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Selected mesenchymal stromal cells to reduce liver inflammation

Submission date 02/10/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 07/11/2017	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 11/04/2024	**Condition category** Digestive System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Primary sclerosing cholangitis is a chronic liver disease that causes the liver to decrease due to scars and inflammation (becoming swollen). Autoimmune hepatitis is an autoimmune disease (where the body attacks and damages its own tissue) of the liver that causes it to become inflamed. A therapy called mesenchymal stromal cells (MSC) could be a safe and effective treatment for these conditions. MSC are found in almost every part of the body. They are known to play a role in tissue repair, renewal and inflammation. When extracted, and used as treatment, they have been shown to reduce the body’s immune response when it is overactive and causing damage. This anti-inflammatory effect of MSC has been utilised in many clinical trials to treat conditions associated with inflammation such as graft versus host disease (GVHD) and Crohn's disease with success. This study uses MSC derived and grown from human umbilical cords as they are readily accessible. The umbilical cords are ethically collected from mothers after childbirth. After collection, the MSC are purified and grown outside the body, before being infused directly into the body. The preparation of MSC we will use is called ORBCEL-C™. This is an 'off the shelf' product consisting of a purer and selected form of MSC. ORBCEL-C™ has not been used in a clinical trial previously however our fundamental laboratory studies have shown ORBCEL-C™ to be safe and effective in reducing liver inflammation. The aim of this study is to investigate whether patients with primary sclerosing cholangitis (PSC) or autoimmune hepatitis (AIH) can be safely and effectively treated with a therapy called mesenchymal stromal cells (MSC).

Who can participate?
Adults aged 18 to 70 years old with either PSC or AIH.

What does the study involve?
This study involves two stages. The first stage determines the highest safest dose to be evaluated in stage 2 by recording any side effects and reactions to the treatment. The second stage uses the dose determined in the first stage to examine the impact on the dose on the body. The treatment is the same in both stages. Participants are informed as to what dose they receive prior to starting the treatment. Participants either receive 0.5 million cells, 1.0 million cells, or 2.5 million cells per kilogram of body weight. Participants receive a single intravenous infusion of ORBCEL-C™ through a needle in a vein in the arm, delivering the cells over 10-15

minutes. An infusion of saline is also given during the infusion. Participants are monitored for four hours after the infusion. Participants attend follow-up visits where they undergo blood tests, scans and questionnaires to determine the treatment impact. Participants attend further follow-up visits at 6, 9, 12, 18 and 24 months. Blood tests are taken at every visit.

What are the possible benefits and risks of participating?
This study will assess whether the ORBCEL-C™ is safe and the effect in the activity of the liver and AIH. There are possible disadvantages and risks of the MSC infuson such as harm to unborn children and pregnancy. There are some mild side effects such as pain or itch at the injection site, high temperature, headache, foul/metallic taste in the mouth. There are few uncommon side effects such as tiredness and bad breath. A serious uncommon side effect is anaphylaxis.

Where is the study run from?
Stage 1 of the study takes place at the University Hospitals Birmingham, Queen Elizabeth Hospital (UK). Stage 2 of the study takes place at Queen Elizabeth Hospital (UK)., Nottingham University Hospital (UK), and the John Radcliffe Hospital (UK).

When is the study starting and how long is it expected to run for?
October 2017 to December 2020

Who is funding the study?
European Commission (EU)

Who is the main contact?
Mrs Helen Coulthard, merlin@trials.bham.ac.uk

Study website
http://fp7merlin.eu/

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
2016-000181-36

IRAS number

ClinicalTrials.gov number
NCT02997878

Secondary identifying numbers
33534

Study information

Scientific Title
An adaptive, single arm, multi-centre phase IIa multi-disease clinical trial investigating the safety and activity of the use of a single infusion of selected Mesenchymal Stromal Cells (MSC) to reduce liver inflammation in the treatment of patients with primary sclerosing cholangitis and autoimmune hepatitis

Acronym
MERLIN

Study objectives
This study seeks to investigate whether patients with primary sclerosing cholangitis (PSC) or autoimmune hepatitis (AIH) can be safely and effectively treated with a therapy called mesenchymal stromal cells (MSC).

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central- Oxford A Research Ethics Committee, 22/03/2017, ref: 17/SC/0032

Study design
Non-randomised; Interventional; Design type: Treatment, Cellular

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied

Primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH)

Interventions

MERLIN is an adaptive, single arm, multi-centre, phase IIa multi-disease clinical trial. It is designed to:
1. Determine dose safety of ORBCEL-CTM
2. Evaluate treatment activity through assessment of biomarkers

This trial has two main stages:
1. Stage 1 determine the highest safe dose that can be administered by observing for occurrence of dose limiting toxicity (DLT).
2. Stage 2 will use the highest safe dose found in stage 1 to and further determine safety and activity outcomes of ORBCEL-CTM.

This study seeks to recruit two cohorts of patients; patients with primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). Both cohorts are recruited from the UK only. Both diseases are related rare autoimmune liver diseases, and both are managed in the same clinic settings.

Dose Safety (Stage 1):
The Dose Safety component of the trial is identical in design and are conducted in parallel for both PSC and AIH cohorts. Participants are recruited in groups of three for this safety component. An identical approach to recruitment is undertaken in both the PSC and AIH cohorts.

As this is a first in man study, the first three patients in both the PSC and AIH cohorts are recruited to dose level A. The first patient in each cohort are recruited to dose level A and followed for the 14 day assessment period for DLT before the next two patients are recruited. Should one DLT be observed in the first three patients then a further three patients are treated at the current dose. If 2/3 DLTs are observed then this dose will be determined unsafe and no further higher dose will be assessed, de-escalation will occur if possible. Escalation occurs to a dose level higher (if possible) if there are no DLTs in the first three patients or less than two DLTs in six patients. The highest dose for which safety is determined will be taken forward to stage 2. An investigated dose level is determined to be safe for the purposes of expansion for stage 2 if we observe less than two DLTs in six patients or in the case of 0/3 DLTs at the highest dose level we will allow expansion to stage 2, with an early look after an additional 3 patients and if < 2 DLTs have been observed, that dose will be declared safe.

After a 28 day screening period, eligible participants receive a single infusion of ORBCEL C. All patients will then be followed up for 56 days for primary safety/ efficacy evaluation, and then followed up long term up to 22 months (720 days post infusion).

It is anticipated that recruitment for both cohorts will take between 18-24 months. An individual patient's involvement spans 24 months including a 28 day screening period prior to MSC infusion.

Stage 2: Activity and Safety
For the primary outcome measure of change in ALP, co-primary analyses of examining
1. Change in ALP at day 28 from baseline and
2. Changes over multiple time-points before and after infusion (Visit 1 to Visit 8) will be conducted on the defined evaluable population.

Intervention Type

Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
ORBCEL-C™

Primary outcome measure
Current primary outcome measures as of 07/06/2023:
Primary outcome measure (all patients):
1. The highest safe single intravenous infusion dose (HSD) of ORBCEL-C™ is measured using the collection of Dose Limiting Toxicities (DLTs) from ORBCEL-C™ infusion to 14 days after ORBCELC™ infusion (Visit 3 to Visit 5)

Co-Primary outcome measures (Patients treated at the HSD only):
2. Safety and tolerability of ORBCEL-C™ infusion are measured using the occurrence of Dose Limiting Toxicities (DLTs) (Visit 3 to Visit 5 only), Serious Adverse Events (SAE) and Adverse Events (AE) up to Visit 8

Co-Primary outcome measures (Patients with PSC treated at the HSD only):
3. Safety and tolerability of ORBCEL-C™ infusion are measured using Change in Alkaline Phosphatase (ALP) after ORBCEL-C™ infusion

Co-Primary outcome measures for (Patients with AIH treated at the HSD only):
4. Safety and tolerability of ORBCEL-C™ infusion are measured using change in Alanine Aminotransferase (ALT) after ORBCEL-C™ infusion

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Previous primary outcome measures as of 04/05/2021:
Patients with Primary Sclerosing Cholangitis (PSC):
Stage 1:
1.The highest safe single intravenous infusion dose of ORBCEL-C™ is measured using the occurrence of Dose-Limiting Toxicity (DLT) over 14 days post-infusion.
Stage 2:
2. The safety and tolerability is measured using the occurrence of DLT, serious adverse events (SAE) and adverse events (AE) over 56 days post-infusion.
3. Clinical outcomes are measured using changes in alkaline phosphatase (ALP) level at baseline, 3, 14, 21, 28 and 56 days post-infusion.

Patients with Autoimmune Hepatitis (AIH):
Stage 1:
1. The highest safe single intravenous infusion dose of ORBCEL-C™ is measured using the occurrence of Dose-Limiting Toxicity (DLT) over 14 days post-infusion.
Stage 2:
2. The safety and tolerability is measured using the occurrence of DLT, serious adverse events (SAE) and adverse events (AE) over 56 days post-infusion.
3. Clinical outcomes are measured using changes in alanine aminotransferase (ALT) level at baseline, 3, 14, 21, 28 and 56 days post-infusion.

Previous primary outcome measures as of 28/04/2021:
Patients with Primary Sclerosing Cholangitis:
Stage 1:
1. Occurrence of DLT over 14 day (Visit 3 to Visit 5) reporting period after ORBCEL-C™ infusion
Stage 2:
2. Safety and tolerability measured using occurrence of dose-limiting toxicity (DLT) (Visit 3 to Visit 5 only), serious adverse events (SAE) and adverse events (AE) throughout trial period (up to Visit 8)
3. Alkaline phosphatase (ALP) level after ORBCEL-C™ infusion

Patients with Autoimmune Hepatitis:
Stage 1:
4. Occurrence of DLT over 14 day (Visit 3 to Visit 5) reporting period after ORBCEL-C™ infusion (Visit 3)
Stage 2:
5. Safety and tolerability measured using occurrence of DLT (Visit 3 to Visit 5 only), SAEs and AEs throughout trial period (up to Visit 8)
6. Alanine aminotransferase (ALT) trend after ORBCEL-C™ infusion

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Previous primary outcome measures:
For both PSC and AIH patients:
Stage 1:
Highest safe single intravenous infusion dose of ORBCEL-CTM over a 14-day reporting period to take forward to Stage 2 of the clinical trial (study). All patients who have been recruited to and completed the 14-day reporting period in stage 1 will continue to be evaluated for outcomes as per Stage 2.

Stage 2:
Safety and tolerability of a single intravenous infusion of ORBCEL-CTM over the period of trial follow up (up to 56 days).

For PSC patients only:
Reduces serum alkaline phosphatase (ALP) in patients with PSC. This is a non-invasive biochemical surrogate of clinical outcomes in PSC

For AIH patients only:
Reduces serum alanine aminotransferase (ALT) in patients with AIH. This is a non-invasive biochemical surrogate marker of hepatic inflammatory activity and outcomes in AIH.

Secondary outcome measures

Current secondary outcome measures as of 07/06/2023:
Changes in the following variables are measured by assessing the change from baseline to visit 8:
1. Circulating inflammatory cells profile (key secondary outcome)
2. Liver biochemistry and function, immunoglobulin G concentrations (in AIH patients) and composite risk scores
3. Non-invasive clinical markers of fibrosis
4. Patient Quality of Life (QoL)
5. Severity of co-existent Inflammatory Bowel Disease (IBD) in patients with PSC

(All patients with PSC):
1. Phenotypic expression of Regulatory T cells (TRegs) measured using flow cytometry (principal secondary outcome)
2. Individual markers of liver biochemistry and function measured using changes in aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), bilirubin, albumin, international normalised ratio [INR] and composite risk scores (Mayo PSC risk score and Model for End Stage Liver Disease [MELD])
3. Non-invasive clinical markers of fibrosis measured using Enhanced Liver Fibrosis (ELF) test and transient elastography (Fibroscan®)
4. Quality of Life measured using Pruritus Visual Analogue Scale, nine-point fatigue severity scale and SF-36v2
5. Severity of IBD measured using the non-endoscopic aspects of the Mayo IBD score – stool frequency, rectal bleeding, and physician's global assessment

(All patients with AIH):
1. Phenotypic expression of Regulatory T cells (TRegs) measured using flow cytometry (principal secondary outcome)
2. Individual markers of liver biochemistry and function measured using changes in AST, ALP, GGT, bilirubin, albumin, INR and composite risk score (MELD)
3. Marker of immune activation measured using changes in immunoglobulin G concentrations
4. Non-invasive clinical markers of fibrosis measured using ELF and transient elastography (Fibroscan®)
5. Quality of Life measured using Pruritus Visual Analogue Scale, nine-point fatigue severity scale and SF-36v2

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Previous secondary outcome measures as of 04/05/2021:
Patients with PSC:
Stage 2:
1. Liver biochemistry and function is measured using changes in aspartate aminotransferase (AST), ALT, gamma-glutamyl transpeptidase (GGT), bilirubin, albumin, international normalised ratio [INR] and composite risk scores (Mayo PSC risk score and Model for End Stage Liver Disease [MELD]) at baseline, 3, 14, 21, 28 and 56 days post-infusion.
2. Non-invasive clinical markers of fibrosis are measured using Enhanced Liver Fibrosis (ELF) at baseline, 3, 14, 21, 28 and 56 days and transient elastography (Fibroscan®) at baseline and 28 days post-infusion.
3. Quality of Life (QoL) is measured using the Pruritus Visual Analogue Scale, nine-point fatigue severity scale and SF 36v2 at baseline and 7 days post-infusion.
4. Severity of Inflammatory Bowel Disease (IBD) is measured using the non-endoscopic aspects of the Mayo IBD score at baseline and 7 days post-infusion.

Patients with AIH:
Stage 2:
1. Liver biochemistry and function is measured using changes in AST, ALP, GGT, bilirubin, albumin, INR and composite risk scores (MELD) at baseline, 3, 14, 21, 28 and 56 days post-infusion.
2. Immune activation is measured using immunoglobulin G concentrations at baseline, 3, 14, 21, 28 and 56 days post-infusion.
3. Quality of Life (QoL) is measured using the Pruritus Visual Analogue Scale, nine-point fatigue

severity scale and SF 36v2 at baseline and 7 days post-infusion.
4. Severity of Inflammatory Bowel Disease (IBD) is measured using the non-endoscopic aspects of the Mayo IBD score at baseline and 7 days post-infusion.

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Previous secondary outcome measures as of 28/04/2021:
Patients with Primary Sclerosing Cholangitis:
Stage 2:
1. Any change from baseline at Visit 7, Visit 8 and throughout the trial period (up to Visit 8) after ORBCEL-C™ infusion of:
1.1. Individual markers of liver biochemistry and function including:
1.1.1. Aspartate aminotransferase (AST)
1.1.2. Alanine transaminase (ALT)
1.1.3. Gamma-glutamyl transpeptidase (GGT)
1.1.4. Bilirubin
1.1.5. Albumin
1.1.6. International normalised ratio (INR)
1.1.7. Composite risk scores (Mayo PSC risk score and MELD)
1.2. Non-invasive clinical markers of fibrosis:
1.2.1. Enhanced Liver Fibrosis (ELF)
1.2.2. Transient elastography (Fibroscan®)
1.3. QoL as measured by Pruritus Visual Analogue Scale, 9-point fatigue severity scale and SF-36v2
1.4. Severity of IBD as measured by the non-endoscopic aspects of the Mayo IBD score:
1.4.1. Stool frequency
1.4.2. Rectal bleeding
1.4.3. Physician’s global assessment

Patients with Autoimmune Hepatitis:
Stage 2:
Change from baseline at Visit 7, Visit 8 and throughout the trial period (up to Visit 8) following ORBCEL-C™ infusion in:
2.1. Individual markers of liver biochemistry and function including:
2.1.1. Aspartate aminotransferase (AST)
2.1.2. Alanine transaminase (ALT)
2.1.3. Gamma-glutamyl transpeptidase (GGT)
2.1.4. Bilirubin
2.1.5. Albumin
2.1.6. International normalised ratio (INR)
2.1.7. Composite risk scores (MELD)
2.2. Immune activation assessed by measuring IgG levels
2.3. Non-invasive clinical markers of fibrosis:
2.3.1. Enhanced Liver Fibrosis (ELF)
2.3.2. Transient elastography (Fibroscan®)
2.4. QoL as measured by Pruritus Visual Analogue Scale, 9-point fatigue severity scale and SF-36v2

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Previous secondary outcome measures:
Stage 2:

1. Single intravenous infusion of ORBCEL-CTM elicits a change over the duration of the study after treatment in patients with PSC and AIH:
1.1. Liver biochemistry and function, immunoglobulin G concentrations (in AIH patients) and composite risk scores
1.2. Non-invasive clinical markers of fibrosis
1.3. Patient quality of life (QoL)
1.4. Severity of co-existent IBD in patients with PSC.
2. Further exploratory research objectives of the trial determine whether MSC infusion modulates the immune response by measuring whether treatment elicits a change in patients with PSC and AIH:
2.1. Markers of immune activation including immunoglobulin values and C-reactive protein concentration
2.2. Markers of biliary injury including total bile acid levels
2.3. Circulating inflammatory cells profile this includes phenotypic expression of T regulatory cells (Tregs) a common mechanistic primary endpoint
2.4. Endothelial cell activation markers such as VAP-1 and ICAM1

Overall study start date
31/10/2017

Completion date
01/10/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 01/08/2023:
Patients with PSC:
1. Aged ≥18 years at visit 1 (screening)
2. Diagnosis of PSC at visit 1 (screening) as evidenced clinically by:
2.1. Chronic biochemical cholestasis (elevated serum alkaline phosphatase (ALP) above the upper limit of normal (ULN) and/or gamma-glutamyl transpeptidase (GGT) above the ULN) > 6 months duration AND
2.2. Radiological AND/OR histological evidence of clinically documented PSC
3. Serum ALP) ≥ 1.5 ULN at visit 1 (screening)
4. Any Serum ALP value change is <40% using two sets of laboratory values obtained during screening. If a participant fails to confirm an ALP at Visit 2 that is within 40% of the ALP at Visit 1, a further screening ALP (Visit 2a) can be arranged, so long as the variation in ALP was <50%, and the Principal Investigator has no other clinical reason to suggest the patient is clinically unstable. If the ALP is within 40% variance at Visit 2a as compared to Visit 1, Trial registration is permitted.
5. At Visit 2 (and Visit 2a if applicable), it should be confirmed that a patient does not meet any of the exclusion criteria

Patients with AIH
1. Aged ≥18 and ≤70 years at visit 1 (screening)
2. Established pre-existing clinical diagnosis of AIH confirmed by clinical expert review consistent with the simplified IAIHG criteria (http://www.mdcalc.com/simplified-scoring-autoimmune-hepatitis-aih/) and must include history of a liver biopsy reported compatible with AIH
3. Active AIH defined by ALT ≥1.1x ULN
4. Serum ALT must be above ≥1.1x ULN at both screening (visit 1) and visit 2

5. At visit 2, it should be confirmed that a patient does not meet any of the exclusion criteria
6. Patients must be on standard-of-care AIH treatment for ≥24 weeks – this includes any AIH therapy except biologics
7. Stable doses of immunosuppression for a minimum period of 4 weeks at the time of screening, and no planned change in immunosuppression for the course of the trial

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Previous inclusion criteria as of 28/04/2021:
Patients with PSC:
1. Aged ≥18 years at visit 1 (screening)
2. Diagnosis of PSC at visit 1 (screening) as evidenced clinically by:
2.1. Chronic biochemical cholestasis (elevated serum alkaline phosphatase (ALP) above the upper limit of normal (ULN) and/or gamma-glutamyl transpeptidase (GGT) above the ULN) > 6 months duration AND
2.2. Radiological AND/OR histological evidence of clinically documented PSC
3. Serum ALP) ≥ 1.5 ULN at visit 1 (screening)
4. Any Serum ALP value change is <40% using two sets of laboratory values obtained during screening. If a participant fails to confirm an ALP at Visit 2 that is within 40% of the ALP at Visit 1, a further screening ALP (Visit 2a) can be arranged, so long as the variation in ALP was <50%, and the Principal Investigator has no other clinical reason to suggest the patient is clinically unstable. If the ALP is within 40% variance at Visit 2a as compared to Visit 1, Trial registration is permitted.
5. At Visit 2 (and Visit 2a if applicable), it should be confirmed that a patient does not meet any of the exclusion criteria

Patients with AIH
1. Aged ≥18 and ≤70 years at visit 1 (screening)
2. Established pre-existing clinical diagnosis of AIH confirmed by clinical expert review consistent with the simplified IAIHG criteria (http://www.mdcalc.com/simplified-scoring-autoimmune-hepatitis-aih/) and must include history of a liver biopsy reported compatible with AIH
3. Active AIH defined by ALT ≥1.5x ULN
4. Serum ALT must be above ≥1.5x ULN at both screening (visit 1) and visit 2
5. At visit 2, it should be confirmed that a patient does not meet any of the exclusion criteria
6. Patients must be on standard-of-care AIH treatment for ≥ 24 weeks – this includes any AIH therapy except biologics
7. Stable doses of immunosuppression for a minimum period of 4 weeks at the time of screening, and no planned change in immunosuppression for the course of the trial

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Previous inclusion criteria:
Patients with PSC
1. Age ≥ 18 , ≤70 years old at visit 1 (screening)
2. Diagnosis of PSC at visit 1 (screening) as evidenced clinically by:
2.1. Chronic biochemical cholestasis (elevated serum alkaline phosphatase (ALP) above the upper limit of normal (ULN) and/or gamma-glutamyl transpeptidase (GGT) above the ULN) > 6 months duration AND
2.2. Radiological AND /OR histological evidence of clinically documented PSC
3. Serum ALP) ≥ 1.5 ULN at visit 1 (screening)
4. Serum ALP value at Visit 2 within +/- 25% of ALP value at Visit 1 as per the formula below:
5. At visit 2, it should be confirmed that a patient does not meet any of the exclusion criteria

Patients with AIH
1. Age ≥ 18, ≤70 years old at visit 1 (screening)
2. Established pre-existing clinical diagnosis of AIH confirmed by clinical expert review consistent with the simplified IAIHG criteria (http://www.mdcalc.com/simplified-scoring-autoimmune-hepatitis-aih/) and must include history of a liver biopsy reported compatible with AIH
3. Active AIH defined by ALT ≥ 1.5 ULN.
4. Serum ALT must be above ≥ 1.5 ULN at both screening (visit 1) and visit 2
5. At visit 2, it should be confirmed that a patient does not meet any of the exclusion criteria
6. Patients must be on standard-of-care AIH treatment for ≥ 24 weeks –this includes any AIH therapy except biologics
7. Stable doses of immunosuppression for a minimum period of 4 weeks at the time of screening, and no planned change in immunosuppression for the course of the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 56; UK Sample Size: 56

Total final enrolment
18

Key exclusion criteria
Current exclusion criteria as of 28/04/2021:
Generic exclusion criteria that will apply to both patients with PSC and AIH:
1. Refusal or lacks capacity to give informed consent to participate in trial
2. Patient who is unable to participate in follow-up assessment
3. Participation actively, or within five half-lives, of another interventional clinical trial
4. Known hypersensitivity to the investigational product or any of its formulation excipients
5. Evidence of active malignancy (within 3 years of Visit 1), other than non-melanoma skin cancer and cervical dysplasia in situ
6. Major surgical procedure within 30 days at Visit 1
7. Prior organ transplantation
8. Active harmful alcohol consumption as evaluated and documented by the Investigator
9. Poor venous access therefore unable to support a 22G needle for infusion
10. Creatinine > 133 µmol/L or being treated with renal replacement therapy at the time of Visit 1
11. AST or ALT >10x ULN
12. ALP >10x ULN
13. Platelets <50 x 10(9)/l
14. Total Bilirubin >2x ULN
15. INR >1.3 (in the absence of concomitant use of Warfarin or equivalent anti-coagulant therapy)

16. Albumin <35 g/l
17. Haemoglobin <10 g/dl
18. Past or present evidence of decompensated chronic liver disease:
18.1. Radiological or clinical evidence of ascites
18.2. Hepatic encephalopathy
18.3. Endoscopic evidence for portal hypertensive bleeding
19. Any active treatment with biologic therapy (monoclonal antibodies)
20. Clinically severe cardiovascular disease as evaluated by the Investigator
21. Pregnancy or breast-feeding
22. Women of child bearing potential who are unwilling to practice effective contraception (i.e. barrier, oral contraceptive pill, implanted contraception, or previous hysterectomy, bilateral oophorectomy) for the duration of the trial up to 90 days after the trial drug is administered. If using hormonal agents the same method must have been used for at least 1 month before study dosing and patients must use a barrier method during that time period.
23. Non-vasectomised men, sexually active with women of child bearing potential, who are not willing to practice effective contraception (condom with spermicide) for the duration of the trial up to 90 days after the trial drug is administered
24. Patients with a history of hepatitis C (present or past infection), known positivity for antibody to HIV or any evidence of current or past hepatitis B virus (HBV) infection
25. Presence of an acute/chronic infection or illness that, at the discretion of the Investigator, might compromise the patient's health and safety in the trial
26. Any symptoms indicative of COVID-19; including fever, chronic/persistent cough, or loss of sense of taste or smell in the preceding 2 weeks
27. Receipt of live vaccination within 6 weeks prior to Visit 1

Exclusion criteria specific to patients with PSC:
1. Documented alternative aetiology for sclerosing cholangitis (i.e. secondary sclerosing cholangitis)
2. A dominant (as determined by Investigator) alternative chronic or active liver injury other than PSC at the time of Visit 1; patients with possible overlap syndrome with AIH are excluded from the PSC cohort if the Investigator considers AIH as the dominant liver injury
3. UDCA dose modification within the last 90 days
4. ALP >10x ULN
5. Evidence of cholangitis within 90 days of Visit 1:
5.1. Documented evidence of cholangitis by physician
5.2. Need for any antibiotics for presumed cholangitis
6. Any patient taking prophylactic antibiotics to combat recurrent cholangitis
7. Presence of percutaneous biliary drain, or internal biliary stent
8. Diagnosed hepatocellular carcinoma or cholangiocarcinoma or high clinical suspicion thereof
9. Dominant stricture clinically suspicious of cholangiocarcinoma (as determined by Investigator)

Exclusion criteria for those with IBD:
1. Unstable disease as evidenced by:
1.1. Documented clinically significant flare within 90 days of enrolment requiring any marked intensification of therapy from baseline maintenance (maintenance therapy = thiopurines, 5-aminosalicylates, or oral prednisolone <10 mg/day; biologics therapy is an exclusion criterion)
1.2. Requirement for daily prednisolone >10 mg
1.3. Mayo Clinic Score ≥2 AND clinician assessment of active disease requiring up-titration of treatment; last colonoscopy within last year used for endoscopic component
2. Any colonoscopic evidence of clinically significant dysplasia at last colonoscopy
3. Patients who have not had their routine colonoscopy within 24 months prior to planned MSC infusion and are unwilling to have their annual colonoscopy examination as per standard care

prior to Visit 3 (treatment)
4. A Mayo score/ Disease Activity Index for Ulcerative Colitis of ≥5 (https://www.mdcalc.com /mayo-score-disease-activity-index-dai-ulcerative-colitis)

Exclusion criteria specific to patients with AIH:
1. A dominant (as determined by Investigator) alternative chronic or active liver injury other than AIH at the time of Visit 1; Patients with possible overlap syndrome with PSC are excluded from the AIH cohort if the Investigator considers PSC as the dominant liver injury
2. AST or ALT >10x ULN
3. Patients on a prednisolone dose of >20 mg at the time of screening
4. Treatment with biologic therapy within 24 weeks of the time of screening
5. Patients with a history of poor compliance with medication
6. Diagnosed hepatocellular carcinoma or cholangiocarcinoma or high clinical suspicion thereof

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Previous exclusion criteria:
Generic exclusion criteria that will apply to both patients with PSC and AIH:
1. Refusal or lacks capacity to give informed consent to participate in trial
2. Patient who is unable to participate in follow up assessment
3. Participation actively, or within 5 half-lives, of another interventional clinical trial
4. Known hypersensitivity to the investigational product or any of its formulation excipients
5. Evidence of active malignancy (within 3 years of visit 1 (screening)), other than non-melanomatous skin cancer and cervical dysplasia in situ
6. Major surgical procedure within 30 days at visit 1 (screening)
7. Prior organ transplantation
8. Active harmful alcohol consumption as evaluated and documented by the investigator
9. Creatinine > 133 µmol/L or being treated with renal replacement therapy at the time of Visit 1 (screening)
10. AST or ALT > 10 x ULN
11. ALP > 10 x ULN
12. Platelets < 50 x 10^9/L
13. Total Bilirubin > 2 x ULN
14. INR > 1.3 (in the absence of concomitant use of Warfarin or equivalent anti-coagulant therapy)
15. Albumin < 35 g/litre
16. Haemoglobin < 10 g/dl
17. Past or present evidence of decompensated chronic liver disease:
17.1. Radiological or clinical evidence of ascites
17.2. Hepatic encephalopathy
17.3. Endoscopic evidence for portal hypertensive bleeding
18. Any active treatment with biologic therapy (monoclonal antibodies)
19. Clinically severe cardiovascular disease as evaluated by the Investigator
20. Pregnancy or breast-feeding
21. Women of childbearing age who are unwilling to practice effective contraception 22. Non-vasectomised men, sexually active with women of child-bearing age, who are not willing to practice effective contraception (condom with spermicide) for the duration of the trial up to 90 days after the trial drug is administered
23. Patients with a history of hepatitis C (present or past infection), known positivity for antibody to HIV or any evidence of current or past hepatitis B infection
24. Presence of an acute/chronic infection or illness that, at the discretion of the Investigator, might compromise the patient's health and safety in the trial
25. Receipt of live vaccination within six weeks prior to visit 1 (screening)

Exclusion criteria specific to patients with PSC:
1. Documented alternative aetiology for sclerosing cholangitis (i.e. secondary sclerosing cholangitis)
2. A dominant (as determined by Investigator) alternative chronic or active liver injury other than PSC at the time of visit 1 (screening); Patients with possible overlap syndrome with AIH are excluded from the PSC cohort if the Investigator considers AIH as the dominant liver injury
3. UDCA use within 8 weeks of the first screening visit (if a patient was taking UDCA a washout period of at least 8 weeks prior to the first screening is required)
4. ALP > 10 x ULN
5. Evidence of cholangitis within 90 days of visit 1 (screening)
5.1. Documented evidence of cholangitis by physician
5.2. Need for any antibiotics for presumed cholangitis
6. Any patient taking prophylactic antibiotics to combat recurrent cholangitis
7. Presence of percutaneous biliary drain, or internal biliary stent
8. Diagnosed hepatocellular carcinoma or cholangiocarcinoma or high clinical suspicion thereof
9. Dominant stricture clinically suspicious of cholangiocarcinoma (as determined by Investigator)

Exclusion criteria for those with IBD:
1. Unstable disease as evidenced by:
1.1. Documented clinically significant flare within 90 days of enrolment requiring any marked intensification of therapy from baseline maintenance (maintenance therapy = thiopurines, 5-aminosalicylates, or oral prednisolone < 10mg/day; biologics therapy is an exclusion criteria; see section 5.2
1.2. Requirement for daily prednisolone > 10mg
1.3. Mayo Clinic Score > = 2 AND clinician assessment of active disease requiring up-titration of treatment; last colonoscopy within last year used for endoscopic component
2. Any colonoscopic evidence of clinically significant dysplasia at last colonoscopy
3. Patients who have not had their routine colonoscopy within 24 months prior to planned MSC infusion and are unwilling to have their annual colonoscopy examination as per standard care prior to study visit 3 (treatment)

Exclusion criteria specific to patients with AIH:
1. A dominant (as determined by Investigator) alternative chronic or active liver injury other than AIH at the time of visit 1 (screening); Patients with possible overlap syndrome with PSC are excluded from the AIH cohort if the Investigator considers PSC as the dominant liver injury
2. AST or ALT > 10 x ULN
3. Patients on a prednisolone dose of > 20 mg at the time of screening
4. Treatment with biologic therapy within 24 weeks of the time of screening
5. Patients with a history of poor compliance with medication
6. Diagnosed hepatocellular carcinoma or cholangiocarcinoma or high clinical suspicion there

Date of first enrolment
31/12/2017

Date of final enrolment
19/09/2023

Locations

Countries of recruitment

England

United Kingdom

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

Sponsor information

Organisation
University of Birmingham

Sponsor details
MERLIN Trials office
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Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
European Commission

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, Ευρωπαϊκής Επιτροπής, Европейската комисия, Evropské komise, Commission européenne, Choimisiúin Eorpaigh, Europskoj komisiji, Commissione europea, La Commissione

europea, Eiropas Komisiju, Europos Komisijos, Európai Bizottságról, Europese Commissie, Komisja Europejska, Comissão Europeia, Comisia Europeană, Európskej komisii, Evropski komisiji, Euroopan komission, Europeiska kommissionen, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
01/05/2024

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No