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Asp-PSC: effect of aspirin on reducing cancer & improving outcomes in primary sclerosing cholangitis

Submission date 19/09/2023	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/11/2023	**Overall study status** Ongoing	
Last Edited 19/07/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Primary sclerosing cholangitis (PSC) is an chronic autoimmune disease of the bile ducts and liver. PSC patients often have inflammatory bowel disease (IBD). Four out of ten people with both PSC and IBD get cancer of the bile ducts, gallbladder, liver or bowel. There are no screening strategies which reduce hepatobiliary cancers and there is no treatment shown to help slow the rate of PSC or reduce cancer risk. Aspirin may have anti-cancer effects and help reduce the PSC-related cancer risk. The main aims of the study are to investigate if daily low-dose aspirin over a minimum of 5 years reduces cancer risk in PSC and IBD patients. The researchers will also be looking at the safety and tolerability of aspirin and liver transplantation rates. There will be future work conducted on samples and imaging to establish if PSC-related cancers can be detected.

Who can participate?
Patients aged 18 years and over at least 12 months after a diagnosis of PSC-IBD

What does the study involve?
Participants will be randomly allocated to take a placebo or 75 mg once daily (oral) aspirin. Participants will be followed for a minimum of 5 years. Patients will attend a screening visit, month 1 phone call, 6 monthly visits over 5 years, and end of treatment. Follow-up data will be collected yearly after 5 years for a maximum of 5 years. Urine and blood samples will be taken at the screening visit and every 6 months over 5 years.

What are the possible benefits and risks of participating?
If the trial shows aspirin significantly and safely improves cancer-free survival and overall survival in patients with PSC-IBD, then this could lead to a change in the standard of care treatment for these patients.
Patients may experience some mild side effects from taking aspirin but risks have been mitigated by careful review of the inclusion and exclusion criteria by healthcare specialists on the Trial Management Group (TMG) to help screen for contraindications for aspirin and the researchers have avoided putting patients with decompensated liver disease onto the trial. They

are monitoring side effects at every visit and patients will have a patient diary and contact number for surveillance of side effects. They are giving disease-related questionnaires to pick up changes in the activity of liver disease and Inflammatory bowel disease to alert clinicians of clinical changes. All side effects will be managed by the local Principal Investigator. All side effects will be reported on the electronic data capture system and reviewed by the clinical trial team as well at committee meetings including the TMG and Independent Data Monitoring Committee (IDMC) to assess signalling for safety.
There is a possibility of redness, swelling and bruising after blood collection and participants may feel lightheaded or faint. The blood samples will be collected at the screening and 6 monthly follow up only. Trained medical staff will be on hand to deal with side effects and the patient will be given a contact card to call for any concerns. There will be some blood collection for research samples, but these are optional.
Patients' travel fees will be reimbursed. These extra visits will be explained in the patient information sheet and there will be a chance to ask questions at every timepoint. Patients have the option to withdraw at any timepoint if they do not feel comfortable attending extra visits.
A women's health professor and Honorary Consultant in Obstetric Medicine was asked to join the Trial Management Group (TMG) to review the requirements for pregnant women to join the trial. It was deemed safe for pregnant women to join this trial. Further advice has been given in the protocol regarding the management of pregnant women and any side effects in this trial.
We will be collecting additional data to monitor these patients and all patients will be monitored closely for side effects for the sub-study. All side effects will be reported on the electronic data capture system and reviewed by the clinical trial team as well at committee meetings including the TMG and Independent Data Monitoring Committee (IDMC) to assess signalling for safety.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
September 2023 to July 2033

Who is funding the study?
Cancer Research UK

Who is the main contact?
Dr Shahid Khan, shahid.khan1@nhs.net

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-aspirin-to-reduce-the-risk-of-cancer-in-people-with-primary-sclerosing-cholangitis-asp

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Additional identifiers

Integrated Research Application System (IRAS)
1007320

Central Portfolio Management System (CPMS)
55190

Protocol serial number
C/45/2022, , MHRA ID: CTA 19174/0447/001-0001

Study information

Scientific Title
Asp-PSC: effect of aspirin on reducing cancer & improving outcomes in primary sclerosing cholangitis

Acronym
Asp-PSC

Study objectives
Primary objective:
To investigate if in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD), a daily low dose aspirin lowers the risk of PSC-related cancer/high grade dysplasia, liver decompensation, the need for liver transplantation and all-cause mortality, compared to placebo, over a minimum 5-year period.

Secondary objective:
Safety and tolerability of aspirin in patients with PSC-IBD and effect on quality of life using disease-specific questionnaires.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/10/2023, Wales REC 1 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0) 2920 785738; Wales.REC1@wales.nhs.uk), ref: 23/WA/0282

Primary study design
Interventional

Study design
Randomized double-blind placebo-controlled parallel-group trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD)

Interventions
Participants will be randomised using OpenClinica and assigned treatment via Sealed Envelope. Each treatment group will receive either 75 mg aspirin or a placebo tablet to take once a day, orally for 5 years. All participants will be screened and have the following visits:
1. Collection of aspirin/placebo visit
2. Month one phone call
3. 6 monthly visits for 5 years
4. End of treatment visit
Endpoint data will be collected yearly after the end of treatment visit.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Aspirin (acetylsalicylic acid)

Primary outcome(s)
The composite primary endpoints are defined as the occurrence of any of the following:
1. Hepatobiliary cancer (including gallbladder cancer/high-grade dysplasia, pancreas, cholangiocarcinoma [CCA] or hepatocellular [HCC]) or colorectal cancer/high-grade dysplasia)
2. Listing for liver transplantation
3. All-cause mortality
Measured from randomisation date to either date of withdrawal of study or end of follow-up period of last patient using patient records

Key secondary outcome(s)
Measured from randomisation date to either date of withdrawal of study or end of follow up period of last patient:
1. Gastrointestinal bleeding risk (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)
2. Progressive liver disease, as evidenced by either ascites, variceal bleeding (any site), hepatic encephalopathy (investigator discretion) or development of cirrhosis with Child Pugh B or C stage
3. Rates of referral for liver transplantation
4. Rates of acute cholangitis
5. IBD flare frequency
6. Rates of colonic surgery/resection for severe IBD
7. Safety and tolerability of aspirin in patients with PSC-IBD and effect on quality of life measured using disease-specific questionnaires
7.1. PSC-PRO
7.2. SF-36
7.3. 5D-Itch Scale
7.4. SIBDQ
7.5. PRO-2
7.6. CLDQ-PSC

Completion date
31/07/2033

Eligibility

Key inclusion criteria
1. Age 18 years or above
2. Able to give written and informed consent.
3. Must have an established clinical diagnosis of large duct PSC-based on a standard disease definition of typical cholangiography findings on endoscopic retrograde cholangiography (ERCP) or magnetic resonance cholangiography (MRCP).

4. An established diagnosis of concomitant colonic IBD either in a pattern of Ulcerative Colitis, Crohn's disease or IBD unclassified.
5. Patients must be at least one-year post PSC diagnosis.
6. If pre-treated with ursodeoxycholic acid (UDCA) – UDCA therapy should remain at a stable dose for 12 weeks prior to screening, and not exceeding 20 mg/kg/day.
7. Must have had a colonoscopy within the last year of randomisation date as part of routine clinical care. If not this must be done within the screening interval.
8. If a patient has cirrhosis, they must have undertaken a hepatobiliary ultrasound (US), MRCP scan, magnetic resonance imaging (MRI) liver or regional computerised tomography (CT) scan within 6 months of screening date as part of routine clinical care. If not, this must be done within the screening interval.
9. If non-cirrhotic, then the patient must have had an US, MRCP, dynamic MRI or regional CT within the last 12 months as part of routine clinical care. If not, this must be done within the screening interval.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Evidence of concomitant disease(s) that causes secondary sclerosing cholangitis
2. Evidence of any of the following diseases: IgG4 related disease, PBC, acute or chronic viral hepatitis, alcohol-related liver disease, Wilson disease, Budd-Chiari syndrome, portal vein thrombosis, alpha-1-antitrypsin disease, hepatic sarcoidosis, cystic fibrosis, Progressive familial intrahepatic cholestasis (PFIC), hereditary haemochromatosis, non-alcoholic steatohepatitis (NASH) – those with simple hepatic steatosis without evidence of NASH or liver fibrosis secondary to fatty liver disease are allowed to participate, other metabolic liver disease, active malignancy in the last 5 years (except treated/excised non-melanomatous skin cancer).
3. Have a previous diagnosis of colorectal cancer, cholangiocarcinoma, gallbladder cancer at any time point.
4. Has received a liver transplant, has been referred for liver transplant assessment, or is listed for a liver transplant.
5. Had any of the following procedures: colonic resection of any nature, including those with a defunctioning ostomy.
6. Consume more than the recommended allowance of 14 units of alcohol per week (as set out by the Department of Health).
7. Current or recent participation in any other clinical trial of an investigational medicinal product (CTIMP) within the last 6 weeks prior to first dose of aspirin/placebo
8. Already taking aspirin.
9. History of non-variceal upper gastrointestinal (GI) bleeding within 1 year.

10. A history of congestive cardiac failure.
11. A known diagnosis of glucose-6 -phosphate dehydrogenase.
12. Child Pugh B or C cirrhosis
13. Untreated thyrotoxicosis or hypothyroidism
14. Familial history of a hereditary cancer syndrome, or confirmed genetic predisposition that heightens cancer risk.
15. Vaccination for varicella zoster in the six weeks prior to screening period
16. Known allergy to aspirin
17. A history of NSAID/ aspirin induced asthma and nasal polyps
18. Concurrently taking non-steroidal anti-inflammatory drugs (NSAIDs) in the four weeks prior to screening
19. History of haemophilia and/or other bleeding disorders where aspirin is contraindicated
20. Taking other anti-platelet or anti-coagulant medication (e.g., clopidogrel, prasugrel, warfarin, apixaban, rivaroxaban, dabigatran or therapeutic heparin preparations)
21. Active, or history of recurrent peptic ulcer
22. Patients who are suffering from gout
23. Severe renal impairment
24. Taking methotrexate at a dose of >15mg/week
25. Taking selective serotonin-reuptake inhibitors

Date of first enrolment
08/01/2024

Date of final enrolment
01/12/2028

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Kings College Hospital
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Denmark Hill
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Study participating centre

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Study participating centre
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	20/10/2023	19/07/2024	No	Yes
Protocol file	version 2.0	20/10/2023	19/07/2024	No	No