiveness (4). Typical radiographic features include irregular duct contour, intra and/or extrahepatic bile duct strictures and saccular dilations creating a classic "beaded" appearance (9, 114). The combination of these classical radiological findings in addition to exclusion of secondary causes of cholangitis, clinical correlation +/- cholestatic liver function tests (LFT's) and +/- concomitant IBD substantiate the diagnosis of large-duct PSC. The addition of an MRI liver has the advantage of addressing concerns regarding cirrhosis, portal hypertension, lymphadenopathy, hepatic malignancy or cholangiocarcinoma (9, 15).

Antibody detection in PSC is high (up to 97% overall), with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) occurring in 26-96% of cases, and antinuclear and anti-smooth muscle antibodies occurring in a smaller subset (9, 115). Atypical p-ANCA or p-ANCA can be detected in PSC. However, antibody measurement has limited value. Several issues exist with their detection (i) their diagnostic sensitivity and specificity is poor, and are therefore insufficient to diagnose PSC, (ii) their corresponding antigen(s) have yet to be elucidated, and (iii) auto-antibody detection does not correlate with disease severity or prognosis (9, 23). Nonetheless, in one Norwegian study (n = 241) ANCA positivity was associated with younger age at diagnosis, lower CCA rates and increased prevalence of HLA-B8 (116). However, conversely a more recent study by Wunsch et al. (117), identified p-ANCA to be associated with an increased risk of CCA in a cohort of German and Polish patients with PSC (relative risk (RR) = 9.8, 95% confidence interval (CI) 1.3-74.4, p=0.03).

Crucially, all newly diagnosed PSC patients should undergo an initial diagnostic ileocolonoscopy to confirm or refute the presence of concomitant IBD. This will then inform future IBD colonoscopy surveillance intervals and PSC-IBD colorectal cancer risk.

### 1.2.6 PSC medical management strategies

Despite its rarity, complexity and heterogeneity, improved understanding of PSC immunopathogenesis is likely to hold the key to potentially effective treatment strategies. With no approved pharmacological therapies for PSC as of yet, liver transplantation remains the gold standard for those who meet minimal listing criteria or have evidence of a cholangiocarcinoma meeting pre-specified criteria. However, prior to liver transplantation, management is primarily focused on prevention and management of acute bacterial cholangitis, hepatic decompensating events, intractable symptoms such as puritis, and surveillance for early detection of associated cancers.

Dominant or clinically relevant strictures may require invasive techniques such as balloon dilation, stenting or liver transplant (118).

UDCA is by far the most comprehensively studied medical therapy in PSC but has failed to prove any significant therapeutic or survival benefit, beyond liver biochemical improvements (119). Early RCTs investigating a range of UDCA doses demonstrated a reduction in liver function tests including ALP and bilirubin, nonetheless no survivorship or transplant-free survival benefit was demonstrated (120). Studies of high dose UDCA (28-30mg/kg/day) demonstrated an increase in serious adverse outcomes including colorectal cancer, liver transplantation and death (121, 122). The 2019 British Society of Gastroenterology (BSG) guidelines for management of PSC do not recommend the use of UDCA (3). In contrast, the updated EASL PSC guidelines were neutral in this regard, suggesting low doses (15-20mg/kg/day) could be considered (weak recommendation) (9), which is a notable shift from their earlier 2009 guidelines where no specific recommendation for low dose UDCA use were issued (119). The use of UDCA in clinical practice is therefore controversial. Despite this, prescriptions of low to moderate doses (13-15mg/kg/day) are still widely practiced (off label), largely owing to its auspicious choleretic, anti-apoptotic, cytoprotective, immunomodulatory and anti-inflammatory properties (120, 123).

### 1.2.7 PSC Clinical trials

There are currently more than 20 ongoing clinical trials (active and/or recruiting) interrogating diverse pathogenic pathways in PSC (Figure 1-6). To date, investigational medicinal products (IMPs) have primarily targeted the immune system (immunomodulatory and anti-inflammatory), bile acid regulators, hepatic fibrogenesis, and the gut microbiome, with several trial results still awaited. None

however have directly targeted the Th17 and IL-17 pathway. The proof-of-concept studies and rational for piloting brodalumab in PSC will be discussed in more detail in Chapter 1.5.4.

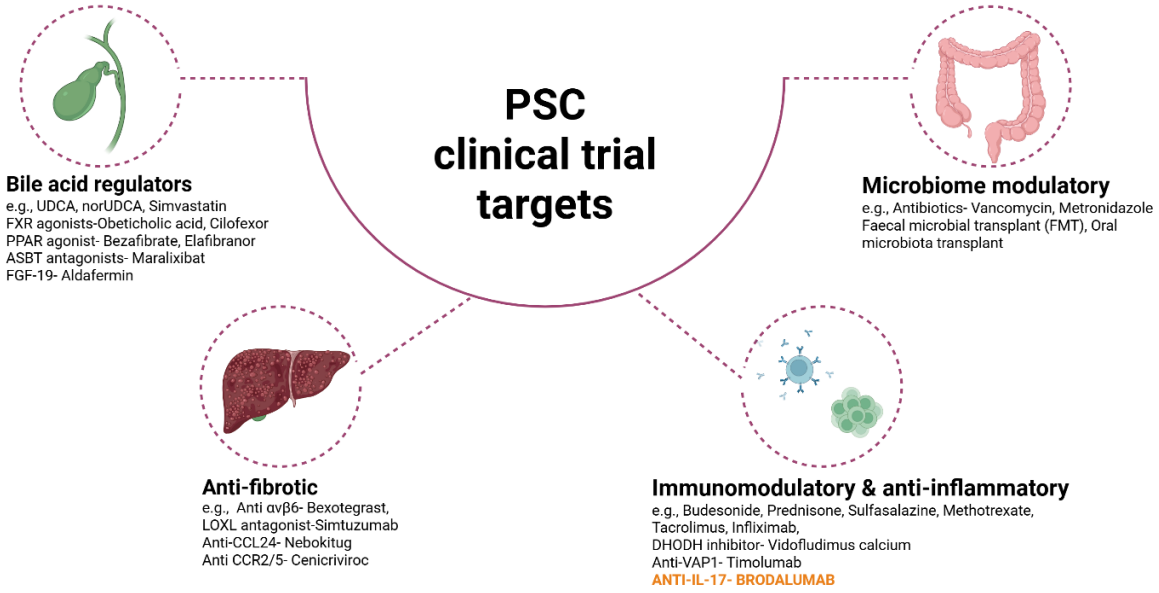



**Figure 1-6.** An overview of prior and emerging therapeutic strategies for PSC, including bile acid regulators, microbiome modulation, anti-fibrotic agents and immunomodulatory/anti-inflammatory therapies. These categories reflect the principal pathogenic pathways under investigation, with several having dual mechanisms of action. Brodalumab, an IL-17 receptor antagonist, investigated as part of the *SABR-PSC* pilot study, and reported in this thesis, is included under the immunomodulatory/anti-inflammatory category. Abbreviations: ASBT, apical sodium bile acid transporter; DHODH, dihydroorotate dehydrogenase; FXR, farsenoid X receptor; LOXL, lysl oxidase-like 2; PPAR, perioxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid; VAP, vascular adhesion protein.

Several agents currently being investigated in PSC have been approved in other conditions e.g., obeticholic acid or bezafibrate (both originally investigated for use in PBC). Therefore, the repurposing of other drugs within this field to treat PSC, is a promising solution to the considerable lag time that occurs in traversing the early stages of clinical trials. Strategically these agents will have already undergone meticulous review of pharmacokinetics, pharmacodynamics and safety profiling in

addition to being approved by major regulatory agencies such as the Food and Drug Administration (FDA) (124).

Whilst several newer agents have been successful in demonstrating a statistically significant reduction in ALP (e.g., cilofexor, bezafibrate) (125, 126), none have been able to translate that success into evidence of improved long term outcomes such as transplant free/survival benefit, reduction in decompensating events or biliary malignancy. An outcome that is likely to be imperative for any pharmacological agent to obtain FDA approval. Yet, interventional clinical trials in PSC are challenging, in part due to PSC's inherent nature of being rare, heterogenous, and slowly progressive with low frequencies of clinically relevant events (e.g., liver transplant or death). To illustrate this point, in a recently published multicentre longitudinal study conducted in Sweden of 512 unselected PSC patients, 10% underwent liver transplant and 4.9% died during five-year follow-up (127).

The following section provides an overview of identified strengths and limitations in selected prior and current clinical trials, while also suggesting areas of methodological refinement for future studies.

**PSC clinical trials- past and present: lessons learnt**

A multicentre double-blind RCT of low dose UDCA (13-15mg/kg) vs placebo was conducted between 1989-1995 (128). The primary outcomes included time to death, liver transplantation, histological progression by ≥ 2 stages, progression to cirrhosis, decompensating events, increase in bilirubin (4-fold) or worsening of symptoms (all defined as treatment failure). Fifty-one patients were included in each arm and completed a mean follow-up of 2.2 years. Inclusion criteria required an ALP ≥1.5x ULN. There was no significant difference in time to treatment failure between the two groups (RR 1.01, 95%

CI 0.6-1.7) irrespective of the histological grade of the disease. However, UDCA was associated with a significant improvement in all liver function tests including ALP in the treatment arm. Patients were stratified based on histological grade of liver disease, including patients with advanced and/or decompensating disease and intention to treat analysis was conducted (128). Additional strengths of this study include the mean duration of follow-up, comparatively PSC trials are of shorter duration (approximately 3-6 months) negating the requisite of being able to fully evaluate long term efficacy outcomes. Nonetheless, with an understanding that the natural history of the disease progresses over decades, the median follow-up time of this study remains conceivably short. Whilst extended follow-up periods to more than a few years is advantageous and desirable this is often impractical in placebo controlled RCTs. Advantageously, this study included several hard clinical outcomes including liver histology, and not just ALP, which if often the principle primary outcome in PSC trials. This study was a well conducted double-blind RCT with a reasonable sample size, successfully achieving its pre-defined sample size to confer 70% power to detect a HR of 2.0 (placebo: UDCA) given an estimated survival free of treatment failure of 3.3 years. It is not uncommon for PSC studies (current and historic) to include small sample sizes (≤20) and/or be single-arm and/or open-label (129-134), thereby introducing type II errors and bias'. Limitations of the study include the heterogeneity of the patients (disease stage as well as presence or absence of concomitant IBD), and inclusion of patients with advanced disease. This patient group are typically expected to have worse outcomes and may be less amendable to therapeutic intervention. Additionally, this study was designed with 70% statistical power, which is lower than the conventional threshold (80-90%) adopted in clinical trials. Whilst this represents a pragmatic compromise between feasibility and statistical robustness in the context of an orphan disease, it increases the risk of committing a type II error.

Two of the largest UDCA placebo-controlled RCTs evaluated moderate-high dose UDCA (17-30mg/kg) (121, 135). Both multicentre studies included larger sample sizes (Olsson: 17-23mg/kg, n = 219 and

Lindor: 28-30mg/kg, n = 149) and a 5-year follow-up duration. The largest failed to recruit their target sample size (n = 346) and was therefore underpowered to detect a statistically significant difference at the 5% level (80% power to detect a 50% reduction in predefined event rates in UDCA vs placebo) in the primary end points of death or liver transplant (135). Whilst the smaller study by Lindor et al. was terminated early due to meeting criteria for futility, demonstrating an increase in serious adverse events, i.e., liver transplant and risk of death (121). Whilst the likelihood of a type II error may be elevated in these studies, the overwhelming body of evidence of UDCA in PSC mirrors these findings: failing to demonstrate a survival benefit. The lack of success of past or present trials in finding a viable therapeutic target for PSC is likely due to the incomplete understanding of PSC pathogenesis as much as the heterogeneity of trial design and end points instituted.

A successful phase 2, dose finding, placebo controlled RCT of norucholic acid (norUDCA) (n = 159), a homologue of UDCA with antifibrotic, choleretic and anti-inflammatory properties, was found to be safe and effective. Treatment was instituted daily for 12 weeks, with a follow-up visit at 16 weeks. The primary end point was mean change (%) in ALP from baseline to 12 weeks (end of treatment). Secondary end points include the degree of reduction in ALP i.e., 50% reduction, normalisation, or partial normalisation defined as an ALP <1.5x ULN. In this study, norUDCA significantly reduced ALP levels in a dose-dependent manner (500mg, -12.3%, p=0.029; 1000mg, -17.3%; p=0.003; and 1500mg, -26.0%; p<0.0001), with the greatest benefit observed at 1500mg (136). Following these encouraging results a phase 3 RCT of norUDCA is currently underway, with full results awaited (NCT03872921). However, a note of historical caution should be taken. Despite the positive trend in ALP reduction in all treatment arms, both the aforementioned high dose UDCA studies also showed a trend towards ALP reduction in the intervention arms. Nevertheless, this was also associated with poorer clinical outcomes when compared to placebo in the trial by Lindor et al (121, 135). Preliminary results from the 96-week analysis of the phase 3 RCT investigating norucholic acid (NCA; previous known as

norUDCA) (NCT03872921, n = 301) demonstrated superiority of NCA over placebo in achieving the co-primary efficacy outcome- defined as partial normalisation of ALP without histological progression (Ludwig stage). Among patients with complete data, 21.7% (30/138) achieved this endpoint, compared with 5.7% in the placebo group (p=0.01). NCA treatment was associated with a statistically significant (p<0.0001) and sustained reduction in liver enzymes (ALP, GGT, ALT) compared to placebo. However, no significant differences were observed in non-invasive markers of fibrosis such as liver stiffness measurements (LSM) (difference in LS means -1.92, 95% CI -4.58-0.74; p=0.16), enhanced liver fibrosis (ELF) score or quality of life (QoL) measures.

It is noteworthy that the initial norUDCA study did not evaluate fibrosis at any stage (histological or non-invasive surrogate markers), which would have provided essential evidence of its potential efficacy on hard clinical outcomes, warranted when planning a phase 3 RCT. However, the inclusion of serial liver biopsies in a 16-week study would understandably have created adverse challenges to recruitment, nonetheless use of non-invasive marker of liver fibrosis such as the ELF score or LSM would have been a pertinent measure to introduce at this stage. Although, it is conceivable that liver fibrosis markers may not materially change in such a short treatment period of 12 weeks, it could be argued that proof of stabilisation of fibrosis markers (ELF/LSM) over the treatment period would have provided reassurances, particularly in consideration of advancing into a phase 3 RCT. To illustrate this point, a similar multicentre, dose finding, phase 2 RCT of cilofexor, a non-steroidal farsenoid X receptor agonist, was trialled in 52 patients with large-duct disease. Patients were randomised 2:2:1 to receive once daily cilofexor 100mg, cilofexor 30mg, or placebo for 12 weeks (later extended to 96-week open-label study) (125, 137). Safety was the primary end point, whilst exploratory efficacy endpoints included ALP and surrogate markers of liver fibrosis (ELF score and FibroScan). Cilofexor treatment was safe, well-tolerated and reduced serum ALP in a dose dependent manner (median difference in ALP from baseline to end of treatment with 100mg cilofexor of -20.5% vs +3.4% in placebo arm;

p=0.029) (137). However, no statistically significant differences were observed in markers of liver fibrosis between the treatment groups and placebo. A subsequent phase 3 RCT of 100mg cilofexor (n = 416), based on these results was conducted, with the proportion of patients with ≥1 stage progression in histological assessment of fibrosis being the primary outcome. The study was terminated at the planned futility assessment of 160 patients, as the estimated probability of meeting the primary endpoint was less than the pre-defined probability of 10% (actual 6.8%). The proportion of patients with ≥1 stage progression in liver fibrosis was not statistically significant between groups (30.8% cilofexor vs 32.8% placebo, p=0.419). The proportion of patients with improvement in liver fibrosis (≥1 stage) at 96 weeks was 25.6% in the cilofexor group vs 17.2% in the placebo arm (p=0.08). In concordance with results from their earlier phase 2 trial, liver stiffness as measured by FibroScan and ELF score equally did not show a statistically significant improvement between the verum arm and placebo.

Very few biologics or small molecule drugs (SMDs) have been evaluated in PSC as part of a clinical trial (Table 1-3) (133, 134, 138, 139). This is in contrast to its concomitant counterpart, IBD. Yet of those studied in PSC, two immunomodulators have proven evidence of clinical benefit to date. A biologic or biological therapy is defined as a substance derived directly or indirectly from living organisms (human, animal or microorganism) (140, 141). Biologics target specific protein receptors on pathogenic cells or tissues e.g., immune cells to treat or modify a disease course, and are usually administered subcutaneously or intravenously (142, 143). Alternatively, SMDs are disease modifying agents that are chemically synthesised from natural compounds (e.g., plants, fungi or microbes), low molecular weight and are orally administered (144). Of particular conceptual interest is the open-label, single-arm, pilot study of small molecule vidofludimus calcium in PSC (133). Vidofludimus calcium (VC) is of particular conceptual interest as a dihydroorotate dehydrogenase inhibitor that promotes lymphocyte apoptosis and suppression of pro-inflammatory IL-17 secretion. Eighteen

patients with a confirmed diagnosis of non-advanced PSC and an ALP ≥1.5X ULN, with or without IBD, were recruited. All participants received VC, orally, once daily for 20 weeks, 16.7% of patients met the primary end point of >25% reduction in ALP and VC was noted to have an excellent safety and tolerability profile. Nonetheless, this was a small study, of short treatment duration and with ALP and other liver biochemistry readouts utilised as the only primary and/or secondary endpoints. There was a notable lack of additional or complementary surrogate biomarkers in this study that may have helped to strengthen the findings. There are widely accepted arguments against using ALP alone as a valid surrogate marker of treatment efficacy. ALP activity is known to be heterogenous, has marked inter and intra-individual variability, frequent evidence of spontaneous reduction and even normalisation without treatment in a significant proportion of patients (145). The corollary being that ALP is an imperfect biomarker when used alone; may imprecisely reflect treatment effect, disease stages or progression (patients can have a normal ALP and advanced disease), and does not currently meet FDA approval as a surrogate marker of treatment efficacy. Therefore, a larger prospective study with hard clinical endpoints such as liver transplant, cholangiocarcinoma or death or use of multiple complementary surrogate biomarkers (e.g., vibration controlled transient elastography (VCTE), Pro-C3 and/or enhanced liver fibrosis score) will need to be undertaken to corroborate these early findings.

A seminal paper evaluating the biologic simtuzumab, a humanised antifibrotic monoclonal antibody targeting lysyl oxidase-like 2 (LOXL2) in a 2b randomised dose-finding placebo-controlled trial enrolled 234 PSC patients (146). Patients were randomised 1:1:1 to 96 weeks of weekly subcutaneously (S/C) injection of 75mg simtuzumab, 125mg simtuzumab or placebo. Mean change in hepatic collagen content measured by morphology on liver biopsy specimens at baseline, mid trial and 96 weeks was the primary outcome. Prevention of liver fibrosis judged from baseline and assessed histologically using Ishak fibrosis staging in addition to frequency of PSC related clinical events were denoted as

secondary outcomes (146). The study failed to demonstrate a significant reduction in hepatic collagen, fibrosis stage, liver biochemistry or PSC progression events with any dose of simtuzumab treatment at week 96 despite being well-tolerated. This well conducted RCT (one of the largest), included several hard endpoints- liver histology, ELF score, LSM, liver biochemistry and PSC progression events including cholangiocarcinoma, ascending cholangitis and decompensating events. However, the study included a wide spectrum of PSC severity including those with established cirrhosis, in which antifibrotics may have less clinical efficacy in this territory. Eighty-six percent of all participants were white and all included patients with IBD had quiescent disease- limiting the generalisability of the study outside of this predefined cohort. Despite this study proving a lack of efficacy for simtuzumab, it succeeded in providing valuable information with regards to PSCs natural history. It confirmed that serum ALP at baseline is an important prognostic factor in PSC, with 34% of patients with an ALP >324U/L having clinical events compatible with disease progression (vs 6% with an ALP just above the ULN) suggesting this should be considered when stratifying patients for clinical trials. Additionally, a 1 kPa increase in the LSM score >8 kPa was positively associated with occurrence of clinical events, providing valuable insight into the utility and prognostication of the LSM as a surrogate marker of liver fibrosis. The study mandated patients to undertake three separate liver biopsies over a 2-year follow-up and clearly demonstrates the will and motivation of patients to participate in research involving invasive investigations. Perhaps this reopens the debate that histological assessment should be part of all PSC trials of investigational medicinal products. Finally, it served to provide further evidence that outcomes such as cholangiocarcinoma (observed in 3/234) and death (0/234) occur all too infrequently to serve as clinical trial primary end points without requiring the need for unfeasibly large sample sizes (146).

A recent systematic review and meta-analysis examining the safety and efficacy of three biologics (infliximab, vedolizumab and adalimumab) in patients with PSC-IBD demonstrated no significant

improvement in liver related outcomes including ALP (147). Despite this, the study provided reassurance that biologics are safe and effective for PSC-IBD. Furthermore, reassuringly biologic treatment of cirrhotic patients was not associated with adverse liver outcomes (147). Whilst informative this study has no bearing on the potential exploration and outcomes of new biologics and advanced immunomodulators targeting different molecular pathways in PSC. It should be noted that the majority of the included studies were relatively small retrospective case series, with a selection bias towards patients with active IBD requiring escalated biologic therapy.

**Table 1-3.** Overview of clinical trials of biologic and advanced immunomodulator therapies in PSC to date

| **Author and Year** | **Hommes et al.(138)** | **Ardntz et al.(134)** | **Muir et al.(146)** | **Carey et al.(133)** | **NCT04595825** |
|---|---|---|---|---|---|
| | **2008** | **2017** | **2019** | **2022** | |
| **Phase/Study design** | Double-blind, placebo controlled RCT (2:1) | Phase 2, single-arm open-label | Phase 2b RCT (1:1:1) | Pilot study; single-arm, open-label | Phase 2a RCT |
| **No. of participants** | 10 | 23 | 234 | 18 | 76 |
| **Intervention** | Infliximab (Remicade) | Timolumab (BTT1023) | Simtuzumab | Vidofludimus Calcium | Nebokitug (CM-101) |
| **Biological type/target** | Anti-TNFα | Monoclonal antibody; VAP-1 | Monoclonal antibody; LOXL2 inhibitor | DHODH inhibitor | Humanised monoclonal antibody; CCL24 |
| **Route of administration** | IV | IV | S/C | Oral | IV |
| **Dose** | 5mg/kg | 8mg/kg | 75mg, 125mg | 15mg once daily for 1 week only; thereafter 30mg once daily | 10mg/kg every 3 weeks, 20mg/kg every 3 weeks |

| | | | | | |
|---|---|---|---|---|---|
| **Comparator** | Placebo | None | Placebo | None | Placebo |
| **Study Duration** | 24 weeks of treatment; EOS 52 weeks | 78-day treatment period. | 96 weeks | 24 weeks of treatment; EOS 28 weeks | 15 weeks, with open-label extension thereafter of 33 weeks; EOS 60 weeks |
| **% Male** | 60% | 83% | 64% | 38.9% | 60.5% |
| **Median age (range)** | Not stated | 45.3 (22-69) | 45 (37-52) | 45.7* (26-70) | 52* (23-75) |
| **PSC phenotype inclusion** | Large and small-duct | Large and small-duct | Large and small-duct | Large-duct | Large-duct |
| **% with IBD** | Not stated | 60.87% | 48% | 66.7% | 61.8% |
| **Patient with cirrhosis included at baseline** | Yes | No | Yes | No | No |
| **ALP cut off for inclusion** | ≥2x ULN | ≥1.5x ULN (with ≤ 25% change between initial two screening visits) | No absolute cut off; cholestatic for ≥6 months (ALP> ULN) | ≥1.5x ULN | ≥1.5x ULN |
| **Primary Outcome measure** | Reduction of at least 50% from baseline to week 18 in serum ALP | Reduction in serum ALP ≥25% from baseline to day 99 | Mean change from baseline in hepatic collagen content | Number of patients with ≥25% reduction in serum | Frequency and severity of treatment emergent adverse events |

| | | | | | |
|---|---|---|---|---|---|
| | | | (measured by liver biopsy) | ALP from baseline to 24 weeks, | |
| **Key Secondary Outcome measures** | Histologic evaluation of liver biopsy | Safety and tolerability; change from baseline to day 99 in ELF score and FibroScan including liver biochemistry | Prevention of progression of fibrosis (Ishak fibrosis stage), PSC- related progression events e.g., variceal haemorrhage, death, liver transplant, cholangiocarcinoma | Improvement in bilirubin, AST and ALT levels at 3 and 6 months compared to baseline. | Serum ALP and ELF score change from baseline to week 15 |
| **Surrogate biomarkers included** | No | Yes; quantitative MRI, ELF score, VCTE | Yes; ELF score, LOXL2, VCTE | No | Yes; ELF score, Pro-C3, Pro-C5 |
| **Liver Biopsy included** | Yes | No | Yes | No | No |
| **Key findings and comments** | Terminated early as failed to meet its primary end point at interim assessment of 10 patients.<br><br>One patient had a reduction in ALP of at least 50% from baseline to week 18. | Failed to meet its primary end point at interim assessment.<br><br>2/18 met primary end point of ≥25% reduction in serum ALP.<br><br>Secondary biochemical and liver fibrosis outcomes were not met. | Mean change from baseline in hepatic collagen content at week 96: -0.5 simtuzumab 75mg (p=0.73) vs +0.5 simtuzumab 125mg (p=0.033) vs 0.0 placebo; No significant difference in frequency of PSC related clinical events of either dose of simtuzumab compared with placebo | 16.7% (3/18) achieved a ≥25% reduction in serum ALP at week 24 (95% CI 3.6-41.4).<br><br>No significant safety signals reported | Full results awaited.<br><br>Preliminary results indicate that Nebokitug is safe and well-tolerated and shows dose dependent efficacy in reducing biomarkers associated with disease progression in moderate/advanced disease (ELF, PRO-C3) |

| | | | | | |
|---|---|---|---|---|---|
| **Evidence of treatment benefit** | No | No | No | Yes | Preliminary results- Yes (dose dependent) |
| **Study Status** | Complete | Complete | Complete | Complete | Ongoing |

Abbreviations: ALP, Alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; DHODH, Dihydroorotate dehydrogenase; EOS, end of study; ELF score, enhanced liver fibrosis score; IV, intravenous; LOXL2Lysyl oxidase-like-2; S/C subcutaneous; ULN, upper limit of normal; VAP-1,Vascular adhesion protein-1; VCTE, vibration controlled transient elastography.

*Mean age presented

In the majority of the above outlined studies participants were recruited with large or small-duct PSC (121, 135, 136, 146). Current understanding reflects an overall better prognosis for those with small-duct disease compared to large-duct disease with and without concomitant IBD, and may be more responsive to treatment (148-151). More recently, PSC trials have sought to include only patients with confirmed large-duct PSC (NCT04595825, NCT03890120, NCT04480840, NCT03722576). Inclusion of participants with small and large-duct disease naturally introduces significant inter and intra-study heterogeneity and bias potentially resulting in a more favourable outcomes, as expected in those with small-duct PSC. To ameliorate this, stratified randomisation of patients with small-duct disease may balance out the heterogeneity between treatment groups in future trial design.

In contrast to one another, early phase clinical trials tend to utilise ALP as a primary endpoint, whereas phase 3 clinical trials have a propensity to include 'harder' end points such as hepatic fibrosis, decompensating events, liver transplant or death (152, 153) in keeping with medicine regulators insistence of at least level 2 markers of therapeutic efficacy (Table 1-4) (134, 154). Studies adopting ALP as the primary end point and demonstrating efficacy may fail when more objective end points such as liver histology or transplant free survival are instituted in later phase studies. Whilst ALP has become an important prognostic marker and potentially a marker of treatment efficacy, as a standalone surrogate marker its reduction is insufficient to provide evidence of improvement in more objective clinical end points such as death, liver transplant or cirrhosis, as previously discussed studies have highlighted. As expected, patients are often reluctant to undertake a liver biopsy, and in one study less than half of patients surveyed indicated they would be willing to undertake a liver biopsy as part of PSC clinical trials (155). Mandating liver biopsies will of course negatively impact patient recruitment, especially in rare diseases and trials with short follow-up periods. Of equal importance is the likelihood that patients willing to undergo serial liver biopsies as part of a clinical trial are likely to be inherently different to those who refrain.

There remains a lack of consensus across early phase trialists on the inclusion ALP cut off for patients, with several studies using an ALP cut off of ≥1.5x ULN as part of inclusion criteria, whilst others have chosen a cut off of ≥ 1 or 2x ULN. Whereas other early phase trials omit an ALP cut off. Naturally, an inclusion criteria citing an elevated ALP cut off above the ULN not only excludes PSC patients with a normal ALP, but perhaps also patients with earlier disease, and those with the most modifiable disease states. It also creates challenges in recruitment, particularly in the knowledge that ALP levels have inter and intra-participant fluctuations, unless a period of chronicity is stipulated in the protocol. On the other hand, including patients with a normal ALP value at screening means the trial will inherently include patients with an overall better long-term prognosis. As such a trialled drug may falsely demonstrate efficacy in this group, which may no longer be observed when trialled in patients with more advanced disease.

In summary, there is a dearth of clinically successful hallmark PSC clinical trials, with none to date leading to regulatory drug approval. This would have allowed for a contemporaneous framework or 'gold standard' on which to base future clinical trials. Rationale for the lack of success seen in current and prior clinical trials is multi-factorial as outlined above. In the main, the lack of success is likely to be attributed to the incomplete understanding of PSC pathogenesis and therefore failure to identify the critical pathway to be inhibited. Additional factors broadly relate to PSC being a rare disease with inherent recruitment challenges and as a result trials are often underpowered, especially in detecting small changes. Significant disease heterogeneity due to sub-phenotypes of PSC leads to clinical heterogeneity of the PSC populations included in clinical trials. Thereby potentially obscuring the true effect size in a more homogenous sub-group. Hard clinical end points such a decompensating event, liver transplant and death are all too infrequently occurring and therefore there is an over reliance on surrogate markers, which inherently have their own limitations (e.g., ALP). Consequently, evidence of benefit in terms of survival, liver transplant or liver histology are perceived as the gold standard and

are required for FDA drug approval. However, this requirement inevitably impacts patient recruitment, potentially rendering studies underpowered for these outcomes. Combined with the aforementioned difficulties, this creates unresolved challenges of perpetual circularity. Furthermore, for interventional clinical trials it is essential that appropriate end points are selected to reflect the pathophysiological target of the drug i.e. inflammation vs fibrosis (156). ALP may be a suitable end point in trials of investigational medicinal products targeting bile acid modulation, however when targeting anti-fibrotic pathways ELF and FibroScan are perhaps more relevant. Clinical trials combining multiple surrogate end points to improve validity has been recommended in an international PSC study group consensus paper (157). The following section provides a detailed discussion of clinical trial endpoints.

There are numerous clinical trials at various stages investigating potential druggable targets for PSC, as mentioned above. It is likely that we will see the first FDA approved therapeutic option for this rare and complex disease very soon. Over the next decade with ongoing interest and proliferation of clinical trials, genetic profiling and exploration of potential disease biomarkers, we may be able to offer more than one drug or combination therapy. Optimistically, the future may hold the ambitious goal of offering precision medicine to patients with PSC, targeting patients' unique fibroinflammatory profiles.

**PSC clinical trials- challenges and unmet need**

PSC has been described as the "last black box of hepatology"(1), and despite significant advancements in our understanding of PSC and its extrahepatic associations/complications there remains substantial unmet clinical need across a spectrum of PSC specific issues. Unique opportunities have been created in more recent times through integrated care pathways, computer-based patient records, refined

international collaboration networks, patient and public involvement initiatives (PPI), and advancing technologies. Combined they provide the potential to address some of the real challenges patients with PSC face.

Broadly challenges and unmet need within PSC relate to the following areas, of which each will be addressed briefly in turn (Figure 1-7):

I. Primary pharmacological therapy
II. Cholangiocarcinoma prevention and surveillance
III. Prognostic markers/biomarkers
IV. Consensus regarding approved clinical trial end points
V. Holistic approaches to PSC-IBD
VI. 'The patients' perspective'- principally mental health and quality of life

Proven pharmacological therapy that prolongs transplant-free survival is lacking. The lack of a pharmacological intervention in combination with the ongoing demand and substantial cost of liver transplantation necessitates the urgent acquisition of novel treatment options in PSC. There is therefore a renewed intensity in PSC research with several ongoing clinical trials aimed at addressing this unmet need, of which the *SABR-PSC* pilot study is one.

There is an urgent clinical need for prevention of cholangiocarcinoma, and its associated morbidity and mortality. Risk prediction markers for cholangiocarcinoma are lacking, which may better enable clinicians to identify at risk individuals, implement appropriate surveillance, and judicious transplant referral. There is a lack of a clear consensus and evidence for an appropriate hepatobiliary malignancy surveillance strategy, leading to global practice differences in internationally published guidelines (9).

Detection of CCA at its earliest stages is crucial to allow for timely curative surgical interventions. CA19-9 is a CCA tumour marker that is widely used in clinical practice, however it is neither satisfactorily sensitive (50-89%) or specific (54-98%) for diagnosis, and is often elevated in benign conditions such as cholangitis or cholestasis (3). A simple, cost effective, safe, and highly sensitive and specific test does not yet exist in PSC, currently distinguishing between benign and malignant biliary lesions is often complex and requires invasive techniques such as ERCP (158). In addition to CCA, increased understanding of the specific PSC-IBD colorectal cancer predisposing factors (above that of IBD only) is required to put forth potential chemo-preventative strategies.

Due to PSC's phenotypic, presentational and disease course variability, diagnosis is challenging. No disease specific biomarker has been elucidated thus far (159). The search for a dependable non-invasive surrogate marker able to accurately predict disease stratification and clinical risk assessment, in place of more invasive end points such as liver biopsy are ongoing. There has been great interest in several newer serological markers e.g., anti GP2 IgA antibodies, P-ANCA, IgG4, ELF score (154). Nonetheless ALP has long been the favoured and most widely studied marker (160). Whilst ALP normalisation or reduction to within less than 1.5x ULN has been associated with favourable outcomes, data from a phase 2 RCT established significant intra and inter subject variability in serum ALP levels over the natural history of the disease in addition to a lack of association between serum ALP with disease progression (112, 161, 162). Moreover, it has been established that serum ALP levels naturally decline with the onset of cirrhosis (113), potentially providing false reassurance. Development of non-invasive risk prediction scores such as the Amsterdam- Oxford model score, Primary sclerosing cholangitis risk estimate tool (PREsTo) and UK-PSC risk score, incorporate a combination of age, clinical and biochemical markers at diagnosis to risk stratify patients into low and high-risk groups (46, 163-165). Of note, all aforementioned models incorporate ALP. Nonetheless, they each have their limitations and are infrequently used in clinical practice. Whilst these alternative

validated tools exist, ALP has stood the test of time and remains the standard outcome measure in early phase clinical trials of investigational medicinal products (160). Nevertheless, serum ALP alone has not been adopted or endorsed by global regulatory agencies. Validated biomarkers not only have the potential to allow clinicians to risk stratify their patients, predicting those with potential for worse outcomes or need for earlier intervention, but may also provide the basis for nuanced follow-up strategies and timely discussions with patients, family, and carers about the future.

In the absence of validated biochemical markers, liver histology remains the gold standard. It serves as a marker of fibrotic disease progression- staging and grading, with overt progression/or prevention of progression to cirrhosis identified as an important disease end point in drug development clinical trials. There are no currently validated histological scoring protocols for PSC liver specimens. A formalised histological scoring system for PSC was developed in 1981 by Ludwig et al (15). Since its development other scoring systems have been created e.g., the Ishak and METAVIR histological scoring system, nonetheless both are infrequently used. Subsequently, the adapted Nakanuma staging and grading system (Table 1-5) has become widely used, deemed to have prognostic value and is independently associated with PSC-related death or liver transplantation (46, 166-168). Liver biopsy is however subject to sampling error due to its patchy nature, and therefore has limited utility, especially in a disease where liver biopsy is not required for the diagnosis of the most common variant of PSC.

Liver transplant, death and cholangiocarcinoma are accepted level one clinical trial endpoints, with cirrhosis qualifying as level two (154, 169). However, due to their low clinical event rate their use in small clinical trials with short follow-up duration remain prohibitive. For many hepatological conditions liver biopsy remains the gold standard, yet this is an invasive and unfavoured approach amongst patients. For a realistic alternative to ALP to be found, or for a level 3 end point to be

upgraded, greater well conducted phase 3 clinical trials, with suitably extensive follow-up durations are required (154). MRCP, MR elastography (MRE) and vibration controlled transient elastography (VTCE) are alternative appealing tools and may in future be combined with other biochemical markers such as ALP to create a more encompassing prognostic model with improved test performance (170). The BSG UK-PSC guidelines do not endorse any single method at present to predict patient prognosis (3).

**Table 1-4.** Qualified clinical trial end points. Adapted from Fleming and Ponsioen (154, 169).

| | | |
|---|---|---|
| **Level 1** | A true measure of clinical efficacy | E.g., Liver transplantation, death, cholangiocarcinoma |
| **Level 2** | A validated surrogate end point | E.g., Progression to cirrhosis |
| **Level 3** | A non-validated surrogate end point, yet "reasonably likely to predict clinical benefit" | E.g., Alkaline phosphatase (ALP), bilirubin, albumin, liver histology |
| **Level 4** | A measure of biological activity, not yet established at a higher level | |

**Table 1-5.** Adapted liver histology scoring systems used to assess disease severity in PBC and of value in PSC. Adapted from De Vries et al.(166).

| **Stage** | **Ludwig criteria (171)** |
|---|---|
| **I** | Portal: portal hepatitis with little or no periportal inflammation or piecemeal necrosis |
| **II** | Periportal: periportal hepatitis with piecemeal necrosis. No bridging necrosis or septal fibrosis. |
| **III** | Septal: bridging necrosis and/or septal fibrous |
| **IV** | Cirrhotic stage: regenerative nodules and fibrous septa |
| **Grade** | **Nakanuma criteria** (172) |
| **A: Fibrosis** | |
| **I** | Portal fibrosis with periportal fibrosis or incomplete septal fibrosis |
| **II** | Bridging fibrosis |
| **II** | Liver cirrhosis |
| **B: Bile duct loss** | |
| **I** | Bile duct loss in <1/3$^{rd}$ of portal tracts |
| **II** | Bile duct loss in 1/3-2/3$^{rd}$ of portal tracts |
| **II** | Bile duct loss in >2/3$^{rd}$ of portal tracts |
| **C: Chronic cholestasis (orcein granule deposition)** | |
| **I** | Deposition of granules in many periportal hepatocytes in <1/3$^{rd}$ of portal tracts |
| **II** | Deposition of granules in variable numbers of periportal hepatocytes in 1/3-2/3$^{rd}$ of portal tracts |
| **III** | Deposition of granules in most periportal hepatocytes in >2/3$^{rd}$ of portal tracts |
| **Nakanuma total score Total derived from summation of individual items in each category** | **Stage:** Total derived from summation of individual items in each category |
| **0** | Stage 1:No/minimal progression |
| **I-III** | Stage 2: Mild progression |
| **IV-VI** | Stage 3: Moderate progression |
| **VII-VIIII** | Stage 4: Advanced progression |

Whilst there are clear national and international guidelines on the management of PSC and IBD as individual disease entities, there is a paucity on consensus of the management of PSC-IBD as a unique combined disease entity. Close collaboration between hepatology and IBD care is essential to deliver comprehensive patient-centred care, providing rich opportunities for shared decision making, greater clinician oversight of both respective diseases and their interplay, fewer hospital appointments to see individual specialists, greater patient satisfaction, greater access to PSC clinical trials and crucially

improved patient outcomes. Licensed therapies for IBD only are routinely used in patients with PSC-IBD however there is a lack of understanding of their safety and efficacy in this very particular cohort.

A diagnosis of PSC brings about anxiety and uncertainty for patients, family, and carers alike, particularly around cancer risk, absence of therapeutic treatment options, and disease trajectory. Individuals living with PSC have been reported as experiencing significant levels of depression, psychological anxiety, and social isolation (173, 174). However there remains a lack of readily available professional psychological support. In a recent survey conducted by PSC Support, the largest UK based charity supporting those living with PSC, up to a third of respondent reported depressive symptoms such as helplessness, furthermore an almost universally shared concern pertained to the lack of psychological support available (175).

Quality of life is arguably one of the most important aspects of PSC management, a domain which is often significantly impaired. A recent systematic review of QoL in PSC uncovered diminished QoL for PSC patients, particularly those with large-duct PSC compared to healthy counterparts, and with a comparable QoL to those with alternative chronic conditions. Furthermore, intractable symptoms such as itch and pain were associated with worse QoL outcomes (176). Incorporation of QoL measures in clinical trial outcomes allows for a more holistic approach to determining drug efficacy and reframing of what is most important to patients living with PSC (177). Patient reported outcome measures (PROMs) are capable of assessing psychosocial wellbeing in addition to physical symptoms, providing a nuanced assessment of PSC burden. Whilst more frequently used in clinical trial settings, its use remains cumbersome, time consuming and ill equipped to be used in a busy clinic setting.

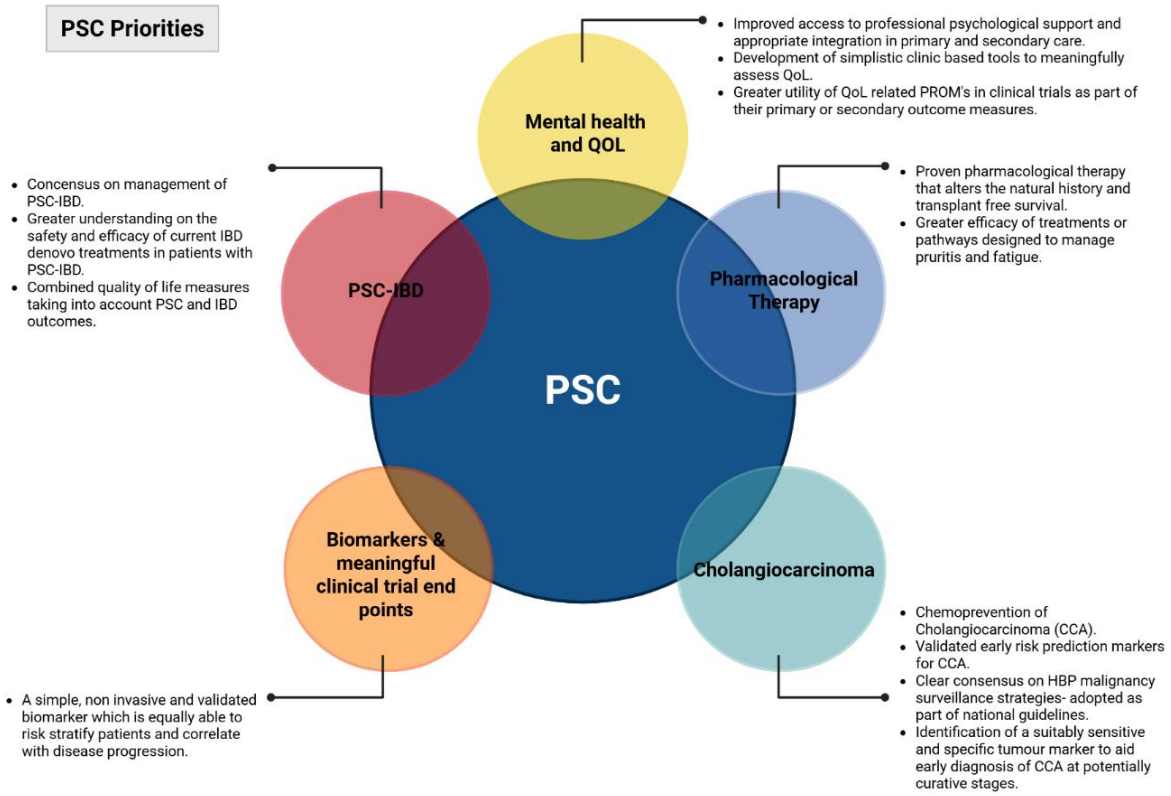



**Figure 1-7.** PSC challenges and unmet need, reflecting potential future research priorities.

## 1.3. Inflammatory bowel disease (IBD)

### 1.3.1 Introduction

Inflammatory bowel disease is a chronic relapsing and remitting idiopathic disorder, triggering gastrointestinal inflammation. Symptoms include abdominal pain, diarrhoea, gastrointestinal bleeding, and constitutional symptoms such as weight loss, fever, and fatigue amongst others. IBD is the umbrella term used to commonly unite two distinct forms: ulcerative colitis and Crohn's disease. IBD-unclassified (IBD-U) is a third subcategory and pertains to a form of IBD that shares characteristics of both UC and CD.

Ulcerative colitis is a non-transmural pathology confined to the colon. It typically starts in the rectum (exception in PSC- where there is rectal sparing) termed proctitis and may extend in a contiguous pattern to affect more proximal parts of the colon (178). UC phenotypes include proctitis, left sided (affecting the colorectum up to the splenic flexure), extensive/pancolitis (affecting the colorectum beyond the splenic flexure) (179, 180). A small proportion of patients (up to 25%) will have 'backwash ileitis' (BWI) a term coined in the 19$^{th}$ century for those with UC who possess terminal ileal inflammation in the distal few centimetres (181, 182). The majority of those with 'backwash ileitis' will have pancolonic disease, and the severity of the ileitis is typically congruent with that seen in the colon and caecal pole (183). Although the exact aetiology is unclear, refluxing colonic contents is proposed as the cause of this phenomenon and has known associations with PSC-IBD (183). Histological features of UC include inflammatory aggregates (acute and chronic), particularly in the lamina propria, accompanied by crypt abscesses, basal plasmacytosis, distortion of colonic mucosal architecture (crypt atrophy and distortion), and goblet cell depletion. Differentiating ileal CD from UC with back wash ileitis can be challenging particularly if hallmark clinical and/or histological features of CD are absent (183). The case burden of UC is slightly greater than that of CD (184). The disease severity and extent of UC has inter-individual variability; however, most patients will experience a mild to moderate disease phenotype (178).

Crohn's disease on the contrary, is a complex transmural inflammatory disease that can affect the entire gastrointestinal tract, from mouth to anus. Hallmark features include variable and discontinuous segmental involvement (skip-lesions), with the development of fibrosis, strictures, fistulae, abscesses, and may include perianal disease- features distinct from UC. Up to 50% of patients will develop such aforementioned complications including bowel obstruction often resulting in the need for surgical intervention (185). Several recognised subtypes of CD exist according to the Montreal classification: terminal ileal CD, ileocolonic CD, colonic CD and isolated upper gastrointestinal CD (186)

(187) Involvement of the terminal ileum is the predominant disease location, occurring in 45% of patients. The colon is affected in 28% , ileocolon in 21%, whilst isolated upper GI involvement afflicts between 4-13% (179, 188, 189). Smoking is a widely accepted risk factor for the development and exacerbation of Crohn's disease, whilst is regarded as protective for UC development (190). The natural history of the disease is highly variable but often involves progression over time from an inflammatory phenotype to that of either stricturing or penetrating disease (i.e., perforation, abscess or fistulae formation) (179). Typical histopathological features of CD include aggregation of acute and chronic inflammatory infiltrate, crypt distortion (crypt disfigurement), villous architectural distortion and non-caseating granuloma formation (191). Albeit considered a hallmark of CD diagnosis, granuloma formation only occurs in 50% of CD patients and is non-specific (188).

IBD can occur at any age, however its peak age of onset is characteristically between 15-30 years of age, with a smaller second peak seen between 50-60 years of age (184). Both UC and CD have largely an equal sex preponderance. Its affliction results in significant morbidity, in a particularly young group of individuals. IBD not only has disease driven consequences and disability, but also social and economic depletion with loss of work or education days.

A typical presentation of IBD would be that of a young adult with a chronic history (>4 weeks) of diarrhoea (bloody or non-bloody) associated with abdominal pain and weight loss. Although presentation is largely determined by IBD subtype and disease location. IBD is a clinical diagnosis, with no gold standard diagnostic test, thus a multimodality approach is mandated to confirm the diagnosis. This approach starts with a thorough history and physical examination and includes the use of surrogate marker of colonic inflammation such as faecal calprotectin (FC) and stool cultures facilitating consideration and exclusion of non-IBD causes e.g., irritable bowel syndrome (IBS) or infectious colitis.

This is further augmented with ileocolonoscopy and biopsy to permit endoscopic and histological diagnosis. However, if ileocolonoscopy and histology is non-confirmatory and suspicion remain high then use of cross-sectional radiological imaging such as ultrasound (USS) small bowel, computer tomography (CT) or magnetic resonance imaging (MRI) may be required e.g., MR enterography. This is particularly relevant in the context of Crohn's disease where disease activity may be isolated to the proximal ileum or GI tract beyond the reach of diagnostic ileocolonoscopy.

There is no cure for IBD. Treatment is directed at inducing and maintaining remission, with mucosal healing being the chief aim. Depending on the distinct IBD subtype the armamentarium of anti-inflammatory and immunomodulatory therapeutics include corticosteroids (e.g., prednisolone, budesonide, methylprednisolone), 5-aminosalycilic acid (e.g., mesalazine), thiopurines (e.g., azathioprine and mercaptopurine), anti-tumour necrosis factors (anti-TNF's) (e.g., infliximab and adalimumab), anti-integrins (α4β7) (e.g., vedolizumab), IL12/23 inhibitor ustekinumab or pan Jak Kinase inhibitors such as tofacitinib amongst others. For those that develop complications or are medically refractory, surgical intervention is required.

Dysplasia, colorectal cancer (CRC) or small bowel neoplasia are associated complications of IBD. Studies have demonstrated a cumulative incidence of 3% at 20 years for IBD- associated CRC (188, 192). Longstanding duration of disease and/or persistence of endoscopic and/or histological inflammation are associated with increased risk of CRC compared to the general population (193). The risk of CRC in PSC-IBD is substantially higher than in IBD only, arising at much younger age, and appears to be independent of both disease duration and/or severity of mucosal inflammation. This phenomenon will be examined in greater detail in Chapter 1.4.

### 1.3.2 IBD epidemiology

The incidence rates of UC and CD appear to be rising globally (194). However, in the industrialised world, traditionally regarded as high incidence areas, chiefly Northern Europe, North America, and United Kingdom the incidence of IBD appears to be plateauing. The converse is true in the developing world and traditionally regarded low-incidence countries such as Asia, Africa and Latin America, where a rapid rise in incidence is being observed (195-197).

Incidence and prevalence rates of IBD in the UK vary widely, largely due to variance in coding and reporting practises. The reported prevalence of IBD in the UK is 400 per 100,000 (198), equating to a conservative estimate of 268,000 individuals in a UK population of approximately 67 million. However, early results of as yet unpublished research commissioned by Crohn's and Colitis reveal that there are approximately half a million patients with IBD in the UK (1 in 123) (199).

The West-East gradient illustrates the variation in global IBD prevalence. The IBD prevalence in Northern Europe is reportedly between 90 to 505 per 100,000, this sharply declines across the lines of longitude to the Far East with reported prevalence of 5 to 57 per 100,000 (67). The explanation for this trend is thought to be multifactorial and includes differences in the prevalence of genetic risk variants (NOD2), geographical differences in diet (highly processed, high fat, low fibre), smoking, breast feeding trends, and the hygiene hypothesis, all of which are risk factors for IBD and intestinal dysbiosis. However, poorer healthcare infrastructure and disease recognition in East and developing countries is also contributory (200, 201).

### 1.3.3 IBD pathophysiology

The exact pathogenesis of IBD is incompletely understood, however similar to PSC, it is postulated to be a complex interplay between genetic predisposition, environment, lifestyle, immune and gut barrier function dysregulation in addition to intestinal microbial dysbiosis (202, 203). Despite the cause of IBD remaining largely unknown, studies have made considerable progress in advancing our understanding in recent years.

**Genetic factors**

By far the largest non-modifiable risk factor for development of IBD is a positive family history (197). The risk of IBD is increased in those with a first degree relative and is greatest in those with a sibling afflicted with the same disease. The strongest substantiation of the contributory effect of genetics factors are observed in concordance studies in twins (197). Concordance rates in monozygotic twins with CD and UC are reportedly as high as 50% and 18.8% respectively (204, 205). Suggesting that the genetic predisposition is of greater importance in CD than UC.

GWAS have implicated 240 non-overlapping genetic risk loci, the majority of which are shared by UC and CD (206, 207). CARD15 (NOD2) was one of the first susceptibility genes implicated exclusively in CD development in Caucasian populations and may predispose to a more aggressive phenotype of CD (197). Mutations in cytosolic nucleotide-oligomerisation domain 2 (NOD2) on chromosome 16 occurs in a third of Crohn's disease patients (206). NOD2's physiological roles include detection of intracellular microbial components, initiating autophagy and therefore regulating T cell response (208). Whilst genetics clearly play a role in IBD susceptibility its overall influence is modest, and other non-genetic factors are essential for IBD development.

Despite 240 genetic risk loci identified for IBD and 23 genetic risk loci identified for PSC to date, a large GWAS of PSC cohorts demonstrated that the genetic correlation between the two pathologies is weak, irrespective of their associations (38, 47). Providing further substantial evidence that PSC-IBD is indeed a distinct clinical entity to IBD only- a topic discussed in greater detail below.

**Gut microbiome**

The gut is populated with a diverse community of microorganisms known as the 'gut microbiome'. Intestinal homeostasis and health is dependent on a diverse array of gut microbiota, whilst an imbalance of this environment is known as 'dysbiosis'. In health, 99% of all gut microbes are derived from Bacteroidetes, Proteobacteria, Firmicutes and Actinobacteria phyla (207). Alteration of this finely balanced complex gut microbial population has been clearly implicated in the promotion of IBD pathogenesis. The intestinal biodiversity is significantly altered in IBD patients compared to healthy controls. In CD there is a marked reduction in Firmicutes and Bacteroidetes, with an exaggeration of opportunistic bacteria enterobacteria species (209). In UC there is reportedly a reduction in clostridium species whilst harmful bacteria such as *Escherichia coli* (*E.Coli*) are more abundant (208). Loss of the normal 'healthy' microbiome is speculated to drive loss of gut epithelial barrier integrity and to perpetuate bacterial access to the submucosa and trigger inflammation (210). However, discerning whether the altered gut microbiome in IBD is as a cause or consequence of the disease has been more difficult to determine.

The role of bile acids, their effect on gut microbial dysbiosis and potential contributory role in IBD aetiology has recently garnered great interest. Colonic microbiota are integral for bile acid homeostasis, with intestinal dysbiosis implicated in bile acid dysregulation. A landmark study by Duboc et al. discovered altered bile compositions and colonic dysbiosis in patients with active colitis (n = 42).

Furthermore, they demonstrated that bile acid dysmetabolism exacerbated colonic inflammation and therefore IBD (211). An accumulating body of evidence implicates the dysmetabolism of bile acids- specifically the reduction in conversion of primary bile acids to secondary in IBD pathogenesis (211-215). However further large-scale studies are required in this area to map out the true contributory role of bile acids in IBD pathogenesis.

**Environment and lifestyle factors**

The disparate incidence rates of IBD between developed and developing counties may of course be partially explained by genetics. However environmental and lifestyle factors would appear of greater importance. Such implicated environmental and lifestyle factors include diet, obesity, sanitation, smoking, antibiotic exposure, access to health care, and industrialisation. Such hypotheses are supported by the increased incidence of IBD observed in urban versus rural regions, and in migrants from low incidence countries having moved to high incidence countries.

There has been significant interrogation of the so called 'western diet'- characterised by macronutrients typically high in saturated fats, red meat, refined grains and simple carbohydrates, whilst relatively lacking in fibre, as being contributory to gut inflammation and IBD risk (216). However, such studies have been small, without adequate methodological rigor and often contradictory. RCT's of dietary manipulation of IBD patients to induce remission has been equally disappointing. A recent systematic review found that CD risk was associated with diets high in ultra-processed (HR 1.71, 95% CI 1.36-2.14) and inflammatory foods, while Mediterranean (0.59, 95% CI 0.43-0.81) and high fibre diets were associated with a lower risk. These associations were not observed in UC (217). Fascinatingly, dietary manipulation in the paediatric CD setting by way of an exclusive enteral

polymeric diet has been shown to reduce intestinal inflammation and induce remission, representing an important treatment adjunct in children with mild to moderate Crohn's disease (218, 219).

The association between smoking and IBD aetiology has been widely studied. As early as 1982 studies have demonstrated the protective effects of smoking on UC development, whilst in contrast smoking is known to increase the risk of CD development and is associated with exacerbations and poor post-operative outcomes (208, 220).

A large recent meta-analysis highlighted the protective effects of reduced environmental sanitation and hygiene in IBD pathogenesis. Specifically large cohabiting families, bed sharing, owning a pet, and living in close proximity to farm animal (221). Whilst breastfeeding (OR 0.74; 95% CI 0.66–0.83) and physical exercise appears protective in IBD and CD respectively (RR 0.63, 95% CI 0.50–0.79) (220).

**Innate immune system**

It is widely accepted that immune dysregulation of the innate and adaptive immune system triggers intestinal inflammation seen in IBD. It is this dysregulation that results in the myriad of features characteristic of IBD i.e., abnormal mucus production, epithelial wall damage, infiltration of the lamina propria of T cells , B cells, dendritic cells and neutrophils (207).

Several proinflammatory cytokines are involved in the initiation and perpetuation of intestinal inflammation. Such cytokines include the IL-17/23 pathway, TNF, IL-13 and IFNy, which are released by the activated lamina propria cells initiating local tissue damage (207). In health the gut remains in

a perpetual state of homeostasis and immune tolerance. In IBD the initial inflammatory insult and immunomodulatory defect in the intestinal mucosa has been theorised to occur due to one of many mechanisms. Central to most of these theories is the exaggerated host immune response that occurs in relation to (i) non-pathogenic organisms (ii) exposure to an infectious pathogens (iii) luminal contents following a breach in the mucus-mucosal barrier (222). However, to date no specific pathogen has been conclusively implicated in the development of IBD. IBD is associated with a 'leaky gut', associated with increased intestinal permeability, and an increased exposure of immune-mediated cells to proinflammatory luminal contents and allowing translocation of microbes (223). This facilitates recruitment of additional immune cells due to cytokine release. In doing so, reducing tight junction adherence in gut vasculature endothelial cells, thus enabling neutrophil recruitment and a self-perpetuating pro-inflammatory cycle (222).

Until recently there was thought to be only two types of T-cells. A Th1 response associated with Crohn's disease and a Th2 response associated with UC. However, the discovery of a third subset known as Th17 cells which produce a family of IL17 proinflammatory cytokines, presented opportunities for new IBD therapeutic immune-mediated targets. Human and animal studies implicated an exaggerated Th17 activity as being instrumental in IBD pathogenesis (224-228). Nonetheless RCT of IL-17 inhibitors in active Crohn's disease, not only failed to induce remission but were also associated with a slight worsening of symptoms in a subset of patients. Nevertheless, recent meta-analyses (of trials in psoriasis, psoriatic arthritis and ankylosing spondylitis) have illuminated that there is no statistically significant increase in IL-17 inhibitors promoting the development or worsening of IBD compared to placebo (229) (230, 231). However, formulating a conclusive argument against IL-17 inhibitors causing paradoxical GI side-effects is challenging. Reported IBD event rates are rare in this setting and are inconsistently reported and investigated in studies. The gold standard investigation is a colonoscopy to confirm or refute the diagnosis; however, this is inconsistently

performed in published studies. Furthermore, the cohort of patients being exposed to anti-IL-17 drugs also have an inherently increased background risk of developing IBD (psoriasis: odds ratio (OR) 2.49 for CD and 1.64 for UC (232)) as an associated immune-mediated disease (233-235). Hence, it is possible we are observing an unmasking of subclinical IBD in an already predisposed population.

Recent unprecedented advancements in our knowledge of IBD has illuminated the cumulative role of environment, genetics, dysregulation of the immune system and altered microbiome being responsible for IBD pathogenesis. However, a defined pathological pathway that unites the four component remains subject to academic conjecture. Nonetheless, it is clear that no single component in isolation is likely to be responsible in its entirety for development of this complex pathology.

### 1.4. Primary sclerosing cholangitis associated inflammatory bowel disease (PSC-IBD)

1924 saw the first definitive descriptions of PSC in published literature. However, it was not until 1965 that the first descriptions and recognition of PSC and IBD as an associated disease entity was published by Smith and Loe (236). Since this period, we have been afforded a greater understanding of PSC-IBD through population based observational studies, systematic reviews and recent meta-analyses.

Ludwig van Beethoven, a critically acclaimed German composer and pianist died of decompensated liver cirrhosis at the age of 57 (67, 237). Beethoven was known to have suffered with abdominal pain, bloody diarrhoea, recurrent jaundice and progressive hearing loss during his life time (238). However, only in 2005 did the collation of all his symptoms lead to the logical supposition that Beethoven had suffered from chronic ulcerative colitis and the extraintestinal manifestation- primary sclerosing cholangitis (239).

### 1.4.1 PSC-IBD epidemiology

PSC and IBD are related diseases, with concomitant PSC and IBD representing a unique phenotype (referred to as PSC-IBD), with its summative risk profile distinctly dissimilar to that of PSC or IBD alone (240). The comorbid relationship between PSC and IBD is a hallmark of the disease and occurs in up to 80% of those with PSC (6, 7, 12, 28, 240-242). Conversely PSC is reported to occur in 2-14 % of those with IBD (4, 67, 243). A higher prevalence of PSC-IBD is reported in Northern America and Northern Europe (Scandinavia), with significantly lower rates reported in the Far East (20% in Singapore) (28, 32, 240). A phenomenon that is poorly understood, and one that remains open to conjecture as to whether there are further PSC phenotype subtypes that are relevant contingent on geographical location, environmental factors and/or ethnicity. In a recent nationwide population based study conducted in the UK, the East of England was identified as having the peak PSC-IBD prevalence (6.4 per 100,000) (244) which cannot be explained by greater utility of diagnostic tools such as MRI or a greater number of PSC or IBD specialists per capita in the region. There is significant heterogeneity between studies and reporting standards globally perhaps owing to the rarity of the disease, global variations in coding, follow-up, diagnostic tools (particularly colonoscopy practises), methodological differences, variable pathophysiological disease contributors between geographical regions and variation in HLA susceptibility amongst different ethnic groups.

In a large nationwide population-based study conducted in England over 10 years the incidence of PSC-IBD was 0.58 per 100,000 in 2016 (245). This parallels contemporary data from the Netherlands (0.5/100 000) (33), but is somewhat greater than that reported in a Danish retrospective population based cohort study (approaching 0.25/100,000) in 2011 (246). However, the global prevalence of PSC-IBD remains unknown, owing to previously aforementioned explanations.

Various studies have documented the temporal rise in incidence of PSC-IBD (245), whilst as previously stated the incidence of IBD alone appears to be stabilising. Of interest, the Trivedi et al. (245) study demonstrated that the geographically distinct regions within the UK with the greatest incidence of PSC-IBD do not correlate with the regions of greatest incidence of IBD only. Thus, illustrating and supporting the pathophysiological differences at play in PSC-IBD compared to IBD only.

### 1.4.2 PSC-IBD natural history

A concomitant diagnosis of PSC can occur at any time point during IBD (247, 248). The diagnosis of IBD typically precedes that of PSC by many years, but the reverse may also occur, and in a small number of cases IBD may be diagnosed post orthotopic liver transplantation (OLT) (4). The natural history and disease course of PSC-IBD is nevertheless heterogeneous.

PSC-IBD patients have a significantly greater risk of colorectal cancer compared with their IBD only counterparts (249). Those with PSC-IBD more frequently undergo colectomy than those with IBD alone. CRC is more common in PSC-IBD necessitating colectomy, however larger studies assert that colectomy is often unrelated to cancer, and likely due to active IBD (245, 246). However, there are countering studies suggesting that colectomy rates in PSC-UC and UC alone for disease severity or continuous chronic colonic inflammation are comparable (Figure 1-8) (69, 250), reflecting that colitis activity is unlikely to contribute significantly to the increased colectomy rates seen in PSC-IBD. The data on colectomy rates in PSC-UC for IBD related events is conflicting, further larger prospective studies are required.

Conflicting data exists as to whether the presence of IBD significantly impacts the clinical course of PSC including OLT and overall survival, and vice versa (251, 252). A handful of studies denounce the association and more over report an inverse relationship between PSC and IBD activity (253, 254). A large international observational cohort study (n = 7121) reported improved transplant free survival in individuals with PSC alone or with a diagnosis of PSC-CD compared with PSC-UC (241). Nonetheless, there is emerging data that active ongoing intestinal inflammation and an intact colon at time of transplantation may adversely affect peri and post liver transplantation complications including rPSC and graft loss (64, 248, 255). It is therefore recommended that every effort should be sought to achieve colonic mucosal healing, expressly in prospective OLT patients (255). Traditional IBD management with biologics (vedolizumab and anti-TNF therapies) appear efficacious in PSC-IBD, however no large RCTs have been performed exclusively in this cohort to assess colonic response rates and evidence to suggest beneficial liver outcomes is lacking (75, 76, 256-258).

Mortality data from the Trivedi et al. group identified a higher all-cause mortality rate in PSC-IBD compared to IBD, with a time dependent hazard ratio of 3.2 (95% CI 3.01-3.40; p=<0.001) (Figure 1-9) (245).

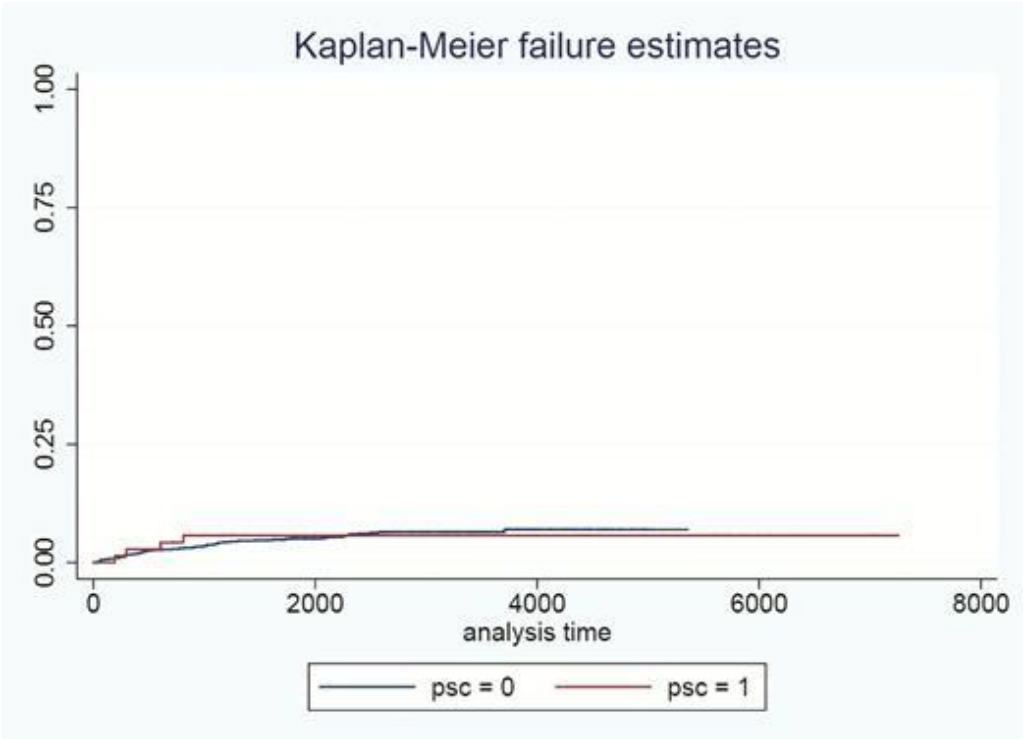



**Figure 1-8.** Kaplan-Meier curve representing colectomy rates for ulcerative colitis disease control; PSC-UC vs UC alone. Kaplan-Meier curves demonstrate comparable cumulative incidence and no substantial divergence in colectomy over time. Adapted from Khan et al.(69).

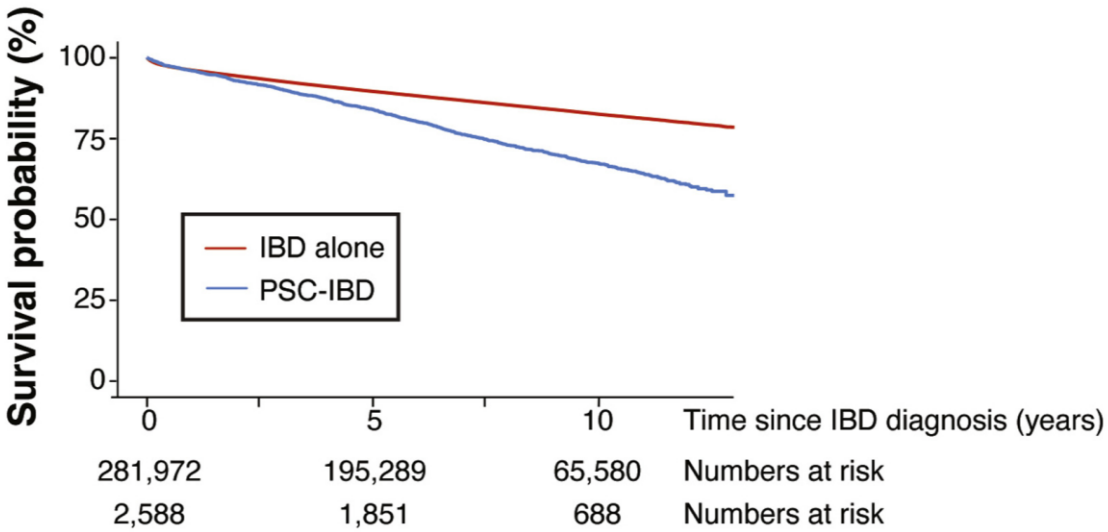



**Figure 1-9.** Kaplan-Meier curve of estimates for all-cause mortality; PSC-IBD vs IBD alone. Adapted from Trivedi et al.(245).

### 1.4.3 PSC-IBD clinical characteristics

The distinct disease distribution of PSC-IBD sets it apart from IBD only (Figure 1-10). Ulcerative colitis (PSC-UC) is the predominant phenotype seen in PSC, accounting for approximately 80%, CD represents approximately 10% with IBD-U accounting for the remainder (240).

PSC-IBD is almost exclusively a colonic and right sided disease. An increased incidence of pancolitis in PSC-UC patients (RR 1.54, 95% CI 1.31-1.75) compared to UC only cases has been widely reported (12, 259). Similarly, backwash ileitis and rectal sparing (RR 3.91, 95% CI 1.31-11.62) are also reported more commonly in PSC-IBD (12, 260). Moreover, higher rates of pouchitis (inflammation of the constructed and anastomosed ileal reservoir) are observed following colectomy and ileal pouch anal anastomosis in PSC-IBD patients compared to their IBD only counterparts, with PSC-IBD pouchitis being more resistant to standard treatment with antibiotics (261, 262). Right sided colonic involvement and rectal sparing (absence of proctitis) is commonly observed at diagnosis of PSC-IBD (259). Furthermore, PSC-UC is suggested to exhibit a milder form of colonic inflammation (despite more extensive disease) compared to UC, and less frequently requiring steroid treatment or hospitalisations (250, 263). Those with PSC-IBD are also less likely to be prescribed anti-TNF therapy (OR 0.26, p=<0.001) (263). A large retrospective Northern American study found that PSC-UC patients were significantly younger at diagnosis than their UC equivalents (26 vs 34 years of age; p=0.02), which is corroborated by a further American cohort study (69, 263). Whilst IBD only exhibits a slight female predominance, PSC with concomitant IBD retains is male predilection (67, 264). Put together, with the fact that PSC-IBD and IBD share little genetic overlap, this provides further support that PSC-IBD and IBD only are distinct clinical entities.

In contrast to PSC-UC, there is a paucity of large datasets on PSC-CD. Nonetheless, several key studies have documented that PSC-CD does not share the characteristic phenotypical or histological features of CD alone (68, 265, 266). Unlike CD, PSC-CD typically presents with colonic involvement (Crohn's colitis) and isolated small bowel disease is seldom a feature (31% vs 6%, p=0.034) (266). Aranake-Chrisinger et al. (265), in a retrospective study detailed that the presence of granulomatous formation, a key diagnostic characteristic of classic CD, is less frequently observed in PSC-CD (67% vs 17%, p=0.08), although this did not reach statistical significance. Finally, additional archetypal characteristics of CD without PSC such as fistulae (penetrating disease) and stenosis (stricturing disease) are rare in PSC-IBD (68, 267).

It has long been accepted that PSC-IBD follows are largely quiescent disease course both clinically and endoscopically (247). This is in contrast to IBD only which is associated with high steroid usage, frequent hospitalisations, and the need to escalate treatment to immunomodulatory or biological agents. However, de Vries et al. reflect that histologically PSC-IBD patients may have active colitis despite macroscopic or systemic incongruence (261), thereby potentially dispelling the prior notion that PSC-IBD is truly quiescent. A supporting study published in 2018 by an American group examined 143 patients in clinical remission (23 with PSC-UC and 120 with UC alone), PSC-UC patients were identified as having significantly greater active endoscopic (OR 4.21, 95% CI 1.67-10.63; p=0.002) and histological activity (adjusted OR 4.87, 95% CI 2.04-11.61; p=<0.001) in the proximal colon compared with their UC alone counterparts (268). Furthermore, in support of the earlier de Vries et al. study, they concurred that there was histologic and endoscopic discordance in the severity of inflammation reported in the proximal colon, whereby histologic descriptions of disease activity were more severe (unadjusted OR 3.14, 95% CI 1.24-7.97; p=0.02) (268). Admittedly, this significant incongruence was not observed in the reporting of left colonic or rectal samples between patients with PSC-UC and UC alone. A large retrospective multicentre study of 7121 PSC patients concluded that PSC-CD is of a

milder phenotype than PSC-UC, with PSC-CD patients typically afforded better outcomes and prognosis than their PSC-UC counterparts (241, 269).

It has been suggested that use of FC to non-invasively assess colonic inflammation cannot be used in the same manner in PSC-IBD. Interestingly, a recent study evaluating the role of FC in PSC-IBD patients, found a strong correlation between biliary and FC levels (r=0.8982, p=0.0024). Elevated FC levels were also associated with biliary complications in patients with endoscopically quiescent PSC-IBD (UCEIS ≤1) (270). This suggests that elevated faecal calprotectin might reflect biliary inflammation in patients with endoscopically quiescent PSC-UC. Nonetheless, a significant limitation of this study was the omission of colonic biopsies to allow parallel histological correlation of the endoscopic scoring of PSC-IBD activity. This once again concurs with results from earlier studies summarising that PSC-IBD activity histologically may be disparate from reported clinical symptomatology and macroscopic activity. However, whilst colonoscopy is mandated at diagnosis of PSC, this is not always adhered to (271). There are no stipulated guidelines on how to manage PSC-IBD and therefore conforms to the same treatment regimens as IBD only, which will continue to delay progress in this area.

### 1.4.4 PSC-IBD associated colorectal cancer

For many patients that develop IBD, PSC confers a lifetime risk of CRC 10 times greater than the general population and 5 times greater than those with IBD alone (9, 33). A hazard ratio of 21 (95% CI 9.6-47.6) was observed in a Danish population (246). This observed risk is greatest in those with pancolitis and/or evidence of longstanding active colonic disease. CRC often develops in the proximal colon (245). In IBD only CRC risk slightly increases in line with active chronic colonic inflammation and advancing age, however in PSC-IBD the greatest risk is seen in those between the ages of 40-50, with a significantly lower median age of CRC in PSC-IBD vs IBD alone (59 years; IQR 47-72 vs 69years; IQR

58-78; p<0.001) (245). This risk is reflected in the annual colonoscopy stipulated by all national guidelines for those with PSC-IBD and a one-off colonoscopy required for all patients not known to have a prior diagnosis of IBD, at initial diagnosis of PSC. As per guidelines, colonoscopy surveillance should routinely include targeted and random colonic biopsies coupled with chromoendoscopy (272). In addition to CRC, colectomy is indicated for flat multifocal low grade dysplasia and high grade dysplasia (67).

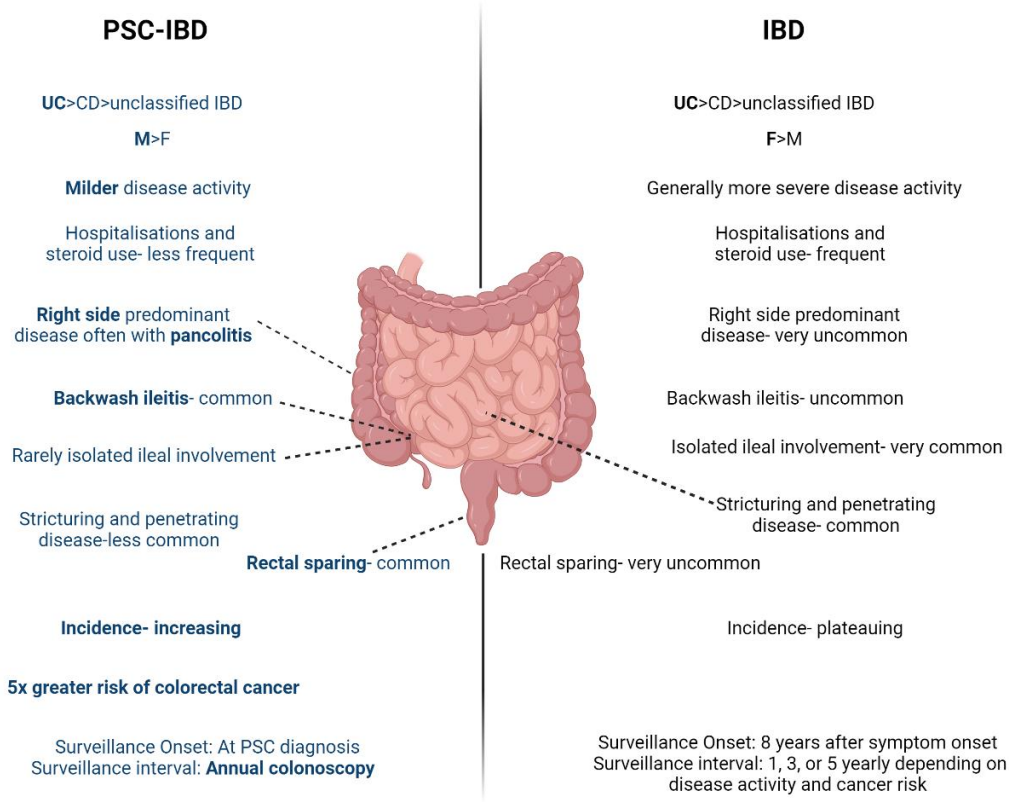



**Figure 1-10.** Comparison of the clinical characteristics and risk factors in PSC-IBD and IBD only**.**

## 1.5 T-helper 17 and the IL-17 pathway

### 1.5.1 Introduction

Brodalumab is the investigational medicinal product (IMP) employed in the *SABR-PSC* pilot study and is part of a family of anti-interleukin 17 inhibitors. A composite understanding of the IL-17 pathway and brodalumab's mechanism of action is crucial to clarifying why IL-17 represents a druggable pathway in PSC, and the rationale for its application in this trial. This chapter first summarises recent insights into T-helper 17 cells, the IL-17 pathway, and proof-of-concept studies in PSC. Finally, it introduces the IL-17 inhibitor- brodalumab, its mechanism of action, pharmacology and safety considerations. Thereby situating the IL-17 pathway within the wider immune landscape of PSC and clarifying the rationale for its clinical investigation.

### 1.5.2 T-helper 17

T cells are regarded as one of the principal drivers of PSC (and IBD) (70, 273, 274). T cells are characterised by their expression of the individual T cell receptors (TCR): alpha/beta and gamma/delta. With the former subdivided based on their expression of either CD4+ (helper) and CD8+ (cytotoxic). The first recognised effector subpopulations of the CD4+ T helper (Th) family included type I (Th1) and type 2 (Th2) cells, understood to play a critical role in adaptive immunity and the regulation of immune and inflammatory conditions. This classical archetype has since expanded to a much larger classification of T helper cells (Figure 1-11).

T-helper 17 (Th17) cells are a functionally and developmentally distinct lineage of CD4+ T helper cells, recognised more recently, in 2005 (275, 276). Since its discovery, Th17 cells have gained notoriety as

principal mediators of numerous autoimmune and inflammatory conditions. As a result, they have become the subject of extensive research in conditions such as psoriasis, ankylosing spondylitis, IBD, rheumatoid arthritis, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune hepatitis (AIH), and multiple sclerosis (277-283).

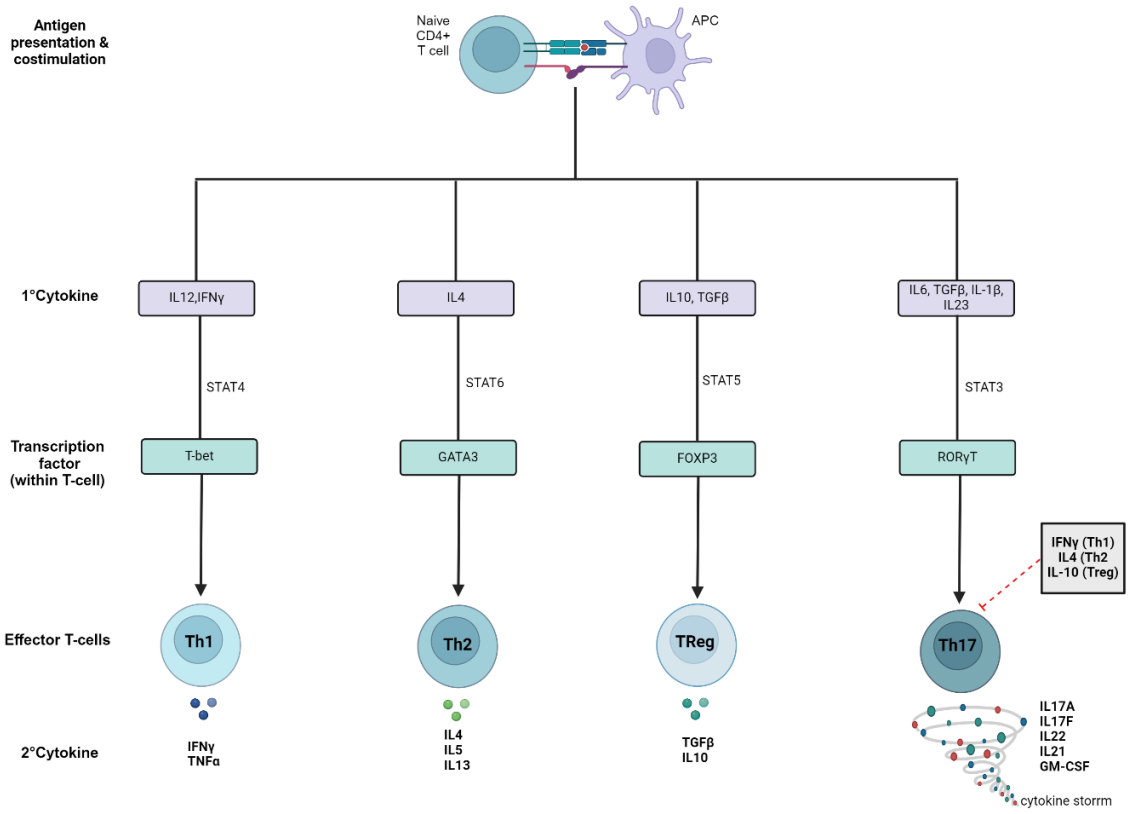



**Figure 1-11** Diagrammatic representation of the T cell lineage activation and associated differentiation, illustrating key cytokines and transcription factors associated with lineage commitment. Abbreviations: APC, antigen presenting cell; IFN, interferon; IL, interleukin; GATA3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony stimulating factor; Th1, T helper 1 lymphocyte; Th2, T helper 2 lymphocyte; Th17, T helper 17 lymphocyte; Treg, T regulatory cell; TGF-β, tissue growth factor beta; STAT, signal transducer and activator of transcription; RORγT, retinoic acid receptor-related orphan receptor γT.

***Th17 differentiation and function***

Th17 differentiation is coordinated by naïve CD4+ cell interaction with antigen presenting cells (APC) and co-stimulation by specific pro-inflammatory cytokines (276). Th17 effector cells differentiate from naive CD4+ cells in secondary lymphoid organs under the combined effect of transforming growth factor-β (TGF-β), and pro-inflammatory cytokines IL-21, IL-23, IL-6 and IL-1β. With IL-1β recognised as being one of the most potent amplifiers of IL-17 production in humans (284, 285).

IL-23 plays a critical role in expanding and stabilising the pathogenic phenotype and subsistence of Th17 cells (286). IL-23 and IL-6 promote activation of the STAT3 transcription factor which in combination with retinoic acid-receptor elevated orphan receptor-γt commences a programme of Th17 stabilisation (287). Retinoic acid-receptor elevated orphan receptor-γt (RORγt) is a master transcription factor expressed in Th17 cells and is a vital regulator of IL-17A/F expression and Th17 development (288, 289). However, naïve Th17 cell differentiation can be antagonised by cytokines released from other Th subsets e.g., IFN-γ and IL-4 from Th1 cells or Th2 cells respectively or IL-10 from regulatory T cells (290).

***Th17 roles and function***

In health, Th17 cell are primarily located within the mucosal tissues, with few circulating Th17 cells, but many 'home' to other tissues via the circulatory system to fight extracellular viral, fungal or bacterial pathogens (291). Th17 cells have two opposing yet finely balanced roles: host defence and disease pathogenesis. Under physiological conditions Th17 cells orchestrate tissue repair, mucosal defence mechanisms, and regulate epithelial barrier integrity by encouragement of antimicrobial peptide secretion thereby protecting against infection (292-294). Additionally, Th17 cells orchestrate chemotaxis of macrophages and neutrophils to the epithelial barrier (292). A host's deficiency in Th17

cells and IL-17 signalling pathways renders them susceptible to fungal infections, particularly mucocutaneous *Candida* (275, 294). Moreover, Th17 cells appear to be essential for pathogen clearance where Th1/2 cells have been inadequate (295). Organs inherently involved in epithelial barrier integrity and host protection from external pathogens contain the largest gradient of IL-17 producing cells. Hence, it is no surprise that the skin, lungs, and intestine are abundant in IL-17 secreting cells (296). Effector Th17 cells secrete pro-inflammatory cytokines IL-17A and IL-17F, in addition to cytokines IL-21, IL-22, IL26, IFNγ, TNFα, and chemokine CCL20 (285, 289).

***Alternative sources of IL-17***

Differentiation from naïve CD4+ T cells into effector Th17 cells takes days, whereas IL-17 expression can be stimulated hours after a stimulus such as infection; suggesting the innate compartment may also be a source of IL-17 secretion (297).

Th17 cells were initially considered to be the sole secretors of IL-17 cytokines; however it is now understood that IL-17$^{+}$ CD8+ T cells (Tc17), natural killers (NK) cells, mucosal associated invariant T cells (MAIT), mast cells, neutrophils, Paneth cells, γδ T cells, and group 3 innate lymphoid cells (ILCs) are all capable of IL-17 production as part of an acute inflammatory or stress response (296, 298). With Th17, MAIT cells and CD8+ T cells identified as the predominant secretors of IL-17 in several chronic liver diseases (96, 299). The commonality between them all being their innate expression of the IL-23 receptor (IL23R), which is also essential to potentiate Th17 differentiation (296). This demonstrates a clear overlap of IL-17 activity shared between the adaptive and innate immune system. Nonetheless, the effective contribution of these cells to IL-17 production in the differing disease models have not been fully elucidated.

***Regulatory T cells and their reciprocal relationship with Th-17 cells***

T regulatory (Treg) cells are a subset of T cells present in the liver and act as regulators of immune response, preventing damage to self. In homeostatic non-inflammatory states Treg differentiation is primed by STAT5, TGF-β and co-stimulatory signals and are classified into natural, peripheral and induced Tregs (287, 299). TGF-β upregulates the expression of forkhead box protein 3 (Foxp3) transcription factor, promoting Treg differentiation and reciprocally opposing Th17 differentiation (299, 300). Treg stabilisation with Foxp3+ is essential for its lineage commitment and function, promoting secretion of anti-inflammatory cytokines IL-10 and TGF-β (287, 299). Classically, Tregs and Th17 regulate one another (289). This balance is critical for regulating homeostasis, chronic inflammation, and autoimmunity. *In vivo* abrogation of Foxp3+ Tregs amplified Th17 activity, gene expression of IL-17 receptor A (IL-17RA) and pro-inflammatory cytokines in murine models. This upregulation correlated with liver fibrosis severity and hepatic enzyme levels (301).

***Th17 instability & plasticity***

Unlike Th1 and Th2 cells which exhibit relative lineage stability, Th17 cells (and Tregs) can exhibit functional and phenotypic environmental adaptations in *vivo* allowing them to deviate from their initial lineage commitment. Contingent on environmental, microbial, or pathogenic factors, Th17 cells can acquire alternative phenotypes (e.g., Treg, Th1) and effector cytokines (302). This flexibility is often referred to as plasticity.

Functional plasticity can either be programmed during early naïve T cell differentiation or later in its development. Th17 cells can upregulate secretion of IL-10, an immune regulatory cytokine, allowing transdifferentiation of former Th17 cells towards a Treg type 1 phenotype contributing to homeostasis, restrained pathogenesis and resolving inflammation (303). Reciprocally, Treg cells can downregulate Foxp3+ expression and reprogramme towards Th17 phenotypical cells (IL-17+Foxp3+)

in animal models under influence from IL-23, IL-1β and IL-6, however the significance of this cross over in human disease models is ill-defined (304).

### 1.5.3 IL-17 family: general principles

Whilst recognition of Th17 cells, as the third subpopulation of CD4+ effector cells, has only emerged in the last two decades, our knowledge of IL-17A preceded that by over a decade (288). 1993 saw the cloning of cytokine IL17A (the signature cytokines of the IL-17 family), and its associated receptor IL-17RA was later described in 1995 (297, 305).

There are six cytokine members of the IL-17 family (305). IL-17A, B, C, D, E (also known as IL-25) and F. Of which, our understanding of cytokines IL17A and IL-17F is the most complete, with considerably less known about IL-17 B, C, D and E (297).

Despite its fundamental role in health, aberrant overexpression of IL-17 cytokine production promotes tissue destruction and contributes to chronic inflammation (276). There are numerous IL-17 cellular targets including macrophages, epithelial cells, endothelial cells, fibroblasts, osteoblasts and chondrocytes (96). IL-17 inhibition has become a druggable target for many chronic inflammatory and autoimmune conditions e.g., psoriasis, psoriatic arthritis, and ankylosing spondylitis (306-309).

**Cytokines IL-17A & F**

IL-17A (originally coined CTLA-8) is the founding member of the IL-17 family (310). Structurally IL-17A & IL-17F are homodimers, composed of two monomers connected by a disulphide bond on a carboxyl terminal cysteine motif (309, 311). IL-17A and F share approximately 50% of their structural homology

and can be secreted as homodimers (IL-17 A & IL-17F) or heterodimers (IL-17A/F) (312, 313). IL-17A appears to be the more potent of the two cytokines, nonetheless, the IL-17A/F heterodimer is produced in greater magnitude than its IL-17A homodimer by peripheral blood mononuclear cells (PBMCs) (314, 315). Whilst biologically similar, and with overlapping functions, IL-17A and F also carry out distinct roles (316). IL-17A appears to be more crucial in activating autoimmunity and priming of the immune system, than its IL-17F counterpart (316). Deletion of IL-17F in mice attenuated experimental colitis, paradoxically deletion of IL-17A resulted in severe disease (317). Evidencing the unpredictability of this pathways' dual roles and suggesting that the specific roles of IL-17A and IL-17F with regards to homeostasis or disease pathogenesis may be contingent on their cellular environment. Nevertheless, there is evidence of a synergistic role between IL-17A and F. Inhibition of IL-17A and F *in vivo*, has been found to have greater clinical efficacy in psoriasis than inhibition of IL-17A singularly (318).

IL-17A also acts upon other innate immune cells promoting expression of IL-8, G-CSF, IL-6 and other chemokines, such as CCL20, to recruit neutrophils and macrophages to sites of infection (319, 320). One of the primary roles of IL-17A is host defence against bacterial and fungal pathogens e.g., *Klebsiella pneumonia* and *Candida albicans* (320). A notable point, requiring due consideration when instituting IL-17 blocking agents in humans.

**Cytokines IL-17B to E**

In contrast, our understanding of the remaining cytokines is incomplete. The structural overlap of the IL-17B to D is less than 30% with IL-17A (321). IL-17 B/C/D are considered proinflammatory, conversely IL-17E activity suggests it has an anti-inflammatory role, inhibiting the IL-17 pro-inflammatory cytokine storm and consequent tissue inflammation (96, 322). IL-17E has a predominant Th2 effect, inducing

expression of IL-4, IL-5 and IL-13, and is considered a potential mediator of allergic airways disease (297, 323). IL-17D is the least well characterised family member. Whilst associated with health, it has also been found to mediate tumour and virus surveillance (324).

**IL-17 Receptors**

There are five IL-17 receptor subunit members: IL-17RA (also known as IL-17R, is the first subunit member identified), RB, RC, RD, and RE (325). Both IL-17A and F homodimers and heterodimers bind to the IL-17RA and IL-17RC receptor subunits (314, 325). Despite being similar, IL-17RA and RC exhibit differing tissue expressions (326). IL-17A binds to the IL-17RA with high affinity (325). IL-17A can additionally signal through IL-17RA/RD, whilst IL-17F can signal independently through IL-17RC/IL-17RC (314, 325, 327). This contrasts to other members of the IL-17 pathway whose receptors are shown in Table 1-6 below.

IL-17RA is expressed ubiquitously throughout the body, including the liver, but found predominantly on haemopoietic tissues, epithelium, endothelium, fibroblasts and myeloid cells. IL-17RC binds IL-17A and F with equal affinity (unlike IL-17RA), and has greater expression in the liver, kidney, and joints, with low relative expression in haematopoietic cells (319). Whilst at present a specific IL-17RC inhibitor does not exist, it is plausible that a specific IL-17RC inhibitor may have greater efficacy in liver disease amelioration, whilst also being more specific. IL-17RA is also the co-receptor for IL-17RB and RE, mediating IL-17E and IL-17C activity respectively (321).

IL-17RA is present on multiple hepatic cell types within the liver including hepatocytes, Kupffer cells (KC), hepatic stellate cells (HSC), biliary epithelial cells (BECs) and liver sinusoidal endothelial cells (LSEC). Such broad expression within the liver may explain its implication in the pathogenesis of a number of liver diseases including primary biliary cholangitis (PBC), MASLD and AIH (283, 328-330).

The IL-17RA/RC receptor is imperative for IL-17A biological activity. B cell, T cells or myeloid cells deficient in this receptor results in IL-17A being unable to bind or activate its downstream biological functions (325, 331, 332).

| Cytokine | Receptor | Sources | Target Cell | Effector role |
|---|---|---|---|---|
| **IL-17A** | IL-17RA/RC | Th17, CD8+ T cells, γδ T cells, NK cells, NKT cells, MAIT cells, neutrophils, ILC3 | Epithelial cells, endothelial cells, fibroblasts, T cells, B cells, keratinocytes, osteoblasts, chondrocytes | Proinflammatory cytokine and chemokine mediation, neutrophil recruitment, mucosal barrier integrity, antimicrobial/antifungal, induces hepatic steatosis and insulin resistance |
| **IL-17B** | IL-17RB/? | Neurones, chondrocytes, pancreas, small intestine, stomach, prostate, neutrophils | Monocytes, endothelial cells | Proinflammatory, neutrophil recruitment, proliferation of cancer cells |
| **IL-17C** | IL-17RA/RE | CD4+ T cell, Dendritic cells, macrophages, keratinocytes, tracheal epithelial cells | Monocytes, epithelial cells | Proinflammatory, neutrophil recruitment |
| **IL-17D** | Unknown | CD4+ T cells, B cells, heart, pancreas, adipose tissue | Endothelial cells, myeloid progenitor cells | Proinflammatory cytokine and chemokine mediation, neutrophil recruitment |
| **IL-17E** | IL-17RA/RB | CD4+ T cell, CD8+ T cells, mast cells, eosinophils, epithelial cells, endothelial cells, thymus | T cells, macrophages, epithelial cells | Eosinophil recruitment, Th2 response to extracellular pathogens, anti-inflammatory role, allergy |
| **IL-17F** | IL-17RA/RC | Th17 cells, CD8+ T cells, γδ T cells, NK cells, NKT cells, MAIT cells, neutrophils, ILC3 cells | Epithelial cells, endothelial cells, fibroblasts, T cell, B cells, keratinocytes, osteoblasts, chondrocytes | Proinflammatory cytokine and chemokine mediation, neutrophil recruitment, mucosal barrier integrity, antimicrobial/antifungal |

**Table 1-6**. IL-17 cytokine family sources and effector function.

Abbreviations: IL, interleukin; ILC, Innate lymphoid cell; Th17, T helper 17; IL17RA, interleukin 17 Receptor A subunit; MAIT, Mucosa Associated Invariant T cell; NKT, Natural Killer T cell; γδ T cells, gamma delta T cell.

**IL-17 cytokine-receptor signalling**

Ligand binding of IL-17A to its associated receptor IL-17RA/RC heteromeric complex creates a conformational change (325). Activating the cytoplasmic protein, Act1 adaptor via the SEF/IL17R (SEFIR) domain- made up of both the IL-17RA and RC subunits (Figure 1-12). This engagement enables rapid recruitment of TNF receptor associated factor 6 (TRAF6) an upstream activator of the transcription factor NF-κB in addition to mitogen-activated protein kinase (MAPK) pathways (312, 314). NF-κB regulates gene expression of pro-inflammatory processes in the nucleus. Activation of this pathway stimulates neutrophil recruitment, cytokines, chemokines (CXCR2), and inflammatory genes leading to a proinflammatory cascade (314).

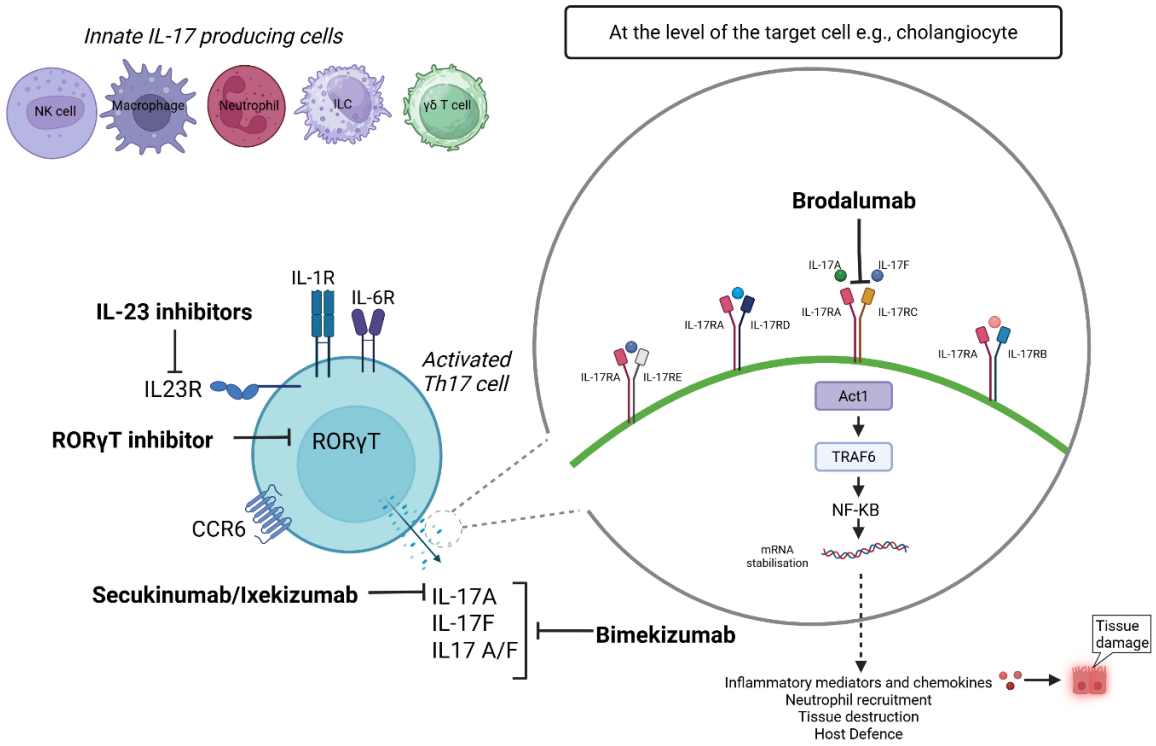



**Figure 1-12** IL-17 signalling pathway, including IL-17 cytokines and receptor members, depicting sites of action of a number of currently approved IL-17 blocking agents. Adapted from Elzubeir et al. (333). Abbreviations: CCR6, CC chemokine receptor 6; IL, interleukin; ILC, innate lymphoid cell; NK, natural killer; γδ, gamma delta; Th17, T helper 17; IL17RA, interleukin 17 Receptor A.

### 1.5.4 Proof of concept: evidence for the Th17/IL-17 pathway in primary sclerosing cholangitis pathogenesis

As discussed previously, the IL-17 pathway and Th17 cells have dual roles, balancing protective immune regulation with pro-fibroinflammatory activity. Over the past decade, a growing body of evidence has implicated the IL-17 pathway as a key driver of the biliary fibroinflammation exemplified in PSC (Table 1-7).

***Biliary epithelial cells as targets of IL-17***

BECs (cholangiocytes) line the bile ducts and are responsible for transporting bile. Recent studies underscore the immunologically active role of cholangiocytes in the chronic inflammation observed in PSC. IL-17 receptors RA, RC and RE are expressed on human cholangiocytes originating from patients with and without PSC (334). IL-17 stimulated BECs secrete pro-inflammatory cytokines IL-6, IL-1β, IL-23, CXCL6, CXCL9, IFN-γ & TNF, amplifying local inflammation and allowing IL-17A signalling on cholangiocytes to trigger a robust biliary immune response (334, 335). Furthermore, IL-17 induces CCL20 expression by BECs, promoting recruitment of Th17 and IL-17+ cells to periductal areas, thereby exacerbating chronic biliary damage (334, 335).

Recruitment of T cell subsets to organ-specific tissues is determined by expression of T cell chemokine receptors (CXCR3 and CCR6) as well as expression of specific chemokine ligands (CCL20) on target tissues. In 2012 Oo et al., conducted a study on a range of chronic liver diseases utilising serum and human liver explants, including PSC (336). BECs were confirmed as driving recruitment of Th17 and IL-17+ CD8 T cells expressing CCR6, CXCR3 and CXCR6 ligands respectively to inflamed bile ducts expressing chemokines CCL20 and CXCL9. CCL20 and CXCL9 expression by injured bile ducts, was

augmented by IL-17, establishing a chronic periductal immune response and positive feedback loop (336).

***Monocytes in IL-17 mediated inflammation***

IL-17A/F signals through IL-17RA and IL-17RC expressed on Kupffer cells (KCs) and infiltrating monocytes, inducing cytokine secretion of IL-6, IL-1β and TGFβ contributing to hepatic fibroinflammation. Human PSC studies have identified enrichment of IL-17RA+ monocytes in fibrotic PSC liver explants. Utilising spatial transcriptomics, IL-17RA+ tissue monocytes and IL-17RA+ T-cell subsets were located at higher frequencies and mapped to fibrotic tissue in end-stage PSC compared to that of the parenchyma (337), suggesting they contribute to disease progression.

***Neutrophils as IL-17 effectors***

Neutrophils are central to acute inflammation in PSC and are heavily influenced by IL-17. Neutrophils are recruited to and perpetuate damage to bile ducts through CXCL8 (IL-8) chemotaxis, either through IL-17 or BEC signalling (338). Patients suffering with PSC exhibit increased biliary neutrophil and $CD103^{+}CD69^{+}CD8$ tissue-resident memory (TRM) T cell infiltration compared to controls which are positioned in closer proximity to the biliary epithelium. IL-17+ biliary resident T cells are also linked to neutrophil recruitment in PSC livers (338). Whilst our understanding of the role of neutrophils in the IL-17 axis is expanding, it has become apparent that neutrophils not only the possess the proclivity to drive IL-17 secretion or skew T-cell differentiation towards a Th17 phenotype through IL-23 production and other means (87), but reciprocally Th17 cells prime and recruit neutrophils to sites of tissue damage and inflammation (87, 275). Interestingly, studies have reported a decrease in hepatic neutrophil accumulation and subsequent liver injury following IL-17 neutralisation (339, 340).

**Th17 skewing in PSC**

A single cell atlas mapping of intrahepatic T cells in PSC patients showed a developmental skewing of tissue resident naïve T cells towards Th17 polarisation as opposed to Foxp3+ Tregs. This propensity was observed to be more abundant in PSC compared to other liver diseases (88). Consistent with this, earlier studies from Christoph Shramm's team identified not only a significant reduction in circulating and intrahepatic Foxp3+ Treg proportions but also functionality in PSC livers compared to healthy controls (98).

A complementary study confirmed pathological biliary resident CD4+ T cells are dominated by Th17 cell aggregates in PSC and non-PSC human cholangiopathies from explanted livers (341). Furthermore, as reported in other studies, Th17 related cytokines IL-17A and IL-17F and associated IL-17RC were found to be upregulated in cholangiocytes after co-culture. Direct cholangiocyte-immune cell signalling facilitates pathogenic Th17 lineage expression. This pathogenic Th17 process appears to be boosted by CD100 mutations (a causal mutation in a Mendelian form of PSC), which contributes to site specific Th17 skewing and consequently localised biliary inflammation (341). This would suggest that cholangiocytes participate in bidirectional cross talk and are not merely passive in the ensuing biliary inflammation observed in PSC pathogenesis (342).

***Bile acids as IL-17 modulators***

Hepatotoxic bile acids have been implicated in driving cholestatic liver injury (343). Pathological bile acid induced IL-23 cytokine signalling during the course of cholestasis synergistically promotes upregulation of the IL-17/Th17 axis, hepatic inflammation, neutrophil accrual and immune dysregulation. In one study, bile acid induced IL-23 production in bile duct ligated (BDL) mice (a cholestatic murine mimic) and mice fed a bile acid diet, promoting Th17 expansion and IL-17A

secretion (339). Additionally, in this same model IL-17 inhibition subdued hepatic necrosis, proinflammatory cytokines and neutrophil accumulation (339).

***Microbial mechanisms***

Th17 cells play a vital role in defending against pathogenic infections. PSC is often complicated by bacterial and/or fungal infection, which may drive IL-17 mediated inflammation. Studies postulate that fungal cholangitis in particular, may expediate disease progression in PSC (344, 345). Katt et al. demonstrated *in vitro* pathogenic stimulation of PBMCs with bacterial and fungal isolates cultured from PSC patient bile samples, stimulated an increase in Th17 cellular expression and IL-17A expressing cellular aggregate in periductal regions in PSC patients compared to controls (97). Furthermore, a later *ex vivo* and *in vitro* study by the same group corroborated their earlier findings, demonstrating amplification of Th17 cells by microbe stimulated PBMCs from patients with PSC (even in early disease stages) when compared to healthy controls and PBC, suggesting heightened Th17 differentiation (90). This was associated with an increase in IL-17A production and pathogen induced IL-1β secreting macrophages around BECs, which in turn promoted cholangiocyte expression of Th17 attracting chemokine CCL20 and proinflammatory cytokines IL-6 and IL-23- cytokines known to drive Th17 differentiation (90). Th17 cell frequencies and IL-17 levels were similarly elevated in patients with PSC alone and PSC-IBD, yet notably lower in those with IBD only. Conversely, Th1 cell frequencies were comparable across PSC, PBC, and healthy controls (90).

PSC-IBD exemplifies the bi-directional gut-liver axis cross talk in PSC pathogenesis. A key study identified significantly greater frequencies of *Klebsiella pneumonia, Proteus mirablis* and *Enterococcus gallinarum* in PSC patients as compared to healthy controls or UC alone *in vivo* (59). When gnotobiotic mice were inoculated with PSC-UC patient microbiota, they developed Th17 mediated hepatobiliary

inflammation (59). Notably, targeting the IL-17 pathway with an ROR-yt inverse agonist supressed Th17 numbers and hepatobiliary injury, as did antibiotics (metronidazole and vancomycin) and an IV administered bacteriophage cocktail targeting *Klebsiella pneumonia* (59, 346). However, IL-17A antibodies were less effective (59), suggesting a more complex role for the IL-17 axis. This study reinforces the pathogen driven Th17 pathway as contributory to the development of bile duct damage, whilst also highlighting our current lack of knowledge as to which aspects of the IL-17 axis require inhibition to ameliorate liver disease.

***IL-17 driven liver fibrosis***

Experimental murine BDL results in biliary fibrosis and obstructive cholestasis, mirroring that seen in human PSC (347-349). A pivotal paper by Meng et al., demonstrated an upregulation in cytokines IL-17A and IL-17F, and their associated receptors IL-17RA and RC in fibrotic livers and serum of BDL mice compared to sham counterparts (347). This correlated with an increase in IL-17+ expressing cells in this compartment, with T cells being the chief source of IL-17A. This was also observed in human disease. Meng et al. concluded that IL-17 signalling likely contributes to liver fibrosis (347). To support this hypothesis, IL-17RA−/− mice were resistant to BDL- induced liver fibrosis (≈75% inhibition), as evidenced by a decrease in collagen deposition, myofibroblasts (of which HSCs are the major source) and pro-fibrogenic cytokines. As a result, liver function tests (ALT) also improved. Conversely, administering anti-inflammatory IL-17E to BDL mice was hepatoprotective. These findings indicate that IL-17A has a fundamental role in liver fibrosis progression in cholestatic disease and is a potential therapeutic target in PSC.

Such observations are also mirrored in several additional studies of cholestatic liver disease, reporting that abrogation of the IL-17 pathway (through either IL-17RA knock out mice or via anti-IL-17A

treatment) results in attenuated hepatic fibroinflammation; as a result of downregulation of pro-inflammatory cytokines, KC, HSC, and/or hepatic neutrophil accrual (339, 340, 350, 351). IL-17A neutralisation in BDL mice has shown promising anti-fibrotic effects by shifting immune polarization from Th2/Th17 towards a Th1 response, improving liver function and restoring autophagy via STAT3 suppression (a key transcription factor in the IL-17 signalling pathway) (351). Somewhat surprisingly, IL-10, an anti-inflammatory cytokine involved in reinforcing the Treg signalling pathway and Th17 suppression, paradoxically mitigated these beneficial effects by stimulating STAT3 activity and impairing essential autophagy (351). Underscoring the complex interplay between immune pathways in PSC.

***PSC and IL-17 controversies***

A study investigating the effect of IL-17+ CD8 T cells on cholangiocytes *in vitro* and murine cholangiocytes *in vivo* found that IL-17A/F inhibition exacerbated cholangitis in autoimmune liver disease (AILD) models (352). The proposed mechanism from this body of work suggested that IL-17+ CD8+ T cells induced programmed cell death ligand 1 (PD-L1) in cholangiocytes, which serves as a protective mechanism by supressing T-cell proliferation and limiting CD8+ T-cell mediated hepatobiliary cytotoxicity. Thus, pan-neutralisation of IL-17 cytokines may inadvertently exacerbate cholangitis (352). However, a separate study on PD-L1 checkpoint inhibitor use in patients with cancer and concurrent autoimmune and cholestatic liver diseases reported that PD-L1 blockade was safe (353). This evidence suggests PD-L1 inhibition does not universally exacerbate liver inflammation. However, it would suggest there is a critical 'tipping-point' in the IL-17 pathway at which point it skews towards chronic biliary disease, these contrasting findings highlight the need for further research in this area.

**IL-17 and cancer risk in PSC**

In one study, IL-17A immunohistochemistry identified greater IL-17A expression locally in PSC associated cholangiocarcinoma (CCA) tissue as compared to CCA de novo (354). In the same study, patient-derived CCA organoids were exposed to five cytokines, IL-1β, IL-6, IL-17A, IFN-γ, TNF-α; of which IL-17A was the only cytokine that demonstrated a significantly increased stimulatory effect on CCA cell proliferation rate (38% ± 16% $p<0.05$) and organoid size (45.9% ± 16.4% $p<0.01$). This potentially implicates IL-17A in PSC-CCA tumour growth *in vitro*.

**Moving from bench to bedside**

Experimental studies targeting direct or indirect neutralisation of the IL-17 pathway have thus far demonstrated encouraging results in PSC and other liver diseases. The promising results from the recent single-arm, open-label pilot study of vidofludimus calcium in PSC, has already been discussed in detail in Chapter 1.2.7.

Matsuda et al. demonstrated that IL-17 blockade can inhibit hepatic fibrosis (355). In psoriasis patients treated with brodalumab (an IL-17RA antagonist), a non-invasive marker of liver fibrosis (fibrosis 4 Index (FIB-4)), was observed to significantly decline compared to both biologic naïve control patients ($p<0.01$) and those treated with the IL-17A inhibitor (secukinumab) ($p<0.05$) (Figure 1-13) (355). This retrospective study was limited due to a small sample size (n = 20) and did not assess patients with concomitant PSC, with steatotic liver disease being the more likely comorbidity. Despite these limitations, the findings suggest IL-17 blockade is safe in patients with liver disease.

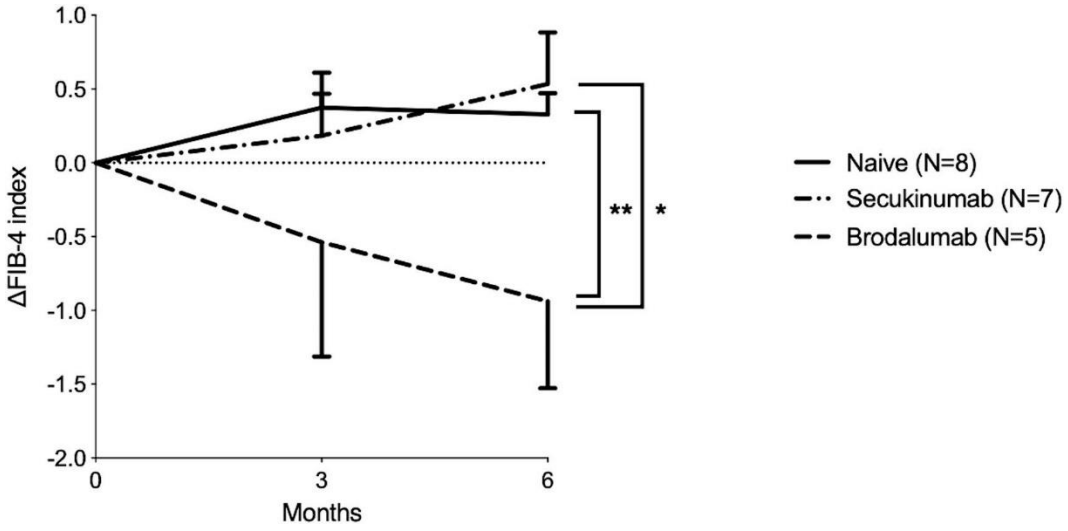



**Figure 1-13** Change in FIB-4 index in psoriasis patients treated with brodalumab, secukinumab or topical therapy only over 6 months. Adapted from Matsuda et al.(355).

In summary, current evidence from both human and murine models support the hypothesis that the canonical IL-17 pathway may be of critical importance to the pathogenesis of PSC and as a result the proposed investigation of an IL-17 inhibitor in PSC is worthy. To the best of our knowledge there are no clinical trials to date targeting IL-17 pathways in PSC. IL-17 inhibition has shown promise in several other autoimmune diseases (e.g., psoriasis). However, its potential benefit in PSC requires clarification. This pilot study assesses whether brodalumab (an IL-17 inhibitor) could represent a new safe, feasible, tolerable, and acceptable treatment in PSC.

**Table 1-7.** Summary findings of research in human and murine models implicating the IL-17 pathway in the development of PSC pathogenesis

| Reference | Year | Main findings | Source |
|---|---|---|---|
| **Meng et al.(347)** | 2012 | Gene expression of IL-17A, IL-17F, IL-17RA and IL-17RC are upregulated in BDL mice livers | Animal |
| | | BDL IL-17RA-/- mice are resistant to liver fibrosis | Animal |
| | | IL-17 stimulation of KC upregulates secretion of pro-fibrogenic cytokines TGF-β1, IL-6 and TNFα and in turn stimulates HSC myofibroblasts conversion and expression of collagen Type 1 | Animal |
| | | Elevated IL-17 expression correlates with severity of liver disease | Human |
| **Oo et al.(336)** | 2012 | Damaged human BECs secrete CCL20 in response to IL-17 and in turn recruit CCR6+ Th17 cells to bile ducts in a positive feedback loop | Human |
| **Katt et al.(97)** | 2013 | Pathogen stimulated PBMC exhibit an augmented Th17 response | Human |
| | | IL-17A+ T cells are aggregated around damaged bile ducts | Human |
| **Hara et al.(350)** | 2013 | Liver fibrosis is attenuated in BDL IL-17-/- mice | Animal |
| | | IL-17A activated KCs upregulate TGF-β1 and TNFα secretion, promoting hepatic fibrosis | Animal |
| | | HSC myofibroblast conversion is enhanced by IL-17A | Animal |
| **O'Brien et al.(339)** | 2013 | IL-17A neutralisation inhibits hepatic neutrophil accumulation, pro-inflammatory cytokines, and liver fibrosis in BDL mice | Animal |

| | | | |
|---|---|---|---|
| | | Cholestasis stimulated hepatic IL-23 secretion, which is critical for the stabilisation and preservation of effector Th17 cells | Animal |
| **Zapeda-Morales et al.(348)** | 2016 | Gene expression of hepatic IL-17A and TGF-β1 are upregulated in BDL mice and correlate with hepatic fibrosis | Animal |
| **Zhang et al.(351)** | 2017 | IL-17A blockade attenuated hepatic fibrosis in BDL mice as demonstrated by a reduction in collagen deposition, improved liver morphology and function, and improved mouse survival rate | Animal |
| **Tedesco et al.(340)** | 2018 | IL-17A is elevated in serum. IL-17 neutralisation in Mdr2-/- mice reduces hepatic fibrosis and detectable IL-17 levels in serum | Animal |
| | | In Mdr2-/- mice IL-17+ γδ T cells are the most prevalent IL-17 producing T cells in the liver compartment. Translocated gut microbiota augment IL-17 secretion | Animal |
| | | Intrahepatic IL-17+ γδ T cells derived from PSC patients' livers secrete IL-17 upon stimulation, compared to controls | Human |
| **Jeffery et al(342)** | 2019 | Injured BEC activated by IL-17 upregulate secretion of CCR6 ligand CCL20 and Th17 polarising cytokines (TGF-β1, IL-6, IL-1β) which in turn upregulates the recruitment and localisation of IL-17+ producing cells in portal tracts, in a positive feedback loop | Human |
| **Nakamoto et al.(59)** | 2019 | Faecal samples from PSC/UC patients inoculated into gnotobiotic mice promotes a Th17 hepatic response and progressive liver injury | Animal |
| | | Antibody mediated IL-17A neutralisation insufficiently inhibited hepatobiliary disease progression | Animal |
| **Kunzmann et al.(90)** | 2020 | Significantly increased frequency of IL-17 secreting T cells are identified in PSC patients compared to PBC and controls in vivo | Human |
| | | Microbial pathogens stimulate monocyte driven Th17 differentiation by upregulating IL-6 and IL-1β | Human |
| | | IL-17 secreting cellular aggregate are located around damaged bile ducts | Human |

| | | | |
|---|---|---|---|
| **Poch et al.(88)** | 2021 | Cirrhotic PSC livers have an enriched CD4+ T cell population located in portal tracts, with a propensity to polarise towards Th17 effector cells as opposed to FoxP3+ T regulatory cells | Human |
| **Moreno et al.(334)** | 2023 | PSC ECO express ILRA, RC and RE receptors and respond to IL-17 treatment by upregulating pro-inflammatory chemokine and cytokine members | Human |
| **Chen at al.(356)** | 2024 | Human placental mesenchymal stem cell derived exosome treatment inhibits hepatic fibrosis in Mdr2 mice by downregulating Th17 differentiation and IL-17 gene expression | Animal |
| **Jiang et al.(341)** | 2024 | Missense- mutation SEMA4D encoding CD100 in autosomal dominant PSC boosts Th17 differentiation. CD 100-expressing biliary resident T cells are dominated by Th17 cells. | Human |

Abbreviations: BDL, bile duct ligate; ECO, extrahepatic cholangiocyte organoids; HSC, hepatic stellate cell; IL-17RA, interleukin 17 Receptor A subunit; IL, interleukin; KC, Kupffer cells; PBMC, peripheral blood mononuclear cells; TNFα, tumour necrosis factor alpha.

### 1.5.5 Brodalumab

The first IL-17A specific blocking agents were licensed in 2015 and 2016 in the form of secukinumab and ixekizumab (outlined in Table 1-8) respectively for psoriasis, psoriatic arthritis, ankylosing spondylitis and axial spondyloarthropathy (357). It was not until 2017 that brodalumab the first, and to date the only, IL-17 receptor A inhibitor was licensed for use. Brodalumab is a fully humanised IgG2 monoclonal antibody (mAb) which binds to the interleukin 17 receptor A (IL-17RA) subunit with high affinity. Consequently, extensively inhibiting the cytokines IL-17A, IL-17C, IL-17E, IL-17F and IL-17A/F heterodimer, and thereby preventing the downstream pro-inflammatory cytokine storm leading to tissue destruction and fibrogenesis. Brodalumab is approved for use in moderate to severe chronic plaque psoriasis (Kyntheum®) (358).

Whilst significant advancements have been made over the past 30 years, a greater understanding of the Th17 cells and IL-17 activity is still required. With Th17 and various members of the IL-17 cytokine family occupying dual roles (anti-inflammatory and proinflammatory), its employment in various chronic inflammatory conditions have led to conflicting and surprising results. Recent scientific studies have implicated Th17 cells in IBD pathogenesis and identified elevated IL-17A activity within the intestinal mucosa of patients with inflammatory bowel disease compared to control or healthy subjects (226, 291, 359-361). Nonetheless, human and animal colitis models have demonstrated contradictory results with regards to IL-17's role in ameliorating or exacerbating colonic inflammation (317, 362, 363). Anti-IL-17 mAb administered to an experimental murine model of induced colitis, dextran sulphate sodium (DSS) induced colitis mice, exacerbated colitis (362). In contrast a study by Zhang et al. demonstrated attenuated colonic inflammation in IL-17R knock out mice (363). Jiang et al. (364), subsequently reported increased IL-17A serum levels in patients with IBD. This and other studies led to the eventual testing of both secukinumab and brodalumab in patients with moderate to severe CD. A double-blind RCT of 59 CD patients were randomised to intravenous secukinumab (n

= 39) or placebo (n = 20). The trial was prematurely terminated due to meeting pre-specified trial criteria for futility i.e., failure to meet their primary efficacy outcomes (Crohn's disease activity index reduction of ≥50 points) (365). The intervention arm saw more adverse events (74% vs 50%) especially with regards to infections, particularly fungal infections. Four patients were noted to have experienced a worsening of their CD (365). In 2016 a phase 2, double-blind, RCT of brodalumab in moderate to severely active CD was conducted in 130 patients across 39 international centres (277). The proportion of patients achieving clinical remission (CDAI <150) at 6 weeks was selected as the primary end point. The study was however terminated early due to a disproportionate accrual of participants presenting with worsening of their CD in the treatment arm (OR 6.64; 95% CI 1.48-29.88), in addition to failing to meet its primary efficacy outcomes. 84 participants completed the study (56 brodalumab arm, 28 placebo arm), with all 130 participants included in the intention to treat analysis (277). The Incidence of adverse events including infections we comparable across both groups (277).

Despite early data suggesting a potential role for IL-17 blockade in CD, results from the above RCTs in CD were surprising and disparate from those seen in other autoimmune diseases such as psoriasis (which shares genetic risk haplotypes with CD) (366-368), where a favourable treatment effect have been observed. Such results highlight the dual functionality and plasticity of the IL-17 pathway, but also its important and perhaps distinct role in CD and the gut compared to other inflammatory conditions (277). Regulatory Th17 cells (rTh17) are also prevalent in the intestine, and secrete anti-inflammatory cytokines (IL-10), which are essential in maintaining homeostasis of proinflammatory Th17 cells. With imbalance of the rTh17/Th17 axis potentially leading to IBD causation. rTh17 cells require IL-17A/F (in low levels), chemokine ligand CCL20 (expressed by inflammatory cells) and its associated receptor CCR6 (expressed by Th17 cells) to re-direct and suppress IL-17 activity within the small intestine (277, 369). Inhibition of rTh17 may result in suppressed migration and development of this anti-inflammatory mediator (370). Targan et al. (277), propose that CD exacerbation may occur

as a direct result of rTh17 inhibition bought about by IL-17 blockade. Alternative hypotheses suggest a role of increased colonic pathogenic microorganisms, particularly *Candida albicans* (371), and loss of the epithelial barrier function orchestrated by drug induced inhibition of IL-17's protective functions (277). The rationale behind these conflicting results remains unclear. The degree to which over-expression of IL-17 activity may be either causatory, consequential or contributory to IBD pathogenesis is undetermined. Remarkably, the attenuation of pathways slightly upstream of and synergistic with the IL-17 pathway, including the IL23/IL17 axis by ustekinamab (372), vidofludimus (373), risankizumab (374), and mirkizumab (375), have proven to be efficacious in IBD, whilst direct targeting of IL-17 to date has not. Plausible explanations include other mediators, such as TNFα and IL-23, having a greater importance in IBD pathogenesis. New therapeutic agents with dual inhibition of TNFα and IL-17 will be interesting in this regard. Alternatively, CD may not be pathologically mediated by IL-17 in humans. IBD has been considered to be primarily orchestrated by Th1 in CD and Th2 and/or Th17 in UC (291) (376). Yet, clinical trials of IL-17 blockade in UC have not been attempted. Other explanations pertain to the biological function of IL-17A/F within the bowel specifically having greater anti-inflammatory magnitude compared to other inflammatory/autoimmune conditions. Nonetheless, the success of IL-17 inhibition in rheumatoid arthritis has also been disappointing (377). Finally, the relative pathogenic contribution of other cells known to produce IL-17 (e.g., CD8+ IL-17 cells, MAIT cells) has not been fully elucidated and to this end we are yet to understand anti-IL-17 drug potency in inhibiting all cellular sources of IL-17. IBD immunology and Th17 biology is clearly complex and further scientific work in this space is still warranted.

Finally, to provide a more comprehensive understanding of IL-17 inhibitors paradoxical role in colitis development, a series of meta-analyses evaluating the risk of development of IBD in psoriasis, psoriatic arthritis, and ankylosing spondylitis during anti IL-17 treatment has been undertaken. Results concluded IBD events were rare and no detectable significant difference in risk of new IBD exists

between treatment and control groups (229, 230). In one study no difference in pooled risk of new onset IBD in the best- and worst-case scenario was observed (worst case scenario RD 0.0008, 95% CI -0.0005- 0.0022) (229).

The introduction to Th17 cells, IL-17 pathway and the IL-17 inhibitors above outlines the critical role of T cells in the potential pathogenesis of autoimmune and chronic inflammatory conditions, and how its aberrancy may be implicit in PSC's pathogenesis. Landmark discoveries have been made in basic science and translational research over the past decade implicating IL-17 and Th17 cell over expression in PSC compared to controls. This founding research highlights the importance of Th17 and IL-17 activity within PSC and has provided the proof-of-concept data to explore an IL-17 inhibitor in patients with PSC. Making IL-17 an attractive therapeutic target in a clinical trial of PSC patients. Therapeutic inhibition of cytokines inevitably carries risk, particularly in the case of IL-17, given its pleotropic protective as well as pathogenic roles. However, the distinct clinical, genetic, and phenotypic characteristics of PSC-IBD suggest that earlier findings in IBD only, should not deter further investigation of IL-17-targeted therapy in PSC.

**Table 1-8** Summary characteristics of licensed IL-17 inhibitors (333).

| | **Secukinumab (Cosentyx)** | **Ixekizumab (Taltz)** | **Brodalumab (Kyntheum)** | **Bimekizumab (Bimzelx)** |
|---|---|---|---|---|
| **Manufacturer** | Novartis Pharma | Eli Lily & Company | Leo Pharma | UCB Pharma |
| **Mechanism Of Action** | Humanised IgG1 Mab | Humanised IgG4 Mab | Humanised IgG2 Mab | Humanised IgG1 Mab |
| **Selective Target** | IL-17A cytokine | Il-17A cytokine | IL-17 Receptor A | IL17, IL17 F & IL17 AF cytokines |
| **Approved Indications** | ● Moderate- severe PsO<br>● PsA<br>● AS<br>● axSpA | ● Moderate- severe PsO<br>● PsA<br>● AS<br>● axSpA | ● Moderate- severe PsO | ● Moderate- severe PsO<br>● PsA<br>● AS<br>• axSpA |
| **First Approval** | 2015 | 2016 | 2017 | 2021 |
| **Route Of Administration** | subcutaneous injection | | | |
| **Device** | 75mg/0.5ml pre-filled syringe | 80mg/1ml pre-filled syringe | 210mg/1.5ml pre-filled syringe | 160mg/1ml pre-filled syringe |
| **Induction Dose** | ● PsO- 300mg weekly for 5 doses<br>PsA/axSpA/AS-150mg weekly for 5 doses | 160mg for 1 dose | 210mg weekly for 3 doses | PsO- 320mg every 4 weeks for 0-16 weeks |
| **Maintenance Dose** | ● PsO- 300mg monthly<br>● PsA/axSpA/AS- 150mg monthly | ● PsO- 80mg alternate weeks for 5 doses, then 80mg every 4 weeks<br>● PsA/axSpA/AS 80mg every 4 weeks | 210mg alternate weeks | ● PsO- 320mg 8 weekly<br>PsA/axSpA/AS- 160mg 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. | | | |

Abbreviations: AS, Ankylosing spondylitis; axSpA, axial Spondylarthritis; IL-17RA, interleukin 17 receptor A; mAb, monoclonal antibody; PsA, Psoriatic arthritis; PsO, plaque psoriasis; SIB, suicidal ideation and behaviour.

*A causal link between brodalumab and suicidal ideation and behaviour (SIB) has not been established; caution is nevertheless advised by the manufacturer in those with a history of depressive disorders or SIB.

## 1.6. Thesis chapter overview

This thesis is structured around works that were undertaken with the aim of answering pertinent questions that would help to inform the design and conduct of the main body of work of this thesis pertaining to the delivery of the single-arm pilot study of brodalumab in the treatment of primary sclerosing cholangitis (*SABR-PSC)* pilot study (Figure 1-14).

**Chapter I:** The opening chapter of this thesis represents an extensive literature review of existing evidence on the three core topics pertaining to this thesis: PSC, IBD/PSC-IBD and the IL-17/Th17 axis.

**Chapter II:** Explores the real-world pre-trial feasibility and eligibility landscape for PSC-IBD patients at the Norfolk and Norwich university hospital (NNUH), the primary site for the *SABR-PSC* trial. This early work assesses the practical feasibility of recruiting patients locally and provides insights into the potential recruitment challenges for this specific patient population.

**Chapter III:** Presents a systematic review and meta-analysis synthesising all available evidence on the safety and efficacy of biologics and small molecule therapies in PSC-IBD patients to date. The primary aim of this work is to contextualise emerging findings from the *SABR-PSC* trial within the broader evidence base from currently available data, thereby providing a critical benchmark for interpreting safety outcomes. In doing so, this chapter also informs the design and rationalisation of key safety endpoints and safety monitoring for the *SABR-PSC* trial.

**Chapter IV:** This chapter represents the design, administration and quantitative findings from the single-arm pilot study of brodalumab in the treatment of primary sclerosing cholangitis (*SABR-PSC* pilot study).

**Chapter V:** Presents qualitative data gathered from the week 16 semi-structured interview conducted as part of the *SABR-PSC* study. This chapter moves on from the numeric pilot data presented in the

previous chapter and focuses on listening to and understanding participants' perceptions and lived experiences of the trial. Exploring their narrative on the design, conduct and overall feasibility. Furthermore, participants' feedback offers practical suggestions for improvement and highlights considerations essential for the planning of a future phase 2 trial investigating brodalumab in PSC.

**Chapter VI:** Summarises the overall results from the research works undertaken within this thesis, discusses the challenges encountered during *SABR-PSC* and considers the design of a larger-scale randomised controlled trial evaluating brodalumab in PSC powered to infer clinical efficacy.

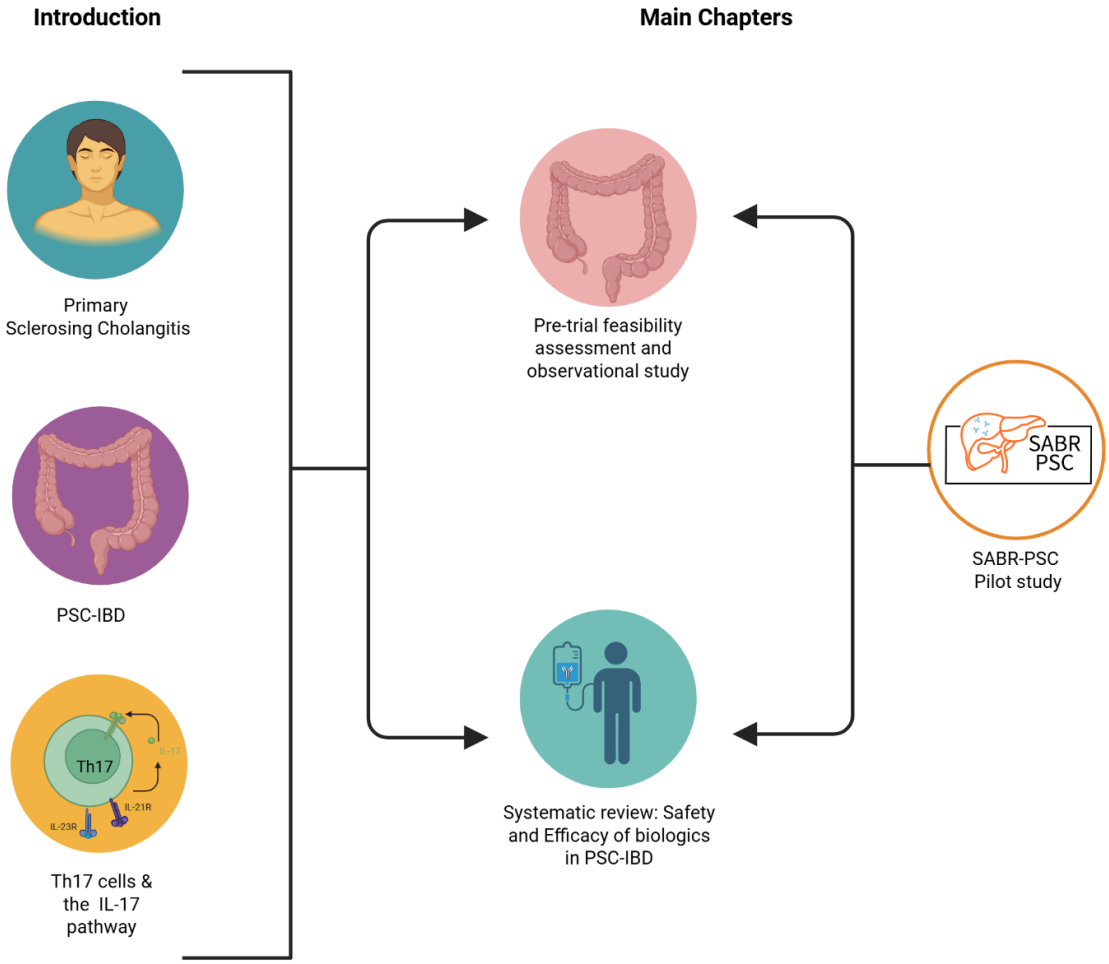



**Figure 1-14** Schematic of thesis overview and structure- including bodies of work and main chapters of the thesis

# Chapter 2 A single centre retrospective review of patients with primary sclerosing cholangitis associated inflammatory bowel disease: A real-world pre-trial feasibility assessment

**University Of East Anglia Research Ethics Application ID (FMH S-REC) Approval gained**

FMH S-REC reference- ETH2425-0257

## 2.1 Abstract


**Background**

Recruitment of patients with rare diseases such as PSC into clinical trials is a well-known clinical challenge, often resulting in trials being underpowered. Local population databases are fundamental to obtaining a granular and comprehensive understanding of the immediate population being treated. Additionally, they can be utilised to inform trial design, inform sample size calculations, likelihood of achieving target trial sample sizes locally, in parallel to providing real-world data on local patient trial eligibility. We evaluated real-world data on the eligibility of a cohort of PSC-IBD patients at the Norfolk and Norwich University Hospital (NNUH) as part of pre-trial feasibility assessment for the *SABR-PSC* pilot study.

**Method**

A retrospective review of PSC-IBD patients managed in the outpatient setting at the Norfolk and Norwich University Hospital between 14$^{th}$ November 2022 and 2$^{nd}$ of September 2024 was undertaken. All PSC-IBD patients aged ≥16 were included. Data collected as part of routine clinical care was extracted from electronic medical care records. We analysed demographics, age at diagnosis, pharmacological interventions used, clinical characteristics and outcomes of both PSC and IBD.

**Results**

A total of 142 patients were included in the study. The median age at PSC diagnosis was 41.5 (IQR 20.5-59), with a male predominance (69%). Large-duct PSC was identified in 81% of cases, and 20% developed cirrhosis over a median follow-up of 9 years (IQR 5–14.5). Twenty-three patients were deemed eligible for the *SABR-PSC* pilot study. The most common reasons for trial ineligibility included

small-duct PSC (19.3%), post liver transplant status (14.3%), active colitis (16%) and age outside the eligible range (13.4%).

**Conclusion**

This real-world data demonstrates that a target recruitment size of five patients for a PSC clinical trial at a single centre such as NNUH is feasible. Use of simulated expanded eligibility criteria doubled the number of eligible patients for the *SABR-PSC* pilot study. Narrow eligibility criteria should only be employed where there is evidence of compelling scientific merit, if recruiting to target in PSC trials is to be successful.

## 2.2 Overview of chapter

This chapter presents a single centre retrospective study investigating the eligibility of patients with PSC-IBD at the Norfolk and Norwich University Hospital ahead of Single-Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis *(SABR-PSC)* (ISRCTN 15271834). The study was conducted in response to challenges in recruiting PSC patients for clinical trials, given the disease's rarity, heterogeneity, and the strict eligibility criteria applied to trial participants. The study utilised real-world data extracted from hospital electronic care records, capturing clinical, biochemical, radiological, and histopathological information. Patients were categorized as eligible, or ineligible based on the inclusion and exclusion criteria for the *SABR-PSC* pilot study.

## 2.3 Introduction

In Chapter 1 challenges around patient recruitment into PSC trials were discussed. It is estimated that up to 85% of all clinical trials fail to meet their target sample size, thereby impeding the studies ability to answer its primary research question with adequate statistical power (378, 379). Recruitment of trial participants with rare diseases, is an even greater challenge at least in part due to the limited patient pool and geographical spread of patients relative to selected trial sites. PSC offers an additional challenge beyond its orphan status, in that it is notoriously heterogenous (114, 380). This heterogeneity is not only seen in PSC's clinical course (i.e., those with cirrhosis awaiting liver transplantation versus those with mild fibrosis but significant symptoms of puritis), but also in its phenotypic heterogeneity (i.e., PSC-IBD versus PSC only, SdPSC versus LdPSC, PSC/AIH overlap versus no PSC/AIH overlap etc). This results in a significant number of patients being ineligible or clinical trial screen failures. Whilst numerous clinical trials are currently underway seeking to evaluate the safety and efficacy of novel pharmacological therapies, there is evidence that poor enrolment is impeding PSC clinical trials. One study exemplifying the difficulties in clinical trial recruitment is a study evaluating curcumin in PSC at a large tertiary care centre in North America (381). Two hundred and fifty-eight patients were screened for eligibility, to enrol fifteen patients. Failure to meet the primary inclusion criteria of a serum ALP ≥ 1.5xULN was the most common reason for participant exclusion (n = 98), supporting the notion that a significant proportion of PSC patients have a normal, near normal, or fluctuating ALP during their disease course. Other screen failures were related to evidence of concomitant liver diseases, uncontrolled IBD, advanced PSC and known or suspected CCA (381).

A comprehensive up-to-date local database using real-world data (RWD) i.e., routinely collected patient data (real-world data refers to information pertaining to a patient's health status and/or health care delivery, that is amassed outside of a clinical trial context) (382), can be exploited to

evaluate the local population characteristics, inform eligibility criteria, anticipate the potential number of ineligible patients, and support recruitment.

The East of England is recognised as having the highest prevalence of PSC-IBD patients in the UK (244). NNUH, based in the East of England, provides care to a large PSC-IBD cohort. Nonetheless, a granular understanding of the local PSC-IBD cohort is lacking, consequently it is unknown how many patients are eligible to take part in local PSC trials, despite NNUH being a prolific PSC trial contributor for several academic and commercial trials. We therefore sought to answer this question as a priority.

The global epidemiology of IBD only has been extensively studied. However, with few exceptions (246), epidemiological studies on IBD associated with PSC remain incomplete or primarily focus on PSC outcomes and prognosis. Data on IBD-specific outcomes including treatment patterns, disease activity, and surgical indications are lacking. Given that more than two-thirds of PSC patients have concomitant IBD and will constitute the majority of all clinical trial participants, a detailed understating of their phenotype, as well as clinical and histological outcomes is essential.

### 2.2.1 Aims & Objectives

The primary aim of this study was to determine the proportion of patients at NNUH who would meet clinical trial eligibility for the *SABR-PSC* pilot study (ISRCTN 15271834). The rationale for this study was to provide a comprehensive overview of the local PSC-IBD cohort as part of a feasibility assessment for *SABR-PSC*, and in direct response to feedback from the NIHR regarding the requirement of a local patient database within which to make trial eligibility estimates. Furthermore, it would facilitate an understanding of the local PSC-IBD population available and eligible for a future phase 2 RCT of brodalumab in the treatment of PSC should the pilot study be successful.

Summary of objectives:

1. To synthesise and characterise PSC-IBD patient demographics (age, gender), prevalence, PSC and IBD phenotypes, medications in use, IBD disease activity, colonoscopy surveillance adherence rates, and disease related outcomes in order to develop a comprehensive and sustainable local database of PSC-IBD patients at NNUH.
2. To pilot the database to assist in the identification and recruitment of eligible patients for the single-arm pilot study of brodalumab in the treatment of PSC study (*SABR-PSC*) (ISRCTN registry No.15271834). In doing so, explore the impact of the *SABR-PSC* pilot study eligibility criteria on the feasibility of successfully recruiting to target at NNUH.

## 2.4 Methods

### Study setting and design

A retrospective review of patients diagnosed with PSC-IBD was conducted between 14th of November 2022 and 2nd of September 2024 at the NNUH. The study protocol was reviewed and approved by the University of East Anglia research ethics committee (ETH2425-0257).

### Data sources

The study was conducted using routinely collected hospital health care data. Clinical data from electronic medical records, hospital prescriptions, radiological and endoscopic databases were interrogated to confirm diagnoses of PSC, IBD and extract information. Five hospital databases were used; (i) ICE, a comprehensive database containing biochemical, histological, endoscopic and radiological patient reports; (ii) EPMA, the primary hospital prescribing system capturing all hospital prescribing practices for both inpatient and outpatient activity; (iii) Electronic document template, capturing all hospital clinic letters and correspondence; (iv) Dimensions, a comprehensive database

containing all inpatient and outpatient endoscopic reports; (v) Synapse, a radiological database containing images and reports for all hospital radiological procedures.

Longitudinal data was obtained from the time of the index PSC diagnosis until censoring, defined as the end of the data collection study period (2nd of September 2024) or death, whichever occurred first. The date of PSC diagnosis was defined as the date of the index MRCP or ERCP for LdPSC, or liver biopsy confirming the diagnosis of SdPSC. The date of IBD diagnosis was defined as the date of the first histological, endoscopic, and/or radiological assessment confirming findings compatible with a diagnosis of IBD. For patients whose primary diagnosis of PSC and/or IBD had been assigned at a referring hospital trust, the diagnosis date was extracted from clinic correspondence. Subsequent in-house imaging, colonoscopy and histology reports were reviewed to corroborate a confirmed diagnosis of PSC-IBD.

**Study population**

Persons aged ≥16 years of age, with a diagnosis of LdPSC or SdPSC conforming to nationally accepted diagnostic criteria (3) (as described in Chapter 1.2.5), under clinical follow-up at NNUH, and receiving a hospital discharge proxy code of PSC (ICD 10 code K83.0) were eligible for inclusion. Provided a confirmed diagnosis of IBD was additionally documented either preceding a diagnosis of PSC or thereafter, and were participating in CRC surveillance. IBD phenotypes were classified as UC, CD, or unclassified as determined by local expertise. Disease location and behaviour were ascribed based on the internationally recognised Montreal classification for UC and CD (180, 188). To avoid diagnostic ambiguity patients with a diagnosis of PSC only, alternative primary liver disease aetiologies including secondary sclerosing cholangitis, PBC, viral hepatitis or an uncertain diagnosis of PSC and/or concomitant IBD were excluded. Patients with a diagnosis of AIH overlap syndrome were eligible

provided this accompanied a primary diagnosis of PSC-IBD. Patients who were deceased before the commencement of the data collection period were also excluded from the study. Ascertainment of PSC-IBD cases had previously been extrapolated by NNUH business intelligence (BI) team as part of a pre-existing PSC-IBD audit and service evaluation.

**Data collection & management**

Clinical characteristic extracted as part of the protocol included: patient demographics (age and sex); PSC and IBD sub-phenotypes and age at diagnosis; alkaline phosphatase at diagnosis or within 12 weeks of diagnosis; presence of PSC/AIH-overlap; surveillance colonoscopy practices; macroscopic and histological evidence of IBD activity at the most recent colonoscopy; dysplasia assessment practices during colonoscopy (i.e., dye spray and/or random ± targeted biopsies); history of colonic dysplasia, colorectal cancer or colectomy; indication for colectomy; evidence of cirrhosis; history of previous liver transplant; PSC and IBD medications used including UDCA, immunomodulators, and biologics.

At the end of data collection all data points were reviewed for plausibility and duplicate records removed prior to analysis. Patients were considered to have cirrhosis based on the following criteria: if corroborated by a radiological and/or histological report, or a reported liver stiffness measurement (LSM) as assessed by transient elastography (FibroScan) of ≥ 14.4 kPa.

All individual level data was extracted into an approved 'master' Microsoft Excel spreadsheet for de-identified downstream analysis on study completion. Only investigators forming part of patient's usual health care team were involved in directly accessing patient records, data collection, and analysis thereby maintaining strict patient confidentiality. On completion of data collection, data was

subsequently anonymised prior to analysis on University of East Anglia (UEA) servers. Informed consent was not sought from patients on the basis that data was anonymised and does not reflect personal information that can be used singularly or in combination with other data to re-identify any one patient. Data was stored in a password protected folder on a secure server at UEA. Incomplete patient datasets were included in the final analysis where it was felt by the Chief Investigator to provide sufficient data from which to draw some conclusions.

Patients were categorised as being eligible or ineligible based on the extracted characteristics collected and assessment against the eligibility criteria from the *SABR-PSC* pilot study (outlined below).

Ethical approval was granted by the University of East Anglia (FMH S-REC reference- ETH2425-0257). The study was conducted in accordance with the Data Protection Act (1998), general data protection regulations (GDPR), Good Clinical Practice (GCP), and Declaration of Helsinki principles.

**Key inclusion and exclusion criteria for *SABR-PSC* pilot study**

The key trial eligibility criteria for the *SABR-PSC* pilot study applied to the inherent PSC-IBD cohort are as outlined below (full eligibility criteria for the *SABR-PSC* pilot study are described in Chapter 4).

<u>Key inclusion criteria:</u>

1. Age ≥18-75
2. 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 both anti-mitochondrial antibodies and causes of secondary cholangitis.

3. An established diagnosis of concomitant colonic inflammatory bowel disease (IBD) with a confirmed diagnosis of quiescent 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.

Key exclusion criteria:

1. 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 non-alcoholic fatty liver disease.
2. 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.
3. Had a total or subtotal colectomy or presence of an ileostomy or colostomy.
4. Has evidence of liver cirrhosis based on liver histology, ultrasound, vibration controlled transient elastography (VCTE) (kPa >14.4) or history of decompensated liver disease e.g., ascites, variceal bleed, hepatic encephalopathy, portal hypertension or hepatic hydrothorax.

## Statistical analysis

Results were summarised as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables according to data distribution. Categorical variables were expressed as frequency and percentage. Statistical analysis was performed using the Chi-squared test (or Fishers exact test where

appropriate) for categorical variables. Continuous variables were analysed using the T-test or Mann-Whitney U test where appropriate. A p-value of <0.05 was considered statistically significant. Cumulative proportions of eligibility and ineligibility for clinical trial enrolment were calculated. Demographic characteristics between eligible and ineligible groups were compared and multiple logistic regression modelling was performed to assess for predictors of eligibility based on cohort demographics. All statistical analyses were conducted using STATA 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

## 2.5 Result

A total of 162 patients were identified. All patient electronic records were reviewed and a total of 20 (12.3%) patients were excluded due to record duplication, incomplete records, death prior to data collection, or inconclusive/doubtful diagnoses of PSC and/or IBD. A total of 142 subjects meeting the inclusion criteria were fully analysed. A flow chart illustrating cohort selection is presented in Figure 2-1. Those identified during data extraction as being lost to follow-up were identified as being alive and deemed to have sufficient clinical information to be included in the study.

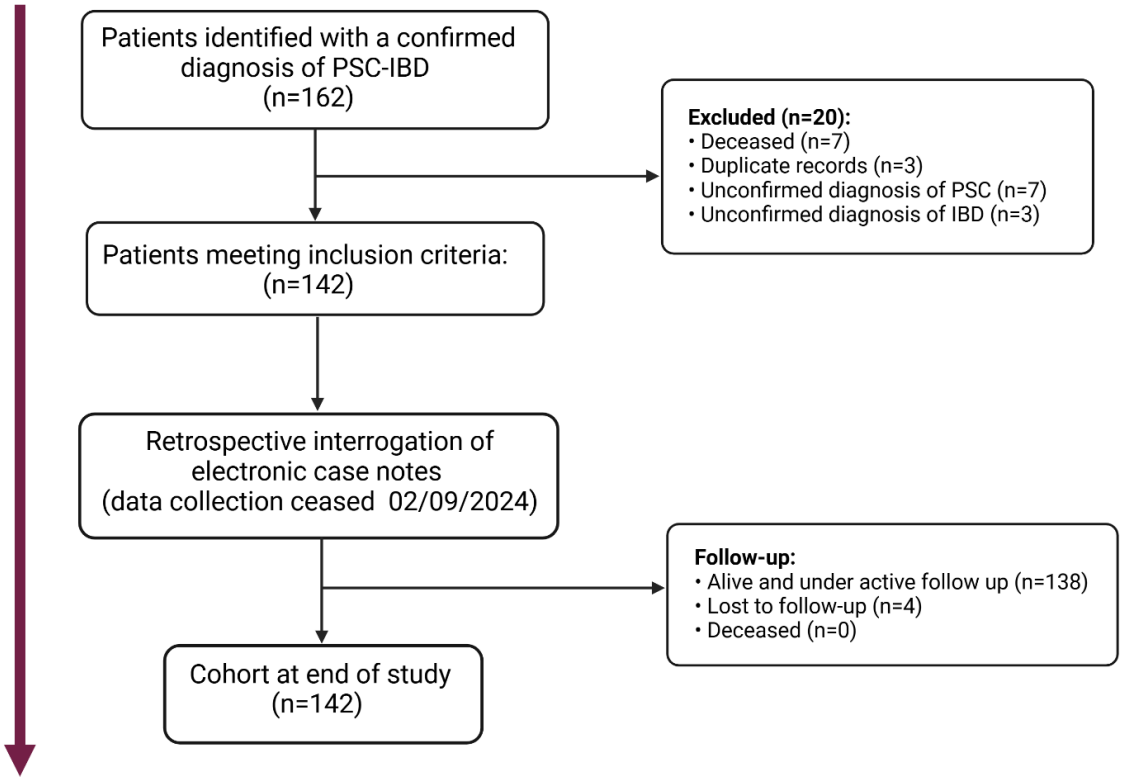



**Figure 2-1** Flow diagram of study cohort identification and exclusion.

**Patient characteristics**

Baseline characteristics for included participants are presented in Table 2-1. The majority of patients were male (69%), with large-duct PSC (81%) and PSC-UC (81%). The mean age at inclusion was 51 years (SD 20.5; range 16-93years) and the mean age at PSC diagnosis was 40.7 years (SD 20.4; range 5-84 ). Twenty-eight patients (19.7%) developed cirrhosis (median follow-up time 9 years, IQR 5-14.5), and 8/142 (5.6%) had PSC/AIH-overlap. The median ALP at diagnosis was 169.5 U/L (IQR 129-327; upper limit of normal = 130 U/L).

The majority of patients were diagnosed with IBD prior to PSC (58.5%), with a smaller proportion diagnosed concurrently (27.5%). Of the evaluable cohort, the majority (61.3%) had quiescent IBD, as confirmed histologically at their most recent annual colonoscopy surveillance.

With respect to treatment, approximately half of all patients were prescribed UDCA, and a comparable proportion (49.3%) received 5-aminosalycilic acid (5ASA). Twenty-one patients (14.8%) were receiving biologic therapy for IBD. At the time of censoring, 138 patients remained under active follow-up, four were lost to follow-up, no deaths occurred during the data collection period (14$^{th}$ of November 2022 and 2$^{nd}$ of September 2024).

**Table 2-1** Baseline characteristics of included cohort

| Characteristic | Patient cohort (n = 142) |
|---|---|
| Age (years), mean (SD) | 51 (20.5) |
| Age at PSC diagnosis, mean (SD) | 40.7 (20.4) |
| Difference in years between PSC and IBD diagnosis, median (IQR) | 3 (0-12) |
| Male, n (%) | 98 (69) |
| PSC Phenotype, n (%): | |
| SdPSC | 25 (17.6) |
| LdPSC | 115 (81.0) |
| Unknown ǂ [1] | 2 (1.4) |
| PSC/AIH-overlap | 8 (5.6) |
| Baseline ALP (U/L) at diagnosis, median (IQR) | 169.5 (129-327) |
| Cirrhotic, n (%) | 28 (19.7) |
| Post liver transplant, n (%) | 21 (14.8) |
| Baseline medications, n (%): | |
| UDCA, n (%) | 74 (52.1) |
| 5-ASA, n (%) | 70 (49.3) |
| Immunomodulator, n (%) | 26 (18.3) |
| Biologic, n (%) | 21 (14.8) |
| IBD phenotype, n (%): | |
| UC | 115 (81.0) |
| CD | 18 (12.7) |
| IBD-U | 8 (5.6) |
| Unknown ǂ [2] | 1 (0.7) |
| Montreal Classification, n (%): | |
| Colonic CD (L2) | 2 (11.1) |
| Ileocolonic CD (L3) | 13 (72.2) |
| Extensive ulcerative colitis/Pancolitis (E3) | 80 (69.6) |
| Active IBD[3], n (%) | 44 (31.0) |
| Colectomy, n (%) | 29 (20.4) |

Abbreviations: ALP, Alkaline phosphatase; 5-ASA, 5-aminosalicyclic acid; AIH, autoimmune hepatitis; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease- unclassified; PSC, primary sclerosing cholangitis; SdPSC, small-duct primary sclerosing cholangitis; LdPSC, large-duct primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

ǂ Frequencies (%) presented for unknown categories reflect the overall proportion of missing data for the relevant covariant.

[1]PSC diagnosis was categorised as unknown if patients had a contraindication to MRCP, declined liver biopsy or were diagnosed at a referring NHS hospital without correspondence specifying PSC phenotype.

[2]IBD-phenotype was categorised as unknown if patients had undergone a colectomy at a referring NHS hospital and no correspondence was available to confirm pre-colectomy phenotype.

[3] Active IBD frequencies (%) also accounted for patients with a prior colectomy who had evidence of pouchitis or disease recurrence in an ileal pouch-anal anastomosis.

**Trial eligibility for SABR-PSC**

On review, only 23 patients (16.2%) met the eligibility criteria for the *SABR-PSC* pilot study. Baseline demographics for both eligible and ineligible groups are presented in Table 2-2. Use of 5-ASA was significantly associated with eligibility status, with eligible patients more likely to be prescribed 5-ASA compared to ineligible patients (74% vs 44%, p=0.01). Eligible patients also had a significantly lower baseline ALP at PSC diagnosis compared to ineligible patients (p=0.02). After adjusting for age at PSC diagnosis, IBD phenotype, UDCA use, 5-ASA use and ALP at diagnosis, lower ALP at diagnosis demonstrated a trend towards significance (adjusted odds ratio [aOR] 0.99, 95% CI 0.98-1.00; p=0.05) (Figure 2-2). No other covariates were significantly associated with eligibility.

**Table 2-2** Baseline characteristics of eligible and ineligible groups

| **Characteristic** | **Eligible (n = 23)** | **Ineligible (n = 119)** | **p value** |
|---|---|---|---|
| Age (years), mean (SD) | 50.7 (18.2) | 51 (21) | 0.94 |
| Age at PSC diagnosis, mean (SD) | 40 (19.4) | 40.8 (20.7) | 0.86 |
| Male, n (%) | 16 (69.6) | 82 (68.9) | 0.95 |
| Large-duct PSC, n (%): | 23 (100) | 92 (77.3) | |
| Baseline ALP (U/L) at diagnosis, median (IQR) | 134 (114-160) | 191 (135-332) | **0.02** |
| Baseline medications, n (%) | | | |
| UDCA, n (%) | 14 (60.9) | 60 (50.4) | 0.17 |
| 5-ASA, n (%) | 17 (73.9) | 53 (44.5) | **0.01** |
| Immunomodulator, n (%) | 6 (26.1) | 20 (16.8) | 0.29 |
| IBD phenotype, n (%): | | | 0.91 |
| UC | 20 (87) | 95 (79.8) | |
| CD | 2 (8.7) | 16 (13.5) | |
| IBD-U | 1 (4.45) | 7 (5.9) | |
| Unknown | 0 | 1 (0.8) | |
| Pancolitis, n (%): | 13 (56.5) | 67 (56.3) | 0.99 |

Abbreviations: ALP, Alkaline phosphatase; 5-ASA, 5-aminosalicyclic acid; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease- unclassified; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

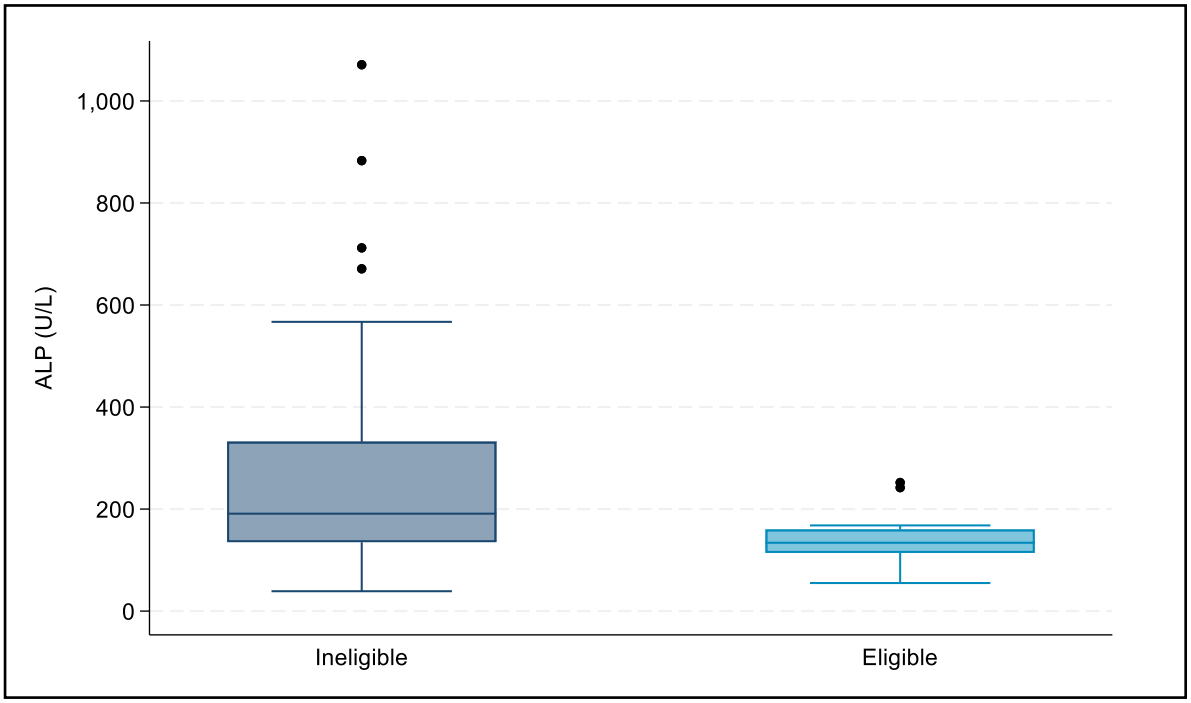



**Figure 2-2.** Box-and-whisker plot illustrating alkaline phosphatase (ALP) values at diagnosis among eligible and ineligible study cohorts. Abbreviation: ALP, alkaline phosphatase.

The most common primary reasons for trial ineligibility included a diagnosis of SdPSC (23/142, 19.3%), post liver transplant (17/142, 14.3%), evidence of active colitis (19/142, 16%), or age outside eligibility criteria (16/142, 13.4%), see Table 2-3. Thirty-five patients (24.6%) met two ineligibility criteria, and five patients (3.5%) met three ineligibility criteria. Where patients met more than one ineligibility criteria, a hierarchy was applied, with the most definitive or immediate reason for exclusion recorded as the primary reason for ineligibility, with additional reasons recorded as secondary.

If the trial eligibility criteria were broadened to include adults ≥16-80 years of age at baseline, an additional four patients would have been eligible. Furthermore, expanding inclusion to patients with histologically quiescent or mildly active IBD at baseline, would have added an additional 23 patients. When both expanded eligibility criteria were applied in combination (age ≥16-80 and quiescent/mild IBD) a total of 50 (35.2%) would have been eligible for the *SABR-PSC* pilot study (Figure 2-3).

**Table 2-3** Classification of reasons for patient ineligibility for *SABR-PSC* pilot study.

| **Main Criteria** | **Ineligible cohort (n = 119)**<br><br>**n (%)** |
|---|---|
| Age<18 years of age or >75 years of age | 16 (13.4) |
| <18 years of age | 2 (1.7) |
| >75 years of age | 14 (11.8) |
| Small-duct PSC (SdPSC) | 23 (19.3) |
| Contraindicated medication | 12 (10.1) |
| Biologic/small molecule inhibitors | 11 (9.2) |
| Methotrexate | 1 (0.8) |
| Cirrhosis, n (%) | 14 (11.8) |
| Post Liver transplant | 17 (14.3) |
| Listed for liver transplant | 1 (0.8) |
| Active colitis | 19 (16) |
| Colectomy | 10 (8.4) |
| AIH Overlap syndrome | 4 (3.4) |
| Other | 3 (2.5) |
| **Total** | **119** |

Abbreviations: AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; SABR-PSC. Single-arm pilot study of brodalumab in the treatment of primary sclerosing cholangitis.

Note: Some patients met more than one ineligibility criteria.

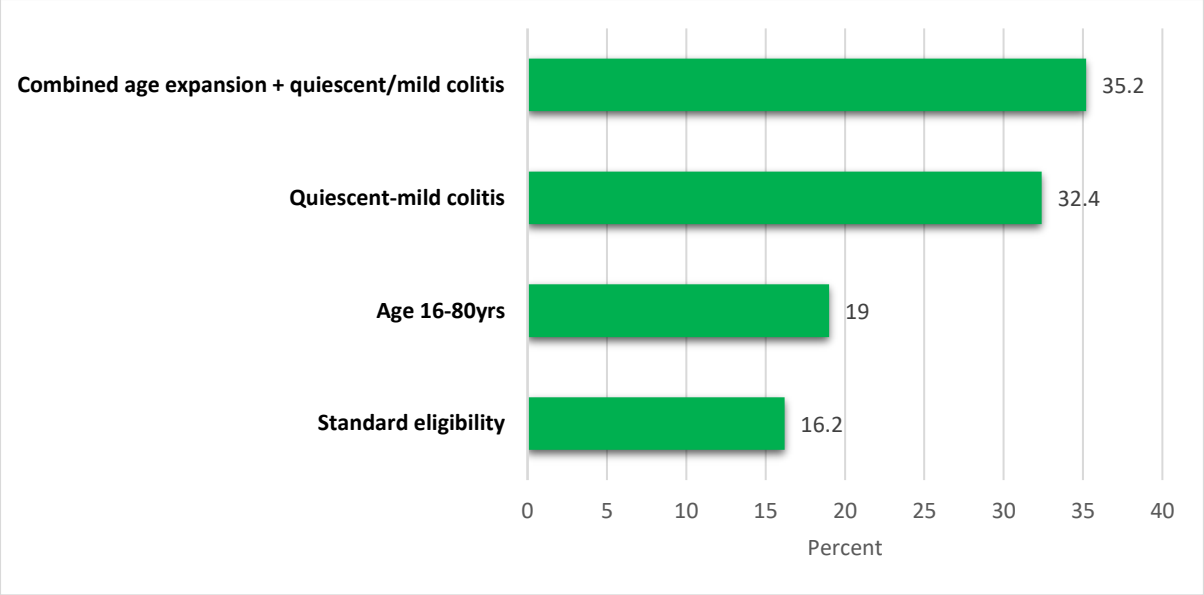



**Figure 2-3** Percentage of the entire cohort eligible for the *SABR-PSC* study under standard eligibility criteria and various expanded eligibility criteria scenarios: (i) aged ≥16-80, (ii) inclusion of patients with quiescent and/or mildly active IBD, and (iii) aged ≥16-80 and/or with quiescent or mild IBD.

## 2.6 Discussion and summary of main findings

There is a notable lack of real-world data evaluating the impact of current PSC clinical trial eligibility criteria on actual enrolment rates. In this study, the demographics of the sampled cohort closely resembled those of reported PSC populations. The majority were male with LdPSC, more than two-thirds having UC, and a proportion having advanced liver disease. Within a tertiary centre in the East of England with a cohort of 142 PSC-IBD patients, we identified a low trial eligibility rate with only twenty-three patients (16.2%) meeting the *SABR-PSC* pilot study eligibility criteria for enrolment. Patients with PSC are a unique cohort, often with a concomitant diagnosis of IBD which carries its own associated extra-hepatic complications and significantly increased risk of intra and extra-hepatic malignancies, which can make recruitment to clinical trials challenging. The findings from this real-world insight into clinical trial eligibility highlights several important points and adds substantially to the literature regarding current PSC eligibility criteria and its impact on trial enrolment.

Our findings highlight, in line with recent evidence, that more than two thirds of PSC-IBD patients have quiescent-mild disease, and excluding this cohort is likely to contribute to exclusion of a large proportion of potential candidates. Whilst active IBD and its associated treatments may contribute to liver biochemistry derangement which may affect outcome measures such as ALP and therefore need to be considered prior to inclusion (145), the extent to which liver biochemical readouts are impacted by mild disease as compared to moderate to severe disease is uncertain. Including patients with quiescent-mild disease in clinical trials would not only improve recruitment but also better reflect the broader PSC-IBD population. The mechanism of action and safety profile of the investigational agent will, of course, influence the suitability of its use in patients with active IBD patients.

Additionally, the arbitrary but widely adopted age cut off of ≥18-75 years for inclusion excludes both younger and older patients without clear justification. Studies looking to target early fibroinflammatory disease may benefit from inclusion of patients aged ≥16, where the study drug may have a greater chance of proving efficacy. However, the increased number of patients with autoimmune sclerosing cholangitis or PSC/AIH-overlap in this younger cohort will have to be carefully considered. Furthermore, with improved healthcare and surveillance the older population is expanding, excluding patients aged >75 without scientific basis or justification warrants further interrogation. The FDA encourages efforts to include older patients in clinical trials where appropriate and discourages arbitrary age exclusions. In our study, simulated relaxation of eligibility criteria more than doubled the original eligibility rate.

A significant proportion (24.6%) met two ineligibility criteria, while 3.5% met three criteria. This suggests that modifying a single criterion may not be sufficient to meaningfully increase enrolment, as many patients have multiple exclusionary factors. However, relaxing overly prescriptive IBD-related eligibility criteria could have the most significant impact on increasing the pool of trial participants,

therefore improving trial recruitment. However patient recruitment targets, generalisability and crucially patient safety all need to be carefully considered.

ALP deserved particular attention. Many PSC clinical trials, employ ALP as an inclusion and outcome criterion. An ALP <1.5X ULN is associated with a milder disease trajectory and improved survival (145, 154, 157). Interestingly, patients with a lower ALP (≤1.5x ULN) at diagnosis were more likely to be eligible for the *SABR-PSC* clinical trial, likely reflecting patients with a less aggressive disease course. *SABR-PSC* intentionally avoided an ALP cut-off. Our findings supports this decision, as incorporating such a cut-off would further reduce recruitment feasibility.

The recruitment challenges identified here mirror those reported in other PSC trials. For example, in the curcumin study only 15 of 258 screened patients were enrolled (381). Uncontrolled IBD, advanced PSC, concomitant liver disease, exclusionary medications and age range were reasons for ineligibility in 27% of patients. These findings reinforce the need for real-world data driven recruitment planning before launching large-scale costly PSC trials.

This study has limitations. Feasibility data was derived from a single NHS hospital site recruiting to *SABR-PSC,* and the retrospective design introduced reliance on diagnostic coding, raising the possibility of missed or misclassified cases. Additionally, diagnoses assigned at referring hospitals could not be independently verified. Nevertheless, this study also has strengths. To our knowledge, this is the first granular real-world feasibility assessment at NNUH, the principle *SABR-PSC* recruiting site. This study provides a clear profile of eligibility and ineligibility and directly informs *SABR-PSC* trial design whilst offering practical considerations for future PSC trial design.

**Conclusion**

In summary, based on the study results it is predicted to be feasible to recruit five PSC patients at the NNUH for the *SABR-PSC* pilot study. Only 16.2% of PSC-IBD patients at NNUH were eligible for *SABR-PSC*, highlighting the challenges of PSC trial recruitment, and recognising the need for trial sample size calculations and planning to consider the potential for high screen-failure rates. The most restrictive yet modifiable trial eligibility criteria related to evidence of active colitis and arbitrary age limits; modifying these parameters more than doubled eligibility. Through adaptive trial design and leveraging patient datasets, collaborative multicentre real-world data can be used to revise and set eligibility criteria, plan patient recruitment numbers, assess pre-trial feasibility, reduce screen failures, identify appropriate PSC rich trial sites, ensure equity of access for marginalised or minority groups and target recruitment efforts, while safeguarding patient safety. Therefore, relinquishing overly restrictive historic eligibility criteria and re-designing PSC clinical trials fit for the future.

# Chapter 3 Safety and efficacy of biologics and small molecule drugs in inflammatory bowel disease patients with concomitant primary sclerosing cholangitis: a systematic review and meta-analysis

## 3.1 Abstract


### Background

Inflammatory bowel disease (IBD) associated with concomitant primary sclerosing cholangitis (PSC) is a distinct phenotype (PSC-IBD). There is a paucity of data characterising the efficacy and safety of advanced therapies on colonic outcomes in PSC-IBD.

### Methods

A systematic review and meta-analysis assessed the safety and efficacy of advanced therapies (biologics and small molecules) in PSC-IBD. MEDLINE, Embase, Cochrane databases, and Web of Science were searched from inception to May 2025. The primary outcome was IBD clinical remission. Secondary outcomes included clinical response, corticosteroid-free remission, endoscopic healing, safety events, and colorectal cancer. A random-effects model was used for pooled estimates. This study protocol was registered with PROSPERO (CRD42024580296).

### Results

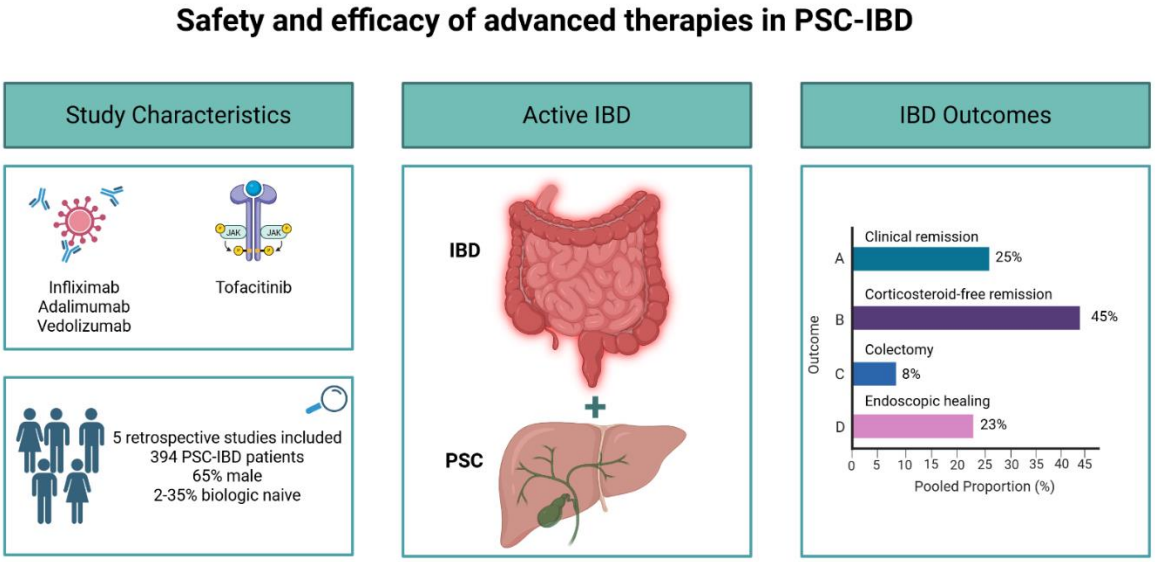
Five studies (394 patients) were included. Overall, pooled clinical remission rates were 24.7% (95% confidence interval [CI] 17.2-33.0%; $I^2$= 0%; p=0.35) at 3 months and 28.6% (95% CI 16.3-42.6; $I^2$ =61.6%; p=0.07) at 6–12 months, with vedolizumab yielding the highest rates. Corticosteroid-free remission occurred in 45.4% (95% CI 33.1-59.1; $I^2$=0%; p=0.38) and endoscopic healing was achieved

in 22.9%.(95% CI 8.0-41.9%; $I^2$=76.1%; p=0.02).Tofacitinib demonstrated a favourable clinical response rate (59.3%, 95% CI 40.0-77.2%) and low adverse event rate. Pooled adverse event-related discontinuation occurred in 9.1%, whilst 31.8% experienced a loss of response. Pooled colorectal neoplasia incidence was 10.5% (95% CI 5.3-17.2%; $I^2$ 0%; p=0.48). Five patients developed colorectal cancer, and two patients developed cholangiocarcinoma during follow-up.

**Conclusion**

IBD advanced therapies are well-tolerated and demonstrate acceptable safety in PSC-IBD colitis, although response rates may be attenuated compared to IBD-only populations. Prospective studies with a control arm and use of standardised IBD outcomes are needed to inform optimal therapeutic strategies.

**Graphical abstract**



## 3.2 Overview of chapter

This chapter provides a comprehensive evaluation of the safety and efficacy of advanced therapies (biologics and small molecule drugs (SMDs)) in patients with inflammatory bowel disease and concomitant primary sclerosing cholangitis, focusing on IBD outcomes and safety profiles. Within the broader context of this thesis, this chapter establishes the current evidence base regarding adverse events (AEs) and safety signals associated with biologic therapies in IBD. These findings directly inform the rationale for the design, safety monitoring and AE reporting frameworks for the *SABR-PSC* trial (described in Chapter 4). Given the increasing use and number of advanced therapies in IBD, data on their performance specifically in PSC-IBD remains limited and poorly characterised. This systematic review and meta-analysis addresses this critical knowledge gap. To the best of our knowledge, this is the first meta-analysis to comprehensively investigate colonic outcomes in PSC-IBD patients treated with biologics and SMDs.

## 3.3 Introduction

In the first chapter of this thesis, previously trialled biologics for PSC were discussed. A small number of additional biologics, principally commenced for active colitis in PSC patients, have been evaluated as part of small retrospective studies (75, 138, 256, 257, 383-385). Several recent systematic reviews and meta-analyses have been conducted summarizing this literature on the efficacy and safety of all biologics evaluated to date on liver outcomes in PSC-IBD patients (147, 386-388). Collectively, the results across these studies have been consistent in that they fail to meaningfully improve liver biochemistry or outcomes in PSC yet appear to be safe with modest efficacy confined to the colonic component of the disease.

Whilst the focus of this thesis centres on the use of a repurposed biologic (brodalumab) in PSC and PSC-IBD patients within the *SABR-PSC* pilot study, where the primary objective was to assess safety outcomes affecting both the liver and colon, the decision to undertake a systematic review and meta-analysis focused on colonic outcomes in PSC-IBD patients was both strategic and complementary. Given several recent publications of high quality meta-analyses evaluating biologics in PSC (147, 386-388), with a particular focus on liver-related efficacy outcomes, conducting a duplicate review would have been redundant. Instead, this review addressed a clear gap in the literature regarding the effectiveness and safety of biologics on colonic outcomes in PSC-IBD, an area previously incompletely reviewed. This approach also aligns with the broader aims of the *SABR-PSC* pilot study, by contextualising the potential impact of brodalumab and other biologics evaluated to date in PSC-IBD, informing expected event rates but also establishing a benchmark against which any emerging *SABR-PSC* trial data, particularly adverse safety signals, serious adverse events (SAEs) or adverse events (AEs) can be evaluated. Particularly given historical concerns surrounding IL-17 mAb use in IBD. Moreover, understanding the incidence of AEs including cholangitis flares, amongst PSC-IBD patients on existing biologics, is critical when developing a safety monitoring plan, interpreting trial data, and discussing any emerging safety signals during trial follow-up with the *SABR-PSC* Trial Safety Committee (TSC) for a drug that has never been trialled in patients with known underlying liver disease. Furthermore, it was important to capture how previous studies of biologics in PSC patients defined and measured IBD outcomes, in order to inform and optimise the design of the *SABR-PSC* trial. Finally, due to the inherent link between PSC and IBD, many patients will receive biologic therapy for their IBD during the course of their disease, as a result, a comprehensive understanding of the efficacy and safety of these therapies is therefore essential to both clinical trial design and clinical practice, informing discussions with PSC-IBD patients about IBD treatment decisions. Looking forward, identifying a therapy that effectively targets both liver and colonic inflammation in PSC, would be of substantial clinical interest.

**Advanced therapies in IBD of relevance to PSC-IBD**

Over the last few decades, advanced therapies have revolutionised the management and outcomes of IBD. The introduction of the first biologic, hybrid anti-tumour necrosis factor α (anti-TNFα) agent infliximab, 26 years ago (389), transformed the therapeutic landscape of IBD, which up until then was limited to corticosteroids, 5-aminosalicylic acid and thiopurines. Subsequently humanised anti-TNFs adalimumab and golimumab were added. Collectively facilitating improved rates of corticosteroid-free remission, mucosal healing, and quality of life (390). Subsequent biologics have targeted other pathogenic pro-inflammatory cytokines including interleukin (IL) 12/23 (ustekinumab) and anti-integrin α4β7 cell migration inhibitor (vedolizumab). More recently drug development has been primed towards small molecules, such as Janus Kinas (JAK) inhibitors (tofacitinib, upadacitinib and filgotinib) and latterly sphingosine-1-phosphate receptor (S1PR) modulator (ozanimod and etrasimod) licensed for moderate to severe UC. Humanised IL-23 subunit p-19 monoclonal antibodies risankizumab (CD), mirikizumab (UC), and guselkumab (UC and CD) are the latest biologics to become licensed for IBD.

**Evaluating IBD outcomes in advanced therapy treated PSC-IBD patients is clinically important**

Whilst effective advanced therapies for active IBD exist and are extensively studied. There is a lack of robust data to establish the safety and clinical efficacy of these agents in the colons of patients with IBD and concomitant PSC. This is of particular importance given PSC-IBD is regarded as immunologically and phenotypically distinct from that of IBD only yet continues to be treated with the same conventional therapeutic agents as those with IBD only. Furthermore, persistent colonic inflammation in PSC-IBD patients, often only evident histologically (268), is associated with an increased risk of dysplasia, CRC and poor peri and post-operative liver transplant outcomes including recurrent PSC and graft loss (64, 255). Therefore, undertreating this patient cohort may have significant clinical consequences.

Of the previous meta-analyses investigating advanced therapy efficacy and safety in PSC-IBD, one review of 411 PSC-IBD patients reported no associated improvement in cholestatic biomarkers of PSC, such as ALP (SMD: 0.05, 95% CI: −0.07 to 0.17; p=0.43), whilst appearing effective in inducing a clinical or endoscopic IBD response (147). Despite recent publications and systematic reviews, gaps still exist. Notably, the review by Shah et al. included papers only up to 2020, incorporating three biologics only- infliximab, adalimumab and vedolizumab (147). IBD outcomes following tofacitinib therapy has been explored in a retrospective case series of PSC-IBD patients, not included in the aforementioned systematic review (383). Available data on colon specific outcomes of advanced therapies in PSC-IBD is derived from a small number of retrospective studies with small sample sizes. Pooling this data in a meta-analysis has the advantage of improving the precision of individual intervention effects. We herein conducted a contemporaneous systematic review and meta-analysis to determine the safety and efficacy of biologics and small molecules on colonic outcomes in PSC-IBD.

## 3.4 Methods

**Search strategy and selection criteria**

This systematic literature review and meta-analysis protocol was prospectively registered with PROSPERO (CRD42024580296) and was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (391).

Electronic databases MEDLINE, Embase, Cochrane Central Register library and Web of Science were searched for inception to May 2025 (full search strategy is detailed below) for studies assessing the efficacy and/or safety of biologics and SMDs in PSC-IBD.

Search terms included the following; ["primary sclerosing cholangitis" OR PSC OR "sclerosing cholangitis"] AND [Biologic* OR "biologic* treatment" OR TNF OR “TNF alpha” OR "Anti TNF" OR "anti-tumour necrosis factor" OR "TNF inhibitor" OR "tumour necrosis factor inhibitor" OR "monoclonal antibod*” OR “immune modul*” OR Vedolizumab OR infliximab OR adalimumab OR “vidofludimus calcium” OR etanercept OR Humira OR “TNF blocker” OR golimumab OR ustekinumab OR “JAK inhibitor” OR Filgotinib OR upadacitinib OR tofacitinib OR “biological products” OR ozanimod OR certrolizumab] (Box 3-1). Included articles were restricted to the English language. Bibliographies of all retrieved articles (including those of relevant systematic reviews and meta-analyses) were reviewed recursively to ensure literature saturation. Authors were contacted for any unpublished data where the study appeared eligible.

1. "Primary sclerosing cholangitis" [ti]

2. PSC [ti]

3. "sclerosing cholangitis" [ti]

4. #1 OR #2 OR #3

5. Biologic* OR "biologic* treatment" OR TNF OR “TNF alpha” OR "Anti TNF" OR "anti-tumour necrosis factor" OR "TNF inhibitor" OR "tumour necrosis factor inhibitor" OR "monoclonal antibod*” OR “immune modul*” OR Vedolizumab OR infliximab OR adalimumab OR “vidofludimus calcium” OR etanercept or Humira OR “TNF blocker” OR golimumab OR ustekinumab OR “JAK inhibitor” OR Filgotinib OR upadacitinib OR tofacitinib OR “biological products” OR certolizumab OR ozanimod

6. #4 AND #5

**Box 3-1.** Detailed search strategy for MEDLINE.

**Eligibility criteria**

Articles were included if they reported original data from randomised controlled trials (RCTs), pilot studies, cohort studies and case series (with a minimum of ≥ 5 patients) and published as full text in peer reviewed journals in the English language and reported on at least one IBD outcome. Studies meeting the following eligibility criteria were included (Table 3-1): (i) adults (aged ≥ 16 years) with a confirmed diagnosis of PSC-IBD irrespective of previous biologic exposure; (ii) studies either evaluating the following biologics or SMDs: infliximab, adalimumab, golimumab, certolizumab, etanercept, ustekinumab, vedolizumab, vidofludimus calcium, tofacitinib, upadacitinib, filgotinib, or ozanimod; (iii) studies including an active comparator or placebo where RCTs exist. Studies were excluded if they: (i) only included liver transplant recipients; (ii) included patients with IBD only (without PSC); (iii) assessed biologic use in autoimmune sclerosing cholangitis patients; and/or (iv) lacked extractable IBD outcomes.

Two reviewers (AE and EH) independently screened titles and abstracts of all identified articles. After excluding ineligible studies, full text articles were retrieved and assessed for inclusion based on pre-defined criteria. Disagreements between reviewers were resolved by discussion with a third author (SMR). Three authors (AE, AK, AM) independently extracted data from selected studies. Data from eligible studies was extracted into a pre-specified data extraction Microsoft Excel spreadsheet. Results were cross-checked with disagreements or discrepancies resolved by consensus.

**Data extraction and quality assessment**

For each eligible study the following summary data was extracted from full texts: author (last name); year of publication; study design; country of origin; total number of patients; proportion of male patients. We also extracted the following data for each study where available: median age of

participants at enrolment; PSC disease characteristics (large-duct vs small-duct disease); IBD disease characteristics (ulcerative colitis, Crohn's disease or unclassified); median age at PSC diagnosis; median age at IBD diagnosis; cirrhosis at baseline; length of follow-up; intervention characteristics (dose, drug, and duration of biologics); concomitant medications, proportion of patients reported as biologic naïve; and IBD outcomes.

Three authors (AE, AK and AM) independently assessed risk of bias using the Joanna Briggs Institute (JBI) critical appraisal tool for case series (10 items) (392), with disagreements resolved by consensus. The JBI critical appraisal tool assessed bias in the following domains: selection of participants (3 items); measurement of outcomes (2 items); selection of reported results (2 items); missing data (1 item), study demographic reporting (1 item), and appropriate statistical analysis (1 item) (392). Risk of bias for each study was evaluated as being low ('yes' scores ≥7/10), medium ('yes' scores ≥5-<7) or high ('yes' scores 0-4) risk of bias.

**Outcomes**

The primary efficacy outcome analysed was the proportion of patients achieving clinical remission. Secondary outcomes included the proportion of patients achieving clinical response; corticosteroid-free remission; endoscopic healing/mucosal healing/endoscopic remission; endoscopic response; histological remission. Changes in disease specific activity indices were assessed from baseline to treatment completion or to last follow-up, using recognised scoring systems such as the Crohn's disease activity index (CDAI), Harvey Bradshaw index (HBI), partial Mayo score (pMayo), total Mayo score or Mayo endoscopic score (MES) where reported. Additionally, changes in faecal calprotectin from baseline, loss of response (primary or secondary) to biologic or SMDs, colectomy and colorectal

cancer rates were also assessed. Primary safety outcomes included adverse events and serious adverse events were reported.

Due to heterogeneity in study definitions and outcome measures of remission and/or response, we extracted and reported definitions as provided in each study. Where studies aligned their outcome definitions in accordance with the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDEII) initiative (393) (Table 3-2), they were noted as such. For studies that did not specify alignment with STRIDE II, outcomes were analysed and interpreted based on the authors own definition.

**Statistical analysis**

Pooled proportions were transformed to stabilize their variances using the Freeman-Tukey double arcsine transformation. Random-effects (restricted maximum likelihood [REML]) models to pool effect sizes and their 95% confidence interval were calculated to give more conservative estimates of effect estimates. Heterogeneity was assessed with the inconsistency index ($I^2$) statistic. Values of < 25%, 25 to <50%, 50 to <75% and ≥ 75% indicated low, moderate, substantial, and considerable heterogeneity, respectively (394). A value of $p<0.05$ was considered statistically significant. Analysis was conducted using the Stata statistical package (StataCorp. 2023. Stata 18. Statistical software. StataCorp LLC).

**Table 3-1.** Inclusion criteria for systematic literature review.

| Item | Inclusion |
|---|---|
| **Population** | • Adult (aged ≥16 years) with a confirmed diagnosis of IBD and associated concomitant PSC. |
| **Intervention** | • Evaluation of the following approved advanced therapies at any doses in bio-naïve or exposed patients:<br>  • Adalimumab<br>  • Infliximab<br>  • Golimumab<br>  • Etanercept<br>  • Certolizumab<br>  • Ustekinumab<br>  • Vedolizumab<br>  • Tofacitinib<br>  • Upadacitinib<br>  • Filgotinib<br>  • Ozanimod |
| **Outcomes of interest** | • Primary efficacy outcome: clinical remission; primary safety outcomes: AEs and SAEs; Secondary efficacy outcomes: clinical response, corticosteroid-free remission, endoscopic response, endoscopic remission/mucosal healing, histological remission/deep remission, changes in pMayo or CDAI score, changes in faecal calprotectin, loss of primary or secondary response, colectomy or colorectal cancer rates |
| **Study design** | • RCT, pilot studies, cohort studies and case series- published in peer review journals in the English language |

Abbreviations: AEs, adverse events; CDAI, Crohn's disease activity index; IBD, inflammatory bowel disease; pMayo, partial Mayo; PSC, primary sclerosing cholangitis; RCT, randomised controlled trial; SAE, serious adverse event; SMD, small molecule drug.

**Table 3-2.** International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) recommendations for treating to target in ulcerative colitis (393).

| Element | Recommendation | Treatment target |
|---|---|---|
| ***Clinical response*** | Decrease of at least 50% in patient reported outcome (rectal bleeding and stool frequency) | Immediate |
| ***Clinical remission*** | Patient reported outcome (rectal bleeding=0 and stool frequency=0) or partial Mayo (<3 and no score >1) | Medium-term |
| ***Endoscopic healing*** | Mayo endoscopic subscore = 0 points, or UCEIS ≤1 points | Long-term |
| ***Histological remission*** | Not currently a treatment target in UC (or CD) but may be used in conjunction with endoscopic assessment of remission to indicate deep healing | |
| ***Biomarkers*** | Normalisation of faecal calprotectin to 100-250µg/g | Intermediate |

Abbreviations: UCEIS, ulcerative colitis endoscopic index of severity.

## 3.5. Results

### Search and selection of studies

The initial search strategy identified 667 studies. After eliminating duplicates, 425 studies proceeded to title/abstract review. After the review process a total of 12 full-text articles were reviewed. Seven articles were excluded due to non-relevance of study characteristics. The study characteristics and patient demographics are detailed in Table 3-3 and 3-4 respectively. Details of the study selection process are outlined in the PRISMA flow diagram (Figure 3-1). The search yielded no eligible clinical trials, with all studies meeting inclusion criteria being case series.

**Characteristics of included studies**

Five retrospective studies, with 394 PSC-IBD patients fulfilling the eligibility criteria were included for qualitative and quantitative synthesis. 65.2% of patients were male. Patient characteristics were generally comparable across studies except for an almost equal proportion of UC and CD patients seen in one study (257). Four of the five included studies reported on biologic naivety (75, 76, 257, 383). When pooling across studies, 20% (51/253) were biologic-naïve. At the study level, the median proportion was 15% (IQR 6-28%; range 2-35%).

The retrieved articles evaluated vedolizumab (n = 211) (75, 76, 257), adalimumab (n = 31) (384), infliximab (n = 110) (384), and tofacitinib (n = 42) (383). No articles met eligibility criteria for the additional IBD advanced therapies listed in Table 3-1.

Included studies were published between 2018 and 2023. All studies (75, 76, 257, 383, 384) were multicentre collaborations across North America, Europe, and/or Australia, reflecting PSC representative populations. One study contributed patient cohorts from the Middle East (383). Table 3-3 and 3-4 present an overview of the study characteristics and baseline patient demographics respectively for included studies.

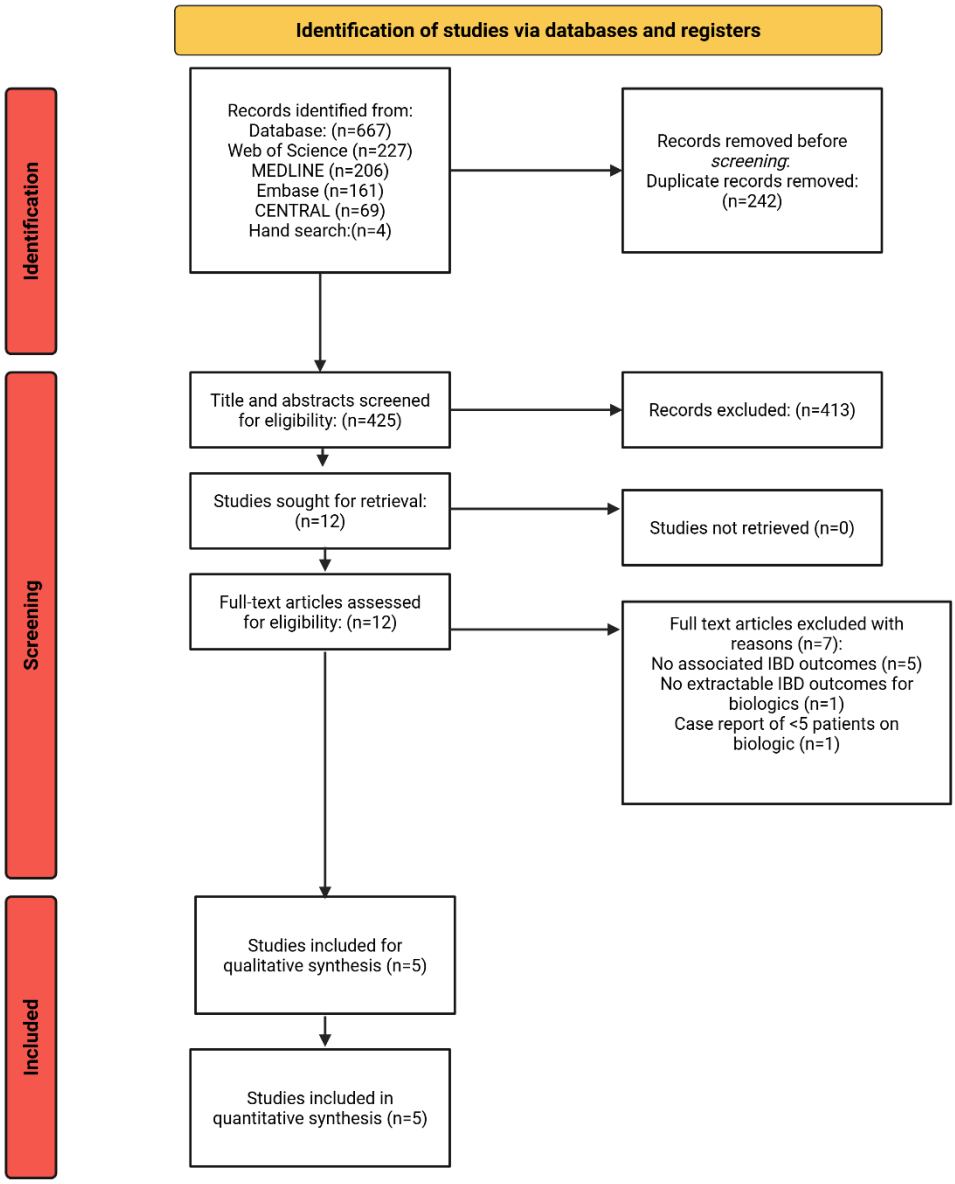



**Figure 3-1**. Study selection PRISMA flow diagram.

**Outcome definitions**

There was significant variation across studies in definitions and reporting of clinical, endoscopic, and/or histological effectiveness, with few adhering to accepted published definitions for IBD outcomes (Table 3-2). The following differences in IBD outcome definitions across studies were observed:

**IBD response**

Response to treatment was defined by Hedin et al. (384) and Schregel et al. (383) arbitrarily as either evidence of endoscopic response, or where endoscopic data was unavailable, by clinician assessment (384) or using disease activity markers, such as faecal calprotectin (383, 384). In contrast, Schregel et al. (383), presented response as a change of at least one point (improvement or deterioration) in full Mayo score.

**Clinical remission**

Hedin et al. (384), defined remission as mucosal healing, utilising the MES in addition to histological assessment. However, in the absence of endoscopic assessment a physician's assessment of clinical remission was accepted. Both Caron et al (76) and Christensen et al. (257) used a HBI of ≤4 to define clinical remission in CD, the pMayo score was instituted for UC and the Simple Clinical Colitis Activity Index (SCCAI) was used in the study by Caron et al. (76) and Christensen et al. (257) respectively. Remission was not explicitly defined by the study, however, from the context provided by Schregel et al. (383), it appeared to correspond to a Mayo score ≤1.

**Endoscopic response**

Endoscopic response was defined as >50% reduction in Simple Endoscopic Score-Crohn's Disease (SES-CD) for CD or an absolute reduction by ≥1 point in MES for UC by Christensen et al. (257). Schregel et al. (383), defined response as a change of at least one point (improvement or deterioration) in MES. Whilst Lynch et al. (75), described endoscopic response as an improvement, worsening or stabilisation of appearances as judged by the treating clinician using endoscopic scores (MES, UCEIS or SES-CD) where available.

**Mucosal healing**

Mucosal healing was defined as a MES of ≤1 for UC and a SES-CD <3 for CD by Christensen et al. (257). Caron at al. (76), defined healing as an absence of ulcers for CD, or a MES ≤1 for UC.

Where authors combined clinical and endoscopic parameters (depending on availability) to define a single outcome e.g., 'response' the results were analysed in the meta-analysis contributing to both clinical and endoscopic outcomes. Where authors defined an IBD outcome outside of accepted STRIDE II consensus recommendations, the outcome was recorded and analysed as per the authors definition, where available. The outcome contributions of included studies are outlined in Table 3-3. Where timepoints for outcomes were reported heterogeneously across studies, we attempted to standardise timepoints to 3, 6 or 12 months where a mean or median assessment timepoint was reported.

**Study quality and risk of bias assessment**

A risk of bias assessment indicated a low risk of bias assessment for four included studies (75, 76, 257, 384) and a moderate risk of bias in one study (383). Details regarding the individual risk of bias

assessments are summarised in Table 3-5. Due to the small number of studies (n = ≤10) it was not possible to examine small study effects.

**Table 3-3.** Summary characteristics of included studies

| Author | Year | Study Design | Country | Single/multicentre | Intervention | No. of PSC-IBD patients | Mean follow-up duration | Primary outcome(s) | Secondary outcome(s) | Effectiveness on ALP | IBD outcome definitions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Schregel et al.(383)** | 2023 | Retrospective case series | Europe, North America & Middle East | Multicentre | Tofacitinib Dose:20mg OD induction;10mg OD maintenance | 42 | 12 months | ALP & bilirubin analysed as surrogate biomarkers of PSC | New diagnoses of cirrhosis, varices or variceal bleeding, bacterial cholangitis, new hepatobiliary neoplasia and need for endoscopic procedures. IBD outcomes; Mayo Endoscopic Score, and faecal calprotectin if available. Full Mayo Score/Disease Activity Index and response to treatment. | Estimated marginal mean ALP difference of -68U/L (95%CI -132 to -4) for those who continued tofacitinib therapy. | Response to treatment defined as either improvement, unchanged or worsening (by at ≥1 point change for improvement or deterioration) in MES ± faecal calprotectin, full Mayo score/disease activity index. Remission denoted as Mayo score ≤1. |
| **Hedin et al.(384)** | 2020 | Retrospective case series | Europe & North America | Multicentre | Infliximab (n=110) & Adalimumab (n=31) | 141 UC:84 CD:52 IBD-U:5 | 12 months | ALP | PSC related outcomes: new onset jaundice, dominant stricture, development of portal hypertension, liver failure, increased puritis, recurrent cholangitis, worsening abdominal pain. IBD outcomes: IBD activity, IBD endoscopic response and remission, clinical response, and faecal calprotectin levels. | A small but significant reduction in ALP noted with ADA (-15%, IQR -29% to -4%) but not IFX (-4%, IQR -24% to 19%; p=0.035) at 3 months. | IBD response defined as endoscopic response or, if no endoscopic data were available, clinical response, as established by the treating clinician or measurements of faecal calprotectin (decrease of ≤30% from baseline or vale <250µg/g). Remission was defined more rigorously as endoscopic mucosal healing, or where endoscopic data was unavailable as clinical remission according to |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | the physical assessment. |
| **Christensen et al.(257)** | 2018 | Retrospective case series | Australia & North America | Multicentre | Vedolizumab | 34<br>UC:18<br>CD:16 | 9 months (7-16)* | Decrease in ALP at weeks 14 & 30 | Changes in total bilirubin, Mayo PSC risk score, ALT, and AST at week 14 and 30 from baseline, including adverse events. IBD Outcomes: HBI for CD and SCCAI for UC. Clinical remission and corticosteroid free remission at week 14 and 30 for those with active disease at baseline. Endoscopic response and mucosal healing (where baseline and follow-up colonoscopy is available after at least 3 months of treatment) using SES-CD for CD or Mayo Endoscopic sub-score for UC patients. Histological improvement and remission also measured. | No change in ALP (249 IU/L, IQR 183-634; p=0.99), other liver biochemical readouts or Mayo PSC risk score at week 30 | Clinical remission defined as HBI≤4 or SCCAI ≤2 for CD and UC respectively. Corticosteroid free remission defined as per clinical remission without concomitant corticosteroid therapy. Endoscopic improvement/response and mucosal healing, defined as >50% reduction in SES-CD and SES-CD <3 respectively for CD or an absolute reduction by ≥1 point in MES and MES 0-1 respectively for UC. Histological improvement defined as an absolute reduction in score of 1 point and histological remission as a score of 0. Biopsies were graded on a 4-point scale from 0= quiescent to 3= severe. |
| **Caron et al.(76)** | 2019 | Retrospective case series | Europe | Multicentre | Vedolizumab<br>Dose:300mg IV at weeks 0.2.6 then 8 weekly | 75<br>UC:49<br>CD:26 | 19.4 months (14.0-29.9)* | Reduction in serum ALP concentration of at least 50% from baseline to week 30 or 54. | Changes in total bilirubin, ALT, AST, GGT, CRP and serum albumin concentration were evaluated at week 30 and 54 compared with week 0. Serum ALP < 1.5xULN. Clinical remission of IBD. | Only 4/54 (7%) and 4/37 (11%) met the primary end point at weeks 30 and 54 respectively. No significant change was observed in liver | Clinical remission of IBD was defined as HBI of ≤4 for CD, and a pMayo score of <3 with a combined subscore for stool frequency and rectal bleeding score of ≤1 for UC. Absence of ulcers endoscopically was used to denote |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | All adverse events collated. | enzymes at either time point. | mucosal healing for CD and a Mayo endoscopic subscore of ≤1. |
| **Lynch et al.(75)** | 2020 | Retrospective<br><br>case series | Europe & North America | Multicentre | Vedolizumab<br><br>Dose:300mg IV at weeks 0.2.6 then 8 weekly | 102<br><br>UC:66<br><br>CD:30<br><br>IBD-U:6 | 561 days (325-790)* | Changes in liver biochemistry (ALP, AST, ALT, bilirubin), proportions of patients with reduction in serum ALP of ≥20% from baseline through to last follow-up | IBD response to treatment and endoscopic score using MES, UCEIS or SESCD. Association between change in ALP and endoscopic IBD response. Liver related outcomes including CCA, liver transplant, decompensating events and death | Median ALP and other liver biochemical readouts increased from baseline to last follow-up (1.5xULN to 1.64xULN, p=0.018). 21/102 (20.6%) were observed to have a reduction in ALP of ≥20% at last follow-up and a further 42/102 (41.2%) had a rise in ALP of ≥20%. | IBD endoscopic response to treatment (improved, worsened/unchanged) as judged by treating clinician. |

Abbreviations: ADA, adalimumab; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; CRP, C-reactive protein; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; GGT, gamma glutamyl-transferase; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; N/A, not applicable; OD, once daily; PSC, primary sclerosing cholangitis; SCCAI, Simple Clinical Colitis Activity Index; pMayo, partial Mayo score; MES, Mayo Endoscopic Score; SES-CD, Simple endoscopic score- Crohn's Disease; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity; ULN, upper limit of normal.

*Reported median (IQR)

**Table 3-4.** Patient characteristics in included studies.

| Author | Age at enrolment, median (IQR) | Sex male, n (%) | Age at PSC diagnosis, median (IQR) | Age at IBD diagnosis, median (IQR) | Median duration of IBD (IQR) | Large-duct, n | Small-duct, n | Overlap syndrome, n | Cirrhotic at baseline, n | Biologic-naïve, n (%) | Median duration of treatment, (IQR) | Concomitant medications (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Schregel et al** | NR | 29 (69%) | 28 (24.25) | NR | NR | 42 | 0 | NR | 9 | 1 (2%) | 13.1 months (16.7) | UDCA 63% |
| **Hedin et al.** | NR | 89 (63%) | 27 (20-38) | 20 (15-30) | NR | NR | NR | NR | 18<br>ADA=16<br>IFX=2 | NR | 457 days (251-1244) | UDCA 59 (42%)<br>Mesalamine 71 (50%)<br>Immunosuppressant 63 (45%), cortisone 73 (52%) |
| **Christensen et al.** | CD: 34 (28.5-38)<br>UC:37 (23-64) | 24 (71%) | UC: 22 (20-43)<br>CD: 24 (20-29) | UC:22 (18-39)<br>CD: 19.5 (17-24) | UC: 10 (3-15)<br>CD: 10.5 (7.5-18.5) | 20 | NR | NR | 2 | 7 (20.6%) | 30 weeks | UDCA 7<br>Tacrolimus 9<br>Immunomodulator 13<br>Glucocorticoids 12<br>Antibiotics 2 |
| **Caron et al.** | NR | 51 (68%) | 26 (18.3-38.4) | 20.9 (16.6-34.2) | 6.2 (3.7-14.5) | NR | NR | NR | NR | 7 (9%) | 54 weeks | UDCA 45<br>Immunosuppressants 18<br>Glucocorticoids 25 |
| **Lynch et al.** | NR | 64 (62.8%) | 31.4 (14.2)* | 26 (12.3)* | NR | 92 | 8 | 2 | 21 | 36 (35.3%) | 412 days (180-651) | UDCA 61 (59.8%) |

Abbreviations: ADA, adalimumab; CD, Crohn's disease; IFX, infliximab; NR, not reported; UC, ulcerative colitis; UDCA, Ursodeoxycholic acid.

*Reported as means (SD)

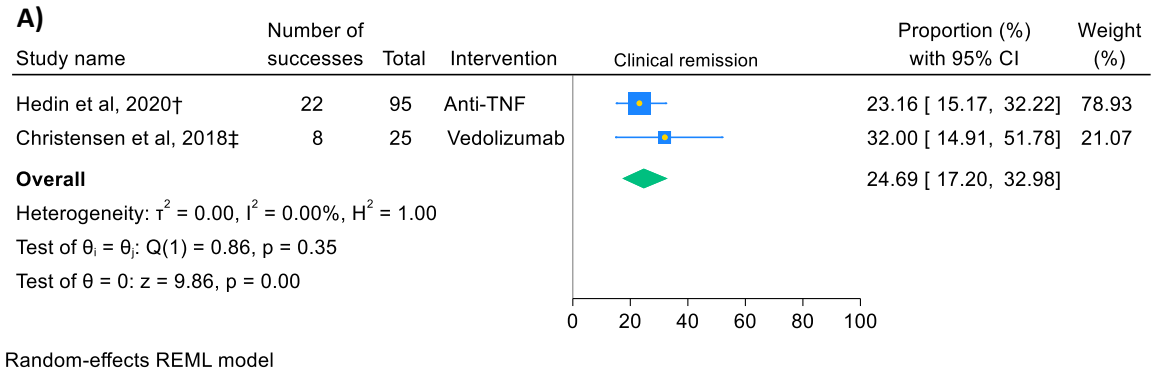
**Table 3-5.** JBI critical appraisal checklist for case series**.**

| Author | 1.Were there clear criteria for inclusion in the case series? | 2.Was the condition measured in a standard, reliable way for all participants included in the case series? | 3.Were valid methods used for identification of the condition for all participants included in the case series? | 4.Did the case series have consecutive inclusion of participants? | 5.Did the case series have complete inclusion of participants? | 6.Was there clear reporting of the demographics of the participants in the study? | 7.Was there clear reporting of clinical information of the participants? | 8.Were the outcomes or follow-up results of cases clearly reported? | 9.Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 10.Was statistical analysis appropriate? | Risk of bias? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Schregel et al.(383) | Yes | Yes | Yes | Unclear | Unclear | No | Yes | No | No | Yes | Medium |
| Hedin at al.(384) | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Christensen et al.(257) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Caron et al.(76) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Low |
| Lynch et al.(75) | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Low |

**Primary outcome**

**Clinical remission**

Two studies (257, 384) contributed to pooled rates at 3 months. Pooled remission rates were 24.7% (95% CI 17.2-33.0; $I^2$=0%, p=0.35) at 3 months (Figure 3-2A). Three studies reported on clinical remission between 6-12 months (257, 383, 384). Amongst these studies, pooled remission rates were 28.6% (95% CI 16.3-42.6; $I^2$=61.6%, p=0.07) (Figure 3-2B). Vedolizumab consistently achieved higher remission rates (3 months: 32%, 95% CI 14.9-51.6; 6-12 months 40%, 95% CI 21.5-60.0%).



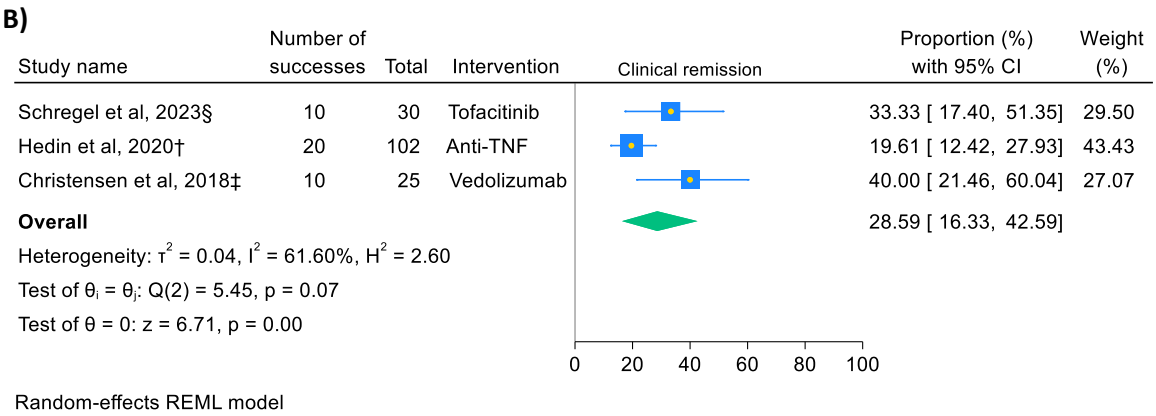




**Figure 3-2.** Forest plot of pooled rates of clinical remission for different biologics/small molecule drugs at: (A). 3 months post biologic, (B). 6-12 months post biologic. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood. Definitions of clinical remission: †defined as endoscopic mucosal healing, or where endoscopic data is unavailable as clinical remission according to the physical assessment; ‡defined as HBI≤4 or SCCAI ≤2 for CD and UC respectively; §Mayo score ≤1.

**Secondary outcomes**

**Clinical response**

IBD clinical response was reported in two studies (383, 384). The pooled clinical response rate was 46.6% (95% CI 26.4-67.5; $I^2$=75.1; p=0.04). Response rates were higher with tofacitinib (59.3%, 95% CI 40.0-77.2) than anti-TNF therapy (37.6% , 95% CI 28.7-49.9).

One study (76) reported significant improvement in disease activity indices with vedolizumab at week 30 (pMayo -2.0 ± 2.6, p<0.001 and HBI index -3.1 ± 6.0, p=0.03). This response was sustained through to week 54, with a further decrease in pMayo (-2.9 ± 3.0, p<0.001) and HBI (-4.2 ± 6.5, p=0.04) compared to baseline.

**Corticosteroid free remission**

Two studies (76, 257) reported data on corticosteroid (CS) free remission rates with vedolizumab therapy at week 30, yielding a pooled estimate of 45.4% (95% CI 33.1-57.9; $I^2$=0%; p0=0.38) (Figure 3-3).

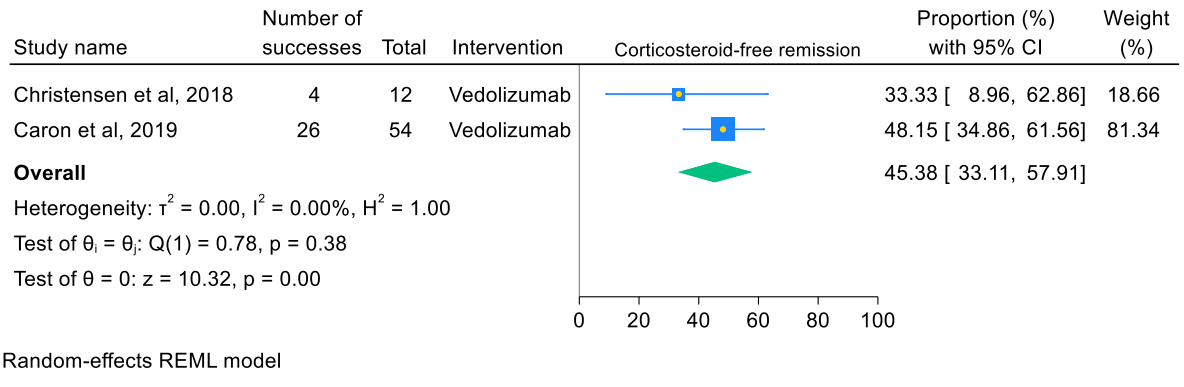



**Figure 3-3.** Forest plot of included studies demonstrating proportion of PSC-IBD patients receiving vedolizumab achieving corticosteroid-free remission by week 30. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

**Endoscopic response**

Three studies reported outcomes on endoscopic response (75, 257, 384), two studies reported on mean changes in MES (75, 383). Pooled endoscopic response was 49.9% (95% CI 41.0-58.9; $I^2$ =24.8; p=0.19), with similar rates observed between anti-TNF (48.0%, 95% CI 38.5-57.7) and vedolizumab therapy (47.1%, 95% CI 23.6-71.3) (Figure 3-4). Variations in clinical practise with regards to the timepoints of endoscopic assessment post-initiation of biologic therapy was observed between studies.

Pooled MES improvement was 0.59 points (95% CI 0.25-0.92; $I^2$=55.7; p=0.13). Both vedolizumab and tofacitinib showed a significant reduction in mean MES post therapy, with the mean improvement in MES post vedolizumab (0.8 points, 95% CI 0.41-1.19) therapy being greater than that observed with tofacitinib (0.45 points, 95% CI 0.22-0.68).

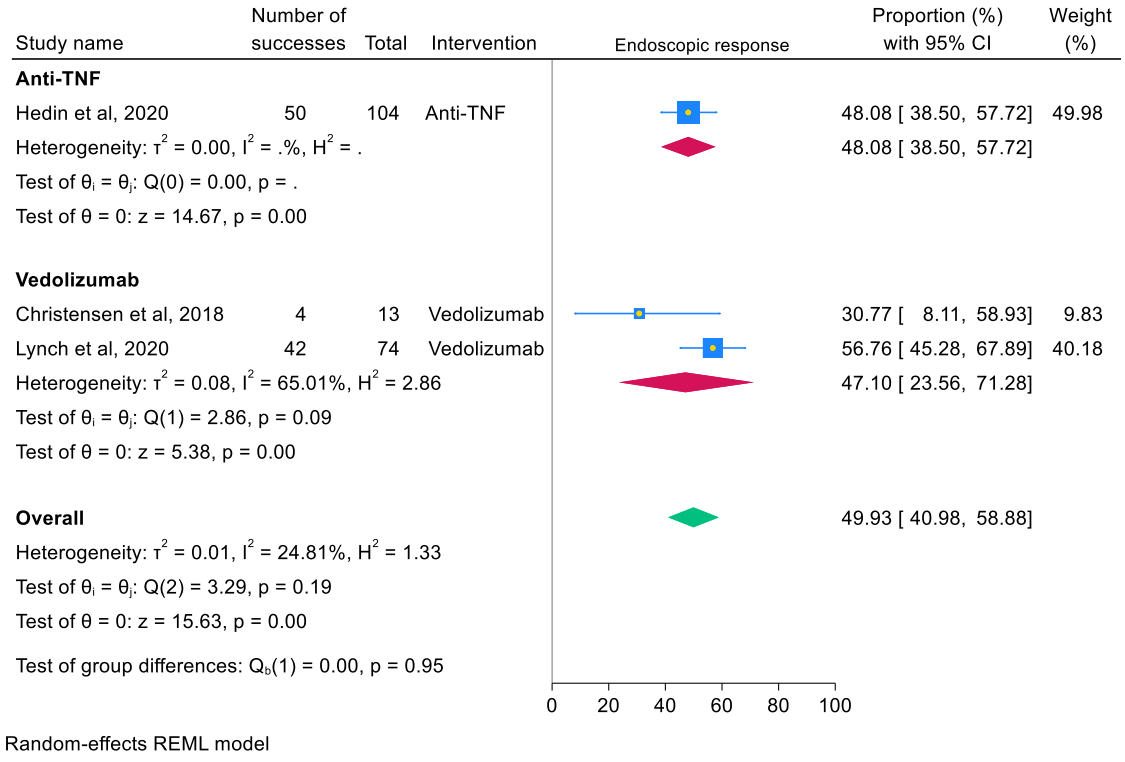



**Figure 3-4.** Forest plot of endoscopic response between 3-7.4 months (biologic exposed and naïve patients included). Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

### Endoscopic healing

Endoscopic healing (EH) (endoscopic remission/mucosal healing) rates were reported in three studies (76, 257, 384). The overall pooled EH rates were 22.9% (95% CI 8.0-41.9) (Figure 3-5). However, considerable heterogeneity was observed ($I^2$=76.05, p=0.02).

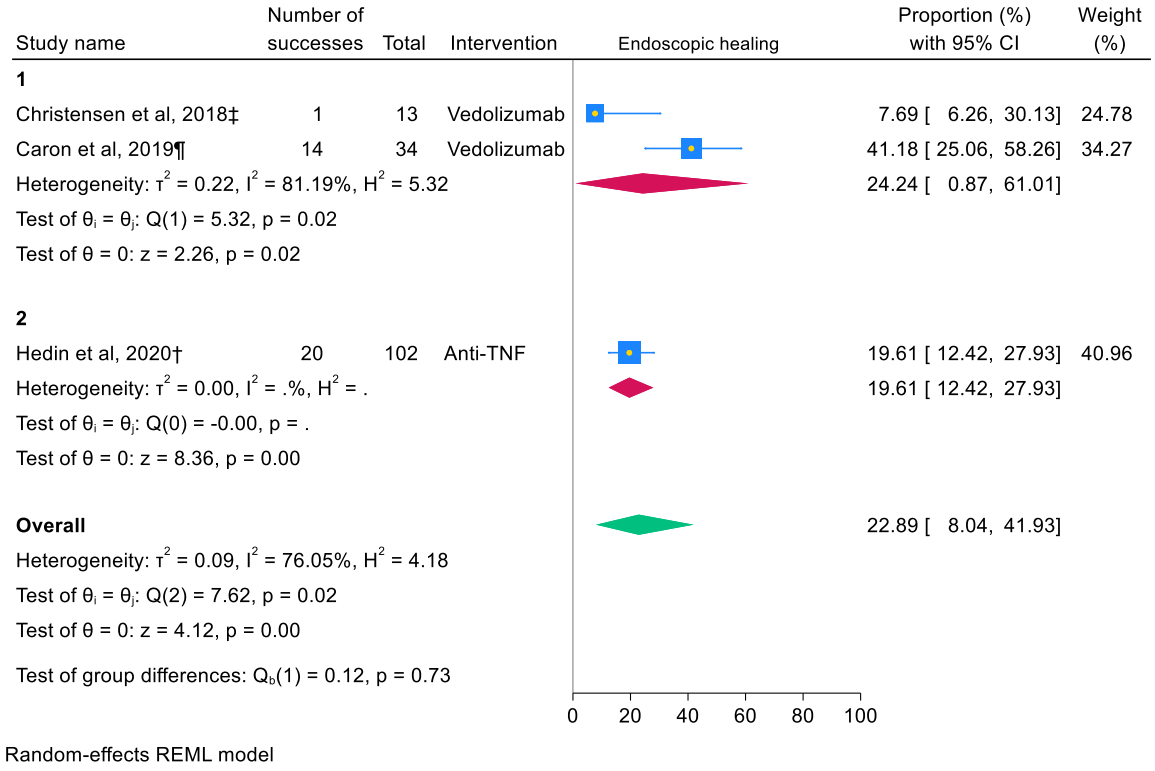



**Figure 3-5.** Forest plot of endoscopic healing (mucosal healing). Definitions of endoscopic healing:[†]defined as endoscopic mucosal healing, or where endoscopic data is unavailable as clinical remission according to the physical assessment; [‡]defined as SES-CD <3 for CD and MES 0-1 for UC. [¶] Absence of ulcers endoscopically was used to denote mucosal healing for CD and a Mayo endoscopic subscore of ≤1 for UC. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

### Histological remission

Histological remission data was limited, a quantitative synthesis could not be conducted. Histological remission was reported in one study (257), with one patient with UC out of 11 (5 CD, 6 UC) achieving histological remission with vedolizumab.

**Change in baseline faecal calprotectin**

Changes in median faecal calprotectin (FC) level was only reported for a small proportion of patients receiving tofacitinib (n = 14). A significant reduction of 458.3 µg/g (p=0.04) was reported at follow-up (median FC at baseline 818 µg/g [IQR 663.9 µg/g] versus 359.7 µg/g [IQR 567.5 µg/g] post treatment), with a median time between baseline and follow-up measurements of 6.3 months [IQR 7.5 months]. Quantitative data synthesis could not be conducted for this outcome.

**Non-response/loss of response**

Overall, 144/439 patients experienced either a primary non-response or secondary loss of response (75, 76, 257, 383, 384) (Figure 3-6), yielding a pooled estimate of 31.8% (95% CI 25.5-38.5; $I^2$=48.9; p=0.08). The lowest rates of non-response/loss of response were observed with adalimumab (23.1%, 95% CI 11.0-37.8).

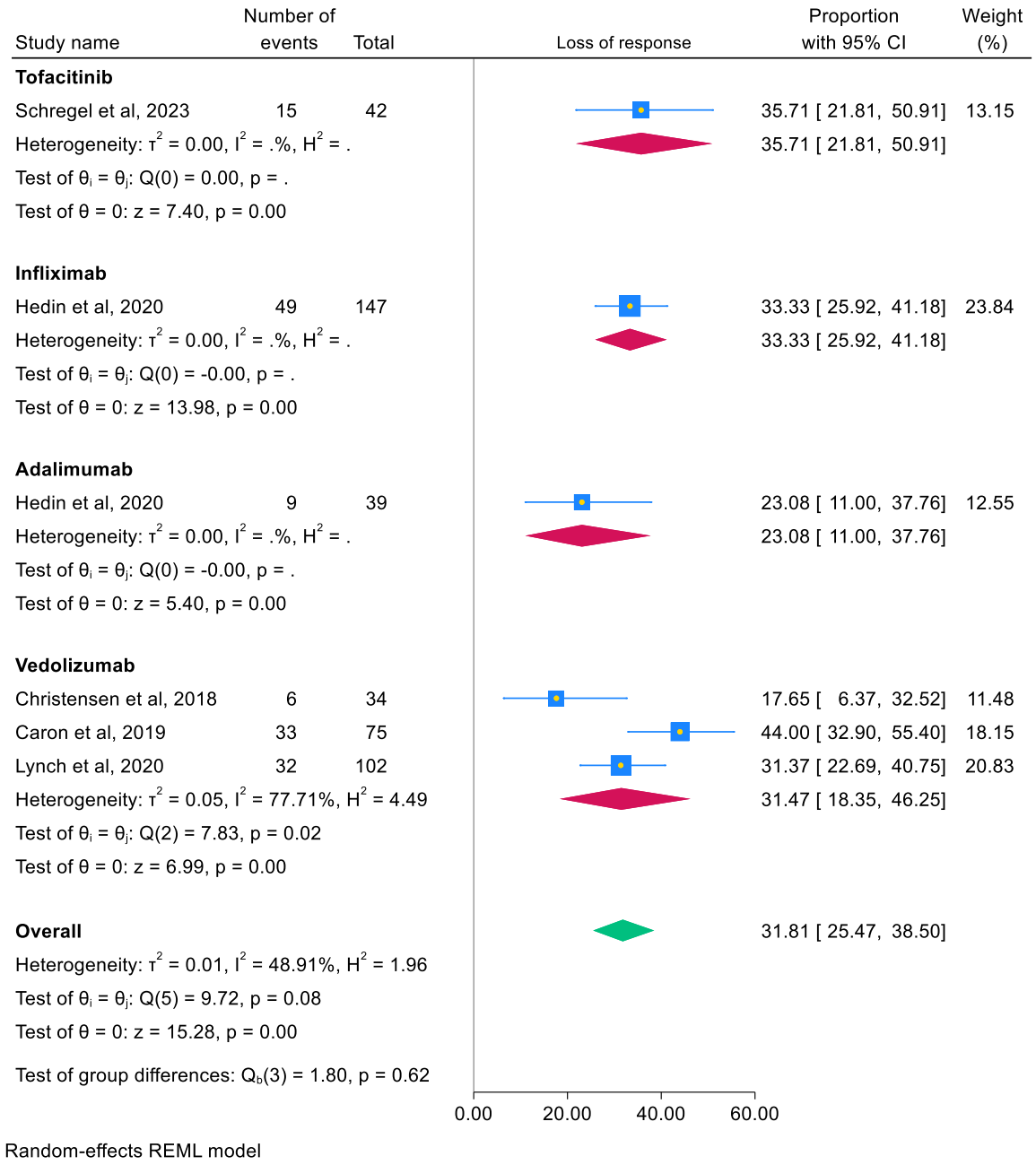



**Figure 3-6.** Forest plot displaying loss of response/non-response to biologic/SMDs. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

**Colorectal neoplasia**

Across two studies (76, 383), 12 of 112 patients (10.5%, 95% CI 5.3-17.1; $I^2$=0%; p=0.48) were diagnosed with colorectal neoplasia, comprising five cases of colorectal cancer (CRC) , six of high-grade dysplasia and one of low-grade dysplasia. The pooled estimate for CRC incidence alone was 4.3% (95% CI 1.0–9.2; $I^2$=0%; p=0.63) (Figure 3-7). When stratified by treatment colorectal neoplasia incidence was higher in tofacitinib treated patients (13.5%, 95% CI 4.1-26.7) whereas CRC incidence was slightly higher among those treated with vedolizumab (5.3%, 95% CI 1.2-11.8).

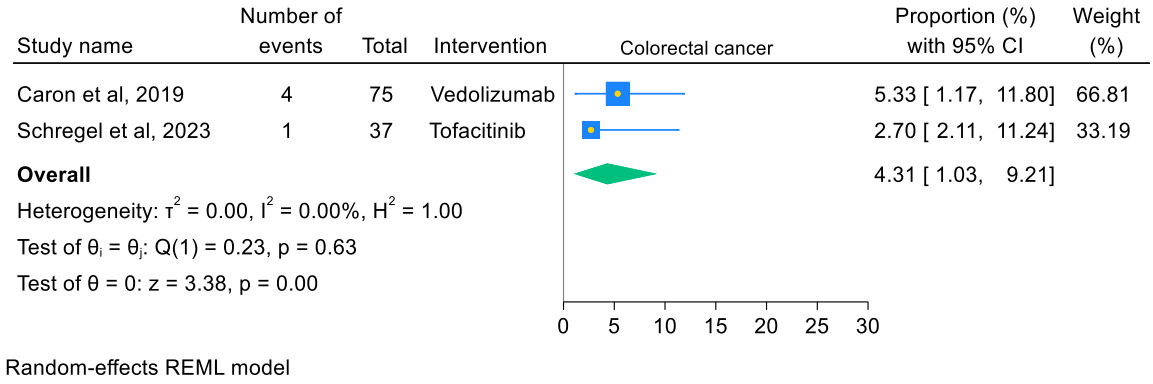



**Figure 3-7.** Forest plot of colorectal cancer event rates at follow-up. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

**Colectomy**

The pooled colectomy rates was 7.7% (95% CI 3.6-12.6; I2=0%; p=0.38), with marginally lower rates observed in vedolizumab treated patients (6.1%, 95% CI 2.1-11.7) compared to tofacitinib (11.9%, 95% CI 3.6-23.7), although this did not reach statistical significance (Figure 3-8). Two studies (257) (76) reported indications for colectomy: six cases were performed for colorectal neoplasia and one for poorly controlled disease.

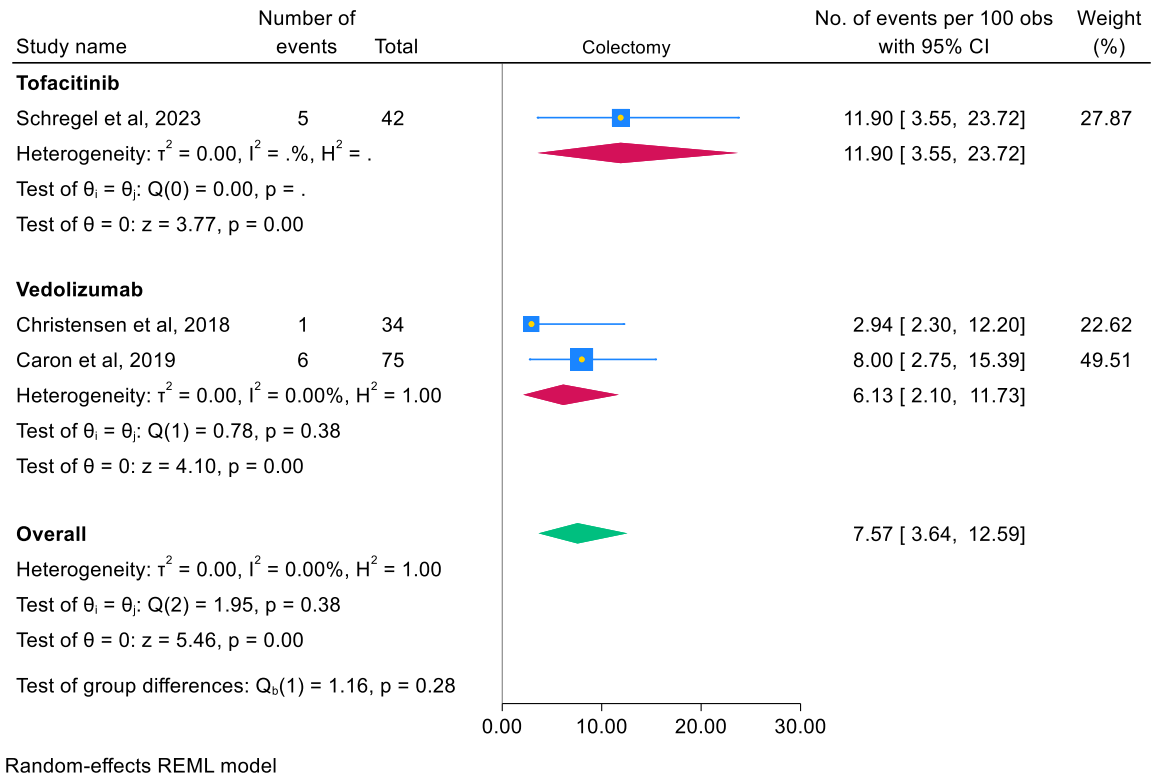



**Figure 3-8.** Forest plot of pooled colectomy rates at follow-up. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

## Safety Outcomes

### Adverse events

Adverse events were reported heterogeneously. Due to the limited data within studies in regard to itemisation of causes for AEs, all adverse events resulting in treatment discontinuation were analysed collectively. Forty-eight out of 439 patients on biologics/SMDs developed an AE of any description warranting treatment discontinuation (Figure 3-9). Pooled AE rates resulting in treatment discontinuation were 9.1% (95% CI, 64.4-15.1; $I^2$= 69.2%; p=<0.01) across five studies with the lowest rates seen with tofacitinib therapy (4.8%, 95% CI 0.08-13.8) and vedolizumab (5.5%, 95% CI 2.6-9.2) (75, 76, 257, 383, 384). Similar results were observed for serious adverse events (10%, 6.6-14.2; $I^2$=0%; p=0.60). For infections excluding cholangitis, pooled rates were 7.2% (95% CI 4.1-11.0; $I^2$=21.0, p=0.29). The lowest infection rates were seen with tofacitinib (2.4%, 95% CI 1.9-9.9) and the highest

rates were seen with vedolizumab (11.8%, 95% CI 6.2-18.7). Two studies (257, 383) reported on the classification of infections, of which 2/337 reportedly had gastrointestinal infections (*Salmonella* and *Aeromonas*).

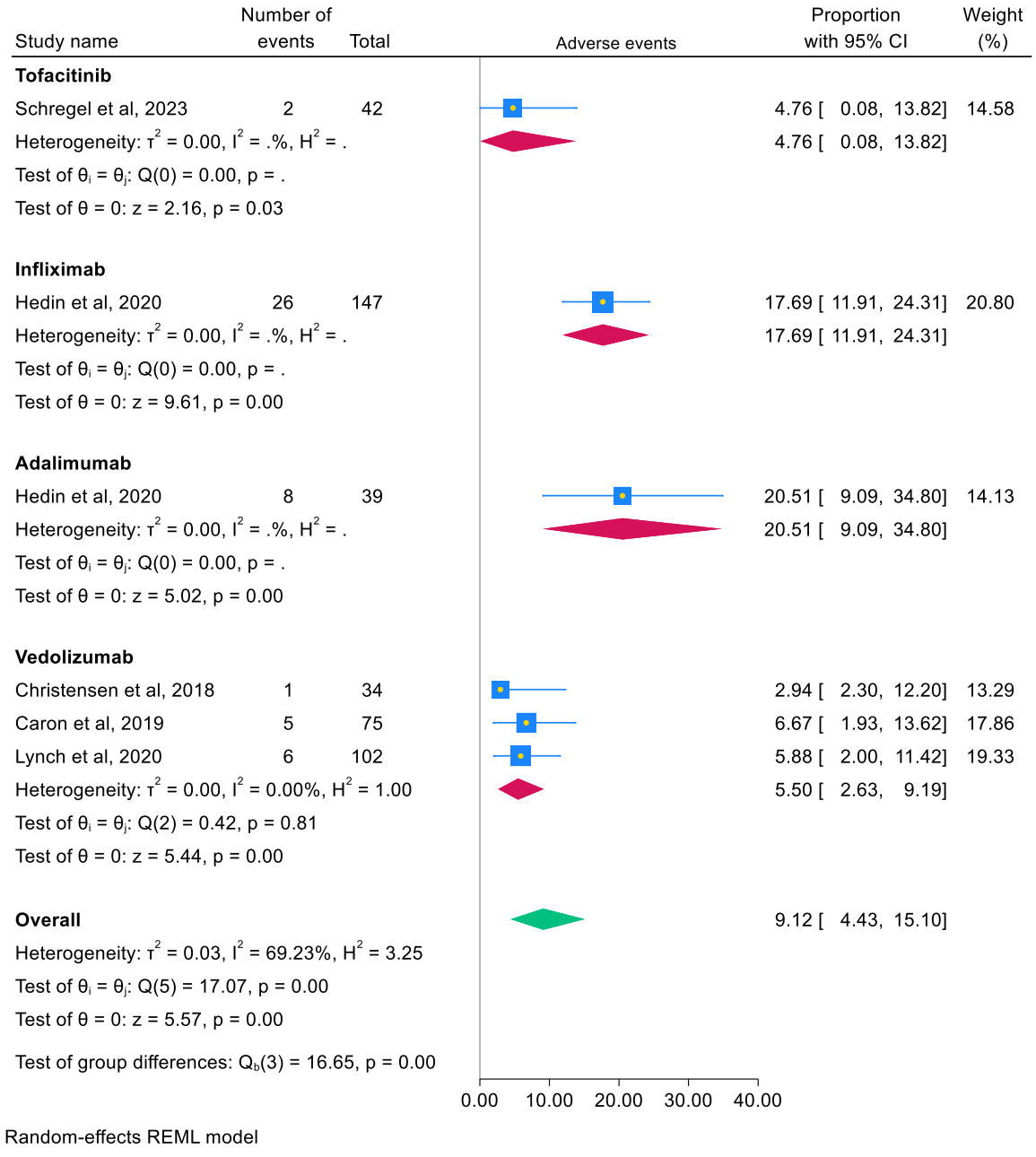



**Figure 3-9.** Forest plot of pooled adverse events resulting in treatment discontinuation at follow-up. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood

**Cholangiocarcinoma and Cholangitis**

Cholangiocarcinoma was rare (2/177 patients; 1.1%) and was only reported in one study evaluating vedolizumab therapy (76). Cholangitis was reported in 5.1% (95% CI 2.9-7.8; $I^2$=0%; p=0.56) with no notable differences between treatments.

**Advanced therapies in liver transplant recipients**

One study reporting on IBD response in seven post-liver transplant patients receiving anti-TNF therapy for a median of 2.3 years post-transplant (384). Early (3 months) response was reported in four patients, with five achieving a clinical response at 12 months. No significant difference was observed in IBD response between liver transplant and non-liver transplant patients at 3 and 12 months (p=0.78 and p=0.69 respectively) among those treated with anti-TNFs (384). Two patients discontinued therapy due to a lack of efficacy and one due to remission. No adverse liver outcomes for liver transplant recipients were reported during follow-up.

## 3.6 Discussion and summary of main findings

This systematic review and meta-analysis of real-world data supports the safety and efficacy of biologics and small molecule, tofacitinib in PSC-IBD. Previous systematic reviews and meta-analyses have demonstrated that biologic therapy confers no clear benefit on PSC outcomes or surrogate biomarker ALP (147, 388, 395). However, this is the first systematic review and meta-analysis, to our knowledge, to examine the IBD specific safety and efficacy outcomes comprehensively and contemporaneously in transplant naïve adults with PSC-IBD and the first to include tofacitinib's reported safety and efficacy outcomes on colitis in PSC patients.

Furthermore, our data suggests these therapies are capable of inducing and maintaining remission over both short and long-term intervals, nonetheless this appears to be attenuated numerically compared to IBD-only cohorts, with current therapies demonstrating variable results in PSC-IBD.

Our results based on limited case-series data indicate that 25% of PSC-IBD patients achieved clinical remission at approximately 3 months, which was sustained through to 1 year. Vedolizumab was consistently superior, with an almost 2-fold increase in remission rates compared to anti-TNF therapy. It should be noted that Hedin et al. (384), reported remission rates for adalimumab and infliximab jointly, and lacked detail on the proportion of patients achieving remission based on clinical assessment, reduction in faecal calprotectin or endoscopic assessment. However, they noted that no significant differences were observed in the proportion of patients achieving response or remission between adalimumab and infliximab (384). Overall, we observed slightly lower rates of clinical remission in PSC-IBD patients with active colitis receiving advanced therapies (Vedolizumab 32%; anti-TNF 23%) as compared to that reported in the IBD only literature (vedolizumab: CD 38% by week 14, 51% by week 52, UC 51% by week 14, 45% at 1 year; anti-TNF therapy: 34.7%-40.2 at 1 year) (396-402). Whilst the data for clinical remission in PSC-IBD is limited, it does support the view that PSC-IBD is a distinct immunological phenotype compared to IBD only.

Tofacitinib, licensed for use in UC, showed variable remission rates based on real-world data, ranging between 32-51% at approximately 12-16 weeks and 27-53% by 52 weeks (398, 403-406). This systematic review and meta-analysis indicates a favourable clinical response and remission rate to tofacitinib in PSC-IBD patients and the results appear comparable to those observed in IBD only cohorts. Its low AE rate and no reported thromboembolic events is reassuring. However, the high colectomy rate and colorectal neoplasia incidence over a relatively short period of time warrants cautious interpretation and clinical vigilance. The late positioning and sequencing of tofacitinib reflects

a particularly refractory cohort of patients with difficult to treat disease with persistent inflammation, and 98% of patients were biologic experienced prior to induction with tofacitinib, which may at least in part explain the observed neoplasia incidence. Other contributing factors may include intensified surveillance and small study size with results appearing inflated due to a few events carrying disproportionate weight. However, these preliminary results support tofacitinib's use for PSC-IBD and are encouraging for more selective JAKi like upadacitinib (selective JAK 1 inhibitor), which has shown superiority over tofacitinib and other biologics in IBD (390).

Endoscopic healing is a crucial long term treatment target, linked to improved disease control and a reduction in risk of colectomy, CRC and hospitalisations (393, 407). The heterogenous definitions of EH across studies may explain variables rates and apparent heterogeneity. Two thirds of the studies failed to clearly define EH, specify which endoscopic scoring systems were used and/or their associated cut off values, impacting interpretability and comparison. The pooled EH rate of 23%% was considerably lower that reported in IBD only patients, and reflecting persistent subclinical inflammation commonly observed in this unique IBD population. A systematic review and meta-analysis evaluating biologics in IBD only patients for induction and maintenance of remission cites a pooled EH rate of 33% (408). EH rates have also been reported as being between 35-40% and 43% (95% CI 24.6-62.0) for anti-TNF therapy and vedolizumab respectively at 12 months in other studies (409). Despite clinical remission PSC-UC patients have objective evidence of ongoing endoscopic and histological inflammation, more so than in UC only counterparts, and with significant discordance between the histological and endoscopically severity (268). We recommend clinicians seek to objectively confirm EH where possible in clinically quiescent patients, with EH as a therapeutic target given the elevated risk of CRC and the known inflammation associated cancer pathway in IBD. Interval endoscopic assessment outside of annual PSC-IBD colonoscopic surveillance practises is likely to be burdensome, costly and time consuming, however application of non-invasive surrogate markers such

as faecal calprotectin, magnetic resonance enterography or the use of intestinal ultrasound as it becomes more widely available may be a helpful and pragmatic tool in clinic. Further research is needed to assess FC levels in clinically quiescent PSC-IBD and to establish a definitive cut-off which reliably correlates with EH as well as its practical use given its co-release from biliary epithelium also.

Severe, chronic colonic inflammation is a well-established risk factor for CRC (410), underscoring the importance of early treatment and sustained remission particularly in PSC-IBD patients, who face a CRC risk significantly greater than that in IBD alone. Robust evidence evaluating the true impact of biologics and advanced immunomodulatory therapy on CRC outcomes in this unique population is lacking (411). In our study, pooled CRC rates were 4.3%, with most cases observed in patients receiving vedolizumab (median follow-up of 19.4months). The unexpectedly high colorectal neoplasia rate may reflect long-standing active inflammation, uncertainty around achievement of histological healing, and the inherent elevated CRC risk in PSC-IBD. Vedolizumabs' mechanism of gut-specific immunosuppression may also diminish mucosal immune surveillance possibly (76, 412). One study demonstrated a reduced risk of CRC in IBD patients receiving anti-TNF therapies (UC OR 0.79, 95% CI 0.73-0.83, $p<0.0001$; CD OR 0.69, 95% CI 0.66-0.73, $p<0.0001$), a benefit not seen with other agents such as vedolizumab or tofacitinib (413). Yet, in a single-centre study of 238 patients with IBD, including 145 receiving vedolizumab, no malignancies were reported amongst those receiving vedolizumab (414). Long-term prospective studies will therefore be essential to clarify if vedolizumab does indeed carry GI malignancy implications in PSC IBD and whether anti-TNFs have the same chemoprotective benefit seen in cases of IBD.

Given the lack of robust evidence of biologics in PSC-IBD patients, when considering treatment escalation to biologics in PSC-IBD patients, therapeutic decisions should be made with full consideration of individualised patient preferences (delivery route), treatment history, comorbidities

including extra-intestinal manifestations, disease characteristics, drug availability, local policy and guidelines with regards to local sequencing practises, in much the same way as for those with IBD alone (412). Irrespective of the chosen treatment sequence, monitoring and assessment of early and sustained treatment response is essential, with the goal of achieving EH. Where there is evidence of primary non-response or secondary loss of response, optimising individual agents through therapeutic drug monitoring and/or treatment escalation as well as timely switching to other potentially efficacious treatments is fundamental to improving long term IBD outcomes. More frequent monitoring of liver function tests is advised during advanced therapies induction and maintenance in PSC-IBD patients, particularly with agents such as vedolizumab, which has been shown to worsen liver blood tests in over a third if patients (75).

This systematic review is subject to several limitations: (i) only, retrospective, case series with few patient contributing to individual outcomes were retried, (ii) there is an absence of clinical trial data and therefore the relative efficacy of advanced therapies in PSC-IBD compared to placebo/standard of care is uncertain, (iii) included studies incorporated heterogenous outcome definitions and assessment timings. A summary of recommended reporting outputs for future studies are outlined in Appendix A. Additionally, including data from studies with mixed clinical and endoscopic definitions for a single outcome could be criticised. Future PSC-IBD studies should therefore align to internationally recognised IBD outcome definitions with accepted standards. Finally, we acknowledge the inherent risk of publication bias and limited data on histological outcomes necessitating cautious interpretation of these findings.

Despite these limitations our study has several strengths. The study protocol was prospectively registered with PROSPERO. The inclusion of several biologics including small molecule tofacitinib allows the incorporation of patients with biologic exposed, difficult to treat disease, reflecting real-

world paradigms. We analysed both short-term and long-term IBD outcomes out to approximately one year, thus offering insights into important long term treatment efficacies. Furthermore, our study includes data from a number of studies covering a variety of health care settings across high PSC prevalence regions with geographical representation from several continents, thereby increasing generalizability of the obtained results. Finally, given the heterogeneity in how remission and response were defined across the included studies, we sought to standardise outcome reporting by aligning the available data as closely as possible with the STRIDE II (393) consensus definitions. Whilst not all studies used uniform criteria, this approach allowed us to apply a consistent interpretative framework—thereby enhancing the comparability of outcomes with those reported in IBD only populations and supporting more meaningful synthesis with the existing body of literature.

**Conclusion**

In conclusion, there is evidence that advanced therapies are safe and can be efficacious in PSC-IBD. Superficially advanced therapies appear favourable in inducing and maintaining remission in PSC-IBD, however at a numerically attenuated level compared to IBD only patients. The short-term colorectal neoplasia burden should be interpreted with caution and likely reflects a small patient cohort enriched with a more severe IBD phenotype, longstanding inflammation and mandated annual surveillance, all of which increase detection. Nevertheless, there is insufficient robust data to make any PSC-IBD specific inferences or suggestions as to the positioning or sequencing of biologics in active colitis in PSC-IBD patients that would traditionally vary from those used in IBD only. Larger prospective studies will be essential to refine treatment algorithms for PSC-IBD patients within the evolving IBD therapeutic armamentarium. In the interim, establishing PSC-IBD registries that consistently capture clinical, endoscopic and histological outcomes will be crucial in validating this data and optimising therapeutic strategies.

# Chapter 4 A single-arm, multicentre, pilot study assessing brodalumab in the treatment of primary sclerosing cholangitis (SABR-PSC pilot study)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**Research Ethics Committee Approval gained:**

London Bridge Research Ethics Committee

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CTA ref: 13630/0015/001-0001

**Clinical Trial registry- Registered with International Standard Randomised Controlled Trial Number (ISRCTN) registry:**

ISRCTN registry No.15271834

**NIHR portfolio study:**

CPMS ID. 57248

## 4.1 Abstract


### Introduction

Primary sclerosing cholangitis (PSC) is a rare immune-mediated hepatobiliary disease. No licensed pharmacological therapy currently exists. Significant advancements have been made in our understanding of the pathophysiology, however the exact aetiology remains elusive. 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, examination of the safety and efficacy of IL-17 inhibition in PSC is lacking.

### Methods

*SABR-PSC* is a phase 2a, single-arm, open-label, multicentre, pilot study conducted to determine the safety of brodalumab, a recombinant human monoclonal antibody that binds with high affinity to interleukin-17 receptor A, in adults with PSC. Eligible patients were those with large-duct, early phase (non-cirrhotic) PSC. Patients received eight brodalumab injections (210mg) subcutaneously for 13 weeks. Primary objectives of this pilot study were to explore the safety, acceptability, adherence, practicality, tolerability and recruitment and retention rates of brodalumab in the treatment of PSC. Exploratory secondary efficacy outcomes included non-invasive assessment of hepatic fibrosis, changes in alkaline phosphatase (ALP) and other liver biochemical readouts, assessment of multi-parametric liver and biliary metrics through MRCP+ and LiverMultiScan (Perspectum, Oxford) and quality of life evaluation. Trial registration: ISRCTN15271834.

### Results

Between 1st February 2024 and 31st March 2025 nine of 29 invited individuals consented to participate (recruitment rate = 31.0%, 95% confidence interval [CI] 15.3-50.8). Six participants (66.7%) were

successfully enrolled and all completed 13 weeks of study treatment (retention rate = 100%, 95% CI 54.1-100). The median age was 37.5 years (interquartile range [IQR] 26-69), 83% were male and 50% had concomitant inflammatory bowel disease. Treatment adherence was excellent (100%, 95% CI 54.1-100). All participants experienced at least one adverse event; the majority were mild; the most frequent were fatigue, sore throat and abdominal pain. No serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) occurred. Two patients (33.3%) experienced >20% reduction in ALP, with one achieving normalisation by week 16. No new diagnoses or exacerbations of IBD occurred. Completion of health-related quality of life questionnaires was high (100%) with no statistically significant differences observed between baseline and week 12. No significant changes were observed in exploratory secondary efficacy outcomes.

## Conclusion

Brodalumab treatment was safe and well-tolerated in this small PSC patient cohort, and the pilot study demonstrated feasibility. While exploratory efficacy signals were observed, further evaluation in a future larger scale, multicentre, dose-ranging randomised controlled trial (RCT) is warranted to investigate safety, tolerability and efficacy.

## 4.2 Overview of Chapter

The emerging basic science and translational research implicating the IL-17/Th17 axis in PSC aetiopathogenesis justifies the conduct of a RCT. However, prior to this, a feasibility study is warranted to inform the design and conduct of a definitive RCT. This chapter outlines the *SABR-PSC* pilot study, which is a phase 2a study exploring the safety and efficacy of brodalumab in PSC patients with and without IBD, and seeks to answer important questions regarding the feasibility and planning of a future definitive multicentre RCT.

## 4.3 Introduction

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic disease, characterised by chronic biliary inflammation, stricturing and concentric fibrosis of the intra and/or extrahepatic bile ducts, leading to biliary cirrhosis and end stage liver disease (1, 3, 415, 416).

In chapter 1.2.7 the challenges of using surrogate end points (in the absence of hard clinical end points) in PSC trials was discussed, particularly in trials of short duration and follow-up. Challenges and questions still remain of how to conduct the optimal PSC trial, and which singular or combination of surrogate end points should be utilised. ALP has prevailed as the conventional non-invasive marker of disease prognostication and treatment outcomes in PSC (employed as phase 2 clinical trial end points), however its inter and intra-individual fluctuations make it an imperfect primary end point in isolation (417, 418). Furthermore, as a result of the low event rate of hard endpoints such as liver transplantation and cholangiocarcinoma, these too are impractical trial endpoints in early-phase clinical trials (154, 157). The ELF score and LSM are reliable predictors of adverse long term clinical

outcomes and advanced fibrosis (419-421), emerging as non-invasive proxy markers for long-term clinical outcomes, and avoiding the requirement for invasive liver biopsies. The *SABR-PSC* study implements novel emerging multi-parametric MRI-based assessments of hepatic and biliary fibroinflammation as part of its exploratory secondary outcomes, together with LSM (FibroScan), ELF score and ALP. Finally, this study capitalises on the opportunity offered by drug repurposing to bridge the gap between mechanistic basic science insights and translational research, representing the first clinical trial to investigate IL-17 inhibition in patients with PSC.

**Study rationale**

In response to recent research implicating the IL-17 pathway in PSC aetiopathogenesis (as outlined in chapter 1.5.4), we undertook, to the best of our knowledge, the first clinical trial evaluating an IL-17 receptor inhibitor (brodalumab) in patients with PSC- a novel therapeutic approach. This pilot study was designed to inform the feasibility, design and conduct of a future phase 2 RCT. Therefore, we aimed to evaluate the safety of brodalumab in PSC, whilst also addressing key feasibility aspects such as recruitment, retention, and sample size considerations. Additionally, we assessed preliminary signs of therapeutic efficacy with regards to periductal disease stability or change (improvement or deterioration) through non-invasive imaging.

To date, few biologics have been trialled in PSC, and only one utilised a subcutaneous (S/C) formulation (as outlined in Chapter 1.2.7). As such, several important questions remain unanswered before proceeding to a definitive trial. Such questions include the acceptability and tolerability of S/C brodalumab among participants, adherence to 13-week treatment regimen, and retention over a 6-month trial follow-up period with intensive assessment. Furthermore, it is unknown how many individuals would be willing and eligible for enrolment, especially in a cohort of patients that (i) are

co-diagnosed with IBD and may have mild colitis at baseline or (ii) may be concurrently prescribed steroids or other biologics for IBD, factors that may influence both inclusion and recruitment rates. An additional concern relates to the historical signal of worsening of CD in patients treated with brodalumab (422). Whilst this has been observed in the context of CD without PSC, evaluating the safety of brodalumab in participants with PSC-IBD is essential before a larger-scale study can be ethically and confidently pursued.

QoL and HRQoL measures are increasingly recognised as important endpoints in clinical trials for both participants and trialist. Any future RCT would be expected to capture these metrics; therefore, it is important to establish patients' views on the use, burden, and acceptability of HRQoL questionnaires, including completion rates to guide appropriate integration of PROMs into a future RCT.

Finally, questions remain with regards to the utility and practicality of introducing quantitative multi-parametric biliary metrics (in the form of MRCP+ and LiverMultiScan) into a multicentre trial of 6 months duration. This pilot study offers insights into the feasibility of deploying specialist quantitative imaging tools across multiple sites further informing endpoint selection and trial design for a future larger-scale RCT.

**Aims and outcomes**

To determine if a future full-scale phase 2 RCT is feasible, the *SABR-PSC* pilot study evaluated the following outcomes:

**Safety outcomes**

1. To determine preliminary data on the safety profile of brodalumab in patients with PSC, a number of outcomes will be captured, these include:
    a. Occurrence of adverse/serious adverse events rates and severity of adverse events- at each study visit.
    b. Monitoring for deterioration (from baseline) in laboratory parameters (e.g., liver function tests) or surrogate markers of liver fibroinflammation e.g., FibroScan.
    c. Quantitative assessment of IBD activity: faecal calprotectin, CDAI, partial Mayo score, and endoscopic scoring.
    d. Incidence of hospitalisations with acute cholangitis, reported cholangitis or colitis flares, as determined by safety reporting procedures.
    e. Evaluation of colonoscopy and histological evidence of disease activity compared to baseline (ileocolonoscopy is required for participants with CD) for those with a confirmed diagnosis of IBD. It is encouraged that the Nancy Histological Index is used by local histopathologists when reporting biopsy specimens from the week 16 colonoscopy/ileocolonoscopy.

**Feasibility outcomes**

1. Acceptability, as determined by eligible participants, of self-administering brodalumab as a S/C injection, its associated number and frequency of study/follow-up visits, assessments, PROM's and investigations. To be evaluated at the end of the study with exit questionnaires, withdrawal questionnaires and semi-structured interview. Participants will be asked in the exit questionnaire if they would want to continue the medication (if this was an option) and if they would be willing to participate in a larger RCT.

2. 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 and exit questionnaire/withdrawal questionnaire.
3. Practicality of administering the study visits and follow-up within the specified time frame across all sites.
4. Tolerability- to assess all eligible participants tolerance of self-administering S/C brodalumab injections. To be evaluated by way of reported side-effects and proportion of study participants discontinuing treatment due to side-effects.
5. Recruitment and retention rates- to assess recruitment and retention of all eligible participants.
6. Adherence- to determine if all enrolled participants adequately adhere to the scheduled intervention regimen i.e., number of administered doses of brodalumab whilst under active follow-up. This was measured by unit pack collection and injection count of unused and returned injection pens at each study visit.
7. Number and reasons for early withdrawal from study (assessed in withdrawal form).

**Efficacy outcomes**

Monitor for signs of deterioration in efficacy outcomes (this study is not powered to measure efficacy), by way of monitoring:

1. Mean ALP change from baseline at 3, 4 and 6 months on an intention to treat basis.
2. Calculation of any change from baseline to 16 weeks in ELF score and LSM (FibroScan).
3. Identification of any change from baseline to 16 weeks in other liver blood test parameters (bilirubin, alanine transaminase [ALT], aspartate transaminase [AST], gamma glutamyl-transferase [GGT], albumin) and international normalised ration (INR).

4. Identification of any change from baseline to week 16 in the MRCP+ and LiverMultiScan as a way of monitoring the trajectory of liver disease.
5. Any deterioration in health by way of review of PROMs i.e., 5-D itch, CLDQ-PSC, and PSC-PRO health questionnaires.

## 4.4 Methods

**Study design overview**

*SABR-PSC* is a phase 2a, multicentre, single-arm, open-label pilot study evaluating the safety and feasibility of brodalumab, in adults with PSC. Individuals with a confirmed diagnosis of early-stage (non-cirrhotic) large-duct PSC were recruited from large NHS hospital trusts. The study was adopted by the UK clinical research network portfolio of studies, as such it received support from research nurses and delivery staff within hepatology. Patients could additionally self-refer or be referred from other hospitals in the UK to NNUH provided (i) their primary hepatologist/gastroenterologist was agreeable for the patient to participate and (ii) the patient was willing to travel to the NNUH for screening and all study visits.

This study additionally incorporated the collection of research samples for future exploratory analyses of cytokine profiles, including IL-17. Optional DNA and urine samples were also obtained to support subsequent translational investigations.

The study protocol was adopted by the National Institute for Health and Care Research (NIHR) as part of a Doctoral Research Fellowship (Award ID: NIHR302616) and was conducted in accordance with the Good Clinical Practice (GCP) guidelines.

Norfolk and Norwich University Hospital sponsored the study (ref: 1006951 (40-02-23) 2021GRANT064). Norwich clinical trials unit (NCTU) maintained oversight of the study and supported all aspects of the study from trial design, management, statistics, trial delivery, and regulatory reporting.

**Study design rationale**

A single-arm pilot design was selected to maximise enrolment in this rare disease cohort. Concerns were raised that inclusion of a placebo arm could hinder participation; a view echoed during a patient forum organised by PSC Support. The safety and adverse event profile for brodalumab is already well characterised through previous clinical trials and pharmacovigilance data and considered sufficiently distinct from the natural history of PSC to be measured without a comparator arm. Finally, *SABR-PSC* was concerned with establishing safety and feasibility, outcomes that can be appropriately addressed without the need for a control group.

**Sample size**

A recruitment target of 20 participants was considered pragmatic in light of recognised recruitment challenges in this rare disease cohort. This target was endorsed by NCTU, the PPI group, leading experts in PSC and clinical trial design who served as primary investigators (PI) at participating trial sites. No formal sample size calculation was undertaken, as the study was not powered or designed to demonstrate statistically significant differences in efficacy outcomes. Instead, quantitative data were collected to monitor for potential deterioration in these outcomes.

**Trial procedures**

Following written informed consent and completion of a six-week screening period, eligible participants commenced scheduled study visits at week 0 (baseline), 2, 4, 8, 12, 16 and 6 months. Over a 13 week treatment period participants received a total of eight S/C injections of brodalumab (210mg/1.5ml) administered weekly during the first 3 weeks (weeks 0, 1, and 2) then every two weeks thereafter (weeks 4, 6, 8, 10 and 12) (Figure 4-1). This regiment mirrors the licensed dosing schedule for moderate to severe chronic plaque psoriasis (423), and repurposed for use in this study. Training in drug administration was provided at the baseline study visit. Participants attended seven study visits, after which they returned to standard of care.

**Study Participants**

Adults aged 18-75 years with a confirmed clinical diagnosis of LdPSC, as defined by the British Society of Gastroenterology (BSG) and UK-PSC guidelines (3) were eligible. Participants could be enrolled with or without a confirmed diagnosis of colonic IBD. For those with IBD, only individuals with quiescent-mild disease were eligible. Disease activity was determined using a combination of clinical indices (history, IBD diary and disease activity index scoring), C-reactive protein (CRP), and endoscopic findings corroborated by histopathology. Only participants with IBD were required to have undergone standard of care annual surveillance colonoscopy in accordance with national guidelines (3), within the preceding 12 months to allow documentation of mucosal disease activity, prior to enrolment. PSC-IBD candidates who lacked a surveillance colonoscopy in the preceding 12 months were deemed ineligible. The protocol did not mandate a new baseline ileocolonoscopy to be performed prior to enrolment. Participants meeting all the inclusion criteria and none of the exclusions were enrolled.

Recruitment of PSC-IBD participants was proposed to be a two-step process. The first ten PSC-IBD participants enrolled were required to have quiescent disease (defined as a CDAI score <150 or pMayo score <2, corroborated by ileocolonoscopy and histology). Following enrolment of these participants, an interim safety committee review would be undertaken to appraise for any adverse colonic safety signals before recruiting the next ten participants with mild disease (CDAI score 150-219, pMayo 2-4 , supported by ileocolonoscopy and histology). The rationale for this staged process was twofold: (i) to allow for early recognition and management of any potential IBD-related adverse events: While PSC-IBD is recognised as clinically and phenotypically distinct disease entity from IBD only (67, 249, 260, 424) (as outlined in Chapter 1.4), and new onset IBD with IL-17 inhibitors appear to be rare, caution was deemed appropriate prior to treatment initiation (234, 425); (ii) it enabled inclusion of disease states representative of the wider PSC-IBD population: The historical view that PSC-IBD is predominantly quiescent is being challenged, with recent studies (including findings from our own pre-feasibility study) showing that mild histological activity is common (68, 261). Including both quiescent and mild disease therefore enhanced the generalisability of the study.

**Eligibility criteria for *SABR-PSC* pilot study (333)**

**Inclusion criteria**:

1. Male or female aged ≥18-75.

2. Written informed consent received.

3. Established diagnosis of LdPSC-based on a standard disease definition adopted by the BSG: (i) cholestatic blood tests; (ii) typical cholangiographic findings on ERCP or MRCP, and absence of both anti-mitochondrial antibodies and causes of secondary cholangitis.

4. Participants may be recruited with or without a confirmed diagnosis of IBD. For those recruited with an established diagnosis of concomitant colonic IBD, a confirmed diagnosis of quiescent-mild disease

must be established prior to enrolment (as part of a two-step enrolment process) (with evidence of standard of care endoscopy performed within 12 months of screening visit) by clinical, biochemical, and endoscopic evidence corroborated by a histopathology report is mandated.

5. Participants on maintenance therapy with 5-aminosalicylic acid (5-ASA) or thiopurine therapy were required to be taking a stable dose for at least 12 weeks prior to screening, with no anticipated dose changes for the duration of the trial.

6. Individuals pre-treated with UDCA therapy should continue on a stable dose for 12 weeks prior to screening, not exceeding 20mg/kg/day.

7. All PSC-IBD patients must have had colorectal cancer screen within 12 months of the screening visit with no signs of malignancy or dysplasia (of any severity), evidenced by a colonoscopy with segmental biopsies or dye spray and histological confirmation of absence of dysplasia.

8. Female subjects of childbearing potential were required to use a highly effective contraceptive method from screening to at least 12 weeks after the last dose of the drug. All hormonal contraceptive methods were to be supplemented by use of a male condom.

**Exclusion criteria:**

1. Gallbladder lesion or polyp (>5mm diameter), cholangiocarcinoma mass lesion, or high suspicion of cholangiocarcinoma, as indicated on imaging such as ultrasound, computer tomography (CT), dynamic MRI or MRCP.

2. Evidence of any other concomitant liver disease including but not limited to overlap syndromes with autoimmune hepatitis, alcohol related liver disease, or clinically significant metabolic dysfunction-associated steatotic liver disease (at investigator discretion).

3. Primary biliary cholangitis, or IgG4-Related cholangitis as judged by the investigator.

4. Liver transplant recipients, listed for a liver transplant or in the opinion of the investigator has an anticipated need for liver transplantation within the next 12 months.

5. Total or subtotal colectomy or presence of an ileostomy or colostomy.

6. Current or recent history of Crohn's abscess, stricturing or fistulating disease.

7. 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 (i.e., 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.

8. Evidence of cholangitis (as defined by Tokyo Guidelines definition (426)) 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 ERCP prophylaxis).

9. Liver cirrhosis based on liver histology, ultrasound, or vibration controlled transient elastography (kPa >14.4) or history of 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 of varices, platelets <150, and/or splenomegaly on recent imaging measuring > 12cm.

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. Active malignant disease or history of malignancy within the past five years including high risk basal cell carcinoma (BCC) (high risk basal cell carcinoma as defined per the National Institute for health and Care Excellence: recurrent BCC, >20mm diameter on trunk and extremities, >10mm on forehead, cheeks, scalp, neck, or pre-tibia, of any size on mask areas of face, genitals, hand, nails, ankle or feet, or histological evidence of incomplete excision margin, perineural invasion below the dermis, infiltrative, micronodular or basosquamous BCC).

13. Existing or intended pregnancy or breastfeeding during study period.

14. Current or recent participation in any other clinical trial involving a CTIMP within the last 6 weeks prior to 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 screening visit.

16. Positive stool culture for *Clostridioidies Difficile* or enteric pathogens within 12 weeks prior to study visit.

**Infectious Disease Exclusion Criteria**

1. Chronic hepatitis B virus (HBV), hepatitis C virus (HCV) or positive hepatitis B core antibody (anti-HBc) at screening.

2. Evidence of 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. Proven previous history of systemic fungal sepsis- as defined by invasive organ infiltration and positive blood cultures (presence of mucocutaneous involvement is not included in this definition).

4. Has congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).

5. 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-TNF$\alpha$, anti-integrin inhibitors), Janus-associated Kinase inhibitor (JAK), ciclosporin, tacrolimus, methotrexate. Antimetabolite therapy established at a steady state for ≥ 12 weeks is permitted.

3. Diagnosis of active depression, 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 the study drug.

**IBD trial entry definitions**

Summary of definition of IBD in *remission/quiescent* at baseline (clinical and endoscopic):

- Ulcerative Colitis:
    - Endoscopic and histological evidence of quiescent colitis in the previous 12 months prior to screening visit in addition to a pMayo score <2 at screening visit.
- Crohn's Disease:
    - Endoscopic and histological evidence of quiescent disease in the previous 12 months prior to screening visit in association with a CDAI <150 at screening visit.
- Note: Where disparity exists in disease activity between the endoscopic and histological report- histology is the gold standard of actual disease activity.

Summary of definition of *mild* IBD at baseline (clinical and endoscopic):

- Ulcerative Colitis:
    - Endoscopic and histological evidence of mild colitis in the previous 12 months prior to screening visit in addition to a pMayo score 2-5 at screening visit.
- Crohn's Disease:

- Endoscopic and histological evidence of mild disease in the previous 12 months prior to screening visit in association with a CDAI 150-219 at screening visit.

Definition of IBD "flare" or relapse during trial:

- The absence of remission (if in remission at screening visit) or worsening of disease (if mild disease at screening visit)
- If in *remission* at screening visit:
    - UC- pMayo score of ≥2 at any point, or an increase of ≥2 in any one sub-category of the pMayo score, or a global assessment of endoscopic severity using Ulcerative Colitis Endoscopic Index of Severity (UCEIS) of >1.
    - CD- CDAI >150 with an increase of more than 70 points in association, or global assessment of Crohn's severity using Simple Endoscopic Score for Crohn's Disease (SES-CD)>2.

- If *mild* disease at screening visit:
    - UC- partial Mayo score of >5 at any point, or an increase of ≥2 in any one sub-category of the partial Mayo score. Or a global assessment of endoscopic severity using Ulcerative Colitis Endoscopic Index of Severity (UCEIS) of >4.
    - CD- CDAI >219 with an increase of more than 70 points in association. Or global assessment of Crohn's severity using Simple Endoscopic Score for Crohn's Disease (SES-CD)>6.

The above is to be used in combination with the discretion of the PIs clinical judgement as diarrhoea is a known common side-effect of brodalumab.

**Inclusion criteria for women of childbearing potential**

For the purposes of the trial a female of childbearing potential (defined as fertile, following menarche and until becoming post-menopausal or sterile and are sexually active) must be able and willing to take two of the following acceptable methods of contraception for the duration of treatment and for at least 12 weeks following the last dose of the intervention to be eligible to participating in the trial:

- Established use of combined hormonal oral contraceptive (oestrogen and progesterone containing) pill, injected, transdermal or implanted hormonal methods of contraception associated with the inhibition of ovulation. All hormonal contraceptive methods must be supplemented by use of a male condom.
- Intrauterine device (IUD).
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- Tubal ligation/occlusion, vasectomised partner, if this is the participants preferred method and in line with their usual lifestyle.
- Barrier methods of contraception (condom or occlusive cap with spermicide, use of spermicide without a form of barrier contraception is not an acceptable form of contraception).
- Alternatively, absolute and continuous abstinence is acceptable, if this is the usual and preferred method for the participant. Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation), concomitant use of male and female condoms or withdrawal are not acceptable methods of contraception.

Women of non-childbearing potential or post-menopausal (i.e., amenorrhoeic for at least 12 consecutive months without an alternative medical cause) were permitted to participate in the trial. It was the responsibility of the investigator to be satisfied that a woman was post-menopausal and to determine if adequate birth control methods were employed to be eligible to participate in the study.

**Participant identification and recruitment**

Potentially eligible participants were identified at participating UK centres by their usual gastroenterology/hepatology health care team, through a locally held and maintained database of PSC patients, referral from non-participating hospitals in the UK, or self-referral through contact with the Chief Investigator. This was the accepted procedure for patients at NNUH. Individuals who were identified as potential candidates and/or had expressed an interest in participating in the study had a retrospective case review if they met inclusion criteria 3 and 4 (p193) by the local clinical trial team. The data captured consisted of: patient demographics, clinical characteristics of PSC i.e., small or large-duct PSC, clinical characteristics of IBD, date of diagnosis of PSC and IBD, current treatment for PSC and IBD, duration of treatment, extent of IBD, medical history, review and documentation of most recent colonoscopy in the last 12 months prior to screening visit, its associated macroscopic diagnosis as determined by the performing endoscopist and associated histological diagnosis.

Individuals who met inclusion criteria 3 and 4 and did not obviously meet any exclusion criteria at pre-screening were then approached. A screening log was maintained for all patients that were approached by the study team. Potential participants were approached either in person by their local clinical trial team physician or site PI/liver research nurse or by way of writing. All participants were issued with an invitation letter and a participant information sheet (PIS) at the point of contact if not already issued at their prior index visit with their treating healthcare team. This method of recruitment was anticipated to allow each site to recruit five patients each. However, in the event of under recruitment at a site, over recruitment was permitted at another site, within the total of 20 patients recruited.

Agreed acceptable recruitment strategies included any of the following:

- Patients could be approached directly by their caring team on attending a hospital outpatient clinic appointment. An invitation letter on hospital headed paper which provided an overview of the study, and a PIS was provided at this encounter/or by post if a teleclinic appointment. The research team would then contact the patient by phone seven days later.

- The clinical team could send an invitation letter by way of postal invitation with or without a PIS along with a reply slip detailing a range of methods for the interested potential participant to contact the local trial team to arrange a screening appointment. This method was adopted for participants who were referred by clinicians outside of the approved NHS trial sites, for self-referred participants or for participants identified through the locally maintained database.

- PSC Support advertised the trial on their website and social media platforms, which included contact details for the Chief Investigator for those interested in the trial. The Chief Investigator could then send a PIS to the interested potential participant.

**Informed consent and screening**

Written informed consent was obtained prior to any study related procedure or investigation, by the PI at the screening visit. Participants read and personally signed the latest approved version of the informed consent form (ICF) (Appendix B) which was also countersigned by the PI . Following consent, trial-related screening investigations were commenced during this visit, as outlined below. Patients meeting all eligibility criteria (after review of screening tests) with a signed consent form were then enrolled in the study to their baseline study visit (week 0). A six week period between consent and commencing trial medication (week 0) was allowed to ensure sufficient time for return and reporting of all pre-screening investigations.

**Participant retention, discontinuation and withdrawal**

Participants were free to withdraw from the study at any time without obligation to provide a reason. Where participant withdrew or exited the study prior to study completion, participants were invited to ongoing follow-up visits for safety analysis. Where possible investigators sought to record the reason for withdrawal, while respecting participant's rights.

Participants who discontinued protocol treatment were invited, if willing, to remain in the study for scheduled study follow-up and safety analysis. Those who voluntarily withdrew were asked to complete a study withdrawal questionnaire. If withdrawal occurred due to an adverse event, the investigator arranged appropriate follow-up visits (in person or by telephone) until the adverse event had resolved or stabilised.

Participants could withdraw or be withdrawn for any of the following reasons :

- Unacceptable treatment toxicity or intolerable adverse event.
- Intercurrent illness, or infection with particular reference to cholangitis, preventing further treatment.
- Progression of trial disease compared to baseline e.g., elevation in serum ALP > 10x baseline result; elevation in serum (conjugated) bilirubin > 3x baseline result; elevation in ALT >5 x baseline result or patient listed for liver transplant.
- Suspected new onset or flare/worsening of CD or UC based on above definitions (investigators discretion was to be used to determine need for treatment withdrawal vs suspension).
- Any change in the participant's condition that in the opinion of the investigator justified treatment discontinuation.
- Intentional overdose.

- Withdrawal of consent by the participant.
- Lack of participant compliance or failure to attend study visits as agreed.
- Protocol violation that come to light after patient enrolment e.g., not meeting inclusion/exclusion criteria.
- Lost to follow-up.
- Evidence or reports of active depression, as judged in combination with the patient health questionnaire (PHQ-9) depression tool with a score of ≥5 (the PHQ-9 score was to be interpreted at the discretion of the PI as PSC and puritis are known contributors of sleep deprivation and severe fatigue. Recognition of other symptoms such as thoughts of suicide/ or hurting oneself, feeling depressed or hopeless were accepted as more likely to be specific to depression in this cohort).
- Where participant's expresses suicidal ideation or behaviours.
- Contraindication to continuing brodalumab treatment as per summary of medicinal product characteristics (SmPC), including pregnancy, breastfeeding or planning pregnancy during the trial.

**Participant screening**

Screening investigations (Table 4-1) comprised full medical and medication history, physical examination, stool (enteric PCR, *Clostridioidies difficile* assay and faecal calprotectin), and urine samples to exclude infection. Baseline physiological tests including height, weight, blood pressure, heart rate, pulse, and temperature. Safety blood tests performed at baseline include carbohydrate antigen 19-9 (CA19-9), ELF score, blood borne virus screening and QuantiFERON testing. Imaging assessments consisted of a baseline MRCP and non-contrast MRI liver, including MRCP+ and LiverMultiScan, and LSM (FibroScan). A urine pregnancy test was performed for all women of childbearing potential. The maximum permitted duration between screening and initiation of treatment was six weeks.

Although brodalumab has previously been associated with suicidal ideation and behaviour (SIB), no causal link has been established (427). Nonetheless, participants were screened at baseline through medical history and consolidated using the PHQ-9 depression tool. Participants with IBD additionally completed IBD symptom diaries (Appendix C), enabling calculation of the CDAI and pMayo score for safety monitoring.

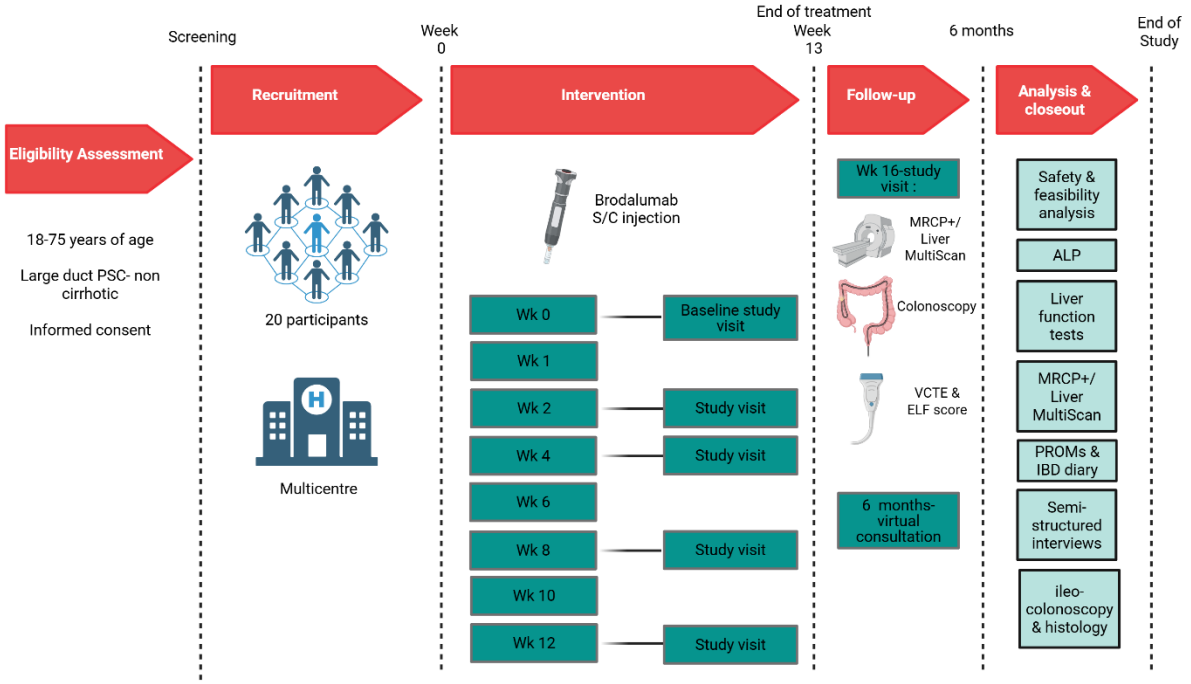


**Figure 4-1.** *SABR-PSC* trial schema. Adapted from Elzubeir et al (333).
Abbreviations: VTCE, Vibration controlled transient elastography; ELF score, enhanced liver fibrosis score; wk, week; ALP, alkaline phosphatase; PROMs, patient reported outcome measures.

## Intervention

Brodalumab (Kyntheum) was supplied as a 210mg/1.5ml pre-filled injection syringe for single use. Brodalumab, licensed for moderate-severe chronic plaque psoriasis was repurposed for evaluation in this study, and supplied by Leo Pharma to participating local hospital pharmacies.

Brodalumab was administered subcutaneously into the thigh, upper outer arm, or abdomen. At baseline, all participants received formal training on subcutaneous self-injection. Thereafter, injections could be self-administered at home, at study visits (if coinciding with their scheduled day of administration), or administered by the research team where participants expresses a strong desire not to self-inject). Each unit pack contained two injection pens, and all unused injection pens were collected and reconciled by the study team.

Brodalumab was dispensed to participants at three timepoints during the study:

(i) Dispensing visit 1- at the week 0 study visit 2x unit packs (4 injections) were issued to the participant (providing the following doses: week 0, 1, 2, 4).

(ii) Dispensing visit 2- at the week 4 study visit, one unit pack containing 2 pre-filled brodalumab injection syringes was issued, providing week 6 and 8 dosages (provided there are no contraindications or safety concerns).

(iii) Dispensing visit 3- at the week 8 study visit, provided there are no contraindications or safety concerns, one unit pack containing 2 pre-filled brodalumab injection syringes was supplied.

**Concomitant medication**

Treatment with 5-ASA, antimetabolites (azathioprine, mercaptopurine), and licensed or guideline-supported anti-pruritic agents (including rifampicin, cholestyramine, and naltrexone) was permissible, provided participants have been established on a stable dose for 12 weeks prior to screening, and no dose changes or treatment escalation were anticipated.

In contrast, concomitant treatment with biologics, small molecules or immunomodulators e.g., infliximab, vedolizumab, tofacitinib, or methotrexate was prohibited. Participants were also ineligible if they received colonic topical or systemic corticosteroids, including budesonide, within three months prior to screening.

For the purposes of this study, the end of trial was defined as 30 days following the last study visit (at 6months).

**Study visits**

At each study visit, participants underwent physiological assessment, physical examination, review of concomitant medication, documentation of missed doses, semi-structured interviews, safety blood sampling, adverse event monitoring, urine dipstick, and research and serum sample collection. PROMs including CLDQ-PSC, PSC-PRO, 5-D itch, and IBD diaries were administered as per protocol. These were distributed electronically ahead of study visits and were expected to be completed by participants ahead of each study visit. Pregnancy testing was performed at screening and subsequently every 4 weeks.

Clinical laboratory tests were performed at screening, baseline (week 0) and each subsequent visit, with the final assessment at six months. Safety blood tests included liver biochemical tests (bilirubin, ALP, GGT, AST, ALT, albumin), INR, full blood count including platelets, urea & electrolytes (U&Es) and CRP.

A single ileocolonoscopy with biopsies was performed at week 16 for all participants as part of colonic safety assessment. This procedure counted towards PSC-IBD participants standard of care surveillance colonoscopy programme; this approach was supported by the PSC patient and public involvement

group. Faecal calprotectin was measured at screening, baseline, week 4 and week 16 to complement IBD diaries and assess intestinal inflammatory activity. Given (i) class specific concerns that IL-17 antagonism may precipitate intestinal inflammation (de novo or exacerbation of pre-existing IBD); (ii) the known discordance between symptoms, endoscopic and histological activity in PSC-IBD, as outlined in Chapter 1.4.3 (67); (iii) the need for a definitive tissue-level safety readout in a first-in-disease IL-17RA study, all participants underwent a week 16 ileocolonoscopy. This approach balanced participant burden with systematic evaluation of the primary safety outcome, while complementing non-invasive monitoring (CRP, faecal calprotectin, IBD diaries).

Additional investigations- including PHQ-9 depression screening, CA19-9, ELF score, VCTE, MRI liver/MRCP with MRCP+ and LiverMultiScan- were conducted at screening and week 16.

All MRI scans were performed at NNUH using a 1.5 or 3 Tesla MRI scanner (Siemens Sola; GE Signa Premier) with acquisition of T1 and T2-weighted sequences. MRI Liver and MRCP sequences were anonymised before being securely uploaded to Perspectum Ltd using a dedicated online portal. Screening and week 16 MRCP images were post-processed using MRCP+ and LiverMultiscan software and were reported independently of the safety MRI liver and MRCP. Safety MRI/MRCP scans were reported by a single radiologist.

Non-invasive artificial intelligence generated MRI liver and biliary metrics is a new novel technology offered by Perspectum (Perspectum LTD, Oxford, UK). MRCP+ software creates 3D biliary tree models, enabling automated measurements of duct length, duct diameter, number of strictures, length of strictures in addition to volume quantification of the biliary tree and gall bladder anatomy (428). LiverMultiScan (LMS) software characterises liver tissue using T1 mapping of extracellular water

content acting as a proxy for fibroinflammatory disease activity, T2* mapping characterising liver iron content, and proton density fat fraction (PDFF) quantifying liver fat (429). 3D MRCP and LiverMultiScan maps were used to build a parametric biliary tree model. Periductal cT1 was quantified over four fixed radial distances surrounding the bile ducts in 2mm acquisitions, from 1.5mm to 9.5mm. Regions of interest (ROI) was defined as 1.5-3.5mm, ROI 2 was 3.5-5.5mm, ROI 3 was 5.5-7.5mm, and ROI 4 was 7.5-9.5mm. Mean periductal cT1 was quantified in each ROI. Evidence suggests that MRCP+ parameters correlate with biochemical scoring systems and are highly predictive of patient outcomes (428, 430, 431), offering a potentially novel prognostic tool for PSC. Recent evidence confirms that mean cT1 in ROI 1 is higher in patients with advanced fibrosis, and that the mean differences in cT1 across ROIs observed in PSC patients are not observed in healthy volunteers ($p=<0.0001$) (432).

**Table 4-1 .** Summary *SABR-PSC* study visit schedule. Adapted from Elzubeir et al (333).

| | STUDY PERIOD | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Treatment | | | | | | | | Close out<br>Week 16 | 6 month follow-up<br>(Teleclinic or video conference) |
| TIMEPOINT | *-2 Weeks Up to 6 weeks prior to week 0 visit)* | *Week 0 (+- 3days)* | *Week 1 (+- 3days)* | *Week 2 (+- 3days)* | *Week 4 (+- 3days)* | *Week 6 (+- 3days)* | *Week 8 (+- 3days)* | *Week 10 (+- 3days)* | *Week 12 (+- 3days)* | *Week 16* | *6 months* |
| **Screening:** | | | | | | | | | | | |
| Eligibility screen | X | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | |
| Physical examination[1] | X | X | | X | X | | X | | X | X | |
| Medical history | X | | | | | | | | | | |
| Medication's review | X | X | | X | X | | X | | X | | |
| **INTERVENTION:**<br>Brodalumab 210mg 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 |
| CA 19-9 | X | | | | | | | | | X | |
| Blood Borne Virus and QuantiFERON[2] | X | | | | | | | | | | |
| Pregnancy Test (urine)[3] | X | X | | | X | | X | | X | X | |
| Urine sample | X | X | | X | X | | X | | X | X | |
| Fibroscan & ELF score | X | | | | | | | | | X | |
| Faecal calprotectin[4] | X | X | | | X | | | | | X | |
| Stool culture[5] | X | | | | | | | | | | |
| MRCP/MRCP+ | X | | | | | | | | | X | |
| Colonoscopy & Biopsy[6] | | | | | | | | | | X | |
| **Questionnaires** | | | | | | | | | | | |
| PSC- PRO | X | | | X | | X | | | X | X | |
| CLDQ-PSC | X | | | X | | X | | | X | X | |
| 5-D itch | X | X | | X | X | X | X | X | X | X | |
| Depression Tool (PHQ-9) | X | | | | | | | | | X | |
| IBD diary review[7] | X | X | | X | X | | X | | X | X | |
| Exit questionnaire† | | | | | | | | | | X | |

1. Physical examination including weight measurements.
2. Blood borne virus and QuantiFERON test collected for all participants at screening, irrespective of previous test results. Test result from screening visit were used as valid result for entry or exclusion from study.
3. Positive urine pregnancy test at any point in the study to result in the participant withdrawal from treatment.
4. A faecal calprotectin result at screening was required prior to enrolment in the study. Stool sample to be returned by participant for testing within 5 days of screening visit.

5. Stool microbiology for enteric pathogens and clostridium difficile. Participant to return stool sample for testing within 5 days of screening visit.
6. Baseline colonoscopy as part of patients' standard of care surveillance colonoscopy, providing it was performed with biopsies within 12 months of the screening visit- permit participant eligibility. An ileocolonoscopy was required at week 16 if the participant has CD, in all other cases a full colonoscopy was accepted.
7. 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) were to be offered the opportunity to complete a withdrawal questionnaire.

## Trial withdrawal criteria

To safeguard participant safety, explicit withdrawal criteria were defined.

- Any participant exhibiting an ALP greater than ten times their baseline value was to be withdrawn from the study.
- A rise in bilirubin exceeding three times baseline or ALT greater than five times baseline could be considered grounds for withdrawal at the discretion of the PI.

## Trial conduct

The trial was conducted in adherence with the Declaration of Helsinki (2008), principles of Good Clinical Practice (GCP), Medicine of Human Use Clinical Trials 2004, Human Tissues Regulations (2007), and UK Data protection Act.

## Safety monitoring and reporting

A trial safety committee was selected and were responsible for providing independent oversight of the trial. The Trial Management Group (TMG) periodically reviewed SAE rates. Any emerging concerns of potential toxicity were to be discussed with the safety committee. Safety data of reported non-serious adverse events and suspected unexpected serious adverse reactions (SUSAR) were also to be presented and reviewed by the safety committee.

Adverse events were captured at each study visit from the first dose of the intervention to week 12 (as per study protocol). All AEs were reported and graded in accordance with Common Terminology Criteria for Adverse Events v5.0 (CTCAE) criteria (1 indicating mild and 5 indicating death). The adverse event form contained the following information: description, severity (using CTCAE v5.0), date of onset, end date or if the AE was ongoing, seriousness. Any SAEs were recorded and promptly reported to the Norwich Clinical Trials Unit (NCTU) within 24 hours of the investigator becoming aware. NCTU was responsible for the reporting of SUSARs and other SARs to the sponsor, regulatory authorities MHRA and the RECs as appropriate. Fatal and life threatening SUSARs were to be reported to the competent authorities within seven days of NCTU becoming aware of the event; other SUSARs were to be reported within 15 days. Acute flares of cholangitis were exempt from being reported as a SAE, due to the natural history of the disease, but were routinely recorded as trial outcome data.

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

**Definitions**

The definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP applied to this trial (Table 4-2)

**Table 4-2**: Adverse event definitions

| Definition | Description |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product. |
| **Adverse Reaction (AR)** | Any untoward and unintended response to an investigational medicinal product related to any dose administered/trial treatment. |
| **Unexpected Adverse Reaction (UAR)** | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorised product or summary of product characteristics (SmPC) for an authorised product or treatment |
| **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)** | Any AE or AR that at any dose:<br>• resulting in death<br>• is life threatening<br>• requires hospitalisation or prolongs existing hospitalisation<br>• resulting in persistent or significant disability or incapacity<br>• is a congenital anomaly or birth defect<br>• or is another important medical condition |
| **Suspected Unexpected Serious Adverse Reaction** | A serious adverse reaction that is assessed as being unexpected, it is unexpected if its nature and severity are not consistent with information known about the medicinal product. |

Adverse events for the purpose of the *SABR-PSC* trial include:

- An exacerbation of a pre-existing illness.
- An increase in the frequency or intensity of a pre-existing episodic event or condition.

- A condition (regardless of whether present prior to the start of the trial) that is detected after trial drug administration (not including pre-existing conditions recorded as such at baseline – as they were not detected after trial drug administration).
- Continuous persistent disease or a symptoms present at baseline that worsen following administration of the trial treatment.
- Any clinically significant laboratory result changes from baseline.
- Hypersensitivity reaction.
- Infections.
- Any hospital admission after trial drug administration.
- New diagnosis or history of depression/suicidal ideation or behaviour.

**Expected adverse events with brodalumab (Kyntheum)**

The SmPC lists all potential adverse reactions reported with brodalumab. The most frequently reported adverse reactions for brodalumab are arthralgia, headache, fatigue, diarrhoea and oropharyngeal pain. Adverse reactions from clinical trials and post-marketing experience are listed by MedDRA (medical dictionary for regulatory activities) system organ class as outlined in Table 4-3. Adverse reactions are ranked by frequency based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

**Table 4-3.** Adverse reactions associated with brodalumab from clinical trials and post marketing surveillance. Adapted from Electronic Medicines Compendium (433).

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| Infections and infestations | Common | Influenza, tinea infections (including tinea cruris, pedis and versicolor) |
| | Uncommon | *Candida* infections (including oesophageal, oral or genital) |
| Blood and lymphatic system disorders | Uncommon | Neutropenia |
| Immune system disorders | Rare | Anaphylactic reaction |
| Nervous system disorders | Common | Headache |
| Eye disorders | Uncommon | Conjunctivitis |
| Respiratory thoracic and mediastinal disorders | Common | Oropharyngeal pain |
| Gastrointestinal disorders | Common | Nausea<br>Diarrhoea |
| Musculoskeletal skeletal and connective tissue disorders | Common | Arthralgia<br>Myalgia |
| General disorders and administration site conditions | Common | Fatigue<br>Injection site reactions (e.g., erythema, pain, haemorrhage, puritis, bruising) |

**Trial oversight and monitoring**

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes relate to participant enrolment, consent, eligibility, adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and to verify

adherence to the protocol, good clinical practice frameworks and applicable regulatory requirements. Independent trial oversight was conducted by the sponsor and NCTU. NCTU conducted central trial monitoring with the sponsor conducting on-site monitoring. In multicentre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the *SABR-PSC* Quality Management and Monitoring Plan.

**Trial Management Group**

A Trial Management Group (TMG) was set up to assist with developing the design, co-ordination and strategic management of the trial. The TMG met at least every 6 months to discuss the general progress of the trial, review all AEs and issues relating to recruitment. Key member included the Chief Investigator, the NCTU research lead, head of research strategy at PSC Support, *SABR-PSC* primary investigators, the trial statistician, including representatives from the sponsor and data management teams.

**Independent Trial Steering Committee**

The Independent Trial Steering Committee (TSC) was established as an independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provided advice to the Chief Investigator, NCTU, the funder and sponsor on all aspects of the trial. The TSC met bi-annually to discuss the general progress of the trial, review recommendations from the safety committee, and provide advice to the TMG on aspects of trial conduct. The TSC has independent and non-independent members. The TSC membership consists of the Chief Investigator, an experienced independent consultant hepatologist at an external institution, an experienced consultant independent gastroenterologist at an external institution (specialising in IBD), and two independent PSC patient representatives.

**Safety committee**

A Safety Committee took the place of a Data Monitoring Committee. A Safety Committee was established, and membership consisted of two experienced independent consultant physicians (one gastroenterologist and one hepatologist at external institutions) independent of the trial with extensive clinical trial experience. The Safety Committee met twice a year for the duration of the trial. The safety committee was established to:

- To review all reports and reported AEs/SAEs/SARs/SUSARs, and to provide an opinion as to whether reported safety events were as expected in this patient cohort.
- To detect any trends, such as increases in un/expected events and take appropriate action.
- To seek additional advice or information from investigators where required.
- Make recommendations to the TSC on trial progress and trial continuation.
- To evaluate the risk of the trial continuing as originally designed and take appropriate action where necessary.
- Meet following the enrolment of the 9$^{th}$ participant with quiescent IBD treated with brodalumab, to ensure there were no adverse safety signals before recruiting the final ten participants with mild IBD.

**Statistical analysis and outcomes**

The prevalence of AEs was calculated together with a 95% confidence interval (using the Clopper-Pearson exact approach). This was done for all major categories of AEs. Within a sample size of 20, there would be an 88% chance of observing at least one AE of any events that occur with a probability of 10% or more within this population; for an event occurring with a probability of 5% or more, the chance of observing at least one will be 64%.

The primary outcomes of the study were feasibility measures, which were summarized using descriptive statistics. Baseline characteristics are presented separately. Categorical variables are presented as frequencies and percentages, while recruitment and retention rates are displayed with corresponding 95% confidence intervals.

Changes in efficacy outcomes are summarized as a mean change from baseline with corresponding 95% confidence intervals under the assumption the change followed a normal distribution. Where normality was not met, a logarithmic transformation was applied. The analysis was exploratory in nature and not intended to provide definitive efficacy inferences but rather to monitor for potential deterioration in these outcomes.

Brodalumab's effect on participants PROM's such as 5-D itch, CLDQ-PSC and PSC-PRO score (outlined below) was assessed at each scheduled timepoint and the absolute change from baseline to week 16 reported with a 95% confidence interval for mean change. Discussions on statistical analysis were coordinated with and approved by the NCTU trial statistician.

**Questionnaires**

- PSC-PRO (434): is a validated disease specific questionnaire frequently employed in clinical trials of patients with PSC to derive QoL outcomes. It covers 42 items across two domains: 'symptoms' and 'impact of symptoms'. Domains one and two are scored separately. A higher score indicates worse disease related QoL. For module one- symptoms, the scores ranges from 0-10. The maximum additive score for module one is 120. For module two- impact of symptoms, the individual domain scores range from 0-5. The summed domain means provides a total for the impact on QoL.

- 5-D itch (435): is a validated QoL questionnaire for patients with chronic puritis and measures itch in five domains: degree, duration, direction, disability, and distribution. The scores of each of the domains are scored separately then summed together to acquire a total 5-D itch score, each domain equating to a maximum score of five. The total scores range between 5= no puritis and 25= most severe puritis. Domain scores for duration, degree and direction correlate to the scores indicted below the response choice (range 1-5). To obtain a score for the disability domain, single highest score on any of the 4 items (i.e., sleep/school/housework and social activities/work and errands) was recorded. The distribution domain contains 16 sited locations of potential itch.
- CLDQ-PSC (436): is a validated PSC specific HRQoL PROM. CLDQ is a shorter form and designed to supplement the PSC-PRO. The CLDQ-PSC PRO is a 24 item PRO represented across five domains (fatigue, sleep, worry, emotional and systemic symptoms). The total score is calculated as an average of the five domains. A higher score indicates better HRQoL.
- Patient Health Questionnaire (PHQ-9) (437): is a validated self-administered instrument to detect severe depression and is frequently used in primary care settings. PHQ-9 is a nine item depression tool itemising depression symptoms, with the cumulative score indicting severity. Each individual question had a maximum score of three with the total score being out of 27. A total score of ≥ 20 indicated severe depression. Questions include: feelings of anhedonia, fatigue, poor sleep, or difficulty concentrating. It was the responsibility and at the discretion of the PI to interpret the results of the PHQ-9 score in the context of PSC as fatigue and puritis are common symptoms in patients with PSC and may influence the results (sleep deprivation/fatigue) without indicating objective evidence of depression.

Patients lived experience and perception of the trial were explored as part of the week 16 semi-structured audio-recorded interview and exit questionnaire (Appendix D and E respectively). The proportion of participants that indicated they would wish to participate in a future larger-scale RCT of

brodalumab (if there was an opportunity to do so) was calculated as a percentage of the total number of trial participants.

**Data Management**

Data was captured using the electronic Case Report Form (eCRF) on the purpose built and approved *SABR-PSC* database by the Chief Investigator, paper CRFs were also held in written form. Data was entered under the participants participant identification (PID) number onto the central database stored on the servers based at NCTU. Access to the database required a unique, individually assigned (i.e., not generic) username and password, and only accessible to members of the *SABR-PSC* trial team, and external regulators where requested. The servers are protected by firewalls and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database and associated code were developed by NCTU Data Management, in conjunction with the Chief Investigator. The database software provided a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

The identification, screening, and enrolment logs, linking participant identifiable data to the pseudonymised PID, were held locally by the trial site. This was held in written form (paper CRF) in a locked filing cabinet at the Norwich clinical research facility.

**Trial approvals**

Ethical approval for this study was granted by the London Bridge Research Ethics Committee (REC23/LO/0718) on the 25/10/2023 (Appendix F). Medicines and Healthcare Regulatory Agency (MHRA) approval was obtained on 26/10/2023 (Appendix G). Sponsor site activation was obtained on the 01/02/2024 at NNUH. The trial was registered with the ISCRTN registry (ISRCTN15271834).

**Protocol Amendments**

The *SABR-PSC* pilot study was originally designed to include patients with PSC-IBD only, and to exclude participants overlapping concomitant liver disease. However, it became apparent following the analysis of results from the pre-trial feasibility study and commencement of recruitment that enrolment would be challenging and likely inadequate to meet the agreed sample size of five participants at NNUH (20 participants total across all sites). Sponsor, NCTU and Health Research Authority (HRA) approval was obtained for two minor amendments in relation to this: (i) firstly, to expand the inclusion criteria to include patient with and without concomitant IBD and (ii) to permit participants with non-clinically significant MASLD, as judged by the recruiting clinician.

The *SABR-PSC* pilot study was initially designed to recruit participants across four large UK NHS hospital trusts (Norfolk and Norwich University Hospital; University Hospital Birmingham; John Radcliffe Hospital, Oxford; Cambridge University Hospital), selected for their prior experience in conducting clinical trials and anticipated ability to deliver the target sample size of 20 participants. However, delays and operational challenges encountered with study set-up at several sites revealed that additional measures were necessary to ensure adequate recruitment. In response, within four months of site activation at NNUH an additional minor amendment was approved by the Sponsor, NCTU and HRA. This amendment enabled (i) the inclusion of additional NHS sites with the requisite

capacity and capability to conduct the study, (ii) over-recruitment at NNUH, provided the overall sample size did not exceed 20 participants, and finally (iii) an extension of the recruitment period from 31st December 2024 to 31st March 2025.

A substantial amendment was submitted on the 4th of September 2025, following NIHR approval of a six month no-cost extension. This amendment sought to further extend the recruitment period to 30th November 2025. Final regulatory approvals from MHRA, HRA and REC remain pending.

**Patient and public Involvement (PPI)**

PSC Support played an instrumental role in design of the study and development of patient-facing documentation through consultation with a dedicated PSC PPI group. A patient forum of 10 individuals suffering from PSC was convened to discuss key trial features, including acceptability of a single-arm open-label design, administration of a novel repurposed subcutaneous intervention, and attitudes towards invasive assessments such as colonoscopy and liver biopsy. Their feedback was incorporated into the protocol to support achievement of the trial's objectives. Forum participants considered the study to be timely, relevant and important. In addition, the Head of Research Strategy at PSC Support served as a member of the TMG, and two individuals living with PSC contributed as members of the Trial Steering Committee. PSC Support also shared details of *SABR-PSC* with the wider PSC community and will assist with dissemination of the study findings on completion.

**Funding source**

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

**SABR-PSC protocol paper**

The *SABR-PSC* pilot study protocol (333) was published before completion of the trial.

The extension of CONSORT 2010 checklist for reporting of pilot and feasibility trials (available in Appendix H) was used for reporting of the results (438).

## 4.5 Results (Quantitative)

### 4.5.1 Baseline demographics and quantitative feasibility outcomes

**Recruitment and retention**

Between 01/02/2024 and 31/03/2025, 244 patients were assessed against the protocol-defined inclusion and exclusion criteria for eligibility as outlined in the CONSORT diagram (Figure 4-2). Of these 215 did not meet eligibility criteria and were excluded. The remaining 29 patient were invited to participate in the study.

Between 16/04/2024 and 31/03/2025 nine patients provided written informed consent and subsequently underwent screening procedures. Of these, three were identified as screen failures (see Figure 4-2 and Appendix I for comprehensive details). One participant was classified as a screen failure due to radiological evidence of hepatic steatosis. However, acknowledging the high global prevalence of hepatic steatosis, and that our cohort was similarly affected, a minor protocol amendment was submitted and approved by HRA on 01/05/2024. Within this, the inclusion criteria were revised to permit enrolment of participants presenting with non-clinically significant MASLD at the clinician's

discretion. Practically, this amendment permitted the inclusion of patients without evidence of hepatic steatohepatitis and/or significant cardiometabolic comorbidities (e.g., obesity, hyperglycaemia/type II diabetes mellitus, dyslipidaemia and/or hypertension). As a result, this participant was later rescreened and enrolled in the study under the revised eligibility criteria.

Of the 244 patients pre-screened for eligibility at NNUH, 29 (11.9%; 95% CI 8.1-16.6) were identified as potentially eligible (i.e., meeting inclusion criteria 3 and 4, without obvious evidence of meeting any exclusion criteria) and were invited to participate. Of these, 20 (69%) declined, were identified as being ineligible after detailed medical review or could not be reached by the study team. Of the remaining nine (31%; 95% CI 15.3-50.8) provided written informed consent to enrol in the study. In total, only 2.5% (6/244; 95% CI 0.9-5.3) of the known available PSC patient cohort at NNUH were eligible and willing to participate in the study.

In total, six participants (6/9, 67% of screened participants) were successfully enrolled in the study and contributed data for safety, feasibility and exploratory efficacy analyses. Table 4-4 outlines the monthly recruitment rates for each selected site. Of the five sites, two received sponsor green light activation however only one (NNUH) was successful in recruiting participants. The average monthly recruitment rate at NNUH was 0.64 (95% CI 0.29-1.22) participants per month. All enrolled participants completed the study and received all scheduled doses of the intervention as per protocol, with a retention rate of 100% (95% CI 54.1-100). There were no participant withdrawals or losses to follow-up over the course of the study.

A total of 19 patients directly contacted the Chief Investigator to express interest in study participation. The majority (58%) were located in Birmingham or London (Figure 4-3), with one patient

located in Northern Ireland and another residing in North America. To enhance recruitment efforts NCTU and Sponsor approved a formal referral process whereby self-referred, interested and potentially eligible patients from external sites could be referred by their primary hepatologist to Dr Rushbrook at NNUH for their ongoing care and appropriate screening. Two of these 19 patients confirmed their ability to travel to NNUH, the sole active recruitment site at the time, and subsequently underwent preliminary eligibility assessment conducted by their primary local hepatologist. One patient was subsequently deemed ineligible due to a history of concomitant liver disease, while another required an updated surveillance colonoscopy for preliminary eligibility assessment, which was not completed before the recruitment deadline.

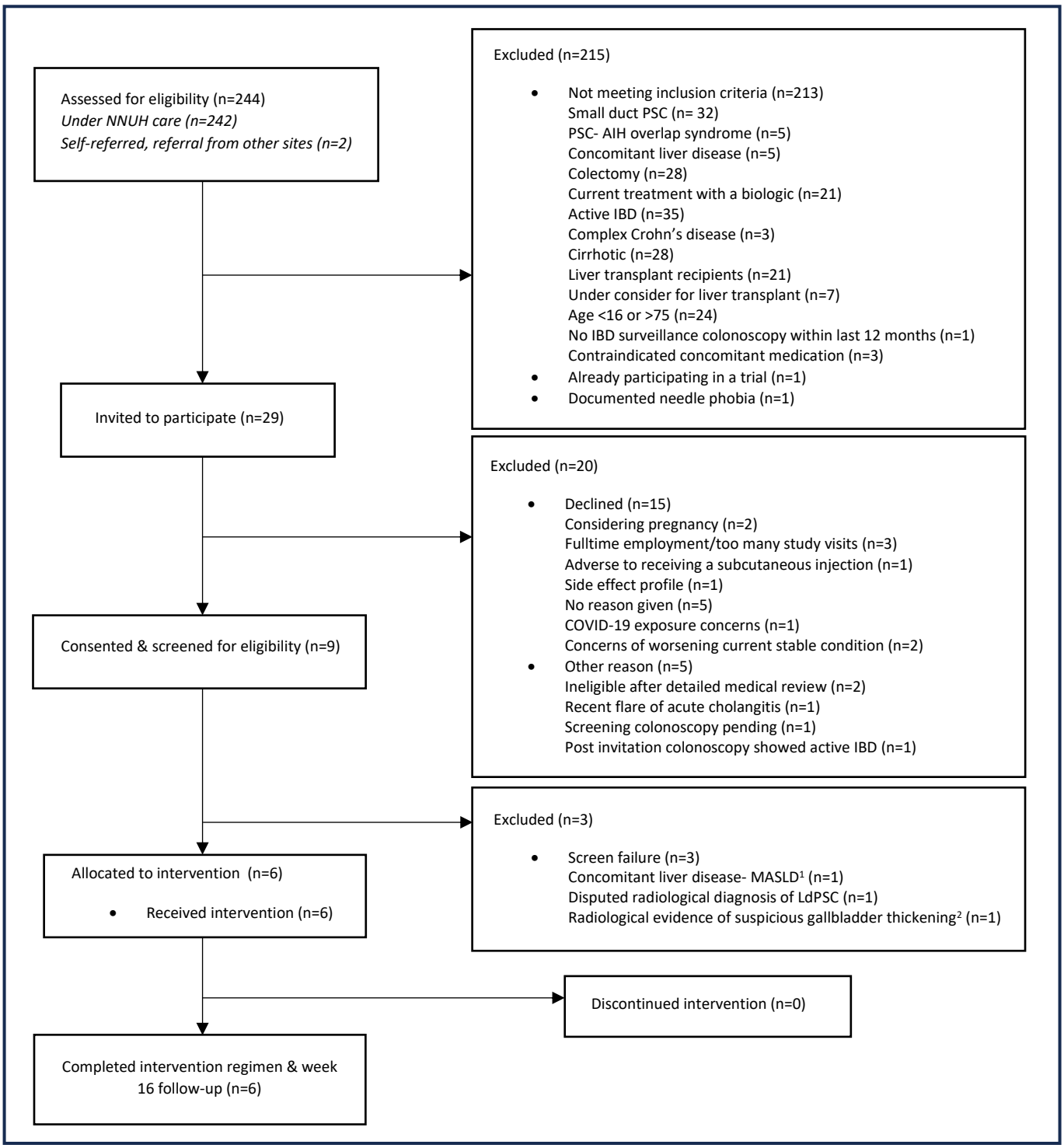


**Figure 4-2.** CONSORT diagram of patient flow

Abbreviations: AIH, autoimmune hepatitis; IBD, inflammatory bowel disease; LdPSC, large-duct primary sclerosing cholangitis; MASLD, metabolic dysfunction associated steatotic liver disease; PSC, primary sclerosing cholangitis; SdPSC, small-duct primary sclerosing cholangitis.

1.Protocol was later amended to allow inclusion of patients with non-clinically significant MASLD, this patient was later rescreened and enrolled in the study.

2. Patient referred for cholecystectomy.

**Table 4-4.** Contributing NHS site enrolment metrics including monthly recruitment rates

| Site | Number | Recruitment time (months) | Rate (95% CI) |
|---|---|---|---|
| Norfolk and Norwich University Hospital (NNUH) | 9 | 14 | 0.64 (0.29-1.22) |
| Nottingham University Hospital (NHT) | 0 | 1.8 | 0 |
| University Hospital Birmingham (UHB) | 0 | 0 | 0 |
| John Radcliffe Hospital (JRH) | 0 | 0 | 0 |
| Addenbrookes Hospital (CUH) | 0 | 0 | 0 |
| **Cumulative Total** | 9 | 15.8 | 0.57 (0.26-1.08) |

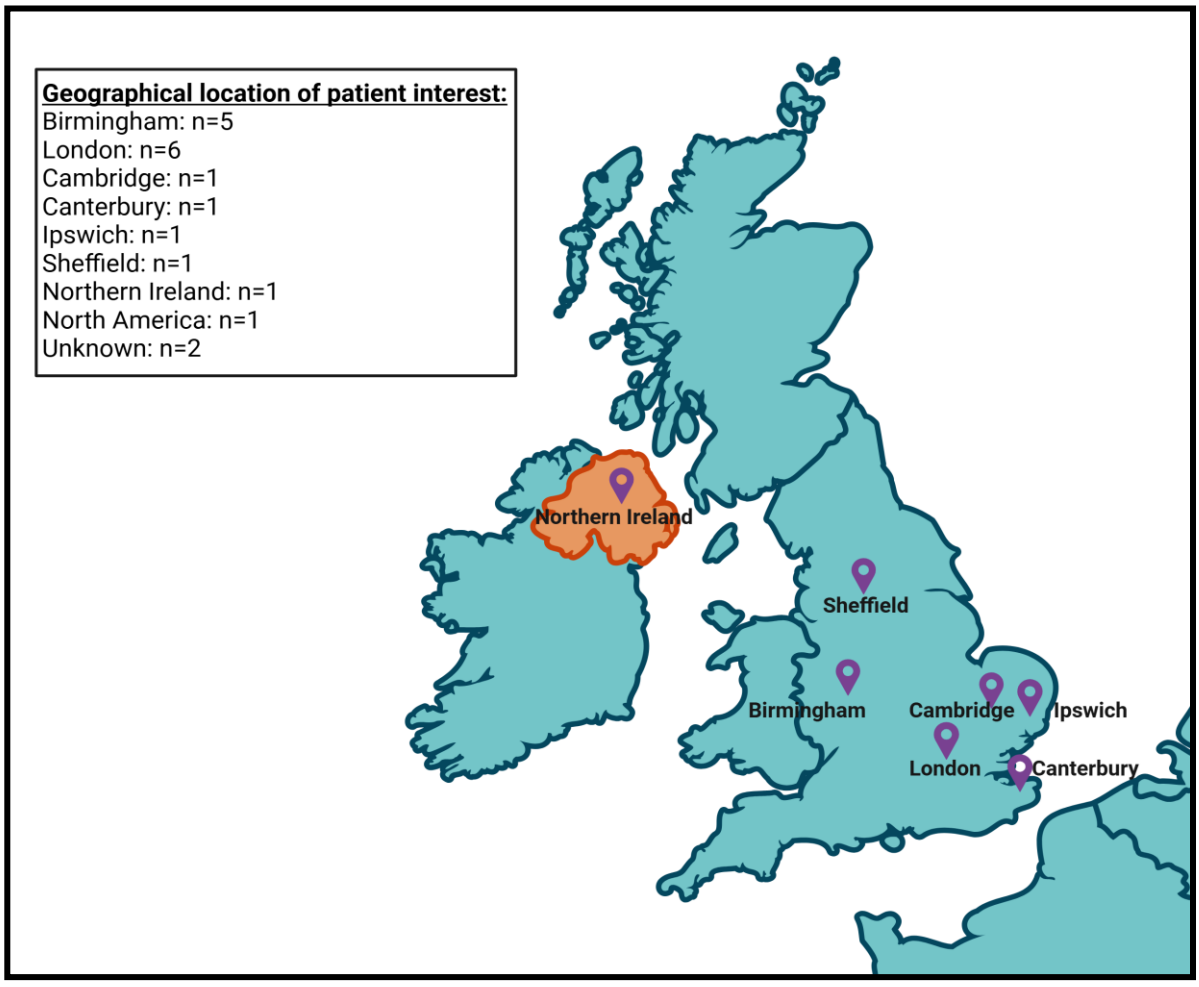


**Figure 4-3.** Geographical distribution of patients expressing interest in *SABR-PSC* trial participation.

**Baseline characteristics**

Baseline characteristics are summarised in Table 4-5 and are reflective of the expected population demographics of PSC. The majority of participants were male (83.3%), and all were of White European decent. The median age at enrolment was 37.5 years (IQR 26-69). Two-thirds (66.7%) of participants were receiving UDCA therapy at baseline, which was maintained throughout the study (no participants were concomitantly treated with fibrates). The median body mass index (BMI) was 28.5kg/$m^2$ (IQR 26.9-29.5). Half of the cohort (50%) had a concomitant diagnosis of PSC associated IBD, with UC as the exclusive phenotype, of whom one-third (33.3%) received 5-ASA therapy. All PSC-UC participants were in remission at baseline, with a pMayo score of ≤1. Assessment of colonic disease activity in all participants at baseline confirmed absence of active inflammation, with a median FC level of 28µg/g (IQR 7-51; ULN 200µg/g). All participants with PSC-IBD demonstrated clinical, biochemical and histological remission at baseline, in accordance with the two-step recruitment process for IBD patients outlined in Chapter 4-4.

**Table 4-5** Baseline demographics and clinical characteristics of participants receiving brodalumab (n = 6).

| **Characteristic** | **Brodalumab (n = 6)** |
|---|---|
| Age at enrolment, years | 37.5 (26-69) |
| Age at diagnosis, years | 32.8 (25.0-34.4) |
| Male, n (%) | 5 (83.3) |
| White race, n (%) | 6 (100) |
| BMI (kg/m$^2$) | 28.5 (26.9-29.5) |
| Smoking status, n (%) | |
| Current | 0 |
| Ex-smoker | 3 (50) |
| Never | 3 (50) |
| **PSC phenotype, n (%)** | |
| Intrahepatic only | 1 (16.7) |
| Intrahepatic and extrahepatic | 5 (83.3) |
| **Inflammatory Bowel Disease, n (%)** | 3 (50) |
| Ulcerative colitis | 3 (100) |
| Crohn's disease | 0 |
| Indeterminate | 0 |
| Faecal calprotectin, µg/g (ULN 200) | 28 (7-51) |
| Concomitant 5-ASA therapy, n (%) | 2 (33.3) |
| Concomitant UDCA therapy, n (%) | 4 (66.7) |
| Alkaline phosphatase (ALP), U/l | 141 (84-211) |
| **Gamma-glutamyl transferase (GGT), U/l** | 139 (59-293) |
| **Alanine aminotransferase (ALT), U/l** | 58 (30-68) |
| **Aspartate aminotransferase (AST), U/l** | 43 (25-67) |
| Bilirubin, µmol/l | 11 (7-20) |
| INR | 1 (0.95-1.03) |
| Albumin, g/dL | 42.5 (40-45) |
| Liver stiffness (VCTE), kPa | 7 (5.7-8.5) |
| Enhanced Liver Fibrosis (ELF) score | 8.5 (8.0-9.6) |

Abbreviations: BMI, body mass index; INR, international normalised ratio; UDCA, ursodeoxycholic acid; VCTE, vibration controlled transient elastography; 5-ASA, 5-aminosalycilic acid.
*Values are presented as median (IQR) or frequency (%) unless otherwise indicated.

**Baseline characteristics between groups**

To assess whether the treated cohort differed meaningfully from other potentially eligible PSC patients, baseline demographics, clinical characteristics and biochemistry of enrolled participants were compared with those of screen-failed individuals (Table 4-6). This data is presented in Table 4-5. Values are presented descriptively only; no formal statistical testing was performed due to small groups sizes (n = 6 vs. n = 3 respectively) and the exploratory intent of this comparison.

**Table 4-6** Comparison of baseline demographics, clinical characteristics and biochemical parameters between participants receiving brodalumab (n = 6) and those recruited but screen failed.

| **Characteristic** | **Brodalumab (n = 6)** | **Screen failed (n = 3)** |
|---|---|---|
| Age at enrolment, years (range) | 37.5 (26-72) | **61 (26-75)** |
| Male, n (%) | 5 (83.3) | 2 (66.7) |
| White race, n (%) | 6 (100) | 3 (100) |
| BMI (kg/m$^2$) | 28.5 (26.9-29.5) | **34.9 (25.4-35.3)** |
| Smoking status, n (%) | | |
| Current | 0 | 0 |
| Ex-smoker | 3 (50) | 2 (66.7) |
| Never | 3 (50) | 1 (33.3) |
| **PSC phenotype, n (%)** | | |
| Intrahepatic only | 1 (16.7) | 1 (33.3) |
| Intrahepatic and extrahepatic | 5 (83.3) | 1 (33.3) |
| Small-duct PSC (revised diagnosis) | | 1(33.3) |
| **Inflammatory Bowel Disease, n (%)** | 3 (50) | **1 (33.3)** |
| Ulcerative colitis | 3 (100) | 1 (100) |
| Crohn's disease | 0 | 0 |
| Faecal calprotectin, µg/g (ULN = 200 µg/g) | 28 (7-51) | **121.5 (4-239)** |
| Concomitant 5-ASA therapy, n (%) | 2 (33.3) | 1 (100) |
| Concomitant UDCA therapy, n (%) | 4 (66.7) | 2 (66.7) |
| Alkaline phosphatase (ALP), U/L | 146.5 (93-189) | **172 (66-377)** |
| **Gamma-glutamyl transferase (GGT), U/L** | 149 (62-276) | **76 (50-496)** |
| **Alanine aminotransferase (ALT), U/L** | 58.5 (36-87) | **80 (48-90)** |
| **Aspartate aminotransferase (AST), U/L** | 45.5 (30-54) | **52.5 (31-74)** |
| Bilirubin, µmol/L | 13.5 (13-16) | 13 (13-20) |
| Liver stiffness (VCTE), kPa | 7.0 (5.7-8.5) | **8.0 (7.1-10.6)** |
| Enhanced Liver Fibrosis (ELF) score | 8.5 (8.0-9.6) | 9 (8.0-9.9) |

Abbreviations: BMI, body mass index; ULN, upper limit of normal; UDCA, ursodeoxycholic acid; VCTE, vibration controlled elastography; 5-ASA, 5-aminosalycilic acid.

*Values are presented as median (IQR) or frequency (%) unless otherwise indicated.

Values deemed to be disparate between the two groups are highlighted in bold.

**Treatment adherence**

Adherence was determined based on the number of participants who administered all intervention injections as per treatment schedule and is presented as a percentage of doses taken. Adherence to the study intervention by all participants was excellent (100%; n = 6) throughout the study. There were no non-compliance, missed doses or drug interruptions over the course of the study.

**Data completeness**

Data completeness was excellent across all study parameters, with no missed study visits or missing entries for PROMs despite the administration of multiple instruments at various timepoints. Overall, the only instances of missing data arose from Perspectum's analyses, where MRCP+ sequences, LiverMultiScan or periductal cT1 data could not be generated due to poor image quality or incomplete sequence acquisition at screening or week 16 MRI/MRCP. The overall missing data rate across all Perspectum generated reports was 16.7% (5/30), reflecting that complete high-quality image acquisition during liver MRI/MRCP was not consistently achievable.

### 4.5.2 Safety outcomes

**Adverse events**

The safety profile of brodalumab was systematically monitored throughout the study period. A total of 36 individual adverse events (AEs) were recorded among the six study participants, with all participants (100%) experiencing at least one AE. The majority of events were mild (Grade 1; 31/36, 86.1%), with only two events each classified as moderate (Grade 2; 2/36, 5.6%) or severe (Grade 3; 2/36, 5.6%). There was one case of Grade 3 pruritis that occurred following study intervention completion, this event was transient and resolved with cholestyramine treatment. The most

frequently affected organ systems were laboratory investigations (25.0%; only one of which required further investigation), gastrointestinal disorders (22.2%) and general disorders (13.9%). No life-threatening (Grade 4) or fatal (Grade 5) events occurred. Three patients had at least one laboratory investigation abnormality, the majority of which were Grade 1 in severity. Table 4-7 summarises the safety data, including AEs, listed according to CTCAE v5.0, while Table 4-8 presents the total number of AEs stratified by severity and organ system. Importantly, no SAEs or SUSARs were observed.

When considering unique AEs (where a given AE experienced multiple times by the same participant is only counted once), the most commonly reported AEs of any cause were sore throat (4/31, 12.9%; 95% CI 3.6-29.8), abdominal pain (3/31, 9.7%; 95% CI 2.0-25.8%), and fatigue (3/31, 9.7%; 95% CI 2.0-25.8%). Both sore throat and fatigue are recognised and expected AEs with brodalumab treatment, events were transient and spontaneously resolved. Other frequently observed unique AEs include: Grade 1 ALT increase (2/31, 6.5%; 95% CI 0.8-21.4%), Grade 1 AST increase (2/31, 6.5%; 95% CI 0.8-21.4%), headache (2/31, 6.5%; 95% CI 0.8-21.4% ) and constipation (2/31, 6.5%; 95% CI 0.8-21.4%), primarily affecting the gastrointestinal, nervous system and laboratory investigations organ system categories. Diarrhoea, a recognised side-effect, was uncommon (1/31, 3.2%). Notably, there were no cases of oropharyngeal candidiasis, systemic infections, neutropenia or suicidal ideation or behaviour reported.

One case of cholangitis was suspected radiologically (transient biliary dilatation) at week 16, with corresponding elevations in their AST, ALT and GGT. However, there were no clinical suspicions or definite diagnosis of acute cholangitis based on the Tokyo guidelines 2018 for acute cholangitis (426) prior to the MRI and the participant remained asymptomatic with no systemic symptoms; no concomitant antibiotics or antifungals were administered. There is no corresponding CTCAE v5.0

grading system for mild biliary tract infections not requiring oral intervention and is therefore listed as ungraded in Table 4-7.

This study systematically captured and reported all instances of liver biochemistry worsening (hepatic safety) relative to baseline, including mild and/or transient changes. Two participants (33.3%) experienced worsening of their liver biochemistry from baseline, most commonly ALT, AST and/or GGT, which met CTCAE v5.0 organ system criteria for an AE. One of these corresponded to the participant with radiologically suspected cholangitis. In both participants, liver enzyme elevations meeting CTCAE criteria were first detected at week 12. In the participant with radiologically suspected cholangitis, GGT elevations at week 12 (Grade 1) progressed to Grade 3 at week 16 (four weeks after the final dose of the intervention), returning to baseline levels at 6 months. There were no instances of ALP elevations meeting CTCAE organ system criteria as an AE.

No deaths, hospitalisations, acute flares of colitis, new diagnoses of colitis, or diagnoses of cirrhosis, hepatocellular carcinoma or cholangiocarcinoma occurred during the study. The safety committee convened on three separate occasions, during which all reviewed AEs were categorised as outcome Category A -'no safety concern'. No formal assessment of the relationship between AE events and trial medication were undertaken, as there was no *a priori* requirement in the study protocol to determine relatedness.

**Table 4-7**. Summary of *SABR-PSC* safety data.

| **Safety data** | **Brodalumab (n = 6)** |
|---|---|
| Total Adverse event, n | 36 |
| Number per participant, median (IQR) | 5 (4-8) |
| Participants reporting ≥ 1 AE, n (%) | 6 (100) |
| **Grade, n (%)** | |
| 1 | 31 (86.1) |
| 2 | 2 (5.6) |
| 3 | 2 (5.6) |
| Pruritis | 1 |
| GGT increase | 1 |
| 4 | 0 |
| 5 | 0 |
| Ungraded† | 1 (2.8) |
| Deaths | 0 |
| AEs leading to treatment discontinuation | 0 |
| **CTCAE System Organ Class, n (%)** | |
| Blood | 2 (5.6) |
| Gastrointestinal | 8 (22.2) |
| Abdominal pain | 5 |
| Diarrhoea | 1 |
| Constipation | 2 |
| General disorders | 5 (13.9) |
| Laboratory Investigations | 9 (25.0) |
| Metabolism and nutrition | 1 (2.8) |
| Musculoskeletal | 2 (5.6) |
| Nervous system | 2 (5.6) |
| Respiratory | 4 (11.1) |
| Skin | 2 (5.6) |
| Infection (biliary tract) | 1 (2.8) |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

Adverse events were classified by the investigator as Grade 1-5 using the Common Terminology Criteria for Adverse Events organ system classification version 5.0.

†Event recorded but not assigned a severity grade due to absence of specific grading criteria in CTCAE v5.0.

**Table 4-8**. Total number of individual adverse events stratified by CTCAE system organ class and severity grade

| CTCAE System Organ Class | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Ungraded |
|---|---|---|---|---|---|---|
| Blood | 2 (5.6) | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal | 8 (22.2) | 0 | 0 | 0 | 0 | 0 |
| General disorders | 4 (11.1) | 1 (2.8) | 0 | 0 | 0 | 0 |
| Laboratory investigations | 8 (22.2) | 0 | 1 (2.8) | 0 | 0 | 0 |
| Metabolism and nutrition | 1 (2.8) | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal | 1 (2.8) | 1 (2.8) | 0 | 0 | 0 | 0 |
| Nervous system | 2 (5.6) | 0 | 0 | 0 | 0 | 0 |
| Respiratory | 4 (11.1) | 0 | 0 | 0 | 0 | 0 |
| Skin | 1 (2.8) | 0 | 1 (2.8) | 0 | 0 | 0 |
| Infection | 0 | 0 | 0 | 0 | 0 | 1 |
| **Total** | 31 (86.1) | 2 (5.6) | 2 (5.6) | 0 | 0 | 1 (2.8) |

*Values presented as frequency (%)

**IBD activity**

Assessment of gastrointestinal activity was undertaken using a combination of clinical evaluation, non-invasive surrogate markers of colonic inflammation (FC), colonoscopy and histological assessment. Faecal calprotectin measurements were collected for all participants, with or without IBD, throughout the study period. The median baseline FC (pre-treatment; n = 6) was 28µg/g (IQR 7-51), and levels remained stable throughout the study period. Median FC values at week 4 week and 16 were 27.5 µg/g (IQR 4-32; n = 6) and 29 µg/g (IQR 26-72; n = 5), respectively. There were no statistically significant differences in FC levels between screening and any follow-up time point ($p > 0.05$; see Figure 4-4). The upper limit of normal for FC in this study was set at 200 µg/g.

Clinical assessment of IBD activity using the pMayo score in participants with PSC-UC demonstrated that brodalumab treatment was not associated with any worsening of baseline pMayo scores at any point during the study. Partial Mayo scores from baseline (pre-treatment) through to week 16 for all PSC-UC participants remained ≤1 (n = 3), consistent with colitis remission. All participants who completed the treatment phase also completed the week 16 colonoscopy, regardless of underlying IBD status. Histological assessment confirmed quiescent disease (as determined by the Nancy histological index in patients with known PSC-UC; Nancy Index ≤1; Appendix J) and no new diagnoses of IBD were made in participants with PSC-only.

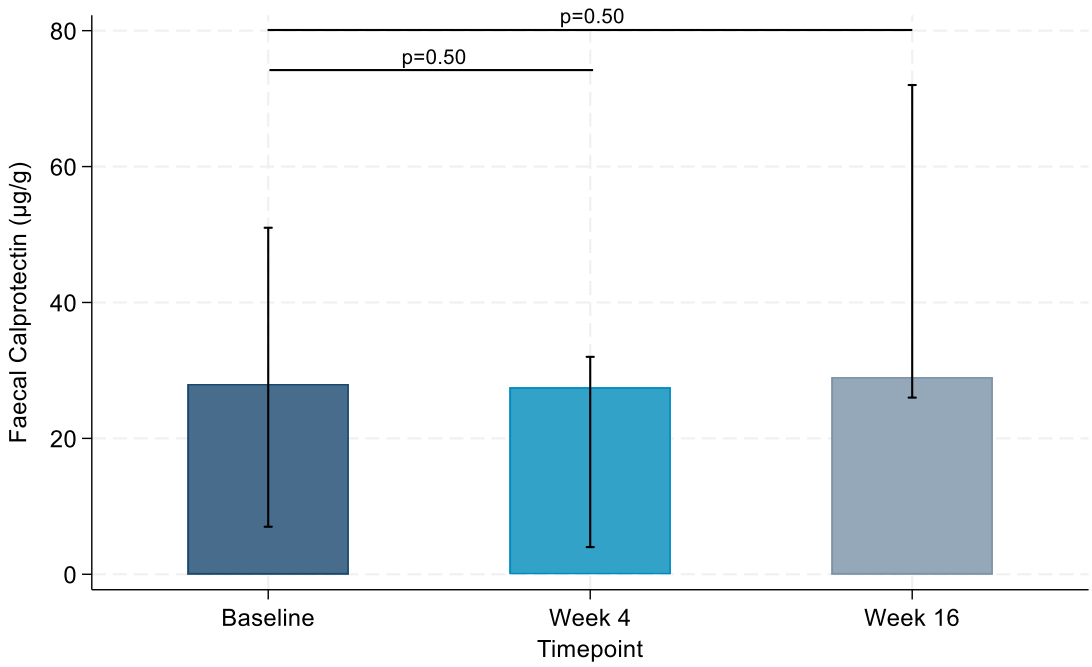


**Figure 4-4.** Faecal calprotectin levels presented at pre (baseline) and post-brodalumab treatment Week 4 and week 16. Faecal calprotectin measurements presented as median values (bars) with IQR shown. Wilcoxon signed-rank test performed for significance.

### 4.5.3 Exploratory efficacy outcomes

**Liver biochemistry and fibrosis markers**

Longitudinal trends and changes from baseline in serum liver biochemistry analytes and non-invasive surrogate markers of fibrosis were evaluated for each participant at each study visit. Despite a non-significant Shapiro-Wilk test for normality (Shapiro-Wilk test, $p > 0.05$), visual inspection suggested skewed distributions for some analytes. Given the positive skew a natural logarithmic transformation was applied to better approximate a normal distribution and stabilise variance. Paired differences were back transformed and geometric mean ratio and associated 95% CI were reported. Statistical analyses were performed using the log transformed values to meet distributional assumptions; however descriptive statistics are presented using the raw data. Given the small sample size and possible non-normality, both mean (with 95% CI) and median (IQR) are reported for each time point.

Table 4-9. summarises the longitudinal trends in all liver biochemical readouts including surrogate markers of liver fibrosis pre and post brodalumab treatment. There is a trend towards a modest reduction in median ALP from baseline (141 U/L, IQR 84-211) following brodalumab treatment to 107 (IQR 90-273) at week 12. This reduction is apparent as early as week 2 (132 U/L, IQR 82-189). At week 16 (4-weeks untreated follow-up period) there is evidence of partial rebound to 114 U/L (IQR 86-115) (Figure 4-5). The mean ALP mirrored this trend. GGT values showed a similar early reduction. Median GGT declined from 139 U/L (IQR 59-293) at baseline to 90.5 U/L (IQR 38-277) at week 4, however the effects were fluctuant at later timepoints. There was little change in median ALT, AST, or bilirubin from baseline to week 12.

**Table 4-9.** Longitudinal trends in liver biochemistry and liver fibrosis markers in participants pre- and post-treatment with brodalumab.

| Variable | Time point | n | Median (IQR) | Mean (SD) | Geometric mean* |
|---|---|---|---|---|---|
| **Alkaline phosphatase (ALP), U/L** | Baseline | 6 | 141 (84-211) | 148.2 (74.5) | 131.7 |
| | Week 4 | 6 | 126.5 (74-191) | 138.3 (72.8) | 122.6 |
| | Week 12 | 6 | 107 (90-273) | 156 (92.9) | 135.8 |
| | Week 16 | 5 | 114 (86-115) | 115 (42.2) | 109.5 |
| | 6 months | 5 | 101 (94-142) | 124.4 (48.8) | 117.7 |
| **Gamma-glutamyl transferase (GGT), U/L** | Baseline | 6 | 139 (59-293) | 181.3 (155.3) | 124.1 |
| | Week 4 | 6 | 90.5 (38-277) | 159.7 (161.1) | 100.0 |
| | Week 12 | 6 | 177.5 (51-267) | 195.3 (155.3) | 141.5 |
| | Week 16 | 5 | 119 (48-196) | 181.6 (194.5) | 114.9 |
| | 6 months | 5 | 142 (44-165) | 126.6 (83.3) | 101.5 |
| **Alanine aminotransferase (ALT), U/L** | Baseline | 6 | 58 (30-68) | 69.8 (62.8) | 51.3 |
| | Week 4 | 6 | 69.5 (25-76) | 71 (55.9) | 53.0 |
| | Week 12 | 6 | 47.5 (37-156) | 92.7 (95.5) | 56.3 |
| | Week 16 | 5 | 38 (20-264) | 96.8 (105.5) | 51.8 |
| | 6 months | 5 | 55 (41-82) | 87.8 (93.6) | 50.3 |
| **Aspartate aminotransferase (AST), U/L** | Baseline | 6 | 43 (25-67) | 45 (20.6) | 40.9 |
| | Week 4 | 6 | 46.5 (25-73) | 47.8 (22.6) | 43.0 |
| | Week 12 | 6 | 47.5 (29-68) | 57.8 (42.1) | 46.1 |
| | Week 16 | 5 | 40 (31-69) | 55 (36.9) | 46.3 |
| | 6 months | 5 | 43 (38-54) | 50.6 (28.5) | 44.8 |
| **Bilirubin, µmol/L** | Baseline | 6 | 11 (7-20) | 18 (18.4) | 12.9 |
| | Week 4 | 6 | 12 (7-31) | 17.2 (13.1) | 13.2 |
| | Week 12 | 6 | 14 (8-35) | 19 (14.5) | 11.9 |
| | Week 16 | 5 | 9 (8-14) | 20.4 (25.7) | 12.7 |
| | 6 months | 5 | 9 (8-15) | 17.2 (17.5) | 12.5 |
| **INR** | Baseline | 6 | 1.00 (0.95-1.03) | 1.01 (0.08) | 1.00 |
| | Week 12 | 6 | 1.01 (0.96-1.08) | 1.01 (0.08) | 1.02 |
| | Week 16 | 5 | 0.98 (0.96-1.03) | 0.99 (0.05) | 0.99 |
| | 6 months | 5 | 1.03 (1.01-1.10) | 1.03 (0.08) | 1.03 |
| **Albumin, g/dL** | Baseline | 6 | 42.5 (40-45) | 42.2 (2.8) | 42.1 |
| | Week 12 | 6 | 41.5 (41-43) | 41.7 (2.9) | 41.6 |
| | Week 16 | 5 | 39.0 (38-39) | 39.8 (2.9) | 39.7 |

| | | | | | |
|---|---|---|---|---|---|
| | 6 months | 5 | 42.0 (42-43) | 42.4 (1.14) | 42.4 |
| **Liver stiffness (VCTE), kPa** | Baseline | 6 | 7.0 (5.7-8.5) | 7.3 (5.0-9.6) | |
| | Week 16 | 5 | 7.3 (5.7-8.4) | 7.6 (3.7-11.6) | |
| **Enhanced Liver Fibrosis** | Baseline | 6 | 8.45 (8.0-9.6) | 8.7 (7.8-9.7) | |
| **(ELF) score** | Week 16 | 5 | 9.67 (9.3-10.4) | 9.6 (8.2-10.9) | |

*Analyte is log transformed for analysis. The back-transformed geometric mean is presented.

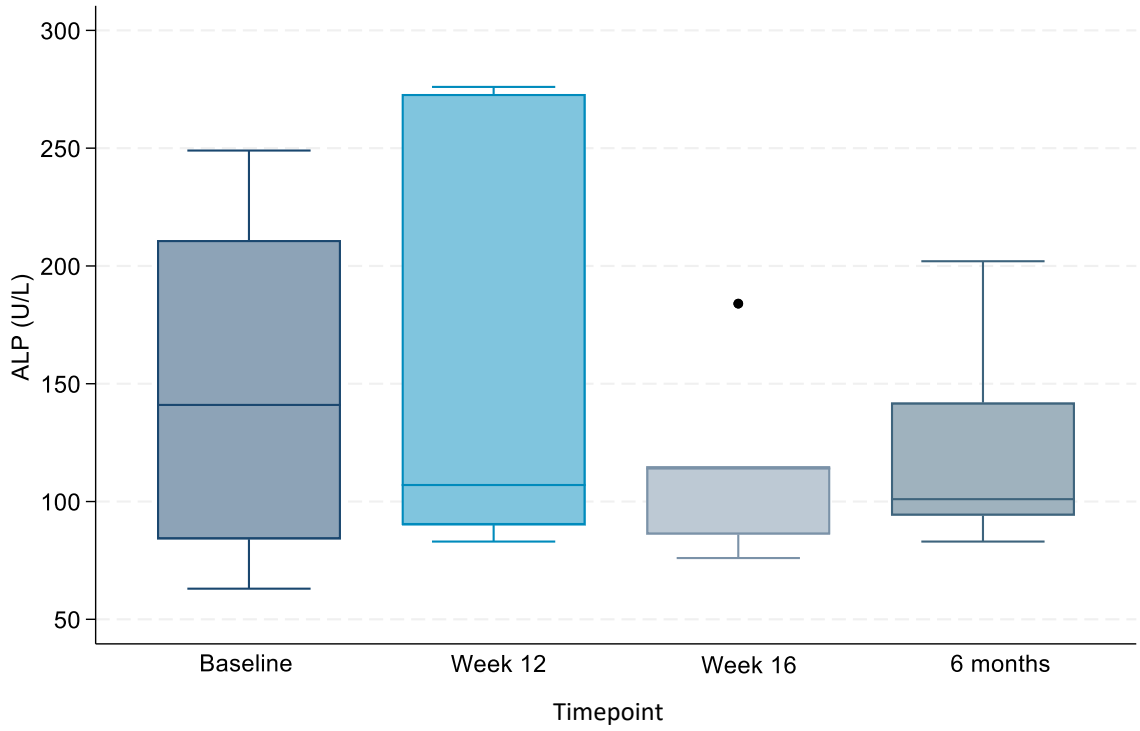


**Figure 4-5.** Box-and-whisker plot showing the distribution of alkaline phosphatase (ALP) levels at baseline and post-treatment in study participants. Number of participants per timepoint: baseline, n=6; week 12, n=6; week 16, n=5; 6 months, n=5.

For more precise analyte changes Table 4-10 summarises changes in liver biochemistry and surrogate fibrosis markers from baseline at each follow-up visit. Median ΔALP concentrations demonstrated a decreasing trend from baseline to week 4 before rebounding back to near/greater than baseline levels at weeks 8–12, with evidence of ALP rebounding to pre-treatment levels by 6 months. The greatest change in median ALP occurred at week 4 (-12 U/L, 95% CI -19.5 to 1.6, p=0.05). This timepoint coincided with the induction phase of the intervention (weekly dosing) before commencing

maintenance dosing on alternate weeks thereafter. This early trend towards reduction is also observed in median GGT up to week 4 (-11.5, 95% CI -83.1 to 8.4; p=0.06), however this did not persist over time and the greatest overall reduction in GGT was observed at 6 months follow-up (median -15, 95% CI -128 to 179; p=0.91). All other parameters (AST, ALT, bilirubin, INR and albumin) remained stable Figure 4-6A and B presents the median change (95% CI) from baseline for ALP, GGT, AST, ALT and bilirubin at each study timepoint.

At the individual level, at week 4, five of six participants had a reduction in ALP (range 0.8-13%). By week 12, 2 participants (n = 6) had evidence of a ≥15% relative reduction in ALP from baseline (17% reduction in one participant and a 41% reduction in another participant). By week 16 the former participants ALP declined further to 20.4%, whereas the later experienced a 46% reduction in serum ALP, normalising their ALP (later participant was not on concomitant UDCA therapy), before inclining again at 6 months. Figure 4-7A and B displays individual ALP and GGT trajectories respectively, over time for each participant, with each line representing one participant's ALP/GGT measurement from baseline to each study timepoint.

Liver fibrosis markers were measured at baseline and week 16. Over the course of the study VCTE scores remained stable whilst ELF scores increased slightly at week 16. There was no evidence of a statistically significant change observed between baseline and week 16 VCTE values (median 0.9kPa, 95% CI -1.5 to 4.6; p=0.36) or ELF score (median 1.02, 95% CI -0.6 to 1.9; p=0.21). A decrease in ELF score by -0.19 from baseline to week 12 has been shown to predict PSC survival from decompensating events, liver transplant or death (162). Of note, two participants experienced a reduction in ELF score of ≥ 0.19 at week 16, one of which had a change of -0.61 and a corresponding reduction of >20% in serum ALP. Three participants had evidence of a >0.19 increase in ELF score post treatment.

**Table 4-10.** Change in liver biochemistry and surrogate markers of liver fibrosis from baseline at each follow-up time point.

| Variable | Time point | n | Median difference (95% CI) | Mean difference (95% CI) | Geometric mean ratio (95% CI)* | p value |
|---|---|---|---|---|---|---|
| **Alkaline phosphatase (ALP), U/L** | Week 2 | 6 | -5 (-20.8 to 28.1) | -1.5 (-20.3 to 17.3) | 0.98 (0.90-1.07) | 0.57 |
| | Week 4 | 6 | -12 (-19.5 to 1.6) | -9.8 (-18.6 to -1.1) | 0.93 (0.87-1.00) | **0.05** |
| | Week 8 | 6 | 6 (-69.2 to 52.4) | -0.6 (-46.5 to 45.2) | 0.98 (0.76-1.27) | 0.83 |
| | Week 12 | 6 | 13 (-80.1 to 94.2) | 7.8 (-56.8 to 72.4) | 1.03 (0.71-1.49) | 0.83 |
| | Week 16 | 5 | -8 (-97 to 52) | -13 (-80.8 to 54.8) | 0.94 (0.54-1.64) | 0.79 |
| | 6 months | 5 | 17 (-69 to 28) | -3.6 (-53.1 to 45.9) | 1.01 (0.72-1.43) | 0.91 |
| **Gamma-glutamyl transferase (GGT), U/L** | Week 2 | 6 | -11.5 (-47.3 to 76.4) | -4.6 (-54.8 to 45.5) | 0.89 (0.73-1.09) | 0.19 |
| | Week 4 | 6 | -11.5 (-83.1 to 8.4) | -21.7 (-58.5 to 15.2) | 0.81 (0.64-1.01) | 0.06 |
| | Week 8 | 6 | -11 (-105.1 to 142.2) | -0.5 (-93.0 to 92.0) | 0.85 (0.61-1.20) | 0.29 |
| | Week 12 | 6 | 20.5 (-138.5 to 145.2) | 14 (-91.3 to 119.3) | 1.14 (0.57-2.28) | 0.65 |
| | Week 16 | 5 | -11 (-174 to 451) | 47.8 (-245.3 to 340.9) | 1.18 (0.28-4.99) | 0.77 |
| | 6 months | 5 | -15 (-128 to 179) | -7.2 (-151.9 to 137.5) | 1.04 (0.39-2.81) | 0.91 |
| **Alanine aminotransferase (ALT), U/L** | Week 2 | 6 | 1.5 (-8.9 to 36.3) | 4.8 (-14.1 to 23.7) | 1.09 (0.84-1.4) | 0.42 |
| | Week 4 | 6 | 2.5 (-17.6 to 13.8) | 1.2 (-11.6 to 14.0) | 1.03 (0.87-1.22) | 0.64 |
| | Week 8 | 6 | -1 (-19.4 to 30.2) | 0.3 (-19.2 to 19.5) | 0.99 (0.71-1.38) | 0.92 |
| | Week 12 | 6 | 6.5 (-28.3 to 89.5) | 22.8 (-26.1 to 71.8) | 1.10 (0.63-1.90) | 0.68 |
| | Week 16 | 5 | -2 (-30 to 100) | 23.4 (-43.9 to 90.7) | 1.01 (0.48-2.16) | 0.96 |
| | 6 months | 5 | 11 (-13 to 58) | 14.4 (-19.3 to 48.1) | 1.10 (0.80-1.50) | 0.46 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Aspartate aminotransferase (AST), U/L** | Week 2 | 6 | 0 (-4.8 to 22.2) | 3.7 (-7.5 to 14.8) | 1.09 (0.89-1.32) | 0.33 |
| | Week 4 | 6 | 2.5 (0 to 6.8) | 2.8 (-0.1 to 5.8) | 1.05 (1.00-1.11) | 0.06 |
| | Week 8 | 6 | 3 (-18.3 to 25.8) | 4.2 (-12.7 to 21) | 1.05 (0.80-1.38) | 0.65 |
| | Week 12 | 6 | 4.5 (-23.7 to 62.5) | 12.8 (-20.5 to 46.2) | 1.16 (0.73-1.84) | 0.45 |
| | Week 16 | 5 | 9 (-27 to 43) | 10.8 (-23.8 to 45.4) | 1.17 (0.65-2.11) | 0.49 |
| | 6 months | 5 | 6 (-13 to 27) | 6.4 (-12.2 to 25.0) | 1.13 (0.82-1.57) | 0.34 |
| **Bilirubin, µmol/L** | Week 2 | 6 | -1 (-15.8 to 0) | -4 (-11.0 to 3.0) | 0.80 (0.62-1.02) | 0.06 |
| | Week 4 | 6 | 0 (-16.2 to 10.1) | -0.8 (-10.7 to 9.1) | 1.03 (0.77-1.38) | 0.78 |
| | Week 8 | 6 | -0.5 (-2.9 to 5.4) | 0 (-3.3 to 3.3) | 0.98 (0.82-1.16) | 0.72 |
| | Week 12 | 6 | 1.5 (-13.6 to 13.9) | 1 (-9.1 to 11.1) | 1.11 (0.78-1.57) | 0.48 |
| | Week 16 | 5 | 1 (-2 to 12) | 2.8 (-4.0 to 9.6) | 1.08 (0.86-1.35) | 0.40 |
| | 6 months | 5 | 1 (-6 to 4) | -0.4 (-5.4 to 4.6) | 1.06 (0.76-1.48) | 0.64 |
| **Liver stiffness (VCTE), kPa** | Week 16 | 5 | 0.9 (-1.5 to 4.6) | 1.04 (-1.8 to 3.8) | - | 0.36ł |
| **Enhanced Liver Fibrosis (ELF) score** | Week 16 | 5 | 1.02 (-0.6 to 1.9) | 0.7 (-0.6 to 2.1) | - | 0.21ł |

Abbreviations: INR, international normalised ratio; VCTE, vibration controlled transient elastography

Values represent the change from baseline for each participant at the specified time point. Negative median and mean values indicate a decrease from baseline.

Note: Due to the small sample size and non-normal distribution of data multiple descriptive approaches are shown. This increases the risk of multiplicity, and therefore results should be interpreted with caution.

*Analyte is log transformed for analysis. The back-transformed mean is the geometric mean ratio. Geometric means <1 indicate a reduction in analyte compared to baseline and >1 indicate an increase in analyte compared to baseline. Tests of hypotheses are performed using a paired t-test on log transformed data.

ŁTest of hypothesis performed using non-transformed paired t-test

Number of participants per timepoint: baseline, n=6; week 12, n=6; week 16, n=5; 6 months, n=5.

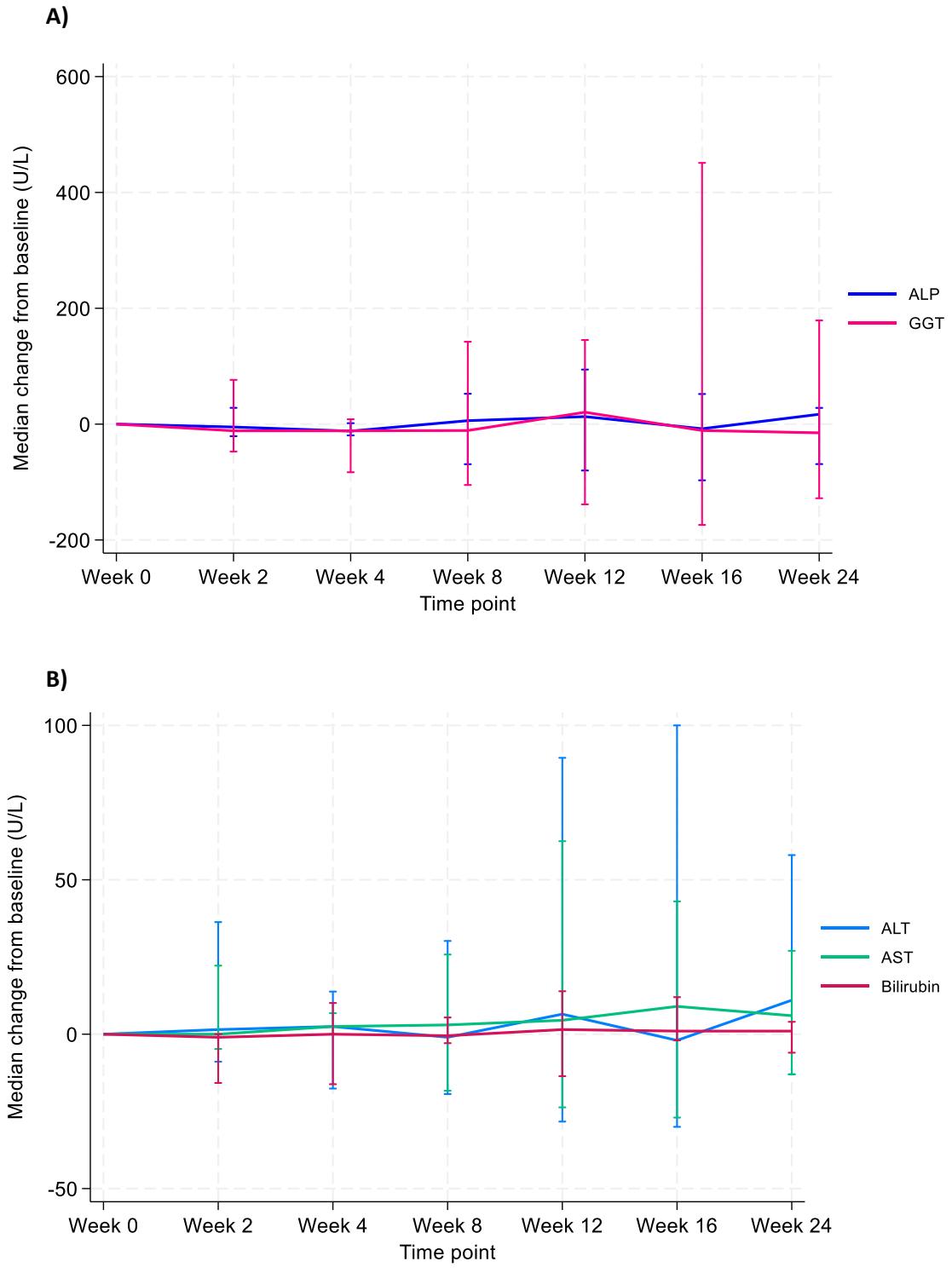


**Figure 4-6.A**. Median (95% CI) change in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) from baseline at each study timepoint. Error bars represent the 95% CI. Negative values represent a reduction in median values from baseline. **Figure 4-6B**. Median (95% CI) change in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin from baseline at each study timepoint. Error bars represent the 95% CI.

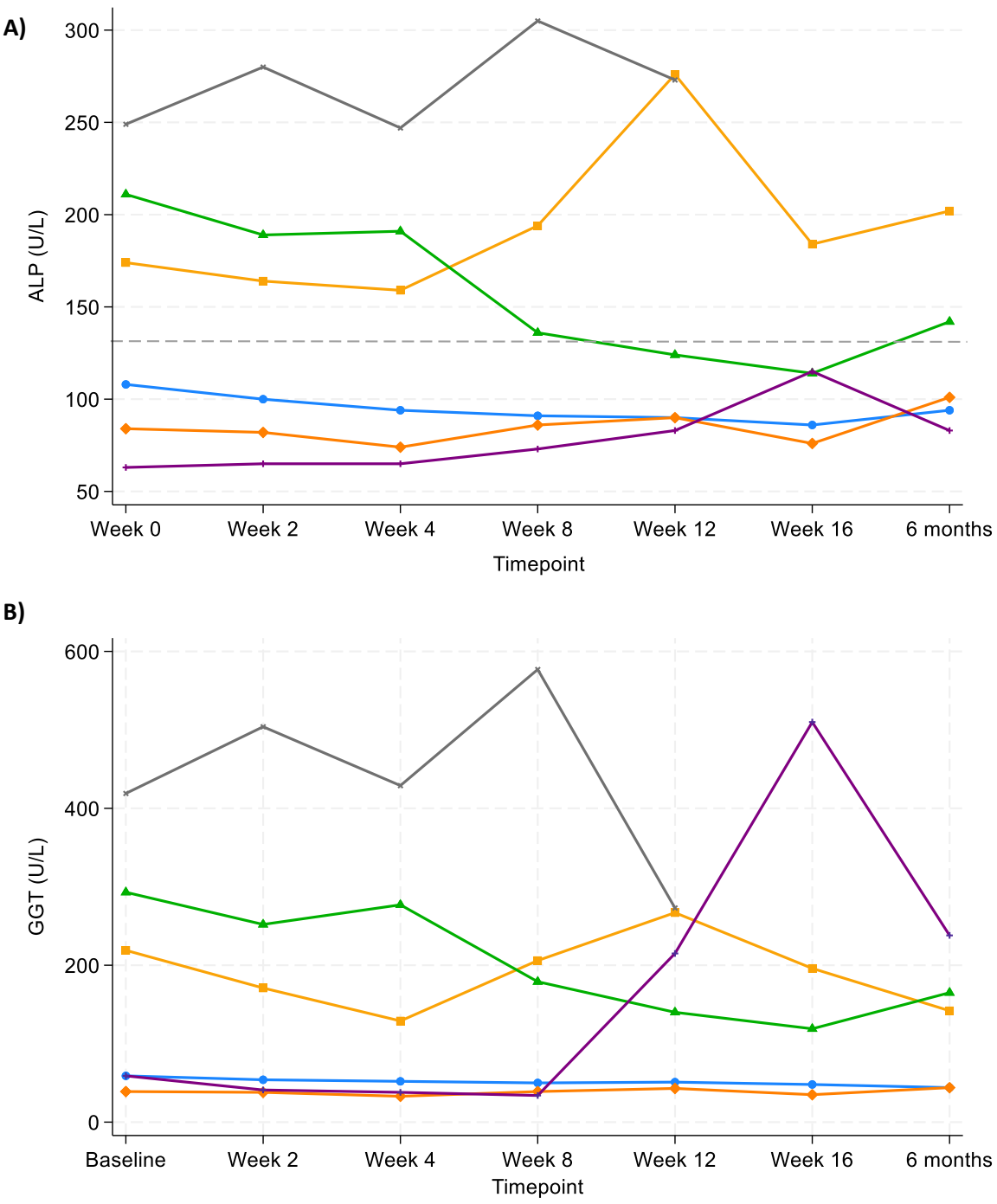


**Figure 4-7A.** Individual alkaline phosphatase (ALP) trends over time for each participant. **Figure 4-7B.** Individual gamma glutamyl-transferase (GGT) trends over time for each participant. Each coloured line represents one participant's ALP/GGT measurement form baseline (week 0) and subsequent study timepoints. The grey dashed horizontal line indicates the upper limit of normal ALP (130 U/L).

**Quantitative MRI metrics (MRCP+, LiverMultiScan)**

All participants (n=6) completed the screening non-contrast MRI liver and MRCP scan, with five participants to date completing their week 16 MRI/MRCP (one participant awaiting week 16 imaging and quantitative post processing). All five participants (with baseline and week 16 imaging) had at least one MRI/MRCP of adequate quality/sequence acquisition to allow for quantitative post processing. Four participants had paired MRCP+ data, and the equivalent had paired LiverMultiScan hepatic cT1 data of adequate quality for analysis and reporting. Three patients had paired periductal cT1 data from combined MRCP+ and LiverMultiScan sequences.

For descriptive purposes all available MRCP+ and LMS data (n=6 at baseline and n=5 at week 16) regardless of pairing are summarized in Appendix K. However, inferential comparisons were restricted to the cohort with paired data available from both baseline and week 16 timepoints.

Paired quantitative MRI metrics for MRCP+ and LMS at baseline and week 16 are shown in Table 4-11. Overall, post-treatment quantitative MRCP+ metrics (n=4) demonstrated no statistically significant change from baseline in ductal or liver parenchymal parameters. The total median number of ducts remained stable (74 [IQR 33-141.5] at baseline vs 73.5 [IQR 48.5-110] at week 16; p=0.56), as did the total median number of candidate strictures (9 [IQR 5-12.5] vs 7 [3.5-9]; p=0.33). Similarly, the total duct length or combined length of strictures and dilations demonstrated no statistical differences (p=0.89 and p=0.87 respectively), although there was evidence of marked inter-individual variability across time points.

On analysis of liver parenchymal tissue characteristics, all pre and post-treatment values remained below the upper limit of normal. Median hepatic cT1 (n = 4) values (ULN: 800ms) decreased modestly

post treatment (738 ms [IQR 702.5-773.5] at baseline vs 718.5 ms [IQR 664.5-772.5]; median difference -19.5ms). Both liver fat fraction (PDFF; ULN: 5%) and iron content (ULN 1.8 mg Fe/g) were low at baseline and remained unchanged at follow-up. Representative MRCP+ and LMS images are presented in Figure 4-8.

One participant exhibited a marked reduction in hepatic cT1 measurement post-treatment. Hepatic cT1 decreased from 706 ms at baseline to 660 ms at week 16 (**Δ**-46 ms). This reduction exceeded that observed in the remainder of the cohort. Figure 4-9 presents individual participants paired hepatic cT1 data (n=4) pre and post-treatment.

Pairwise comparisons of periductal cT1 (n=3) (ULN: 800ms), in ROI (region of interest) 1 showed no significant difference after 13 weeks of treatment (Table 4-12). A nonsignificant but consistent trend towards reduction in periductal cT1 from baseline to week 16 in ROI 2-4 was observed. ROI 1 demonstrated a negligible change (mean 778 to 774.7 ms). In contrast, ROI 2 decreased from 779.7 ms to 750.3 ms (mean difference -29.3 ms) and ROI 4 from 762.3 ms to 741 ms (mean difference -21.3).

Overall, parenchymal and ductal MRI analysis demonstrated stability. Hepatic cT1 and periductal cT1 in ROI 2-4 demonstrated a trend towards reduction. These finding suggest that brodalumab may stabilise or attenuate hepatic and periductal fibroinflammation in PSC, although interpretation should remain cautious due to the small sample size. Further evaluation in larger cohorts is warranted.

**Table 4-11.** Paired MRCP quantitative metrics pre and post-treatment with brodalumab (n=4).

| Quantitative MRI metrics | Baseline median (IQR) | Week 16 median (IQR) | Median difference (95% CI) | Mean difference (95% CI) | p value |
|---|---|---|---|---|---|
| **Number of ducts** | 74 (33-141.5) | 73.5 (48.5-110) | -24.5 (-59 to 46) | -15.5 (-91.5 to 60.5) | 0.56 |
| **Total number of candidate strictures** | 9 (5-12.5) | 7 (3.5-9) | -0.5 (-9 to 0) | -2.5 (-9.4 to 4.4) | 0.33 |
| **Total length of ducts (mm)** | 1667 (638.8-2696.5) | 1762 (1067.9-2125.2) | -237.3 (-998.8 to 1188.7) | -71.1 (-1556.3 to 1413.0) | 0.89 |
| **Total length of candidate strictures and dilatations (mm)** | 136.4 (73.4-248.5) | 163.6 (102.3-197.2) | 16.2 (-184.1 to 107.1) | -11.2 (-206.9 to 184.6) | 0.87 |
| **Liver cT1 (ms)*** | 738 (702.5-773.5) | 718.5 (664.5-772.5) | -19.5 (-46 to-7) | -19.5 (-56.5 to 17.5) | 0.19 |
| **PDFF- Liver fat fraction (%)†** | 2 (1.5-2.5) | 2 (1.5-3.0) | 0 (0 to 1) | 0.3 (-0.5-1.0) | 0.39 |
| **Liver iron concentration ł (mg Fe/g dry tissue)** | 0.5 (0.5-0.6) | 0.6 (0.6) | 0.1 (0 to 0.1) | 0.1 (0 to 0.3) | 0.06 |

Abbreviations: cT1 iron corrected T1; Fe, iron; PDFF, proton density fat fraction.

*ULN:800 ms

†(ULN: 5%)

ł ULN:1.8 mg Fe/g

Paired t-test performed for statistical significance.

Note: Due to the small sample size and non-normal distribution of data multiple descriptive approaches are shown. This increases the risk of multiplicity, and therefore results should be interpreted with caution.

**Table 4-12.** Paired periductal liver inflammation and fibrosis score measured by iron corrected T1 (cT1) pre and post-treatment (n=3) for each region of interest.

| | Baseline | Week 16 | Difference between measurements |
|---|---|---|---|
| **Periductal cT1 (ms)-ROI 1** | | | |
| **Mean** | 778 | 774.7 | -3.33 |
| **Median** | 783 | 804 | 16 |
| **IQR** | 733-818 | 686-834 | -47 to 21 |
| **Periductal cT1 (ms)- ROI 2** | | | |
| **Mean** | 779.7 | 750.3 | -29.3 |
| **Median** | 788 | 779 | -27 |
| **IQR** | 720-831 | 668-804 | -52 to -9 |
| **Periductal cT1 (ms)- ROI 3** | | | |
| **Mean** | 769 | 743.7 | -25.3 |
| **Median** | 782 | 775 | -19 |
| **IQR** | 713-812 | 663-793 | -50 to -7 |
| **Periductal cT1 (ms) -ROI 4** | | | |
| **Mean** | 762.3 | 741 | -21.3 |
| **Median** | 782 | 776 | -15 |
| **IQR** | 709-796 | 666-781 | -43 to- 6 |

Abbreviations: cT1, iron corrected T1; ROI, region of interest.

Periductal cT1 upper limit of normal (ULN):800 ms

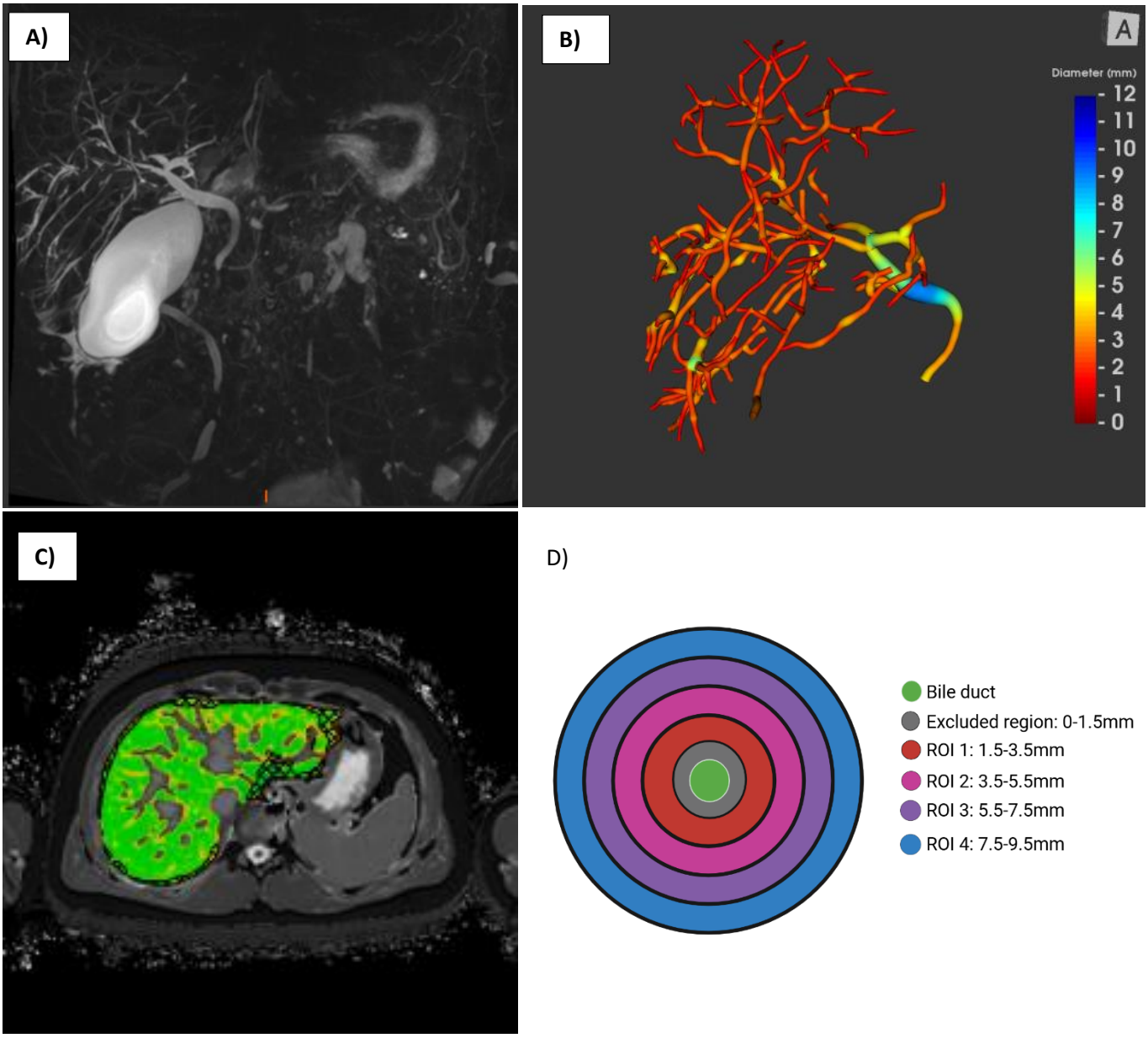


**Figure 4.8 A & B.** Example maximum intensity projections of 3D MRCP and corresponding participant MRCP+ demonstrating strictures and dilatations. **Figure 4.8C.** Example case of hepatic cT1 mapping with depicted colour reference range (yellow and green) within normal limits. **Figure 4-8D.** Graphic representation of periductal cT1 regions of interest (ROI) corresponding with reported periductal cT1 regional data. Adapted from Selvaraj et al. (439).

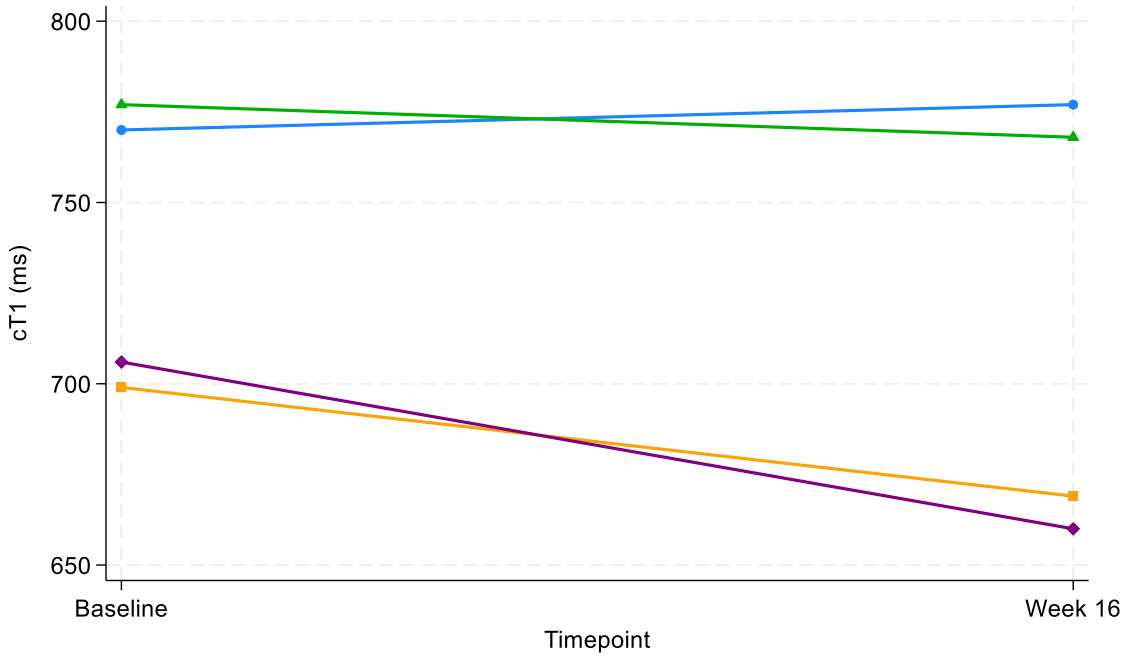


**Figure 4-9.** Paired LiverMultiScan hepatic fibroinflammatory measurements (cT1) for individual participants pre and post-treatment (n=4).

**Health-related quality of life (HRQoL)**

Completion of health-related quality of life (HRQoL) questionnaires was excellent. Overall completion was 100% for all administered questionnaires throughout the study period. Table 4-13 and Figure 4-10 present the median scores for 5-D itch score pre and post-treatment. Baseline 5-D Itch scores ranged from 5-15, 50% of participants had no/mild pruritis at baseline. Differences between pre (baseline) and post-treatment (week 12) 5-D Itch total scores were minimal (9.2 at baseline vs 8.7 at week 12, mean difference -0.5; p=0.85), indicating there was no worsening of pruritis whilst receiving the trial medication. A slight trend towards worsening of pruritis at week 16 was observed. One participant exhibited marked improvement if 5-D Itch scores post-treatment (16 at baseline vs 5 at week 12), having also experienced a 17% reduction in serum ALP at week 12.

Median baseline, week 12 and week 16 scores for the disease specific CLDQ-PSC and PSC-PRO are summarized in Table 4-14 and Figure 4-11. Although the individual responses were variable across the two questionnaires, patient reported outcomes showed no statistically significant change in pre and post-treatment (week 12) questionnaire scores. Analysis of PSC-PRO domains suggests a trend towards improved HRQoL at week 12 in the domains of work productivity, emotional impact and quality of life impact scores compared to baseline. However, there is an observable trend towards worsening HRQoL at week 16 in all CLDQ-PSC domains, and slight worsening of symptom severity at week 16 in the PSC-PRO score compared to baseline.

**Table 4-13.** Summary of longitudinal trends and absolute differences in 5-D Itch scores between baseline to week 16 follow-up.

| Instrument | Time point | n | Median (IQR) | Mean (95% CI) | Median difference (95% CI) | Mean difference (95% CI) | p value* |
|---|---|---|---|---|---|---|---|
| **5-D Itch** | Baseline | 6 | 7.5 (5-14) | 9.2 (4.0-14.4) | - | - | |
| | Week 12 | 6 | 7.5 (5-9) | 8.7 (3.5-13.8) | 2 (-10.3 to 4.0) | -0.5 (-6.9 to 5.9) | 0.85 |
| | Week 16 | 5 | 13 (7-17) | 13.8 (4.4-23.2) | 3 (-9.0 to 20.0) | 3.8 (-10.0 to 17.5) | 0.35 |

Lower values represent a lesser impact of itch on quality of life.

*Test of hypotheses for paired differences tested using paired t-test

5-D itch was score from 5 (no pruritis) to 25 (most severe pruritis).

Note: Due to the small sample size and non-normal distribution of data multiple descriptive approaches are shown. This increases the risk of multiplicity, and therefore results should be interpreted with caution.

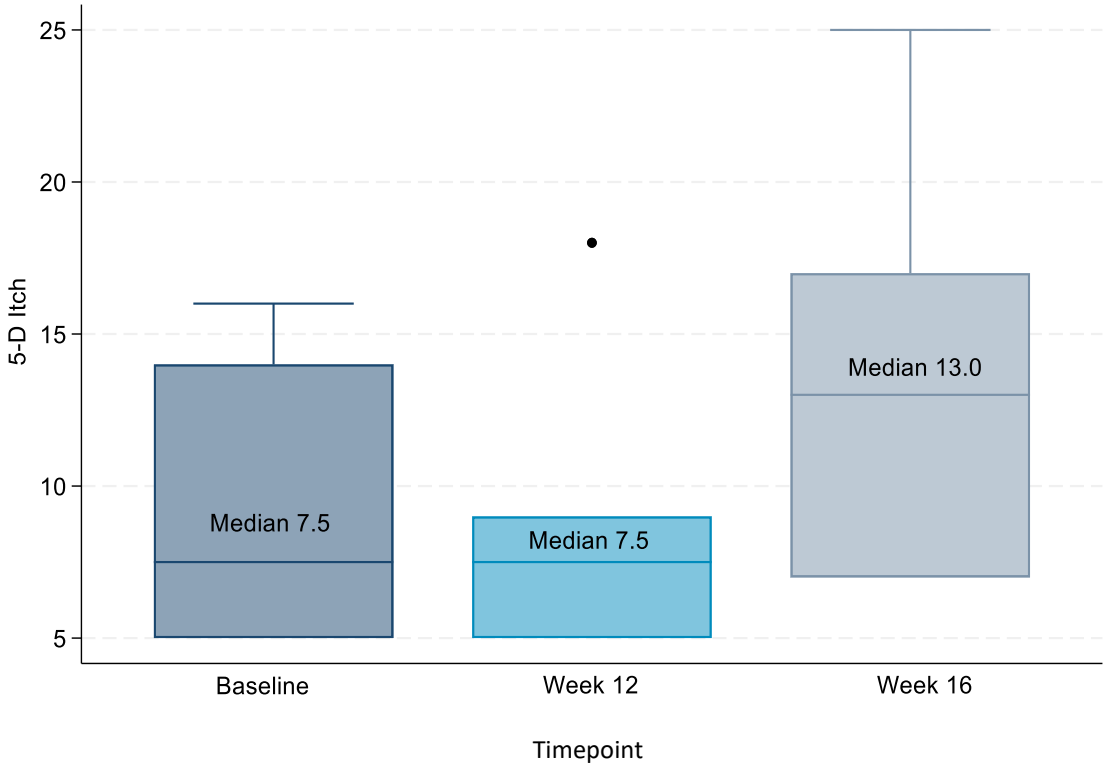


**Figure 4-10.** Box-and-whisker plot of 5-D Itch scores pre and post-brodalumab treatment. Number of participants per timepoint: baseline, n=6; week 12, n=6; week 16, n=5. Five is the minimum score allowable for the 5-D itch tool. Lower values represent a lesser impact of itch on quality of life.

**Table 4-14.** Longitudinal trends in validated disease specific health-related quality of life indices in enrolled participants in the SABR-PSC trial (CLDQ-PSC and PSC-PRO) captured at baseline to week 12 and week 16.

| Instrument | Domain | Baseline median (IQR) | Week 12 median (IQR) | Week 16 median (IQR) | Median (95% CI) change from baseline to week 12 |
|---|---|---|---|---|---|
| **CLDQ-PSC** | | n = 6 | n = 6 | n = 5 | n = 6 |
| | Systemic symptoms | 5.1 (3.5-6.3) | 4.4 (3.3-5.8) | 4.3 (4-4.3) | -0.3 (-3.2 to 0.6) |
| | Emotional health | 5.9 (3.8-6) | 5.4 (5.2-6.4) | 2.4 (1.8-5.8) | 0.2 (-0.6 to 1.3) |
| | Fatigue | 4.6 (3-5.5) | 4.0 (2.5-5.3) | 2.0 (1.8-3.3) | -0.1 (-1.5 to 1.4) |
| | Worry | 4.4 (2.4-6.8) | 5.8 (3.4-7) | 2.0 (1.4-5.4) | 0.2 (-1.3 to 2.7) |
| | Sleep | 5.6 (2.8-5.8) | 4.9 (2.5-6) | 2.5 (1.8-2.5) | -0.1 (-1.2 to 0.5) |
| | Total CLDQ-PSC score | 5.4 (2.8-5.5) | 5.1 (3.7-5.7) | 2.9 (2-3.9) | -0.1 (-1.4 to 1.2) |
| **PSC-PRO** | | n = 6 | n = 6 | n = 5 | n = 6 |
| | PSC Symptoms | 14 (12-17) | 16 (9-25) | 27 (7-46) | -4 (-31.5 to 11.3) |
| | Physical activity impact | 5.5 (4-8) | 5 (4-8) | 8 (4-9) | 0 (-7.4 to 1) |
| | Activities of daily living impact | 7 (6-9) | 6.5 (4-10) | 8.(4-12) | -2.5 (-5.9 to 3.9) |
| | Work productivity impact | 5.(0-6) | 2 (0-11) | 0 (0-8) | 0 (-5.6 to 7.4) |
| | Role function | 4.5 (4-6) | 6.5 (4-8) | 8 (4-9) | 1 (-11.7 to 5.7) |
| | Emotional impact | 7 (5-14) | 5 (4-8) | 5 (4-8) | -1 (-10.3 to 1.8) |
| | Social/leisure impact | 6 (4-7) | 5 (4-6) | 8 (4-8) | -0.5 (-10.9 to 0.9) |
| | Quality of life impact | 7.5 (4-10) | 4.5 (4-7) | 7 (4-8) | -1.5 (-12.1 to 0.9) |
| | Total Impact of symptoms | 6.5 (5-7) | 5.0 (4-9) | 7 (3-8) | -1 (-8.3 to 2) |

Number of participants per timepoint: baseline, n=6; week 12, n=6; week 16, n=5.

1. CLDQ-PSC higher scores reflect better health status.
2. PSC-PRO higher scores reflect worse health status.

Note: Due to the small sample size and non-normal distribution of data multiple descriptive approaches are shown. This increases the risk of multiplicity, and therefore results should be interpreted with caution.

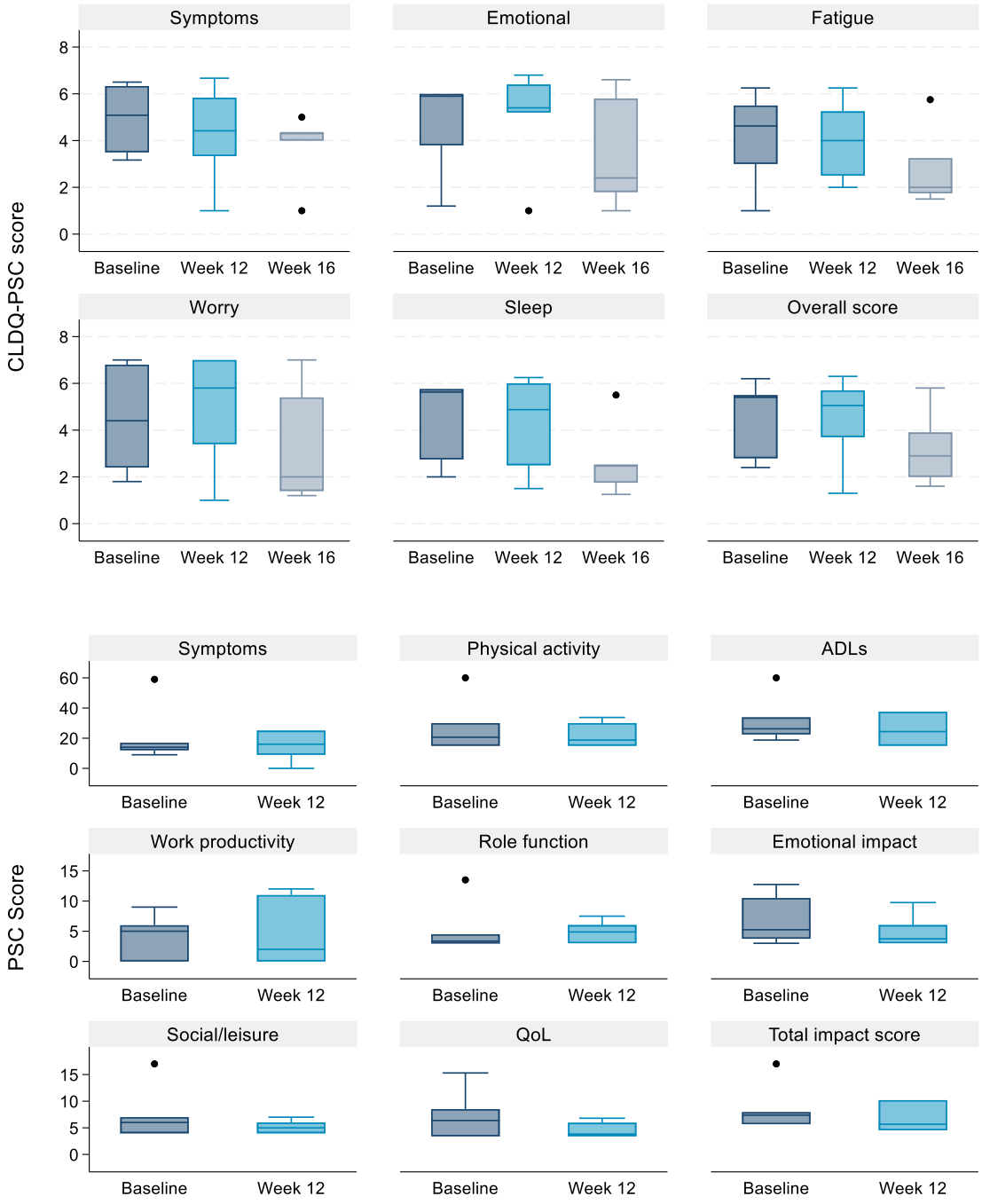


**Figure 4-11.** Box and whisker plot illustrating changes in CLDQ-PSC and PSC-PRO domain scores over time. Higher scores represent better health status in CLDQ-PSC, whilst in PSC-PRO higher scores reflect poorer health status/health quality. Number of participants per timepoint: baseline, n=6; week 12, n=6; week 16, n=5.

**Exit questionnaire**

Exit questionnaires included eight standardised questions (template available in Appendix E) relating to participants experience of the trial overall, acceptability of the intervention and trial processes, willingness to continue the study medication if it were made available, and participants perceived likelihood of future trial engagement. All exit questionnaires were completed remotely by participants. Exit questionnaires (quantitative data) were administered prior to semi-structured interviews (qualitative data detailed in Chapter 5). The two instruments were designed to complement one another.

1. Participant experiences: As part of the exit questionnaire completed at week 16, participants were asked "how would you rate your experience of participating in the *SABR-PSC* study overall?" Overwhelmingly, participants indicated they had a positive experience. All participants rated their experience as either 'good', or 'very good'.
2. Trial acceptability: 100% of participants 'agreed' or 'strongly agreed' that the number and frequency of study visits and questionnaires was 'about right'.
3. Intervention acceptability: When asked if they found "administering an injection under the skin an acceptable way of taking medication", the majority (60%) strongly 'agreed', with the remainder being 'neutral'.
4. Side-effect tolerability: No participant considered the side-effect profile of brodalumab to be unacceptable. Four out of five (80%) participants found the side-effect profile 'acceptable' or 'very acceptable'.
5. Future engagement: 100% of respondents would choose to participate in the study again given the opportunity and would be willing to consider participation in a larger scale RCT of brodalumab in the future.

### 4.6 Discussion and summary of main findings

#### Summary of main findings

*SABR-PSC*, to the best of our knowledge, is the first clinical trial of a repurposed IL-17 inhibitor in PSC. Theoretically, brodalumab combines the following approaches to treat PSC: IL-17 inhibition, with a prominent influence on Th17 aggregate, reduction in neutrophil recruitment and pro-inflammatory cytokines resulting is attenuation of fibroinflammatory activity. Rendering brodalumab a promising intervention for the treatment of PSC.

The *SABR-PSC* pilot study is a single-arm, open-label, multicentre pilot study evaluating brodalumab in adults with large-duct, non-cirrhotic PSC. The primary outcome was to determine the interventions safety and trial feasibility using a mixed-methods approach, to inform the design and conduct of a future larger-scale RCT, powered to determine its clinical efficacy. Secondary exploratory efficacy outcomes included changes in serum ALP values including other liver biochemical readouts, non-invasive surrogate markers of liver fibrosis, and assessment of hepatic and biliary metrics through quantitative multiparametric MRI software. Results from six participants treated with brodalumab for 13 weeks and five to date followed up for a total of six months are reported. Findings from this study offer descriptive insights into brodalumab treatment in PSC, addressing a gap in current literature. Nonetheless, the sample size is small and a larger RCT is required to definitively assess the efficacy of IL-17 inhibition in PSC cohorts.

Overall, 2.5% (6/244; 95% CI 0.9-5.3%) of all known eligible PSC patients at NNUH were enrolled in the study, 67% (6/9) of screened participants enrolled and received the intervention. The *SABR-PSC* study was designed to recruit 20 participants across four large tertiary NHS hospitals across the UK. However, due to operational and logistical difficulties at other sites this was later extended to include

a fifth site. Overall, across the five sites, two received green light sponsor activation and opened to recruitment. On average one participant was recruited every two months (monthly recruitment rate: 0.64; 95% CI 0.29-1.22). Retention rates and treatment adherence were excellent (100%).

Baseline characteristics of trial participants were in keeping with the expected population demographic for PSC. The adverse events profile was largely in keeping with the expected side-effect profile of brodalumab. Adverse events were typically mild, transient and self-limiting, none required treatment discontinuation. There was one case of radiologically diagnosed cholangitis, not requiring treatment. Importantly, there were no cases of cholangiocarcinoma, progression to cirrhosis, new diagnoses of IBD, flares of concomitant IBD or depression/SIB. These findings provide important reassurance regarding the gastrointestinal safety of brodalumab in this cohort, with no signal of drug-associated worsening or induction of colitis. The protocolised week 16 colonoscopy with biopsies mandatory for all participants despite exceeding standard of care in non-IBD PSC – provided a tissue-level safety assessment, not achievable with evaluation of symptoms or non-invasive biomarkers alone. There were no deaths, SAEs or SUSARs. Completion rates of PROM questionnaires was excellent (100% of all administered items were completed). Overall, the results suggest the intervention is safe and well-tolerated in this PSC cohort and that a future larger scale RCT is feasible. No formal causality assessment was undertaken to determine the relationship of adverse events to brodalumab, which may limit the ability to attribute specific adverse events to the study drug. Figure 4-12 summaries the trial findings, recommendations for a future trial and next steps.

Owing to the exploratory nature of secondary efficacy outcomes, the study was not designed to detect any statistically significant differences in clinical efficacy outcomes. Analysis of serum liver biochemistry demonstrated temporal heterogeneity, with no consistent change from baseline in ALP or GGT. AST, ALT and bilirubin remained largely unchanged throughout treatment. The greatest

absolute median reduction in serum ALP was observed at week 4 (Δ-12, 95% CI -19.5 to 1.6; p=0.05), with GGT (Δ -11.5, 95% CI -83.1 to 8.4) following a similar trend. However, this effect was not sustained at other timepoints. Inter-individual variability in ALP was observed. ALP levels naturally fluctuate and can normalise in a proportion of PSC patients, making observed reductions difficult to attribute to the intervention or the natural history of PSC. Two participants experienced a ≥20% absolute reduction in ALP by week 16, with one participant experiencing a reduction of >45% and normalising their ALP. Of interest, the same two participants experienced a corresponding 19% and 59% reduction in GGT at week 16, with one corresponding participant experiencing a pronounced absolute reduction in ELF score of -0.61. Indicating that brodalumab may have a beneficial biological effect in a subset of patients, justifying its further evaluation in a future RCT. A reduction in mean serum ALP of ≥ 20% at 12 week is regarded as clinically meaningful (136). Although these results from this small sample size should be interpreted with caution and will require a larger-scale trial to evaluate further.

The absence of a uniform response for ALP across all participants or a signal suggesting clear benefit is not surprising given the small sample size, short trial duration and likely insufficient dosing of brodalumab to penetrate the bile ducts. Several preceding early-phase interventional PSC trials have also demonstrated stability or no clear biochemical signal of efficacy despite compelling early basic science and translational evidence. Perhaps the best example of this is the recent phase 2 RCT of aldafermin (NGM282) (fibroblast growth factor 19 analogue [FGF-19]), where there was no evidence of a significant difference in mean ALP 12 weeks post-treatment with 1mg of aldafermin (n= 62, mean difference -14U/L, 95% CI -68 to 28; p=0.43). However, significant improvements in fibrosis biomarkers such as ELF score (LS mean difference -0.4, 95% CI -0.8 to -0.1; p=0.02) and PRO-C3 (-14.3; p=0.001) were observed with 3mgs of aldafermin (440), challenging our current understanding of ALP's utility as a clinical trial endpoint and marker of treatment response. There is conflicting data on the significance of ALP reduction on long term clinical outcomes. Results from *SABR-PSC* showed there

was no pronounced cohort wide change in surrogate liver fibrosis markers (ELF score and VCTE) at week 16, despite a subset experiencing a modest reduction. The significance of this change following 12 weeks of treatment is unclear. Liver fibrosis is unlikely to have changed markedly over the short duration of this study with likely sub-optimal dosing and biliary penetration.

Emerging multiparametric MRI techniques are increasingly used alongside biochemical and non-invasive liver fibrosis markers across a number of chronic liver disease studies (viral hepatitis, AIH, MASLD), of which MASLD is the best studied indication (430, 441-443). For cT1 scores, healthy controls fall below 800 ms (444), with 800 ms widely used as a pragmatic ULN. Across MASLD studies cT1 correlates with histological activity/fibrosis composites and tracks clinical risk surrogates (445, 446).

A small number of studies have begun to evaluate LMS (cT1) and MRCP+ in PSC (447-450). In one cohort of 70 LdPSC patients and 20 health controls, peribiliary cT1 scores were higher in more advanced PSC (432). In that study, a mean peribiliary cT1 cut-off of 774 ms in ROI 1 discriminated advanced fibrosis defined by LSM (area under the curve = 0.73), which is below the manufacturer's referenced hepatic cT1 ULN of 800 ms-emphasising that biliary-adjacent ROIs behave differently depending on the underlying liver disease aetiology (i.e., parenchymal vs biliary). However, these data remain preliminary and future PSC-specific validation studies are required to confirm these early findings. The mean periductal cT1 score (ROI 1) in *SABR-PSC* was 778 ms. Separately, higher parenchymal cT1 scores (>825 ms) and/or greater MRCP+ intrahepatic dilation severity (>7; a metric not captured by Perspectum for the *SABR-PSC* study) has been associated with worse HRQoL in PSC (450), and quantitative ductal burden (number of intrahepatic duct dilatations/strictures) has been linked with transplant-free survival and high-risk stratification (428, 430, 448). In a prospective series of 29 PSC patients with repeat quantitative MRCP at approximately 12 months, MRCP+ detected ductal changes (rising biliary strictures count) in over half of the cohort, despite stable ALP,

aminotransferases and LSM (447). This divergence suggests that quantitative MRI metrics may capture subtle disease progression that routine laboratory investigations may miss.

In *SABR-PSC*, most MRCP+ ductal metrics were stable to week 16. However, hepatic and biliary cT1, a marker of fibroinflammatory activity, demonstrated a consistent numerical reduction at week 16, compatible with a modest fall in fibroinflammatory activity over the treatment period. Notably, one participant exhibited a marked decrease in hepatic cT1 (-46 ms; 706 ms to 660 ms), accompanied by parallel reductions in periductal cT1 measurements across all ROI. This observed change occurred despite little or no parallel reduction in ALP or VCTE in the corresponding participant; however, a corresponding reduction in their ELF score was observed. Given that cT1 reflects fibroinflammatory activity, even modest reductions may be clinically and biologically meaningful. Novel technologies such as LiverMultiScan cT1 mapping may be able to detect fibroinflammatory changes earlier than liver biochemistry or surrogate markers of liver fibrosis. Conversely, the participant with the greatest reduction in ALP and GGT at week 16 demonstrated only a modest reduction in their biliary and hepatic cT1 score, whilst the participant with the greatest reduction in cT1 values experienced stable ALT/AST values at week 16. It is possible that the modest cT1 change in this participant reflects limited hepatic fibroinflammation at baseline, reducing the capacity for cT1 mapping to demonstrate improvement. However, these conflicting results also highlight the potential discordance between conventional PSC serum based surrogate biomarkers and more sophisticated image based measurements. Additionally, this discordance highlights that serum cholestatic enzymes, transaminases, LMS and MRCP+ interrogate different biological compartments and may diverge over short treatment and follow-up. Underlining the need for future studies to combine conventional PSC end points with imaging biomarkers, as a multi-modal strategy to fully characterise treatment response.

Whilst there a number of exploratory studies highlighting quantitative MRI as a potentially complementary diagnostic or prognostic tool, prospective, biopsy-anchored thresholds and minimally important changes in peribiliary and parenchymal cT1 score post-treatment in PSC are not yet established; peribiliary cT1 is particularly early in its validation. Until PSC-specific multiparametric MRI clinically meaningful change thresholds have been defined and correlated with histological scoring systems, LMS (cT1) and MRCP+ should be interpreted as complementary, hypothesis generating biomarkers, not a standalone surrogate of efficacy. Development of a PSC-specific core outcome set is currently underway, and will hopefully clarify the role and recommended use of quantitative MRI metrics in future trials (451).

Differences between pre (baseline) and post-treatment (week 12) 5-D Itch, CLDQ-PSC and PSC-PRO scores were minimal and are likely as a result of the small sample size. It may have been overambitious to expect scores to change dramatically over 12 weeks of treatment. In select domains across PSC-PRO (work productivity, emotional impact and quality of life impact scores) participants reported slight improvement in HRQoL. However, there was a trend towards slight worsening HRQoL scores across all questionnaires at week 16 which may indicate that participants perceived clinical benefit of the intervention was lost at this timepoint, possibly indicating that any early stability of PROM scoring was short-term and was not sustained once treatment was withdrawn. The decline in week 16 PROM outcomes may also reflect participants' awareness that treatment, close follow-up and the trial were coming to an end. Such psychological effects could contribute to changes in PROM scoring and could possibly amplify participants' perceptions of symptom burden or reduced well-being once treatment was withdrawn.

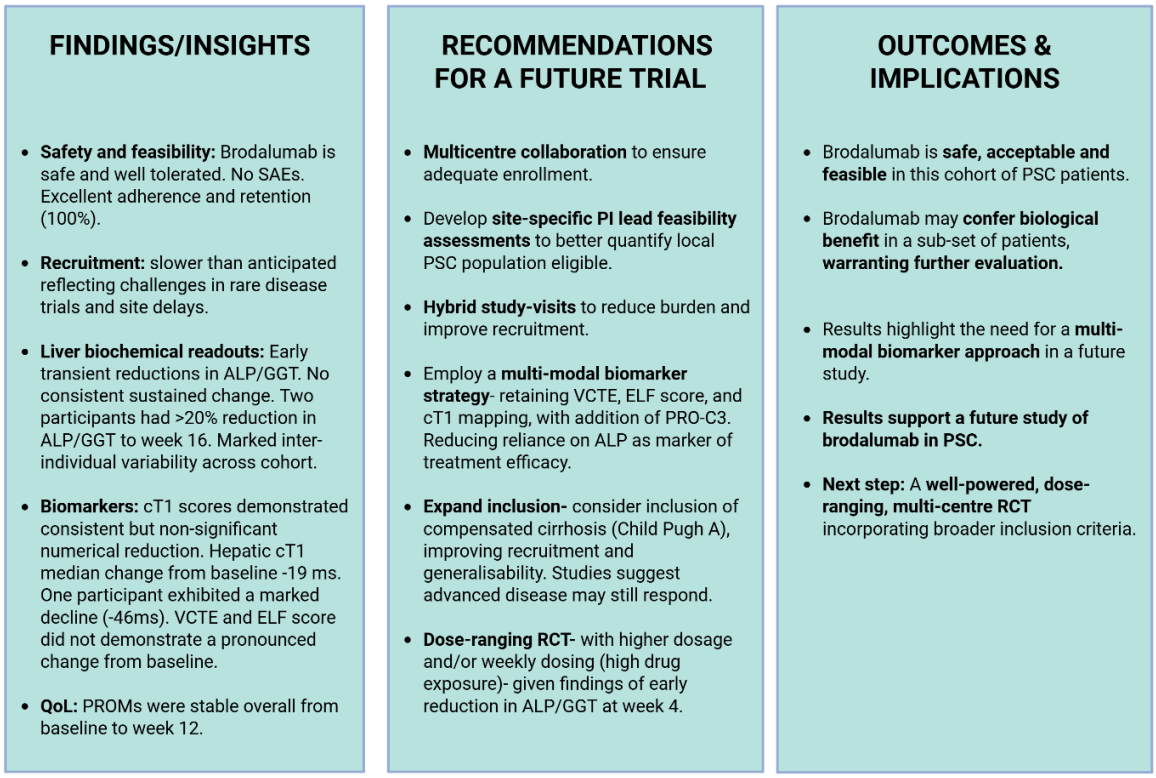


**Figure 4-12.** Summary of trial findings including recommendations for a future trial and next steps.

**Trial interpretation**

***1. Recruitment and retention***

This trial demonstrated that participants with PSC were willing to enrol in a clinical trial of a novel repurposed therapy, and there is clear appetite among the PSC community to engage in clinical trials where available. However, the pool of eligible patients for such a trial is small, as illustrated by the limited number of eligible participants identified at NNUH. Underlining the need for multicentre recruitment to ensure adequate sample sizes. The logistical and operational challenges experienced by selected *SABR-PSC* recruitment sites resulted in their being unable to open to recruitment, this had a significant impact on the sample size, despite over recruiting at NNUH. This highlights the importance of sustained efforts to accelerate trial set-up and reduce regulatory and administrative delays.

Despite initial projections of recruiting 1-2 participants per month, the actual recruitment rate was lower, at 0.64 participants per month (95% CI 0.29-1.22). For rare diseases such as PSC, trialists and trial sites must develop a realistic understanding of the geographical distribution of PSC patients in the UK and the true pool of eligible patients at their respective centres. This could be achieved through creation of a patient-generated PSC national registry or via conducting clinician led feasibility assessments locally, as described in Chapter 2. Nonetheless, despite the lower than expected recruitment rate, this should not be seen as a barrier to a future study, as it is likely to be sufficient for a multicentre trial powered for clinically efficacy and conducted over a longer recruitment period.

Of those invited to participate, just under a third (n = 9; 31%; 95% CI 15.3-50.8%) were recruited. Reasons for declining varied, however the most commonly cited reasons included family planning (among women of childbearing age) and concerns over the frequency of study visits. Whilst the former reflects unavoidable personal factors in a disease that predominantly afflicts the young, the later could be addressed in a future trial, by considering fewer study visits and/or adopting a hybrid (phone or virtual) study visit model where appropriate.

The recruitment rate and performance across a single centre (NNUH; including over-recruitment) should be seen as favourable despite other selected sites being unable to open and recruit within the available time frame. The NNUH data provides valuable insight into anticipated recruitment trajectories in a rare disease context, providing a rate that was previously unquantified. The recruitment rate for NNUH, with the longest period of active recruitment, should be regarded as a realistic estimate of expected rates for a future trial.

The retention rate in *SABR-PSC* was excellent (100%, 95% CI 54.1-100) with 100% completing the study protocol and no participant withdrawals. However, owing to the small sample size, generalizability to a future larger scale RCT is limited. Nonetheless, these results are encouraging. Positive factors likely contributing to retention include strong participant-clinician rapport, close monitoring and contact with the trial team. Exit questionnaires confirmed that enrolled participants found the trial a positive experience, found the trial design acceptable, were willing to engage in a future trial of brodalumab and viewed the side-effect profile of brodalumab as tolerable.

Taken together, these finding are reassuring and supports the feasibility of conducting a larger-scale RCT of brodalumab in PSC, provided that strategies are implemented to optimise recruitment efficiency, address participant burden and leverage carefully selected multicentre collaboration.

***2. Adherence***

Adherence to the trial intervention was excellent (100%) throughout. Suggesting that administration of a subcutaneous injection administered weekly/alternate weeks is feasible and tolerable by participants. Whilst these early results are encouraging, it is not possible to draw conclusive inferences on adherence rates in a future study of longer duration. The positive impact of frequent study visits, study visits coinciding with the day of intervention administration, and one participant having all their injections administered by the study team, likely significantly improved adherence.

***3. Safety***

Results from this study indicate that brodalumab is safe and well-tolerated, this inference is however limited by the small sample size. Nonetheless, reported adverse events were largely in keeping with the known side-effect profile of brodalumab. There were no SAEs. One participant (1/6, 17%) was

diagnosed radiologically with acute cholangitis, despite the small sample size in this study this is similar to results from the simtuzumab trial where 13% (31/234) developed ascending cholangitis (162). Two participants experienced a rise in their ALT/AST or GGT meeting CTCAE grading criteria. All elevations were transient and subsequently normalised by 6 months. Only one participant required further investigation, in the form of a repeat MRCP, which demonstrated cholangitis as the cause. Importantly, there were no findings of cholangiocarcinoma, depression/SIB or new/exacerbations of IBD. Given the tolerable side-effect profile as reported in the exit questionnaire and the absence of SAEs this study demonstrates no concerning safety signals with brodalumab use in individuals with PSC and PSC-IBD; supporting the feasibility of brodalumab's use and further exploration in a future trial.

***4. Clinical outcomes***

This study was not powered to detect clinically significant efficacy outcomes with any degree of certainty. Exploratory efficacy outcomes were measured to detect any change (improvement or deterioration) from baseline. Interpretation of these findings should be made with caution. The findings are helpful in generating hypotheses for a future well-powered larger-scale study to determine efficacy. On analysis of the liver biochemistry analytes, there is evidence of a reduction in serum ALP and GGT as early as week 2, with the most pronounced median difference occurring at week 4 (Δ-12). A third of participants experienced a >20% mean decrease in ALP and GGT out to week 16. A previous study investigating norucholic acid in patients with PSC demonstrated a mean change of +1.2% change in serum ALP over 12 weeks of treatment in the placebo arm (136). Therefore, the findings of a third of participants experiencing a reduction of ALP of ≥ 20% at week 16 may suggest a biological signal. Of note, a similar finding in a similar proportion was recorded in a study of another biologic, vedolizumab in PSC-IBD (75). However, for the majority of participants any initial improvements were not sustained past week 4. The median serum ALP and GGT decreased to week

12 compared to baseline suggesting a general trend towards reduction across the cohort. However, median differences suggested an overall rise at week 12 reflecting the influence of heterogeneity and individual participants with increases in serum ALP values. AST, ALT and bilirubin demonstrated variable fluctuations over time, with no evidence of pronounced improvement or deterioration by week 16, suggesting stabilisation. There is clear evidence of heterogeneity and inter-individual variability in response. Overall, the results do not suggest evidence of a clear-cut biochemical response to brodalumab at week 12, across the entire cohort. For participants with evidence of possible biological efficacy with regards to those with the most pronounced reductions in ALP and GGT, the corresponding VTCE scores also declined slightly. Overall, VTCE across the cohort showed stabilisation. ELF scores across the cohort non-significantly increased (1.02, 95% CI-0.2-1.6; p=0.21). Although the increase in ELF score did not reach statistical significance, two participants experienced a ≥ 0.19 unit reduction at week 16. A change of 0.19 units in individual participants may be clinically relevant. The median difference in hepatic cT1 across the cohort was -19.5 (95% CI -56.5 to 17.5), demonstrating potential beneficial biological efficacy with regards to attenuating fibroinflammatory activity. Given the small sample size, these findings should be interpreted with caution, but they raise the possibility of subtle biological effects not captured by statistical testing.

A number of factors could explain the observed fluctuations in clinical outcomes:

(i) **Dose:** The dose of brodalumab administered in this trial, was equivalent to that licensed for chronic plaque psoriasis. The selected dose (210mg) was intentionally cautious and may have been insufficient to observe a meaningful biological signal in the peribiliary compartment in this small cohort. Doses up to 700mg have been successfully trialled in IBD, without evidence of a statistically significant increase in adverse events or signs of toxicity (277), with doses of up to 420mg trialled in healthy adults (452). The dose required to penetrate the bile ducts and meaningfully modulate biological effects on peri-biliary Th17 cell and pro-inflammatory milieu, remains uncertain. It is conceivable that a higher dose

would be necessary to alter pro-inflammatory activity within the biliary tree. This is consistent with the observation that serum ALP declined in most participants at week 4 (during weekly dosing), before administration was reduced to alternate weeks. The safety profile reported in this study is reassuring. A future dose-ranging study would be pertinent to evaluate this hypothesis.

(ii) **Disease stage and biomarker sensitivity:** Participants with the greatest degree of fibroinflammatory activity are likely to derive the greatest benefit from treatment with brodalumab. Inclusion criteria in this pilot study were intentionally broad, to facilitate both recruitment and enhance real-world generalisability. However, without stratification by disease stage or restriction of disease duration, it is possible that participants most likely to derive benefit from brodalumab were underrepresented. Patients with elevated biomarkers such as cT1 or PRO-C3 may be most responsive to fibroinflammatory inhibition with brodalumab, yet none of the participants in this study had an elevated cT1 score at baseline. Nonetheless, this was a pilot study, designed primarily to assess safety and feasibility. Importantly, this pilot study is novel in that it incorporated both biochemical markers, non-invasive surrogate markers and multi-parametric MRI derived markers of disease activity, providing a more comprehensive assessment of disease activity. In the phase 3 norucholic acid (NCA) study (NUC-5), a co-primary endpoint of partial normalisation of ALP to <1.5xULN and no worsening of disease stage on histological assessment in PSC patients, was achieved in 15.1% of participants (453). Yet, surrogate markers of fibrosis (VCTE and ELF) showed no improvement compared to placebo, whilst histology improved significantly in the treatment arm (≥1 Ludwig stage improvement: 25% vs 11% in the placebo arm; p=0.02) (453). Highlighting the discordance between liver biochemistry and surrogate markers of fibrosis in PSC. Repeated liver biopsy is invasive and impractical in a short-term study like *SABR-PSC*. PRO-C3, a biomarker of type III collagen reflecting fibrogenic activity, has recently garnered interest in the PSC community as a potential biomarker, having been shown to predict transplant-free survival in PSC (454). PRO-C3 performed well in combination with the ELF score in the recent trial investigating aldafermin. Participants with a higher baseline ELF score (>9.8) experienced greater reductions in ELF score post-treatment, than those with an ELF score <9.8

(440). This trial also included participants with compensated cirrhosis (Childs Pugh A). Recent preliminary results from the phase 2 RCT evaluating Nebokitug (CM-101) in PSC, an anti-fibroinflammatory, observed corresponding findings with regards to participants with more advanced disease (LSM >8.7kPa) experiencing the greatest reduction in exploratory efficacy markers (455). Questioning prior assumptions that those with early disease are most likely to benefit from anti-fibrotic/fibroinflammatory therapy. Interestingly, in *SABR-PSC*, the two participants with the greatest reduction in ALP sustained to week 16, both had an ELF scores >9.6. Interpretability of this finding is nonetheless limited. It is possible that brodalumab may have fibroinflammatory benefits that were not adequately captured by VCTE or ELF score, particularly during a short-duration exploratory study like *SABR-PSC*. In retrospect, assessing VCTE and ELF score at week 12 (end of treatment), may have provided greater sensitivity in detecting any short-term changes. By week 16, four weeks after treatment cessation, any transient effects may have diminished towards baseline, possibly obfuscating any detectable differences, if indeed present. Taken together, a future RCT of brodalumab in PSC should consider incorporation of novel biomarkers such as PRO-C3, with less reliance on ALP as a marker of compartmentalised fibroinflammatory efficacy or treatment efficacy more generally. Serum ALP is unlikely to represent the best surrogate biomarker of fibroinflammation. Finally, expanding inclusion criteria in a future study to include patients with compensated cirrhosis is likely to improve recruitment and enhance generalisability. Data from both the aldafermin and NUC-5 study, suggest that even patients with more advanced disease may be responsive from anti-fibrotic or anti-fibroinflammatory strategies, supporting consideration of their inclusion in a future study of brodalumab.

(iii) **Transient and reversible effects of brodalumab:** An alternative explanation for the observed reduction in ALP/GGT up to week 4, which diminished thereafter, may reflect the transient and reversible effects of Th17 inhibition. It is conceivable that a compensatory adaptive response subsequently ensued, without adequate suppression, restoring the homeostatic functions of the IL-17-Th17 pathway previously discussed in Chapter 1.5.

(iv) **Sample size and study design:** Finally, the small sample size limits interpretation. Even if the target sample size of 20 participants had been achieved, this pilot study was not powered to detect clinically significant changes in efficacy outcomes. The study was designed to primarily establish safety and feasibility and to generate hypotheses for future research.

### *5. Quality of life*

Completion of HRQoL questionnaires was excellent throughout the study, with the entire cohort reporting that the number and frequency of trial related procedures including questionnaires was acceptable. There were no complaints from participants suggesting participants experienced questionnaire fatigue. Overall, this demonstrates feasibility of inclusion of HRQoL assessment in a future study including repeated instrument administrations. There was no evidence of a meaningful change from baseline to week 12 in 5-D itch, total CLDQ-PSC and PSC-PRO. Whilst there is no evidence of a significant improvement in week 12 HRQoL results, their relative stability is reassuring.

### *Strengths and limitations*

This study has several strengths. Firstly, it met its primary objective of determining safety and feasibility of a larger scale RCT of brodalumab in patients with PSC and PSC-IBD. We were able to establish that the intervention and trial procedures were acceptable to participants, clinicians and research staff. This pilot study provided conservative estimates of recruitment rates, and importantly through pre-screening of all known adult PSC patients at NNUH, we have now developed a real-world understanding of the number of potentially eligible patients for a future study at NNUH. *SABR-PSC* combined several trial endpoints, incorporating conventional PSC biomarkers such as ALP, in addition to surrogate markers or fibrosis and MRI hepatic and biliary metrics. Furthermore, this study was novel as an ALP cut-off value was not specified for inclusion, otherwise frequently adopted in other studies.

Inclusion of such a cut-off would have significantly impeded recruitment to this pilot study, and limited generalisability. This study has highlighted several areas of study design that will need to be addressed in a future RCT, relating to choices of inclusion criteria, method and frequency of follow-up, intervention dosages to be explored, and choice of outcome measures. We were able to establish effective trial-specific procedures at NCTU as a result of this early pilot study, which will be built upon in a future study. Such procedures include, risk assessment, safety management plans, quality-management and monitoring plans. Finally, this is the first trial of an IL-17 inhibitor in adults with PSC, to the best of our knowledge, seeking to answer a critical question regarding the safety, feasibility and exploratory efficacy outcomes of brodalumab therapy in PSC.

This study also has limitations. Firstly, the small sample size which was compounded by persistent recruitment issues. This open-label pilot study did not include a placebo arm, preventing attribution of causality, and was designed with a relatively short follow-up period. Recruitment was only successful at NNUH, which may render recruitment, retention, and adherence rates optimistic and less generalisable when expanding across other sites. As the host site for the doctoral research fellow, NNUH functioned as an enthusiastic trial recruitment centre that may not be directly comparable with other sites. Efficacy outcomes were exploratory in nature and will therefore require further evaluation. Additional limitations include the lack of high quality paired MRCP+ and LMS data for the entire cohort. Finally, whilst the sample size was small all participants were Caucasian, demographics which do not necessarily reflect the global PSC population demographics. All these factors limit the conclusions that can be drawn and therefore necessitate caution when interpreting these findings. Despite these limitations, it does not preclude the design and implementation of a future RCT of brodalumab in PSC.

We acknowledge that *SABR-PSC* did not generate pharmacodynamic evidence of IL-17 pathway inhibition by brodalumab within the main study. To address this limitation, we prospectively banked serum research samples pre and post-treatment for planned future analyses (Table 4.4). Because few studies have profiled circulating serum cytokine levels pre and post-brodalumab treatment, the optimal biomarker for treatment response is uncertain (456). Accordingly, our follow-on work will quantify: (i) drug exposure using brodalumab trough levels and (ii) assess functional pathway suppression using downstream IL-17 responsive chemokines e.g., IL-8 and CCL20. We will also measure IL-17A/F, IL-23, and TNF-α, to provide more sensitive and specific pharmacodynamic readouts of IL-17 pathway inhibition. A recent study has reported paradoxical increases in serum IL-17A levels detected at 12 weeks post brodalumab therapy, in keeping with a peripheral accumulation of IL-17A secondary to brodalumab's known mechanism of action and associated pan IL-17 cytokine blockade (456). The initial findings from *SABR-PSC* should be interpreted as safety/feasibility and hypothesis generating, with pharmacodynamic validation built into the next phase to explore observed clinical or surrogate marker changes within the context of evidence of IL-17 pathway antagonism.

***Key lessons and considerations for a future trial design***

- Recruitment was slower than anticipated- multicentre collaboration to achieve adequate enrolment will be essential in a future trial. Recruitment could be improved through early local site feasibility assessments to understand patient eligibility, which should be encouraged early in the planning phase of a future study. A hybrid study design with fewer face-to face visits and use of virtual or phone consultations may improve recruitment for adults of working age as part of a future study. However, maintaining key touchpoints will be essential for safety monitoring. As evidenced by the excellent retention in *SABR-PSC* the strong participant-research team rapport and regular monitoring were invaluable and will be strongly

emphasised in a future study. Recruitment timelines will need to be pragmatic, however a longer study with extended recruitment window will be essential for any future study.

- ALP exhibits high inter-individual variability and does not consistently reflect fibroinflammatory activity. A future study will persist with inclusion of a multi-modal strategy including surrogate markers of fibrosis (VCTE and ELF score) in addition to LiverMultiScan cT1 scoring, however I would incorporate PRO-C3 as an additional biomarker. A combined approach may provide a more accurate reflection of peri-biliary compartmentalised treatment response.
- Recent studies indicating patients with more advanced disease, including compensated cirrhosis, remain responsive to anti-fibrotic therapies, challenges perceptions that only early/intermediate disease states are likely to be responsive to treatments like brodalumab. Expanding inclusion criteria to include patients with compensated cirrhosis (Child Pugh A) in a future study would not only improve recruitment and generalisability of results but may capture a subset of patients that may derive some therapeutic benefit. Brodalumab pharmacokinetics in cirrhotic patients are unknown at present and is unlikely to be explored in the next clinical trial of brodalumab in PSC, where safety still requires testing in a larger cohort.
- The optimal dosing of brodalumab remains uncertain. Higher doses have been used safely in other trials. It is plausible that greater therapeutic exposure (higher dosage and/or more frequent dosing) may be required to penetrate the biliary tree and modulate hepatobiliary Th17 mediated fibroinflammation, as suggested by early ALP and GGT reductions to week 4. A future dose-ranging study would be informative.

**Conclusion**

In summary, this is the first clinical trial of an IL-17 inhibitor in PSC patients. The reported findings from this single-arm, open-label, multicentre study demonstrate that a larger-scale interventional clinical trial is safe and feasible. Whilst there was no evidence of a uniform ALP response to brodalumab across the cohort, a subset of participants experienced a ≥ 20% reduction, which for some correlated with a reduction in surrogate markers of fibroinflammation, with one participant normalising their ALP. However, this study was not powered to determine evidence of efficacy. Lessons learnt throughout the trial highlight that recruitment in PSC trials is inherently challenging. However, the excellent retention rate observed in *SABR-PSC*, alongside participants reported satisfaction, and reported willingness to engage in a future clinical trial, is encouraging and supports the viability of testing brodalumab in this rare disease cohort. Importantly, we were able to establish that brodalumab is a safe and tolerable therapy in PSC and PSC-IBD patients. Estimated recruitment and retention rates, drug adherence, safety profiles, and completion of trial related procedures from *SABR-PSC* will help inform the design of a future trial of brodalumab in adults with PSC. Finding from this pilot study underline the necessity to establish the optimal dose of brodalumab to inhibit peri-biliary IL-17 activity. Finally, the combined reported results justify the need for a well powered larger-scale study to evaluate brodalumab's safety and efficacy in PSC.

# Chapter 5 Qualitative results- participants perceptions of the *SABR-PSC* pilot study. Moving beyond numbers to understand what truly matters to PSC participants.

**Research Ethics Committee Approval gained as part of the SABR-PSC study:**

London Bridge Research Ethics Committee

REC referenceREC23/LO/0718

## 5.1 Abstract


**Introduction**

Recruitment and retention to randomised controlled trials (RCT) is often challenging. The orphan status of primary sclerosing cholangitis (PSC) further compounds these difficulties, due to small patient populations, geographical spread and limited trial opportunities. Embedding qualitative methodology within clinical trials can yield invaluable insights into participant perspectives, enabling identification of barriers and facilitators to recruitment and retention. However, PSC interventional trials seldom incorporate qualitative approaches, leading to a gap in understanding the lived experience of participants. A qualitative component was embedded in the *SABR-PSC* pilot study, exploring participants experiences of trial participation to assess feasibility, and inform the design and conduct of a future large-scale RCT.

**Methods**

Six participants enrolled in the *SABR-PSC* pilot trial took part in in-person semi-structured interviews following treatment completion. All interviews were recorded, transcribed verbatim and analysed using reflexive thematic analysis.

**Results**

Three overarching themes emerged representing the lived experience of *SABR-PSC* trial participants: (1) being part of a greater good- strong altruistic motivations underpinned by a desire to contribute to PSC research; (2) overcoming fear and obstacles- managing concerns and apprehension about side-effects, injections and trial participation; and (3) ease of process- the offering of practical suggestions for improvement.

**Conclusion**

Participation was largely driven by altruism, often combined with a desire for reciprocal benefit (conditional altruism). All participants reported a positive trial experience, found the trial acceptable and tolerable, and expressed willingness to participate in a future larger-scale RCT of brodalumab. These findings confirm the feasibility of the *SABR-PSC* pilot study design and intervention, in addition to providing practical guidance on improvements for a future trial of brodalumab in PSC.

## 5.2 Overview of chapter

Chapter 4 presented important quantitative safety and exploratory efficacy data for the *SABR-PSC* study, contributing critical insights towards feasibility assessment of a future phase 2 RCT investigating brodalumab for the treatment of PSC. Building on these findings, this complementary chapter presents the results from qualitative assessments- specifically the week 16 semi-structured interviews- to provide a more granular understanding of participants perceptions and lived experiences of the *SABR-PSC* study.

By listening directly to the voices of people living with PSC, the *SABR-PSC* study moves beyond numbers to understand what truly matters to participants—and uses those insights to shape the future of clinical research in this disease.

## 5.3 Introduction

The *SABR-PSC* study was designed not only to evaluate the safety and feasibility of brodalumab in PSC (numerically), but also to understand the perspectives of those directly impacted. Such approaches, ensure participants have a direct and meaningful influence on the design (empowering patients), delivery, recruitment and selection of outcome measures of future studies of brodalumab in PSC. Interviews were conducted not only to gain participants opinions and experience of the trial, but also to better understand their motivations and impact of the intervention on participants health and quality of life (positive and/or negative). Semi-structured interviews are one of the most common qualitative approaches applied for this purpose, a method felt best able to capture the nuanced realities of PSC patients' perspectives and therefore employed in the *SABR-PSC* study.

Integrating qualitative research into traditional clinical trial design not only provides a more comprehensive understanding of the phenomena in question, but also enriches the design, conduct and interpretation of trial results (457). There is strong evidence that trials with embedded qualitative methodologies can effectively shape and improve clinical trial design (457, 458). Despite evidence of the advantages of embedding qualitative methodology in interventional trials, a 2021 scoping review identified a notable underrepresentation of participants' perspectives and experiences in interventional clinical trials across a range of medical specialities, with oncological trials performing best in this regard (459). PSC-related clinical trials including pilot and feasibility studies rarely incorporate qualitative methodology, and where they do, the qualitative findings are often not explicitly reported within the main trial publications. To address this gap and to ensure participants lived experiences and perceptions directly inform a future trial, a deliberate decision was made to embed qualitative methods in the *SABR-PSC* study. This approach was intended to generate deep, rich

insights that will help inform both the design, improve feasibility and practical delivery of a future RCT in this area.

### 5.4 Methods

Qualitative data was systematically extracted and analysed from week 16 semi-structured interviews (guide available in Appendix D) of participants having completed the *SABR-PSC* treatment phase, employing an inductive qualitative approach. The aim was to evaluate the following key feasibility aspects:

1. Acceptability: participants perspectives of self-administering brodalumab via subcutaneous injection, the number and frequency of study/follow-up visits, study assessments, PROMs and investigations. This also includes insights into participants perceptions of taking part in a pilot study of a novel repurposed drug.
2. Tolerability: the degree to which participants were able to tolerate self-administering subcutaneous brodalumab injections.
3. Future engagement: participants views on whether they would have wished to continue the intervention if this was an available option, as well as their willingness to participate in a future larger-scale RCT.

Week 16 semi-structured interviews were audio-recorded to ensure faithful representation of participants answers. All participants were required to provide prior written informed consent. Verbal consent was additionally obtained prior to the commencement of each interview. Audio-recording were later transcribed verbatim by a professional transcription company. The week 16 semi-structured interview was a mandatory part of the study protocol. However, where participants declined to be audio-recorded, their answers were transcribed fully during the study visit by the PI. All

audio-recording were checked for quality and anonymised prior to transfer to a professional transcription company for verbatim transcription. For reporting, participant quotations were anonymised with alphabetical participant codes which were randomly assigned and bear no relation to the original study identifiers or recruitment order.

Participants were interviewed using a pre-specified semi-structured interview guide to ensure uniformity of content across all interviews. However, each interview question was designed to be open-ended, allowing participants to talk freely and to cultivate their own narrative of their trial experience. Most questions also contained prompts to facilitate discussion points if required. All semi-structured interviews were conducted by the PI. Participants were aware of the PIs role and aims within the study. To acknowledge and mitigate the potential influence this dual role may have had on participants' responses, the PI engaged in ongoing reflexive practice.

The study was reported in line with COREQ (consolidated criteria for reporting qualitative research) guidelines, a 32-item checklist for qualitative interviews (Appendix L) (460). Analysis of the data was undertaken using reflexive thematic analysis and analysed in NVivo version 14, a computer assisted qualitative data analysis software tool. Transcripts of the semi-structured interviews were coded, creating common themes, a respected approach used by Braun and Clarke (461). Thematic analysis is the method for systematic and rigorous identification, exploration and interpretation of themes within qualitative data, with emphasis on recognising patterns and meaning within the dataset (461). Thematic analysis involves six phases (all phases were undertaken by the author):

(i) Data familiarization

(ii) Generating initial codes

(iii) Generating initial themes

(iv) Theme development and review

(v) Refining themes

(vi) Writing the report

Ethical approval was granted by the London Bridge Research Ethics Committee (REC23/LO/0718) on the 25/10/2023 as part of the *SABR-PSC* pilot study.

## 5.5 Results

In-person, semi-structured interviews were conducted with all six participants (100%). None had prior clinical trial experience. The Primary Investigator conducted all semi-structured interviews at the Norwich Clinical Research Facility. Interviews lasted approximately 15-30 minutes.

Three core themes were identified from semi-structured interviews: The themes reflect: (i) their experience and perceptions of the trial- 'being part of a greater good'; (ii) challenges experienced within the trial and initial barriers to participation- 'overcoming fear and obstacles'; and finally, (iii) recommendations and considerations for trial engagement- 'ease of process'.

**Experience and perceptions of the trial, study visits and investigations**

**Theme 1: Being part of a greater good**

Overall, participants described the trial as a positive experience. Participants felt that their participation in the trial was 'enjoyable' and 'worthwhile', with may expressing pride and satisfaction in contributing to PSC research.

*"I think it's been a worthwhile trial. It's been a good experience for me, and I can't think of any negatives whatsoever." (Participant BT)*

Another participant expressed sadness that the trial had come to an end *"I can't think of a bad thing. Finishing it was I think is the worst part." (Participant YS)*

Participants expressed a range of motivations that were key determinants in their trial participation. Altruism was a strong motivator *"the incentive to me, really, was to be part of something that's bigger"*. *(Participant BT)*

Being part of a greater good or participating in something that may benefit others and/or PSC research more broadly in the future, even if they themselves did not derive any direct benefit was a frequently reported incentive *"if you can do something to help someone else, why not?" (Participant YS).* This was echoed by *Participant JZ*:

*"Just the possibility. Just the possibility of what, what can come out of it……..maybe after this something else can come up and we can go somewhere with it. So, I think that just that idea that something [positive] can happen…… it's a good feeling, yeah."*

For others their motivation for engagement in the study was intertwined with it being mutually beneficial- both offering personal benefit or hope, whilst engaging in research to also possibly benefit others in the future- a form of conditional altruism *"at the end of the day it's going to help me and other people" (Participant ZS)*

Many of the participants felt a sense of pride in being involved in research *"I've been proud to be, glad to be part of the trial" (Participant BT)*, another participant echoes this sentiment *"yeah, and that's what it takes [for PSC research to evolve], and if there aren't people like me about to do it then you don't develop drugs" (Participant AA).*

Participants motivations were deeply rooted in their epistemological standings of their current condition and the lack of treatment options available to them outside of the trial. It was clear that the opportunity afforded to participants of regular monitoring, frequent one-to-one study visit consultations and personalised feedback of test results was perceived as a significant benefit and potential motivator for participants. Despite half of the participants being employed or having significant childcare responsibilities the frequent study visits were not seen as a significant barrier; however, their employers/family support and flexibility was cited as a major contributory factor. Without which, their engagement in research may have been difficult if not impossible.

*"For me, without a doubt [the greatest benefit] was getting a check-up with the doctor every time I came here. How often do you get……. It's a benefit to me because you're keeping check of my health. Everything that was done to me, as far as I'm concerned, I know it's for your research but that was for my benefit, because whatever you would have found, you would have told me about it." (Participant BT)*

Another example of the importance to participants of regular follow-up is exemplified by this participant: *"I was getting a check-up every month [laughs] and I used to say to a lot of people, that's brilliant, I get a check-up every- well, it was every two weeks to start with." (Participant YS)*

The expectation for closer monitoring as part of the trial was likely derived from the patient information sheet outlining the number of study visits and investigations.

The interaction between participant and PI was integral to resolving any questions or concerns at enrolment about the trial, side-effect profile, and intervention whilst empowering participants by ensuring they felt fully informed. Many participants commented that the face-to-face consultation at the screening visit and opportunity to meet the research team at the clinical research unit was particularly important. Giving them the opportunity to meet the individual that would directly oversee their care as part of the trial for the next 6 months, imbued a sense of safety and reassurance of the trial and its purpose.

*"I think it was really important how, how it was presented to me……and then just explaining it in a way that was helpful. I was reassured about what would be ahead of me." (Participant JZ)*

*"Definitely positive. Very easy. You made everything- you explained everything, which is the most important thing especially for me……..But everything was explained very well and I found it very positive, yeah." (Participant YS)*

When participants were questioned on their perceptions of how the intervention affected their health or quality of life one participant reported beneficial effects on their mental health as a result of being monitored frequently "*Well to be honest, it has made me happier in as much as I feel happier in myself that you're keeping a check on me". (Participant BT)*

Participants also commented on perceived benefits to their physical health *"gradually feeling my well-being and energy levels increasing" (Participant CQ)* as a consequence of their engagement in the trial was one of the most positive aspect of taking part in the study according to one participant. Notably, this participant talked about renewed interests and plans to start a new business, something their fatigue limited them from engaging in previously. Interestingly, despite their acknowledgement of their general well-being and fatigue improving this was not reflected in the CLDQ-PSC total score or more specifically their CLDQ-PSC fatigue score. Others noted more specific liver changes "*my liver pain has reduced. I had liver pain quite a lot and I didn't realise that I had it until I didn't have it" (Participant AA).* For this participant the significant perceived reduction in liver pain correlated with a reduction in their week 16 ELF score and serum ALP. Without direct questioning, it is impossible to discern when participants experienced the maximum benefit to their health and well-being, and if this correlated with the point of maximum reduction in their serum ALP and/or GGT.

None of the participants found the frequency of study visits or PROMs too onerous. All participants welcomed a single colonoscopy counting towards their standard of care surveillance colonoscopy as a positive factor that contributed towards their decision to participate in *SABR-PSC*. Many commented that their condition mandated a colonoscopy as part of their standard of care, therefore despite not finding the procedure enjoyable, it was acknowledged that it was a procedure they would incur at regular intervals during the course of their disease. Thus, the colonoscopy associated with trial was not seen as an additional burden.

An initial concern discussed with experts in the field including research nurses at the design stage was the frequency and number of PROMs being administered to participants. There was a concern that participants may experience PROM fatigue. Despite the numerous PROMs being administered at repeated intervals, participants did not find this problematic. They found that after initial orientation

that overall, the PSC specific PROMs would take between 10-20 minutes collectively. Participants welcomed the use of electronic PROMs that were able to be completed remotely using a smart-phone or computer, finding this a positive aspect of the trial.

*"I think that made it easier because we could just sit [at home], turn the television on, you know, mute the television and go through them with more concentration, and you can just easily think about them." (Participant BT)*

Another participant found that there was less pressure doing them at home compared to study visits *"where if you do it here [study visit], you feel a little bit under- not under- you know what I mean, a little bit under pressure to get through it. Where at home you aren't under any pressure to get through it." (Participant YS)*

For one participant, completing the questionnaires at home was an opportunity to share the experience and involvement in the trial with their partner.

*"Yeah, [redacted] would read them out, I'd answer them, it would be 10 or 15 minutes." (Participant BT)*

Whilst the number and frequency of the questionnaires was not perceived to be an issue, minor frustrations were voiced on the overlapping questions across PSC-PRO and the CLDQ-PSC PROMs. The greatest frustration experienced was the reversed scoring system between the CLDQ-PSC and PSC-PRO, which could at times be "confusing". Participants did not cite a preference between the two PROMs (CLDQ and PSC-PRO), despite some similarities in questions, they did not mind completing

both. However, the scoring system in CLDQ-PSC (1 equating to being the worst perceived health outcome) seemed counter intuitive, and therefore when switching between the two questionnaires additional time was required to ensure they were using the correct scoring system.

**Challenges encountered during the trial and initial barriers to participation**

**Theme 2: Overcoming fear and obstacles**

Whilst most participants adapted well to the trial, there were challenges and apprehensions also. Several reported apprehension, particularly around self-administering the subcutaneous intervention. Early injections were described as moments of hesitation, quickly overcome through training, support and familiarity.

Participants were trained by the PI on how to administer the intervention subcutaneously at the first study visit and thereafter all, but one participant was able to self-inject at home. Participants found the training session appropriate in content and detail, citing no additional requirements or revision to the training provided. Overall, participants reported mixed feelings about the self-administration of the subcutaneous intervention.

*"You know, it's just like jumping in a cold stream. You've just got to do it. And as long as you just pinch yourself and you dig your nail in so that the nails hurt more than the needle then you don't feel it. So, I didn't find any issue whatsoever. I didn't look forward to it, but it's got to be done, you do it. And if that's a benefit to health then…". (Participant BT)*

Most participants cited anxiety and apprehension in administering their first injection on their own.

*"The first injection, a tiny little bit [scared]. You know, a tiny little bit, you're hovering there with it [laughs], you put your glasses on, the needle looked twice as big. Do you know what I mean? Really? Have I got to really? But no, you're a bit hesitant for the first injection, that was all." (Participant YS)*

Two participants described finding the process as unproblematic. This was particularly so for those with a concomitant autoimmune disease or IBD, where treatment in the way of injectables is commonplace.

*"The needle wasn't as frightening as you would think. It's as thin as a hair, isn't it? It's only once a fortnight." (Participant ZS)*

However, one participant preferred an oral medication, citing refrigeration of the intervention, time to warm to room temperature before administration and disposal into a sharps box thereafter as inconveniences. Whilst not expressly cited by participants in the semi-structured interviews, several participants throughout the course of the study raised concerns about travelling abroad with the medication.

*"I think a tablet probably would help in the long run because obviously, when I pick up the medication from here, then obviously I've got to drive home then obviously, I'm restricted to how long it can be out of the fridge and things like that." (Participant ZS)*

For many, the option of enlisting a family member, the research nurse or PI to administer the injections was beneficial. For one participant who had a mild phobia of self-injecting, the absence of this option would have made their participation unlikely.

Despite the prospect of a subcutaneous injection causing some trepidation in participants, concerns also centred on the side-effect profile (notably fatigue and fungal infections). For others, commencing an intervention that could worsen their currently stable clinical condition caused hesitancy. This sentiment was also expressed in responses from those that were invited but declined to be enrolled. Finally, some participants expressed initial concerns of being one of the first patients with PSC to trial brodalumab for an unlicensed indication. Nonetheless, many also perceived the fact that the intervention had been trialled in other autoimmune conditions and repurposed in this study as reassuring, despite its utility in liver disease being unknown.

*"The only thought that made me hesitant was that because I've had fungal problems, they said you could get it [in the] throat, didn't they? And that was the only thing, ooh, I don't know if I'd want that. That was the only thing." (Participant YS)*

*"For me, I was concerned about being the first patient and not knowing if the drug would work. The drug was also found not to work in IBD before, so not knowing if it would worsen the colitis." (Participant CQ)*

However, participants accounts suggest that any apprehensions lessened as they as they were able to ask questions and learn more detail about the trial during the screening appointment.

Fatigue is a debilitating symptom for many patients who suffer with PSC, and a major contributor to HRQoL impairment. Despite fatigue being a known and listed side-effect, others were not deterred. Nonetheless, perceived trial benefits outweighed any perceived risk. This was exemplified by one participant response:

*"Because I'd rather have fatigue, chronic fatigue than I would be dead." (Participant ZS)*

No participant reported significant impact on their quality of life. Another participant rationalised that all interventions come with a list of *"a thousand things that could go wrong" (Participant YS)* and that even treatments as conceivably innocuous as aspirin has multiple side-effects also.

**Recommendations and considerations for trial engagement**

**Theme 3: Ease of process**

Participants viewed the trial design positively, finding it well-run and minimally burdensome, with few suggested changes. All participants suggested that they would be willing to take part in a larger-scale trial of brodalumab in the future if there was evidence that it may be beneficial for PSC.

Recommendations focused on practical adjustments to reduce participant burden:

(i) Sample handling: Participants expressed that the additional travel to the clinical research unit to return faecal calprotectin samples was time consuming and costly. One recommendation included being able to return samples to their local GP. Another alternative was for sample pots to be issued in batches at the beginning of the study and returned when attending their corresponding study visit.

(ii) Visit format: Some participants proposed flexibility in visit formats, i.e., alternating face-to-face study visits with a virtual consultation, to accommodate full-time employment. Whilst another participant felt that the face-to-face study visits were an integral part of the trial, valuing the in-person format for building rapport and valuing reassurance over convenience.

(iii) PROM scoring: PROM completion was not seen as onerous, however adhering to one format with regards to scoring of questionnaires was preferable.

## 5.6 Discussion and summary of main findings

This small-scale mixed-methods study generated early feasibility insights to guide a follow-on trial. The *SABR-PSC* pilot study embedded a qualitative approach to acquire a more granular understanding of participants real-world experience of trial participation and recommendations for a future larger-scale trial of brodalumab in PSC.

The qualitative findings indicate that the trial and intervention were acceptable, feasible and tolerable to participants (see Table 5-1). Participation was motivated by a combination of altruism, anticipated personal health benefit, and trust in the research team, with the hope of generating results that would be beneficial to the wider PSC community. Whilst participants were not deterred by the subcutaneous route of administration, there were initial hesitancies around self-injection and side-effects. Importantly, these were mitigated by clear training, supportive research team relationships and perceived health monitoring benefits. Participants proposed low-burden procedural trial refinements- particularly regarding FC sample returns and visit flexibility- to enhance future trial recruitment and retention.

These findings align with the broader trial literature where altruism, reassurance and clinical rapport influence engagement, whilst procedural burden and uncertainty can act as barriers (462). Early PSC interventional studies rarely incorporate and/or publish qualitative approaches. Insights from the *SABR-PSC* study highlight the added value of embedding qualitative methods in PSC trials to capture outcomes of feasibility not captured using quantitative metrics, addressing a gap in the literature.

**Interpretation in context of feasibility and design recommendations for phase 2 RCT**

Participants overwhelmingly expressed acceptability of the trial, and its related processes as evidenced through feedback on perceptions that a single colonoscopy as part of the study counting towards their standard of care surveillance reduced burden, their positive assertions of the PROMs/electronic PROMs (ePROMs) and frequency of study visits. This is similarly reflected in the exit questionnaire responses, retention rate, absence of participant withdrawals or early discontinuation as reported in Chapter 4.5.1.

> **Phase 2 design recommendations:** A future larger-scale RCT would maintain ePROMs, but provide additional early guidance to reducing scoring confusion between the CLDQ-PSC and PSC-PRO. Furthermore, amendments will be made to avoid administration of the CLDQ-PSC and PSC-PRO at the same timepoints. A future trial will retain the count-towards standard of care colonoscopy as this was well received, echoing early PPI steering group discussions which endorsed this aspect of the trial at the design stage.

Overall, participants were content with the number and frequency of in-person study visits, many cited the rapport built with the research team as part of these visits as being a valuable aspect of their experience. Some participants recommended consideration of a future hybrid visit model to reduce participant burden. In a recent survey conducted across 30 countries by PSC Partners exploring patient

barriers to trial participation, 22% cited too much time off work, with 17% citing frequent or long study visits (463) as being barriers to research participation. An externally-led, patient-focused drug development meeting hosted by PSC Partners, an FDA initiative, endorsed visit flexibility and the use of remote services to expand PSC clinical trial research engagement and minimise participant burden (463).

**Phase 2 RCT design recommendations:** A future clinical trial will incorporate structured PPI engagement (e.g., focus groups, surveys) to evaluate preferences for inclusion of remote study visits in a larger PSC cohort to inform this aspect of trial design. Recruitment to PPI activities will seek to gather perspectives across age, gender, socio-economic status, digital access/literacy and geographical (locoregional) context to ensure diverse perspectives are represented. It is essential that key 'touchpoints' in-person study visits are preserved, however a hybrid model will be considered where clinically appropriate.

All participants expressed willingness to participate in a future RCT of brodalumab, which supports overall acceptability and participant interest. Corroboratory evidence of patient acceptability and interest in the *SABR-PSC* trial has already been discussed in Chapter 4.5.1, where it was reported that 19 additional patients from across the United Kingdom directly contacted the Chief Investigator to register their interest.

**Phase 2 RCT design recommendations:** To increase future recruitment and retention, a brief frequently asked questions checklist addressing off-label use of brodalumab in PSC, safety over-sights and real-world side-effect frequency as obtained from the *SABR-PSC* study could be issued to participants as part of the PIS. It is clear that the role of the clinician in presenting the study to participants is central; their enthusiasm, ability to build a rapport and foster trust, intricate knowledge of the study/process, adverse events profile and ability to transparently answer questions and concerns can facilitate recruitment outcomes. Selection of clinical

trialists and research team members with a similar passion and commitment to the study will need to be carefully considered in the future.

Training provided for self-injecting was practical and well-received, resulting in the majority of participants being able to self-inject at home.

**Phase 2 RCT design recommendations:** A standardised video could be created and made available online to participants at enrolment demonstrating the process of self-injection and describing common side-effects and associated management. This would ensure uniformity of training and advice across a multicentre study.

Whilst employment and caring responsibilities were not a significant barrier for enrolled trial participants a future study would aim to minimise travel burden and costs.

**Phase 2 RCT design recommendations:** A future RCT will permit batch issue of FC pots following screening completion and confirmation of participant eligibility. Alternatively, a mail-back/courier system could be employed.

**Table 5-1** Feasibility insights and phase 2 randomised controlled trial design recommendations.

| Feasibility Domain | Participant insight (themes) | Phase 2 design recommendations/action |
|---|---|---|
| **Acceptability** | Altruistic motivation (*being part of a greater good*); reassurance from frequent monitoring; positive experience of trial; content with “counts towards" surveillance colonoscopy; positive experience of ePROMs; willingness to join future trial | Retain ePROMs and trial colonoscopy as counting towards standard of care |
| **Acceptability** | PROM duplication/scoring confusion (CLDQ-PSC vs PSC-PRO) | Avoid co-administering CLDQ-PSC and PSC-PRO at same study visit |
| **Practicality** | Extra trips to return FC pots were burdensome; mixed views on virtual consultations (*ease of process*) | Batch issue FC kits; consider courier/pre-paid return; preserve key in-person ‘touchpoint’ visits; active PPI activities to seek opinions on hybrid trial approach |
| **Tolerability** | Self-injection anxiety – mitigated with training/support; side-effects not adversely affecting QoL (*overcoming fear and obstacles*) | FAQ checklist with side-effect frequencies; standardise self-injection 10 minute training video; retain nurse/family administration pathways |

Abbreviations: ePROMs, electronic patient reported outcome measures; FC, faecal calprotectin; FAQ, frequently asked questions; PPI, patient and public involvement.

**Strengths and limitations**

Strengths of this study include the acquisition of rich participant-centred data, a 100% interview completion rate, and direct translation of feedback into concrete phase 2 RCT recommendations. The complementary approach derived from administration of semi-structured interviews and exit questionnaires demonstrated concordance of participant responses, increasing confidence in observed results. This study addresses a gap in existing literature reporting on participant perspectives from within an interventional trial.

Limitations include (i) absence of a qualitative expert as part of the supervisory panel. This was mitigated where possible by early external qualitative expert input from both the Clinical Trials Unit (Dr T Katangwe-Chigamba) and the University of East Anglia (Dr S Hanson) and qualitative training by the interviewer; (ii) a key limitation of this work is that perspectives and acceptability findings were derived primarily from trial participants, as decliners and non-participants were not included in the semi-structured interview programme. Introducing the potential for volunteer bias, whereby the perspectives captured may over-represent individuals who were more research engaged, altruistic, less risk-averse, or better able to accommodate intensive research schedules and study procedures, thereby limiting external validity or generalisability, and threatening transferability to a broader PSC population; (iii) this study includes a small sample size, with limited demographic diversity (only one female participant); (iv) recall bias may have been introduced as semi-structured interviews were conducted four weeks post final dose and 16 weeks post self-injection training. Although proximity to other core events (colonoscopy, MRI, PROMs, study visits) likely limited its impact; (v) the semi-structured interview guide was not piloted prior to administration in *SABR-PSC*; (vi) participant transcripts were not returned to participants for their comment or correction prior to analysis; and (vi) there was potential for the introduction of social desirability bias given the established interviewer-participant rapport over >16 weeks. Social desirability bias occurs where participants are

reluctant to report negative or socially undesirable attitudes, reciprocally overreporting more positive aspects (464). To minimise social desirability bias the interviewer built a rapport with participants based on trust, additionally the interview was conducted in private, maintaining confidentiality. The interviewer tried to put participants at ease and encouraged critical feedback, with all interviews conducted in an impartial and respectful manner. Trustworthiness was supported through a common interview guide and external input.

**Conclusion**

In this small PSC cohort, *SABR-PSC* procedures were acceptable, feasible and tolerable. Semi-structured interviews identified clear, actionable refinement for a future phase 2 RCT to enhance recruitment, particularly around sample handling and visit flexibility. Qualitative insights highlight aspects of participant experiences and perceived well-being not fully captured by PROMs, underscoring the value of embedding qualitative methods in PSC trials and the potential dissonance between some participants subjective health improvements and PROM data scores.

# Chapter 6 Overall discussion and future work

## 6.1 Introduction

This thesis presents the findings of, to the best of our knowledge, the first clinical trial of a novel repurposed IL-17 monoclonal antibody in patients with PSC (*SABR-PSC* pilot study*)*, including individuals with and without concomitant IBD. The introductory chapter (**Chapter 1**) highlighted several key points underpinning the premise for this main body of work: (i) no licensed medical therapy currently exists for PSC that alters the natural history of the disease, leaving a significant unmet need for new therapies in this rare disease cohort; (ii) over the past decade early basic science and translational research has increasingly implicated the IL-17 pathway and Th17 cells in its pathogenesis; (iii) despite this mounting evidence, the safety and efficacy of IL-17 inhibition in people living with PSC has not been formally explored in a clinical trial, prior to this study. This thesis reports on original research conducted across three interconnected studies. Firstly, **Chapter 2**, presented findings from an early pre-trial feasibility assessment of patient recruitment and eligibility at a single centre. Secondly, in **Chapter 3**, the safety and efficacy of biologic therapies in PSC-IBD was systematically evaluated to guide *SABR-PSC* protocol development and safety management plans. Finally, **Chapter 4 and 5**, reported on the findings from the *SABR-PSC* pilot study- an early-phase trial focused on determining the safety and feasibility of brodalumab therapy in PSC cohorts to justify and inform a larger-scale RCT.

This final chapter synthesises the findings across these chapters, situating itself within the context of wider PSC research, reflects on lessons learnt, and considers implications for future works and clinical trial design considerations.

## 6.2 Synthesis of main findings

Robust pre-trial feasibility assessments undertaken in PSC trials at site level are rarely undertaken and/or reported. Omission of this critical step may have contributed to a high screen-failure rate, resulting in a disproportionate number of screened participants to enrol one eligible participant (17:1 screen-to-enrol ratio in a study evaluating curcumin), and/or under-recruitment in several recent multicentre PSC studies (137, 381, 465-467). Such inefficiencies carry significant cost implications particularly for non-commercial trials.

At NNUH a real-world single-centre pre-trial feasibility assessment was conducted to evaluate recruitment potential for *SABR-PSC* based on pre-specified inclusion criteria. Few patients from the known local PSC-IBD cohort met eligibility criteria (23/142, 16.2%). Although baseline characteristics were comparable across eligible and ineligible, eligible participants had a lower ALP (<1.5xULN) at diagnosis, although this did not reach statistical significance on multiple logistic regression. Importantly, no ALP threshold was mandated for *SABR-PSC*. The feasibility assessment indicated that recruitment of five patients at NNUH was feasible and informed the decision to broaden inclusion to patients with and without concomitant IBD and mild colitis. These findings illustrated the practical challenges of conducting trials in a rare heterogenous disease and underscored the requirement of broad inclusion criteria. This pre-trial local level cohort scrutiny resulted in greater efficiency when identifying patients for the *SABR-PSC* study and minimised screen-failures.

Many PSC trials adopt similar eligibility criteria (137, 152, 466-468) (NCT05642468): adults (18-75) with non-cirrhotic LdPSC, absence of concomitant liver disease (including MASLD), stable/quiescent IBD (if IBD is present), on a stable dose of UDCA, and ALP >1.5X ULN. Results from the feasibility assessment as well as lessons learnt from leading and managing the *SABR-PSC* pilot study suggest that a critical

reappraisal of inherited eligibility criteria, especially for early-phase studies assessing safety and tolerability, is warranted. Particularly where unnecessarily restrictive criteria impede recruitment and create a trial population unrepresentative of the intended treatment targeted population. Prior to this work, no systematic site-level assessment of PSC trial eligibility had been performed at NNUH, despite its role as a tertiary centre running several trials concurrently. The pre-trial feasibility assessment proved integral in confirming trial feasibility locally, refining *SABR-PSC* protocol development and informing the design of a future trial of brodalumab in PSC.

Successful clinical trials in PSC depend not only on pragmatic design and realistic recruitment strategies but also on careful selection and rigorous assessment of safety and efficacy outcomes. Only a small number of studies have evaluated biological therapies in PSC-IBD cohorts, with variable incorporation of IBD-specific disease activity outcomes. Given that brodalumab was associated with worsening Crohn's disease in an earlier phase 2 RCT (277), it was critical that *SABR-PSC* included robust IBD assessment outcomes and safety monitoring. To address this a systematic review and meta-analysis evaluating the safety and efficacy of biologics and SMDs in PSC-IBD was undertaken. The review served multiple purposes: firstly, to clarify the fragmented evidence base for the safety and efficacy of biologics in PSC-IBD with a focus on IBD specific outcomes; secondly to guide the choice of IBD outcomes and assessments incorporated in *SABR-PSC*; and thirdly, to guide *SABR-PSC* risk assessment and quality management plans. A treatment that can improve PSC outcomes without exacerbating IBD and ideally one that demonstrates efficacy in both hepatic and colonic compartments- would represent a major therapeutic advantage.

The review highlighted the scarcity and heterogeneity of clinical trials of biologics in PSC-IBD, with substantial methodological variation, small sample sizes and frequent departure from accepted IBD outcome definitions and targets, all of which limit interpretability. This review directly informed *SABR-*

*PSC* methodology most notably through adoption of IBD definitions and outcomes consistent with STRIDE II criteria. Overall, biologics and SMDs (e.g., infliximab, vedolizumab, adalimumab and tofacitinib) appeared safe and well-tolerated, although IBD efficacy was numerically attenuated compared to IBD only cohorts. However, the findings underscored the need for rigorous trial design, incorporation of robust IBD outcome measures and adoption of accepted definitions of remission and exacerbation. Notably, previous meta-analyses of biologic therapy in PSC-IBD have inconsistently reported IBD outcomes. **Chapter 3** of this thesis presents, to the best of our knowledge, the first meta-analysis to comprehensively evaluate colonic outcomes in PSC-IBD, directly addressing a critical knowledge gap. Reporting on these findings should highlight the need for trialists to include more robust and consistent practices in PSC-IBD trials where hepatic and colonic outcomes are of interest.

Together, the pre-trial feasibility assessment reported in **Chapter 2** and the systematic review and met-analysis reported in **Chapter 3**, within this thesis, were the necessary preparatory work that informed the design of the *SABR-PSC* pilot study. The former demonstrated that the recruitment target was achievable and the later ensured appropriate IBD outcome measures and safety monitoring were incorporated alongside hepatic outcomes. **Chapter 1.5.1** details the evidence base of the Th17-IL-17 pathway being implicit in PSC pathogenesis. *SABR-PSC* takes this early evidence, moving from bench to bedside, with the first clinical trial of brodalumab in PSC. *SABR-PSC* contributes to the evidence base and therapeutic landscape represented in Figure 1-6 by evaluating brodalumab for the first time in PSC. Furthermore, it informs the design of a future phase 2 RCT powered to determine brodalumab's efficacy. In **Chapters 4 and 5** the qualitative and quantitative findings for *SABR-PSC* were reported.

Overall, recruitment to *SABR-PSC* was lower than anticipated, with only 6 of the intended 20 participants being recruited over 14 months from a single centre. The pre-trial feasibility assessment

outlined in Chapter 2 over-estimated feasibility (and thus under-estimated recruitment difficulty) for a PSC-IBD-restricted cohort at NNUH; as only 3/6 *SABR-PSC* recruits had PSC-IBD. The *SABR-PSC* study confirmed early results from the pre-trial feasibility assessment indicating that a limited pool of patients were eligible to participate in a trial of a novel repurposed drug at NNUH, reflecting challenges for a future larger-scale RCT and the need for pragmatic eligibility criteria in a future study. Importantly, the pre-trial feasibility assessment and *SABR-PSC* study identified practical modifications to the eligibility criteria to expand recruitment. Inclusion of patients with PSC and PSC-IBD as well as those with non-clinically significant MASLD were pragmatic modifications instituted early in *SABR-PSC* to increase recruitment numbers. Further modifications included recruitment of patients with mild PSC-IBD as part of a phased recruitment strategy. Recruitment to clinical trials of rare diseases are particularly challenging. A larger multicentre trial, ideally with international collaborators, recruiting simultaneously across large tertiary centres with large cohorts of PSC patients will be required for a successful future phase 2 RCT of brodalumab in PSC. Nonetheless, retention, treatment adherence, completion of HRQoL questionnaires, participant reported acceptability and desire to participate in a future trial of brodalumab were excellent, suggesting that a future larger-scale trial is feasible. National patient interest identified as part of this study and presented in Figure 4-3 provides evidence that patients are interested and willing to be recruited to trials of novel repurposed interventions. No SAEs were observed, and the reported AE profile was consistent with that reported in other studies and post marketing experience of brodalumab (277, 278, 433). Importantly, participants reported that the side-effect profile was tolerable. There were no cases of cholangiocarcinoma, depression/SIBs, *Candida* infections, or new diagnoses/exacerbations of IBD which are collectively important and reassuring findings. The absence of a gastrointestinal safety signal with brodalumab in PSC-IBD is particularly reassuring given the concerns raised in earlier anti-IL-17 trials in Crohn's disease . Overall, this study demonstrated that brodalumab was safe and generally well-tolerated in this small patient cohort, supporting feasibility for a future trial in PSC. The limited sample size should not be viewed as a limitation to pursuing a future RCT.

The clinical efficacy outcomes in this study were intended to be exploratory. Outcomes in this small cohort should be interpreted with caution. Lack of any significant and sustained reduction in liver biochemistry analytes and fibrosis markers were not unexpected, possible contributory factors were discussed in detail in Chapter 4.6. The dose adopted in this study was deliberately cautious, with higher doses likely required to demonstrate meaningful biological activity periductally, if such an effect exists. Exploratory efficacy outcomes revealed heterogeneity in response across a number of outcomes. Whilst a two participants achieved a >20% reduction in ALP sustained to week 16, with one demonstrating at >45% reduction and ALP normalisation. However, no consistent reduction was observed across the cohort. These finding are consistent with several recent studies discussed in earlier chapters, highlighting the inter-individual variability in ALP response and aligning with data that ALP alone is an imperfect biomarker of clinical response. Surrogate markers of fibrosis remained largely stable, with individual participants possibly demonstrating potential biological signals of benefit. HRQoL measurements demonstrated minimal change from baseline to week 12. A considerable strength of this pilot study was the inclusion of non-invasive quantitative MRI metrics, particularly hepatic and periductal cT1 scoring suggesting a possible trend towards reduction in hepatic fibroinflammatory activity.

Semi-structured interviews and exit questionnaires were a further strength of the trial design, providing rich detailed insights of participants lived experience of the trial and generating practical suggestions for future trial design improvement. The rich insights captured using this mixed-methods approach could not have been attained had a purely quantitative approach been employed. Participant suggestions regarding reducing participant burden with regards to incorporation of a hybrid study visit programme and continuing to adopt remote completion of HRQoL questionnaires will inform a future larger-scale study.

We acknowledge, however, that the semi-structured interview programme and exit questionnaire captured acceptability findings only from trial participants who enrolled, and that perspectives of decliners and non-participants are also critical for understanding generalisability and optimising future trial design. Systematic differences are likely to exist between participants and non-participants/decliners, and triangulating both sets of views is important to develop effective recruitment and retention strategies. The importance of eliciting decliner/non-participant perspectives is well recognised in trial methodology literature, with qualitative studies consistently demonstrates that motivations and barriers can differ from those who enrol (469, 470).

Although decliners/non-participants were not interviewed, we recorded reasons for non-participation among otherwise eligible individuals, where a reason was provided (Figure 4.2). The most commonly cited barriers were family planning, the frequency/burden of study visits, and concerns about uncertainty or the perceived risk of destabilising a currently stable condition. These findings mirror responses from a recent PSC patient-focused drug development survey exploring barriers to trial participation (463). However, the decliner responses in *SABR-PSC* were captured opportunistically, were not systematically elicited using a standard framework, and were not explored with the depth afforded by semi-structured interviews. Consequently, they cannot be treated as an equivalent qualitative dataset and may under-represent more sensitive or practical consideration (e.g., concerns about IBD flare risk, perceived immunological risk, loss of income, childcare costs or reimbursement adequacy).

Notwithstanding these limitations, the partial decliner data are informative for future trial planning as they highlight barriers likely to influence recruitment and external validity in PSC, and may contribute, at least in part, to the low enrolment of female participants in *SABR-PSC.* A future multi-centre RCT should incorporate an a priori "decliner pathway" at screening, including (i) standardised reasons for

decline categorises with optional free text and (ii) an ethically approved opt-in brief interview option (telephone/remote). This would enable quantification of modifiable barriers and support targeted adaptations (.e.g., travel support, remote/decentralised study visits or assessments and streamlined visits) to improve recruitment and retention.

In light of the cumulative findings, we hypothesis that if IL-17 inhibition were to be shown to be a viable treatment strategy at higher doses, it would be most likely to be effective in a cohort of patients with Ludwig stage 1-3 disease histologically, with less efficacy seen in those with more advanced disease. Figure 6-1 presents a schematic of the proposed "window of opportunity" for brodalumab therapy within the natural history of PSC.

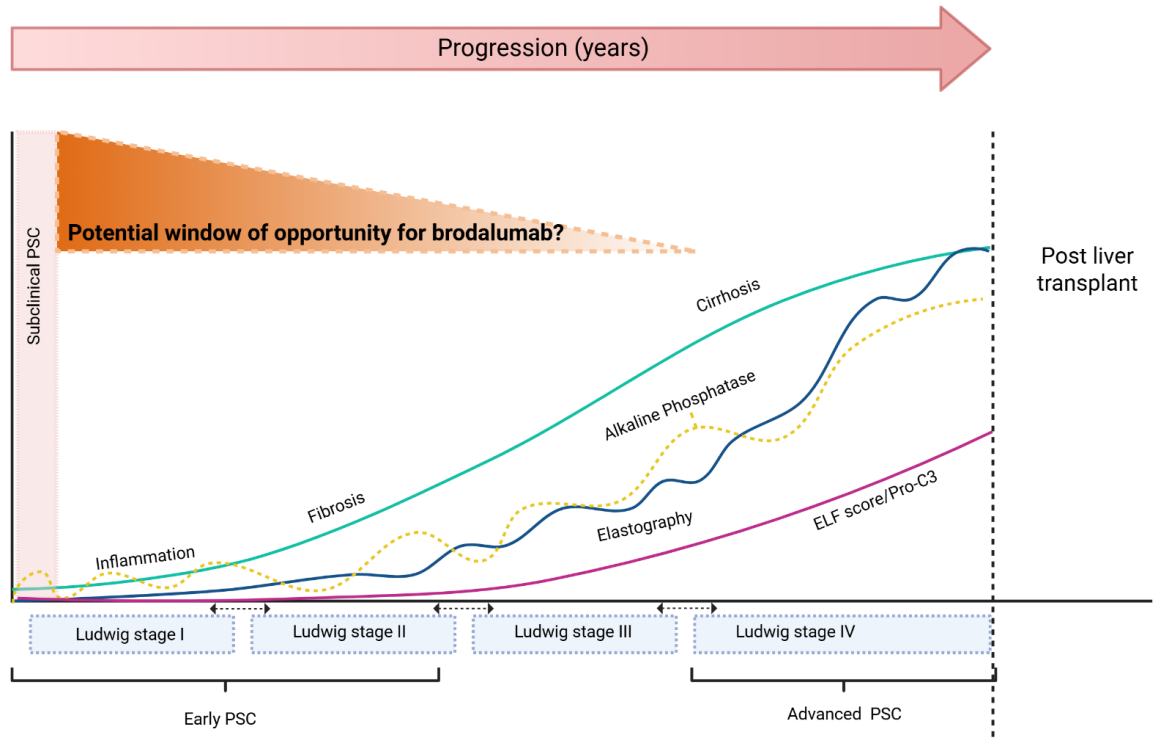


**Figure 6.1**. Schematic representation of the possible window of opportunity for targeted treated with brodalumab within the fibroinflammatory stage of PSC's natural history. The schematic presents how changes

in liver biochemistry, fibrosis markers and histology can fluctuate over time and even regress. Modified adaptation from Karlsen et al. (4).

Taken together, *SABR-PSC* has provided critical insights, demonstrated brodalumab is safe and tolerable in this small cohort of patients, justifying future evaluation of efficacy in a well-powered dose-ranging RCT.

### 6.3 Difficulties encountered and lessons learnt

Several challenges were encountered during the set up and undertaking of the *SABR-PSC* trial. All of which have contributed to important lessons being learnt relating to the undertaking of clinical trials. The greatest difficulties were encountered early on the course of trial set up and regulatory approval, having significant and direct impact on trial recruitment. Setting up and conducting a trial within in a three year period, even for a small pilot study like *SABR-PSC*, is a significant undertaking.

The first difficulty encountered related to gaining sponsor and UEA approval for site activation following MHRA and REC approval, received in October 2023. There were contractual concerns triangulated between sponsor, UEA as grant holder, and Perspectum, in relation to (i) sponsors concerns of storage of anonymised patient images in an offshore cloud; (ii) where ownership of intellectual property would sit; (iii) whether Perspectum's involvement in *SABR-PSC* constituted as a 'sub-study' or whether they would act as 'sub-contractors' using standard subcontracting terms and conditions. These concerns were only relayed to the research team following regulatory approval. As such contractual agreement between the respective parties and approval from the NIHR was protracted taking several months to finalise. This was further incumbered by frequent staff turn-over at Perspectum and within the UEA legal and contracting office. Once it was established that this matter was unlikely to be resolved quickly, the author proposed a temporary resolution. Greenlight site

activation would be issued on the condition that no images would be shared with Perspectum until the matter was formally resolved and contracts signed. Sponsor green light site activation was received on the 1st of February 2024 at which point recruitment efforts commenced. This delay lessened the potential recruitment window by three months (23rd October 2023-1st February 2024), which in light of the estimated recruitment rate would have been the difference between recruiting an additional 1-2 participants at NNUH during this period of delay. It was not until the 23rd of July 2024 that this matter was finally resolved, with standard sub-contracting terms and conditions employed. This early challenge provided early learning opportunities in leadership, management, problem-solving and inter-agency communication, which were applied throughout the study.

*SABR-PSC* was registered on the NIHR clinical research network portfolio, which provided additional funds for research nurse support. However, due to research nurse staff shortages with experience in running liver related clinical trials and multiple clinical trials (both academic and commercial) running concurrently at NNUH, this led to the author conducting all aspects of the trial single handedly for the duration. Leaving the author to act as the CI, local PI, and trial manager. Whilst this position afforded a fuller understanding, consistency in trial conduct, facilitated excellent participant-researcher rapport and provided invaluable learning opportunities in clinical trial management from design to delivery, it may have also introduced bias that could have affected the reliability of some of the study findings. The author conducted all trial-related activities, including study monitoring and the conduct of semi-structured interviews. Whilst this fostered an excellent relationship with participants, this rapport may have confounded the excellent retention rates, adherence, HRQoL completion rates and positive responses received during the semi-structured interviews. Resulting in inflated estimates. The possibility of social desirability bias was discussed in Chapter 5.6. By contrast, demand characteristics- well established in psychological research (471)- may also have influenced participant behaviours and, in turn, trial outcomes. Demand characteristics refers to participants subconscious modification of

behaviours and alignment of their responses to assist the investigator achieve their study aims, engendered once the investigators agenda has been established. Whilst this concept is less well studied in non-laboratory studies, its effects could be far reaching (472). Trial participants, in the knowledge that no currently approved therapy exists for PSC, may have subconsciously been inclined to positively assist the research aims to increase the likelihood of the trials' success. This would have been particularly relevant with regards to completion of HRQoL assessment, retention rates, adherence and feedback during the semi-structured interview. This may also have been compounded by participants knowledge that the *SABR-PSC* forms a significant part of the authors future research endeavours. The potential influence of confounding factors such as social desirability bias and demand characteristics on trial outcomes cannot be excluded in this single-arm, open-label study with direct oversight and study involvement of the author. It is possible that such biases might have been mitigated had the semi-structured interviews been conducted by a research nurse or an alternative member of the research team. Similarly, whilst additional bias may have arisen from the oversight and conduct of all trial activities by a single investigator, supervisory oversight and adherence to pre-specified protocols were intended to promote transparency and minimising undue influence.

Recruitment efforts at NNUH were successful and resulted in over-recruitment at this single site. This success was likely as a direct result of the author driving efforts and timelines at the coordinating trial site. However, challenges in opening research sites in multicentre trials are well documented, and include negotiating excess treatment cost, site logistics, competing academic and clinical priorities of investigators, signing of contracts and staffing availability (473). Several unique site specific impediments arose throughout the *SABR-PSC* study rendering the University Hospital Birmingham, John Radcliffe Hospital-Oxford and Cambridge University Hospital unable to open to recruitment before the end of the recruitment period. These are briefly outlined below:

- Cambridge University Hospital- the local PI relocated to a different institute early on in the trial process and a replacement was unable to be found.
- University Hospital Birmingham- had several ongoing competing academic and commercial trials. Whilst efforts were made to prioritise *SABR-PSC* trial related procedures such as the healthy volunteer scan required by Perspectum for quality assurance and/or the single colonoscopy for all patients created logistical challenges that were not quickly overcome. The recruitment period was exhausted, by the time these issues were resolved.
- John Radcliffe Hospital- also had several competing academic and commercial trials. Additionally, pharmacy cited lack of capacity and capability to run *SABR-PSC* within the available funds as an impediment.

Interest and support was garnered from additional centres- Nottingham University Hospital, The Royal Free Hospital London and the Freeman Hospital in Newcastle, following formal presentation of the study by the author to potential local PIs and their respective R&D teams. Nottingham were able to prioritise the study and opened to recruitment in February 2025, seven months later. However, with less than two months of the recruitment window remaining, this limited timeframe did not allow sufficient opportunity to recruit participants.

Whilst site specific operational and logistical challenges contributed to delays in sites opening and consequent under-recruitment, other impediments may also have played a role and are considered herein. Sustained engagement and enthusiasm from local PI and R&D teams are essential for effective collaboration and will need to be maintained over the course of several years. Local PIs endorsement and reprioritisation are crucial where multiple competing interests and studies exist. In retrospect, involving local PIs earlier in study planning and protocol development would likely have fostered stronger enthusiasm, improved PI-CI communication, and provided greater understanding of the

study timelines engendering shared research goals for *SABR-PSC*. PIs were selected on the basis on their extensive trial experience, research capabilities, and history of successful collaboration on previous projects. However, sites resources, staffing levels and competing study commitments were less well established during the selection process. Once *SABR-PSC* was established, a formal kick-off meeting was conducted, supplemented by regular touchpoints and updates by email or virtual meetings. These measures fostered regular communication, shared problem-solving around recruitment and site opening, and shared recognition of the trials' importance. The professional relationships now established with PSC experts across the UK will be instrumental in the development and successful delivery of a future RCT.

In efforts to increase recruitment a six month no-cost extension was approved by the NIHR in August 2025. Any additional increase in the sample size will only benefit the study in generating more robust results and more precise estimates.

## 6.4 Future recommendations for a phase 2 study

The aim of the *SABR-PSC* trial and therefore this thesis was to establish the feasibility of conducting a phase 2 multicentre RCT of brodalumab adequately powered to demonstrate clinical efficacy in PSC cohorts. This section will outline suggested trial design changes to be implemented in a future study to ensure its success. Figure 6-2 outlines the proposed design of a future phase 2 study based on *SABR-PSC* pilot findings.

**Design and Intervention**

Whilst *SABR-PSC* benefited from being a single-arm study, which is likely to have been favourable amongst participants, a future trial would necessitate a dose-ranging placebo-control RCT. 210mg of

brodalumab appeared to be well-tolerated amongst PSC participants. However, this dose was deliberately cautious, and any future study will need to utilise an adaptive design to enable testing of a broad range of exposures. Doses up to 700mg intravenously have been successfully trialled in other autoimmune conditions and healthy volunteers (277, 452). Brodalumab exhibits partially non-linear pharmacokinetics and target-mediated drug disposition (474). Once near maximal IL-17 receptor saturation is achieved, significant dose increases may not yield greater therapeutic benefit, but rather slow clearance with higher circulating levels. Equally if the dosing is inadequate receptors may not reach saturation allowing the drug to be cleared more quickly, trough levels to drop and receptor inhibition to deplete to below the threshold required for fibroinflammatory pathway inhibition. *SABR-PSC* findings raise the possibility that the psoriasis-licensed dose of 210mg may be insufficient for PSC, although the small sample size precludes definitive conclusions. Brodalumab's partially non-linear pharmacokinetics may contextualise the observed biochemical response in ALP/GGT during weekly dosing in *SABR-PSC* but not during alternate week dosing, resulting in loss of biochemical effect. Dosing decisions for a future trial are therefore not straightforward. However, we propose a future randomised double-blind dose-ranging phase 2 study, evaluating the safety and efficacy of 12 weeks treatment of brodalumab in patients with PSC. Patients should be randomly assigned a 1:1:1:1 ratio according to computer generated randomisation to receive placebo, brodalumab 210mg S/C Q2W (benchmark), or 210mg S/C weekly, or 350mg S/C on alternate weeks. Retaining a subcutaneous method of administration retains validity estimates of participants acceptability of this route. Similar variable dosage schedules of brodalumab have been trailed in Crohn's disease, asthma, psoriasis and rheumatoid arthritis and were well-tolerated (277, 475-477). Further, justification of weekly dosing of 210mg comes from an earlier study where weekly dosing of 210mg S/C showed greater efficacy than alternate week dosing in a small study evaluating brodalumab in hidradenitis suppurative (NCT04979520).

We propose maintaining the same duration of treatment (12 weeks), as clinically significant changes in disease activity have been observed within 2-6 weeks in other trials of brodalumab (277) (478). Whether such early responses occur in PSC is unknown, but a 12-week duration provides a pragmatic timeframe to detect potential treatment signals. This is likely to be more acceptable to both investigators and participants, reducing the burden of trial involvement. This will also ensure feasibility estimates derived from *SABR-PSC* remain valid. Finally, a trial significantly longer in duration is likely to be financially prohibitive at this stage. A future study will incorporate a reduced number of face-to-face study visits whilst retaining the option to submit HRQoL questionnaires remotely. Close contact with the trial team will still remain at key points with participants able to contact the research team with questions or concerns and a remote consultation 1 week after the participants first administered injection. A reduction in study visits is likely to benefit patients who have work commitments or caring responsibilities, reduce overall trial costs and would appear pragmatic given the reassuring safety profile established within *SABR-PSC* to date.

**Eligibility criteria**

Eligibility criteria would largely remain the same in order to retain feasibility estimates derived from *SABR-PSC.* Importantly, this includes retaining the absence of an ALP cut-off, provided there is evidence of a historical elevated ALP and ALP is <10x ULN at screening. We would continue to include patients with non-clinically significant MASLD and quiescent-mild IBD (phased approach). Whilst expanding the eligibility criteria to include patients with Child Pugh A cirrhosis (as previously discussed in Chapter 4-6) would increase the pool of potential patients, thereby improving recruitment, and providing important insights into its potential efficacy in more advanced disease stages (compensated), at this stage the pharmacokinetics of brodalumab in cirrhotic patients remains unknown and re-evaluating safety in a larger more robust cohort of non-cirrhotic patients is the

primary goal in any trial succeeding *SABR-PSC* and retains feasibility estimates acquired from *SABR-PSC.*

**Study assessments**

The multi-modal outcome approach used in this early phase study was a significant strength. Completion of all outcome assessments at week 16 in *SABR-PSC* were feasible. A future study should retain use of multi-parametric MRI as well as conventional assessment of liver fibrosis (VCTE and ELF score) but should be augmented by use of PRO-C3.

**Sample size**

PSC interventional trials seek to demonstrate safety alongside a meaningful change in biomarkers (biochemical or fibrosis) that can be used to prognosticate long-term clinical outcomes e.g., transplant. Liver biopsy is invasive, carries a risk of complications and is not suitable for routine use in early phase studies. Moreover, given the short duration of follow-up in such studies, it is not feasible to power them to detect rare clinical events such as liver transplant or death. As a result, ALP is frequently employed as a primary end point in PSC trials. However as previously discussed, ALP may not be the ideal surrogate marker of biliary fibroinflammation. Any future trial of brodalumab should consider a composite endpoint of mean change from baseline to week 12 (end of treatment) in ALP or fibrosis scores such as ELF score or periductal cT1 score, as a pragmatic solution to this challenge.

A sample size calculation was undertaken to estimate the number of participants required for a future phase 2 double-blind, placebo-controlled, dose-ranging trial. The calculation assumed a clinically meaningful response defined as 30% reduction in serum ALP after 12 weeks of brodalumab treatment. Based on an estimated SD of 39.2 (estimated from *SABR-PSC* pilot data). A sample size of 28 patients

per arm would be required to provide 80% power, at a two-sided alpha level of 0.05. Participant retention in *SABR-PSC* was excellent, however this is likely attributable to the strong participant-investigator rapport, reducing the likelihood of participants withdrawing. Which is unlikely to be replicable at scale in a multicentre study. To account for this a 10% drop-out rate was assumed based on observations from prior clinical trials, increasing the required sample to 31 patients per arm (124 total). Assuming rates from the *SABR-PSC* feasibility work (which account for the impact of competing trials) are accurate and applicable then across a minimum of 20 centres 124 patients could be recruited in 3-3.5 years with a buffer of 10% for staggered site activation. A collaborative approach will be required for future success.

Recent research has uncovered a biologically plausible role of IL-17 inhibition in attenuating the fibroinflammatory processes in PSC that leads to disease progression. This is supported by mounting evidence from basic science and early translational research. Nonetheless, clinical equipoise is maintained. As outlined in previous chapters there is evidently a fine balance between IL-17's homeostatic and pathogenic role. A well-powered RCT to definitively determine safety and clinical efficacy of brodalumab in PSC cohorts is required. Whilst very different diseases, one should not ignore that equally favourable early research pointed towards IL-17 inhibition as a potential treatment target for Crohn's disease- results that were later disproved in clinical trials.

| | PILOT STUDY | FUTURE MAIN TRIAL |
|---|---|---|
| QUESTION | Is a trial of brodalumab safe and feasible in PSC? | Is brodalumab efficacious in PSC (does it significantly reduce ALP and fibroinflammatory markers), is it safe, what is the optimal dose? |
| DESIGN | Single arm, open label, multi-centre pilot study | Phase II double blind, placebo-controlled, multicentre, dose-ranging study |
| POPULATION | Adults (18-75), with non-cirrhotic LdPSC. With or without IBD and non-clinically significant MASLD. | |
| INTERVENTION | Brodalumab 210mg S/C alternate weeks | 1:1:1:1<br>Brodalumab 210mg S/C alternate weeks<br>Brodalumab 210mg S/C weekly<br>Brodalumab 350mg S/C alternate weeks<br>Placebo |
| COMPARATOR | None | Placebo pre-filled injection pen |
| OUTCOME | **Primary outcome:** Safety and feasibility<br>**Exploratory efficacy outcomes**: Liver biochemical readouts, VCTE, ELF score, MRCP+/LiverMultiScan, HRQoL | **Primary composite endpoint**: Change in ALP and ELF score from baseline to week 12<br>**Secondary endpoints:** safety, other liver biochemical readouts, VCTE, MRCP+/LiverMultiScan, HRQoL, PRO-C3 |
| NUMBER OF SITES | 4 | Minimum of: 6 |
| NUMBER OF PARTICIPANTS | **Target:** 20<br>**Actual:** 6 | 31 patients per arm<br>124 total |

**Figure 6-2.** Proposed outline of a future phase 2 dose-ranging study based on the feasibility findings from *SABR-PSC*. Abbreviations: ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; HRQoL, health-related quality of life; MASLD, metabolic dysfunction-associated steatotic liver disease; MRCP, magnetic resonance cholangiopancreatography; S/C, subcutaneous; VCTE, vibration controlled transient elastography.

## 6.5 Final conclusion

PSC is a complex disease for which approved therapies are urgently required. This thesis set out to address a series of interlinked questions culminating in the design and delivery of the *SABR-PSC* pilot study. Each chapter provided novel insights, contributing to the existing knowledge base, and directly informed the design of *SABR-PSC* carrying with it wider implications for a future trial of brodalumab in PSC.

Taken together these complementary studies provided a unified set of insights: that PSC trials are feasible but require pragmatic design and multicentre collaboration to overcome recruitment challenges; that safety monitoring and appropriate outcome selection are critical when evaluating equally important colonic and hepatic outcomes in PSC-IBD; that brodalumab is safe and well-tolerated in PSC cohorts; and that innovative trials should incorporate endpoints beyond ALP, and include a combination of fibrosis biomarkers, imaging biomarkers and HRQoL assessment to holistically capture treatment effects. In summary, the research undertaken in this thesis contributes to the evolving landscape of PSC research and provides a clear roadmap for the design of a future phase 2 RCT evaluating the efficacy of brodalumab in PSC.

It is intended that a competitive application for NIHR funding to evaluate brodalumab in a phase 2 multicentre RCT will be submitted within the next 6-9 months following completion of this Doctoral Research Fellowship.

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## Appendices

Appendix A- Future PSC-IBD study minimum output reporting recommendation

Appendix B- Informed Consent Form

Appendix C- IBD diary (non-validated questionnaire)

Appendix D- Week 16 Semi-structured interview

Appendix E- Exit Questionnaire (non-validated questionnaire)

Appendix F- Research approvals for studies

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Appendix H- CONSORT 2010 checklist

Appendix I- Full details of screen failures

Appendix J. Nancy histology Index for ulcerative colitis

Appendix K MRCP+ and LiverMultiScan metrics for all participants

Appendix L COREQ checklist for qualitative research

## Appendix A- Future PSC-IBD study minimum output reporting recommendation

| Variable | Explanation |
|---|---|
| Study design | • RCT/prospective/retrospective; single vs multicentre; country |
| Demographics | • Age at enrolment<br>• Sex<br>• Age at PSC diagnosis<br>• Age at IBD diagnosis |
| Baseline characteristics | • PSC phenotype: large-duct vs small-duct PSC<br>• Overlap syndrome i.e. autoimmune hepatitis<br>• Cirrhosis status at baseline<br>• Transplant status: naïve vs post-liver transplant<br>• IBD phenotype: UC vs CD vs IBDU<br>• Montreal classification of disease extent and location<br>• Biologic naïve<br>• Median duration of IBD |
| Baseline disease activity | • IBD clinical index used: pMayo,SCCAI, HBI, CDAI<br>• Faecal calprotectin result (if applicable)<br>• Endoscopic scoring system used: UCEIS, MES, SESCD |
| Intervention details | • Agent used<br>• Treatment dose and regimen(for induction and maintenance)<br>• Route of administration<br>• Concomitant medications: UDCA, steroids, immunomodulators, antibiotics<br>• Corticosteroids at baseline: agent, dose and weaning regimen<br>• Duration of treatment and reasons for discontinuation (primary non-response secondary loss of response) |

| | |
|---|---|
| IBD outcomes (standardised definitions and timepoints) | • Clinical response/remission: report the index used with associated cut-off values<br>• Corticosteroid-free remission: define steroid-free remission and how it was confirmed<br>• Endoscopic response/mucosal healing: report the score used and cut-off values<br>• Histological outcomes (if done): report the scoring system used e.g., Nancy histology index, Geboes score<br>• Health related quality of life: tool used, timepoints<br>• Changes in baseline faecal calprotectin (if used)<br>• Non-response/loss of response<br>• Colectomy: proportion and primary indication (active disease vs colorectal neoplasia)<br>• *Mean/median timepoints for assessment of each of the above should be outlined* |
| PSC/hepatobiliary outcomes | • Cholangitis: definition used; culture proven vs radiological<br>• Cholangiocarcinoma<br>• Liver transplant<br>• Death<br>• *Length of time from induction of therapy to detection of outcome* |
| Timepoints | • Induction: report exact window i.e., 8-14 weeks<br>• Maintenance: report exact window i.e. 6 months and 52 weeks<br>• Duration of follow-up |
| Safety | • Adverse events/ Serious adverse event (proportions and rates)<br>• Adverse event related discontinuation (proportions and rates)<br>• Infections: serious vs non-serious, site specific, and pathogens named<br>• Colorectal neoplasia (low grade, high grade, colorectal cancer)<br>• *Length of time from induction of therapy to detection of outcome* |
| Statistics and reporting | • Denominators stated for each outcome<br>• Continuous outcome: mean +/- SD or median +/- IQR<br>• Binary outcome: n/N (%) |

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease unclassified; IQR, interquartile range; MES, Mayo endoscopic score; pMayo, partial Mayo score; PSC, primary sclerosing cholangitis; RCT, randomised controlled trial; SCCAI, simple clinical colitis activity index; SESCD, simple endoscopic score Crohn's disease; SD, standard deviation; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity; UDCA, ursodeoxycholic acid

## Appendix B- Informed Consent Form


NHS
Norfolk and Norwich
University Hospitals
NHS Foundation Trust


8. I agree to the collection, transfer, storage and analysis of blood, faecal, urine, and biopsy samples for use in translational research associated with the SABR-PSC trial. ☐

9. I understand that if I withdraw from the trial, any samples and data that have been collected up to the date of my withdrawal will be analysed and used as part of the research ☐

10. I understand that it is entirely *optional* to provide an additional blood sample for DNA analysis and urine samples to be stored as part of this trial and used in future research to help better understand PSC. ☐

11. **DELETE AS APPROPRIATE** -I agree/do not agree to the collection, storage and analysis of the *optional* blood sample for DNA analysis for future research in PSC. ☐

12. **DELETE AS APPROPRIATE** -I agree/do not agree to the collection, storage and analysis of the *optional* urine samples for future research in PSC. ☐

13. I understand that an voice (audio) recording will take place at the week 16 study visit as part of the semi-structured interview, and any quotes used will be anonymised before publication. **DELETE AS APPROPRIATE**- I give my permission/do not give permission for my voice to be recorded during the week 16 semi structured interview. ☐

14. I understand that as part of my MRI (Magnetic Resonance Imaging) scan a private company (Perspectum) will be involved in making more detailed analysis of my liver disease to better understand how this medication works in PSC. If my hospital offers this service. I understand that any data shared with the company will be anonymous. ☐

15. **DELETE AS APPROPRIATE**: I give my permission/ do not my give permission for Perspectum to use my anonymised images or data for internal research, presentation, or development. (Perspectum will not share my images or information with any 3rd parties.) ☐

16. I agree to take part in the above study. ☐

| | | |
|---|---|---|
| _____ | _____ | _____ |
| Name of Participant | Date | Signature |
| _____ | _____ | _____ |
| Name of Person seeking consent | Date | Signature |

SABR-PSC Pilot Study
Date:04/12/2024
Version:0.3
IRAS No. 1006951

## Appendix C- IBD diary (non-validated questionnaire)

**PSC-IBD Diary: Ulcerative colitis/IBD-Unclassified**

Date completed: __/__/__

Trial participant number: ☐

Please fill in this diary, documenting your symptoms for the *previous 7 days*.

When you are well, on a normal day, how often (on average) do you have a bowel movement per day? ☐

This diary should be completed, ideally the day before you attend your scheduled study visit appointment. By keeping this diary as accurate as possible, it will provide your trial team with information they need to assess flare ups of your IBD.

Please either complete the diary electronically and send it to the trial team the day before your appointment at the following email address SABR.PSC@uea.ac.uk, or complete it on paper and bring it along with you to your appointment.

| Question- relating to the previous 7 days | Response | Tick | Score |
|---|---|---|---|
| **On average how often do you have a bowel movement per day?** | Normal for you | ☐ | 0 |
| | 1-2 stools/day more than normal | ☐ | 1 |
| | 3-4 stools/day more than normal | ☐ | 2 |
| | >4 stools/day more than normal | ☐ | 3 |
| **Have you noticed blood in your bowel movement?** | No-None | ☐ | 0 |
| | Streaks of blood with your stool but occurring<50% of the time | ☐ | 1 |
| | Visible blood with your stools occurring >50% of the time | ☐ | 2 |
| | Passing blood only when you open your bowels | ☐ | 3 |
| **Have you had any pain in your stomach/belly?** | No. None | ☐ | 0 |
| | Mild | ☐ | 1 |

| | | | |
|---|---|---|---|
| | Moderate | ☐ | 2 |
| | Severe | ☐ | 3 |
| **How would you describe your general wellbeing?** | Good | ☐ | 0 |
| | Average | ☐ | 1 |
| | Poor | ☐ | 2 |
| | Very poor | ☐ | 3 |

Please calculate your total score ☐

*To be completed by trial team only:*

| | | |
|---|---|---|
| **Physician rating of disease activity[1]** | **Normal** | **0** |
| | **Mild** | **1** |
| | **Moderate** | **2** |
| | **Severe** | **3** |

Total partial Mayo score ☐

Date completed __/__/__

Completed by (initials) ☐

Signature of investigator: …….

**PSC-IBD Diary: Crohn's disease**

Date completed: __/__/__ Trial participant ID: ☐

Participant initials: ☐ Study visit number: ☐

Please fill in this diary, documenting your symptoms for the *previous 7 days*.

When you are well, on a normal day, how often (on average) do you have a bowel movement per day? ☐

This diary should be completed daily ideally before going to bed. By keeping this diary as accurate as possible, it will provide your trial team with information they need to assess flare ups of your IBD.

Please either complete the diary electronically and send it to the trial team the day before your appointment at the following email address: SABR.PSC@uea.ac.uk, or complete it on paper and bring it along with you to your appointment.

| Question- relating to the previous 7 days | Response | Number | Tick | Score |
|---|---|---|---|---|
| **How many liquid or soft stools have you had per day?** | Day 1 | ☐ | | |
| | Day 2 | ☐ | | |
| | Day 3 | ☐ | | |
| | Day 4 | ☐ | | |
| | Day 5 | ☐ | | |
| | Day 6 | ☐ | | |
| | Day 7 | ☐ | | |
| **Have you had any pain in your stomach/belly?** | No. None | | ☐ | 0 |
| | Mild | | ☐ | 1 |
| | Moderate | | ☐ | 2 |
| | Severe | | ☐ | 3 |

| | | | |
|---|---|---|---|
| **How would you describe your general wellbeing?** | Well | ☐ | 0 |
| | Slightly under par | ☐ | 1 |
| | Poor | ☐ | 2 |
| | Very poor | ☐ | 3 |
| | Terrible | ☐ | 4 |
| **Have you taken medications such as loperamide or codeine for diarrhoea within the last 7 days?** | No | ☐ | |
| | Yes | ☐ | |

*To be completed by trials team only:*

| | | | |
|---|---|---|---|
| **Total liquid stools per day** | | | **X2** |
| **Abdominal pain** | | | X5 |
| **General wellbeing** | | | X7 |
| **Use of antidiarrheal medication** | | | X30 |
| **Body Weight (kg)** | (ideal-observed)/ideal x100 | | X1 |
| **Haematocrit (Hct) (Expected men=47, women=42)** | Expected- observed Hct | | X6 |
| **Abdominal mass palpable** | No | 0 | X10 |
| | Questionable | 2 | |
| | Definite | 5 | |
| **Extraintestinal complications (1 per finding)** | Arthritis/arthralgia | 1 | X20 |
| | Mucocutaneous lesions | 1 | |
| | Iritis/uveitis | 1 | |
| | Anal disease (fissure/fistulae etc) | 1 | |
| | External fistula | 1 | |
| | Fever >37.8 (in the past 7 days) | 1 | |

Total CDAI score ☐

Date completed __/__/__

Completed by (initials) ☐

Signiture of investigator: …….

# Semi structured interview

## Week 16

Participant ID: ……  Particiant Initials:……..

Date: __/__/__

| Interview Audio-recorded? Yes ☐ No ☐ |
|---|

Semi-structured interview and Exit interview questionnaire to be completed at week 16.

**Objective:**

To gain an understanding of participants experiences and elicit participants:

1. General wellbeing whilst taking Brodalumab
2. Changes in mental health whilst taking Brodalumab and being involved in the study
3. Side-effects or adverse events
4. To detect any un-anticipated events relating to the trial or Brodalumab
1. Experience and opinion of the trial and related investigations
2. Experience and opinion of the trial medication
3. Suggestions of modifications of study design to improve future studies and recruitment rates

**Thank trial participant for taking the time to be part of the trial and this semi-structured interview**

**General questions:**

1. How has your general health been since we last met?

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……

2. Have you noticed any changes in your mental health since we last met?

……
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……..

3. Have you experienced any side-effects or reactions since your last administration of Brodalumab?
    - *If yes, explore nature of side effect/reaction, time, date, duration, requirement of any treatments, medical attention sought?*

……
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……

5. Have you taken or been prescribed any medications since we last met?
    - *If yes list on concomitant medications page*

……
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……

**<u>Trial specific questions</u>**

1. Overall, how would you describe your experience of the trial?

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……

2. What was the best thing about taking part in this study?

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……

3. What was the worst part about taking part in this study?

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4. Was there anything in the design of the trial that put you off taking part in the study at the beginning?

……
……
……

5. Were there any specific aspects of the study that you found difficult or challenging?
- *Prompt if required, possible prompts include:*
- *Number of study visits*
- *Frequency of questionnaires and diaries needing to be filled in*
- *Number of medication injections required over 12 weeks*
- *Administering subcutaneous injections*
- *Number of investigations- if so, explore which ones in particular*

……
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……

6. Thinking back about the questionnaires and IBD diaries- how would you describe your experience of them?

*-prompt if required, possible prompts include:*
*- Were there too many questionnaires*
*- Were the questionnaires and IBD entries too time consuming*
*- what was the best thing about filling them in?*
*- what was the worst thing about having to fill them in?*

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7. How easy or difficult was it to give yourself the injection treatment?

……
……
……

8. Was the training you received on how to inject yourself with brodalumab sufficient?

……
……
……

9. If you experienced side effects during the trial- did the side effects impact your daily activities and/or quality of life?

……
……
……

**Trial modification questions**

1. Is there anything you would change about the study if you could?
   - *Prompt if required, possible prompts include:*
   - *Reducing the number study visits to the hospital*
   - *Reducing the number of questionnaires needing to be filled in*
   - *Reducing the number of entries in the IBD diary*
   - *Any suggestions on how to improve training for delivery of subcutaneous injections*

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2. Is there anything that you think would have made you happier to participate in the study at the beginning?
   - *Prompt if required, possible prompts include:*
   - *More/less study visits*
   - *More money reimbursed for travel*
   - *Shorter duration of the trial*
   - *More assessments and reviews completed virtually*

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**Close out**

3. Are there any other aspects of your experience of the trial and/or medication that we have not discussed that you would like to share?

……
……
……

Investigator initials……

Investigator signature……

## Appendix E- Exit Questionnaire (non-validated questionnaire)

Participant ID: …….  Particiant Initials:……

Date: __/__/__

1. Thinking about all aspects of the study over the past 16 weeks, how would you rate your experience of participating in the SABR-PSC study overall?

☐ VERY GOOD  ☐ GOOD  ☐ FAIR  ☐ POOR  ☐ VERY POOR

2. The frequency of the study visits was just about right?

☐ STRONGLY AGREE  ☐ AGREE  ☐ NEUTRAL  ☐ DISAGREE  ☐ STRONGLY DISAGREE

3. The frequency of completing the questionnaires and IBD diary was just about right

☐ STRONGLY AGREE  ☐ AGREE  ☐ NEUTRAL  ☐ DISAGREE  ☐ STRONGLY DISAGREE

4. I found administering an injection under the skin an acceptable way of taking medication

☐ STRONGLY AGREE  ☐ AGREE  ☐ NEUTRAL  ☐ DISAGREE  ☐ STRONGLY DISAGREE

5. How acceptable or unacceptable did you find the side effects of Brodalumab?

☐  ☐  ☐  ☐  ☐

| VERY ACCEPTABLE | ACCEPTABLE | NEUTRAL | UNACCEPTABLE | VERY UNACCEPTABLE |
|---|---|---|---|---|

6. Given the chance again, would you still choose to participate in this study?

YES ☐ NO ☐

7. After this study would you choose to continue using Brodalumab as an injection treatment if it could treat your condition?

YES ☐ NO ☐

8. Would you choose to participate in a larger clinical trial of Brodalumab in the future, if there was an opportunity to do so?

YES ☐ NO ☐

Please use the space below to write any comments or feedback for the research team about the trial and your experiences

……
……
……
……
……
……
……
……
…….

**Thank you for filling out this exit interview & for taking the time to participate in this study**

Appendix F- Research approvals for studies

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Amera Elzubeir
University of East Anglia
Bob champion Research and Education Building,
Norwich research Park
Norwich
NR4 7UQ

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

25 October 2023

Dear Dr Elzubeir

**HRA and Health and Care Research Wales (HCRW) Approval Letter**

| | |
|---|---|
| **Study title:** | **A Single Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis** |
| **IRAS project ID:** | **1006951** |
| **Protocol number:** | **1** |
| **REC reference:** | **23/LO/0718** |
| **Sponsor** | **Norfolk and Norwich University Hospital Foundation Trust** |

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

**How should I work with participating non-NHS organisations?**
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

**What are my notification responsibilities during the study?**

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

**Who should I contact for further information?**
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **1006951**. Please quote this on all correspondence.

Yours sincerely,

Laura Hodgin
Approvals Specialist
Email: approvals@hra.nhs.uk

*Copy to:* *Amera Elzubeir, University of East Anglia*

NHS
Health Research Authority

**London - London Bridge Research Ethics Committee**
2 Redman Place
Stratford
London
E20 1JQ

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

25 October 2023

Amera Elzubeir
University of East Anglia
Bob champion Research and Education Building, Norwich research Park
Norwich
NR4 7UQ

Dear Dr Amera Elzubeir

| | |
|---|---|
| **Study title:** | **A Single Arm pilot study of BRodalumab in the treatment of Primary Sclerosing Cholangitis** |
| **REC reference:** | **23/LO/0718** |
| **Protocol number:** | **1** |
| **EudraCT number:** | |
| **IRAS project ID:** | **1006951** |

Thank you for your letter of 11 October 2023, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair Ms Jane Smith.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Good practice principles and responsibilities**

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

**Conditions of the favourable opinion**

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and research project identifiers).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

CTIMPs submitted for combined review via IRAS will be registered automatically with the ISRCTN Registry. You do not need to notify the REC of the registration details. The lawful basis for processing your personal data for this purpose is official authority under the NHS Care Act 2014 (for further information please see our privacy notice).

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

**N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months**.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at:
https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**After ethical review: Reporting requirements**

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

**Ethical review of research sites**

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Cover Letter [MHRA Cover letter] | | |
| GP/consultant information sheets or letters [SABR-PSC GP letter] | 1.0 | 11 October 2023 |
| Interview schedules or topic guides for participants [Study visit interview theme] | 0.1 | 28 July 2023 |
| Interview schedules or topic guides for participants [Semi structured interview week 16] | 0.1 | 28 July 2023 |
| Investigator Brochure/SmPC [Kyntheum (Brodalumab) SmPC] | 28.0 | 10 January 2023 |
| Letter from funder [NIHR Award Acceptance Report] | N/A | 15 August 2022 |
| Letter from funder [Letter of Intent] | N/A | 08 August 2022 |
| Letters of invitation to participant [Patient Invitation letter] | 0.1 | 28 July 2023 |
| Letters of invitation to participant [SABR-PSC patient reply slip] | 0.1 | 28 July 2023 |
| Miscellaneous [IBD Diary- Crohn's] | 0.1 | 28 July 2023 |
| Miscellaneous [IBD Diary-UC] | 0.1 | 28 July 2023 |
| Non-validated questionnaire [SABR-PSC Withdrawal questionnaire] | 0.2 | 11 October 2023 |
| Non-validated questionnaire [SABR-PSC Exit Interview] | 0.2 | 11 October 2023 |
| Participant information and informed consent form [SABR-PSC Informed Consent Form] | 0.2 | 11 October 2023 |
| Participant information and informed consent form [SABR-PSC Patient information sheet] | 0.6 | 11 October 2023 |
| Participant information and informed consent form [Brodalumab patient Information leaflet] | 0 | 12 October 2023 |
| Protocol [SABR-PSC Protocol] | 1.1 | 02 October 2023 |
| REC Application Form [Ethics] | | 12 October 2023 |
| Response to Request for Further Information [SABR-PSC MHRA | 0.1 | 11 October 2023 |

| | | |
|---|---|---|
| and Ethical review applicant reponses] | | |
| Sample diary card/patient card [Participant Card] | 0.1 | 28 July 2009 |
| Suitability of the investigator/Investigator CV [Amera Elzubeir Investigator CV] | 0.1 | 28 July 2023 |
| Validated questionnaire [PSC-PRO Questionnaire] | 0.1 | 28 July 2023 |
| Validated questionnaire [5D-Itch Questionnaire] | 0.1 | 28 July 2023 |
| Validated questionnaire [Patient Health Questionnaire (PHQ-9)] | 0.1 | 28 July 2023 |
| Validated questionnaire [CLDQ-PSC Questionnaire] | 0.1 | 28 July 2023 |

**Statement of compliance**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Learning**

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

**IRAS project ID: 1006951 Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

On behalf of
**Ms Jane Smith**
**Chair**

Email: londonbridge.rec@hra.nhs.uk

University of East Anglia
Norwich Research Park
Norwich. NR4 7TJ

Email: ethicsmonitor@uea.ac.uk
Web: www.uea.ac.uk

**Study title:** A single centre retrospective observational review of primary sclerosing cholangitis associated inflammatory bowel disease (PSC-IBD).

**Application ID:** ETH2425-0257

Dear Amera,

Your application was considered on 14th October 2024 by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee).

The decision is: **approved**.

You are therefore able to start your project subject to any other necessary approvals being given.

If your study involves NHS staff and facilities, you will require Health Research Authority (HRA) governance approval before you can start this project (even though you did not require NHS-REC ethics approval). Please consult the HRA webpage about the application required, which is submitted through the IRAS system.

This approval will expire on **30th September 2025**.

Please note that your project is granted ethics approval only for the length of time identified above. Any extension to a project must obtain ethics approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) before continuing.

It is a requirement of this ethics approval that you should report any adverse events which occur during your project to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) as soon as possible. An adverse event is one which was not anticipated in the research design, and which could potentially cause risk or harm to the participants or the researcher, or which reveals potential risks in the treatment under evaluation. For research involving animals, it may be the unintended death of an animal after trapping or carrying out a procedure.

Any amendments to your submitted project in terms of design, sample, data collection, focus etc. should be notified to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) in advance to ensure ethical compliance. If the amendments are substantial a new application may be required.

Approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) should not be taken as evidence that your study is compliant with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. If you need guidance on how to make your study UK GDPR compliant, please contact the UEA Data Protection Officer (dataprotection@uea.ac.uk).

Please can you send your report once your project is completed to the FMH S-REC (fmh.ethics@uea.ac.uk).

I would like to wish you every success with your project.

On behalf of the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee)

Yours sincerely,

Dr Paul Linsley

## Appendix G- MHRA approval

Medicines & Healthcare products Regulatory Agency

MHRA

**MHRA**
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

**gov.uk/mhra**

Dr Amera Elzubeir
UNIVERSITY OF EAST ANGLIA
BOB CHAMPION RESEARCH & EDUCATION BUILDING,
ROSALIND FRANKLIN ROAD, COLNEY
NORWICH
NR4 7UQ
UNITED KINGDOM

26/10/2023

Dear Dr Amera Elzubeir

**THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031**

| | |
|---|---|
| Our Reference: | CTA 13630/0015/001-0001 |
| IRAS ID: | 1006951 |
| Product: | Brodalumab 210 mg solution for injection in pre-filled syringe |
| Protocol number: | 1 |

**NOTICE OF ACCEPTANCE OF AMENDED REQUEST**

I am writing to inform you that the Licensing Authority, having reviewed your application in collaboration with the Research Ethics Committee, accepts your amended request for a clinical trial authorisation (CTA), with effective received date of 28/07/2023.

COMBINED REVIEW MEDICAL - Remarks: MHRA Clinical conditions of approval

The definition of WOCBPs and contraception requirements are confusing.

The protocol should use wording consistent with the CFTG guidance

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

As brodalumab is an IMP where assessment of the completed necessary non-clinical studies does not indicate teratogenicity/fetotoxicity, section 2.2.4 is relevant. An acceptable effective contraceptive method (section 4.2) or highly effective method (section 4.1) is acceptable for WOCBPs. There is no requirement for male patients.

If these conditions are met, the trial is authorised and you do not need to respond to this letter. If your trial does not meet these conditions, your trial does not have authorisation and therefore you cannot proceed with the trial. You must inform the MHRA immediately if the trial does not meet the above conditions. All changes to the terms and conditions of this trial must be made as a request for a substantial amendment to this clinical trial authorisation.

Remark (for future consideration only. No response is required.)

Regarding pregnancy, no additional testing during the trial is necessary unless a woman is suspected to have become pregnant.

If you have a query on these comments, please contact Dr Marie-Christine Bielsky

marie.bielsky@mhra.gov.uk

HRA

Acceptable

PHARMACEUTICAL

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

You are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed, changes made as part of your amended request may need to be notified to the Ethics Committee. If not already provided, please follow the guidance on our website on informing us of the registration status of your trial (where applicable).

***You are reminded that from 1 January 2022 you will need to comply with the requirements specified in the following guidance, where applicable:***

- ***Import of IMPs from listed countries to GB:***

***https://www.gov.uk/government/publications/importing-investigational-medicinal-products-into-great-britain-from-approved-countries***

- ***Supply of IMPs to Northern Ireland:***

***https://www.gov.uk/guidance/supplying-investigational-medicinal-products-to-northern-ireland***

- ***Substantial amendments to clinical trials:***

***https://www.gov.uk/guidance/guidance-on-substantial-amendments-to-a-clinical-trial***

***Any required substantial amendment to your Clinical Trial Authorisation should be submitted and approved as soon as possible and before 1 January 2022.***

Yours sincerely,

**Clinical Trials Unit**
**MHRA**

Medicines and Healthcare Products Regulatory Agency

# CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a pilot or feasibility randomised trial in the title | p182 |
| | 1b | Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials) | p182 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial | p186-187 |
| | 2b | Specific objectives or research questions for pilot trial | p187-190 |
| **Methods** | | | |
| Trial design | 3a | Description of pilot trial design (such as parallel, factorial) including allocation ratio | p186, 191 |
| | 3b | Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons | p220 |
| Participants | 4a | Eligibility criteria for participants | p193 |
| | 4b | Settings and locations where the data were collected | p219 |
| | 4c | How participants were identified and consented | p200 |

| | | | |
|---|---|---|---|
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | p204 |
| Outcomes | 6a | Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed | p206 |
| | 6b | Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons | N/A |
| | 6c | If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial | N/A |
| Sample size | 7a | Rationale for numbers in the pilot trial | p191 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | N/A |
| | 8b | Type of randomisation(s); details of any restriction (such as blocking and block size) | N/A |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | N/A |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | N/A |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | N/A |
| | 11b | If relevant, description of the similarity of interventions | N/A |
| Statistical methods | 12 | Methods used to address each pilot trial objective whether qualitative or quantitative | p216 |

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective | p222 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | p223, 225 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | p222 |
| | 14b | Why the pilot trial ended or was stopped | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | p228 |
| Numbers analysed | 16 | For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers<br>should be by randomised group | p231-256 |
| Outcomes and estimation | 17 | For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any<br>estimates. If relevant, these results should be by randomised group | p231-256 |
| Ancillary analyses | 18 | Results of any other analyses performed that could be used to inform the future definitive trial | p280-290 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | p231-236 |
| | 19a | If relevant, other important unintended consequences | N/A |
| **Discussion** | | | |
| Limitations | 20 | Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility | p270 |
| Generalisability | 21 | Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies | p257-272 |

| | | | |
|---|---|---|---|
| Interpretation | 22 | Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and<br><br>considering other relevant evidence | p257-272 |
| | 22a | Implications for progression from pilot to future definitive trial, including any proposed amendments | p257-272 |
| **Other information** | | | |
| Registration | 23 | Registration number for pilot trial and name of trial registry | p220 |
| Protocol | 24 | Where the pilot trial protocol can be accessed, if available | p24 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | p221 |
| | 26 | Ethical approval or approval by research review committee, confirmed with reference number | p220 |

## Appendix I- Full details of screen failures

| Reason | Frequency |
|---|---|
| **Failed to meet the following inclusion criteria:** | 1 |
| A. 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. | 1 |
| Met the following exclusion criteria: | 2 |
| A. Gallbladder lesion or polyp (>5mm 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. | 1 |
| B. 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 metabolic dysfunction-associated steatotic liver disease (MASLD). | 1 |
| **Total** | 3 |

## Appendix J. Nancy histology Index for ulcerative colitis

Nancy histology index for ulcerative colitis (479).

| Grade | Activity | Histological description |
|---|---|---|
| **0** | Quiescent | Chronic inflammatory infiltrate: None or mild.<br>No histological significant disease. |
| **1** | Quiescent | Chronic inflammatory infiltrate: Present and increased; easily apparent.<br>Acute inflammatory infiltrate: None (Absence of mucosal neutrophils). |
| **2** | Mild | Neutrophils: Few or rare neutrophils in the lamina propria or epithelial cells; difficult to see.<br>Ulceration: Absent. |
| **3** | Moderate | Neutrophils: Multiple clusters in the lamina propria and/or epithelial cells; easily visible.<br>Ulceration: Absent. |
| **4** | Severe | Neutrophils: Multiple clusters in the lamina propria and/or epithelial cells; easily visible.<br>Ulceration: Present. |

†The Nancy Index is a validated histological tool, describing five grades of activity, based on the presence of and severity of acute and chronical inflammatory infiltrates, as well as ulceration. The composite score provides a classification of histological disease activity in UC.

## Appendix K MRCP+ and LiverMultiScan metrics for all participants

**Table .** MRI quantitative metrics pre and post-treatment with brodalumab for all participants (n=5) irrespective of pairing.

| **Quantitative MRI metrics** | **Baseline**<br>**(n = 6)** | **Week 16**<br>**(n = 5)** |
|---|---|---|
| **Number of ducts** | 51 (34-114) | 73.5 (48.5-95) |
| **Total number of candidate strictures** | 8 (3-10) | 7 (3.5-9) |
| **Total length of ducts (mm),** | 962.8 (737.4-2596.6) | 1761.5 (1067.8-2125.2) |
| **Total length of candidate strictures and dilatations (mm)** | 106.1 (65.1 -166.7) | 163.6 (102.3-197.2) |
| **Liver cT1 (ms)**<br>**(ULN:800 ms)** | 738.0 (702.5-773.5) | 768 (669-777) |
| **PDFF- Liver fat fraction (%)**<br>**(ULN: 5%)** | 2 (2-3) | 2 (2-4) |
| **Liver iron concentration (mg Fe/g dry tissue)**<br>**(ULN:1.8 mg Fe/g)** | 0.5 (0.5-0.6) | 0.6 (0.6-0.6) |

## Appendix L COREQ checklist for qualitative research.

COREQ checklist adapted from Tong et al. (460).

| No | Item | Guide questions | Page Number |
|---|---|---|---|
| **Domain 1: Research team and reflexivity** | | | |
| **Personal Characteristics** | | | |
| **1.** | Interviewer/facilitator | Which author/s carried out the interview or focus group? | p279 |
| **2.** | Credentials | What were the qualifications of the researcher? | N/A |
| **3.** | Occupation | What was their professional role at the time of the study? | N/A |
| **4.** | Gender | What the researcher gender? | N/A |
| **5.** | Experience and training | What prior experience did the researcher have? | p295 |
| **Relationship with participants** | | | |
| **6.** | Relationship established | Was contact/rapport established before the study began? | p295 |
| **7.** | Participant knowledge of the interviewer | What did participants know about the researcher/research team? | p295 |
| **8.** | Interviewer characteristics | Were personal attributes or assumptions of the interviewer reported? e.g. *Bias, assumptions, reasons and interests in the research topic* | p279 |
| **Domain 2: study design** | | | |
| **Theoretical framework** | | | |
| **9.** | Methodological orientation and Theory | Was the methodological of the study reported? | p278-280 |
| **Participant selection** | | | |
| **10.** | Sampling | How were participants chosen? | p278 |
| **11.** | Method of approach | How were participants invited? | Reported in Chapter 4 |
| **12.** | Sample size | How many participants were included in the study? | Reported in Chapter 4 |
| **13.** | Non-participation | How many withdrew or declined? Reasons? | Reported in Chapter 4 |

| | | | |
|---|---|---|---|
| **Setting** | | | |
| **14.** | Setting of data collection | Where did interviews take place? e.*g. home, clinic, workplace* | p280 |
| **15.** | Presence of non-participants | Who else was present besides the participants and researchers? | N/A |
| **16.** | Description of sample | What were the key characteristics of the group? | Reported in Chapter 4 |
| **Data collection** | | | |
| **17.** | Interview guide | Were questions, prompts, guides provided? Was it tested beforehand? | p278 |
| **18.** | Repeat interviews | Were repeat interviews carried out? | |
| **19.** | Audio/visual recording | Did researchers use audio or visual recording? | p278 |
| **20.** | Field notes | Were field notes made? | N/A |
| **21.** | Duration | What was the duration of the interviews? | p278 |
| **22.** | Data saturation | Was data saturation reported? | N/A |
| **23.** | Transcripts returned | Were transcripts returned to participants for comment and/or correction? | p295 |
| **Domain 3: analysis and findings** | | | |
| **Data analysis** | | | |
| **24.** | Number of data coders | How many data coders were there? | p279 |
| **25.** | Description of the coding tree | Did authors provide a description of the coding tree? | N/A |
| **26.** | Derivation of themes | Were themes identified in advance or derived from the data? | p278 |
| **27.** | Software | What software, if applicable, was used to manage the data? | p279 |
| **28.** | Participant checking | Did participants provide feedback on the findings? | p295 |
| **Reporting** | | | |
| **29.** | Quotations presented | Were participant quotations presented to illustrate the themes / findings? | p280-290 |
| **30.** | Data and findings consistent | Was there alignment between data presentation and the findings? | p280-290 |
| **31.** | Clarity of major themes | Were major themes clearly described? | p280-290 |
| **32.** | Clarity of minor themes | Were minor themes or divergent cases discussed? | p280-290 |