

Restoring immune function in liver failure

Submission date 14/02/2025	Recruitment status Recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 19/02/2025	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 04/03/2025	Condition category Digestive System	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

Liver failure occurs when liver cells are damaged significantly and are no longer able to function. In some patients their liver may suddenly stop working and this is known as acute liver failure. In these patients they may have no evidence of liver disease before being hospitalised. In other patients the liver may already have sustained damage but has managed to keep functioning well then something happens which means that it is no longer able to perform all its functions adequately. This is known as acute decompensation of cirrhosis. Cirrhosis is the result of long-term damage to the liver which causes scarring. Patients with liver failure have increased susceptibility to infection which usually leads to further deterioration in liver function. The purpose of this study is to investigate how we can improve the function of immune cells in patients with liver failure, ultimately helping to reduce infection. There is no expectation that liver function will be restored. The researchers will be collecting samples and data to investigate whether an anti-PD1 drug can be used to help defects in the immune response in patients with liver failure. There is currently no targeted treatment for this.

Who can participate?

Patients aged 18 years and over with acute liver failure (ALF) or acute decompensation of cirrhosis (AD)

What does the study involve?

The study involves a single dose of a drug (nivolumab) by injection. Blood samples will be taken before the injection and then every 5 days for 20 days.

What are the possible benefits and risks of participating?

There is no guarantee of any benefit from participating in this study. There is a small risk that the drug could cause temporary inflammation of the liver.

Where is the study run from?

Imperial College London (UK)

When is the study starting and how long is it expected to run for?

December 2020 to December 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Mark Thursz, m.thursz@imperial.ac.uk

Contact information

Type(s)

Public, Scientific, Principal Investigator

Contact name

Prof Mark Thursz

ORCID ID

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Contact details

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

313128

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

22SM7474, CPMS 53156

Study information

Scientific Title

Inhibition of PD-1 to restore monocyte/macrophage function in liver failure

Acronym

Normalise

Study objectives

Antibodies targeted at the PD1 molecule will restore immune function in patients with liver failure

Ethics approval required

Ethics approval required

Ethics approval(s)

Approved 22/11/2022, Harrow Research Ethics Committee (Level 3, Block B, Whitefriars, Bristol Research Ethics Committee Centre, Bristol, BS1 2NT, United Kingdom; +44 (0)207 104 8012; harrow.rec@hra.nhs.uk), ref: 22/LO/0397

Study design

Non-CTIMP physiological assessment

Primary study design

Interventional

Secondary study design

Non randomised study

Study setting(s)

Hospital, Laboratory, University/medical school/dental school

Study type(s)

Other

Participant information sheet

Not available in web format

Health condition(s) or problem(s) studied

Liver failure (acute liver failure and acute decompensation of cirrhosis)

Interventions

Nivolumab (anti-PD1 antibody)

Non-CTIMP, physiological assessment in two groups of patients:

1. Patients (n = 19) with acute liver failure (ALF)
2. Patients (n=59) with acute decompensation of cirrhosis (AD)

The study will follow patients up for 30 days. Patients should commence treatment within 48 hours of study enrolment. Anti-PD1 antibody (nivolumab or pembrolizumab) will be administered as a single 240 / 200 mg dose (120 / 100 mg dose in the first sentinel cohort patients) diluted in 100 ml of 0.9% saline and administered intravenously over 30 minutes.

Intervention Type

Biological/Vaccine

Pharmaceutical study type(s)

Physiological assessment of response to PD1 inhibition

Phase

Phase 0

Drug/device/biological/vaccine name(s)

Nivolumab, pembrolizumab

Primary outcome measure

HLA-DR expression on circulating monocytes measured using flow cytometry on day 15 compared to baseline

Secondary outcome measures

1. Monocyte phagocytosis measured using pH-Rodo uptake in flow cytometry on days 5, 10, 15 and 30 compared to baseline
2. HLA-DR expression on circulating monocytes measured using flow cytometry on days 5, 10, 15 and 30 compared to baseline
3. Incidence of clinically diagnosed infection during the 30 days of follow-up
4. Incidence of bacteraemia diagnosed on blood cultures during the 30 days of follow-up
5. Changes in lipopolysaccharide-induced tumour necrosis factor alpha secretion from monocytes measured by ELISA test on days 5 and 15 compared to baseline
6. Changes in circulating bacterial 16S-ribosomal DNA (16S-rDNA) at days 5 and 10 compared to baseline measured using real-time polymerase chain reaction assays

Overall study start date

16/12/2020

Completion date

31/12/2025

Eligibility

Key inclusion criteria

Inclusion criteria – Group 1 (ALF):

1. Male and female patients aged 18 years or older at screening
2. Clinical diagnosis of acute liver failure:
 - 2.1. Presence of jaundice (bilirubin > 40 uMol/L)
 - 2.2. INR > 1.5
 - 2.3. Any degree of encephalopathy
 - 2.4. No history of cirrhosis or advanced chronic liver disease
3. Informed consent (provided by a relative or a professional legal representative when the patient lacks capacity)

Inclusion criteria – Group 2 (AD):

1. Male and female patients aged 18 years or older at screening
2. Clinical diagnosis of acute decompensation of cirrhosis including acute-on-chronic liver failure characterised by at least one of:
 - 2.1. Ascites
 - 2.2. Spontaneous bacterial peritonitis
 - 2.3. Encephalopathy (any degree)
 - 2.4. Variceal haemorrhage
3. Evidence of cirrhosis based on any of the following:
4. Liver biopsy (at any time)
5. Elastography (at any time) FS >10 KPa

6. Radiological imaging (at any time)
7. Informed consent (provided by the patient or a relative or a professional legal representative when the patient lacks capacity)

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

78

Key exclusion criteria

1. Candidates for liver transplantation within 2 months
2. Duration of clinically apparent jaundice >3 months before baseline visit
3. Evidence of acute viral hepatitis
4. Biliary obstruction
5. Hepatocellular carcinoma
6. Any known autoimmune disorder, including autoimmune-mediated liver failure
7. Previous treatment with any checkpoint inhibitor
8. Untreated sepsis
9. Evidence of current malignancy (except non-melanotic skin cancer)
10. Patients with known hypersensitivity or contraindications to anti-PD-L1 antibody (nivolumab or pembrolizumab)
11. Pregnant or lactating women
12. Currently enrolled in a CTIMP
13. Known HIV infection

Date of first enrolment

01/12/2022

Date of final enrolment

30/11/2025

Locations**Countries of recruitment**

England

United Kingdom

Study participating centre

Imperial College Healthcare NHS Trust

The Bays
St Marys Hospital
South Wharf Road
London
United Kingdom
W2 1BL

Study participating centre**Kings College Hospital NHS Trust**

Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre**St George's Hospital NHS Trust**

Blackshaw Road
London
United Kingdom
SW17 0QT

Sponsor information

Organisation

Imperial College London

Sponsor details

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W2 1PG
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r.nicholson@imperial.ac.uk

Sponsor type

University/education

Website

<https://www.imperial.ac.uk/research-and-innovation/support-for-staff/joint-research-office/hrs/stakeholders/rgit/>

ROR

<https://ror.org/041kmwe10>

Funder(s)

Funder type

Government

Funder Name

Medical Research Council

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Publication and dissemination plan

The study will be published in peer-reviewed journals. The expectation is that a successful study would lead to an application for a Phase II trial to assess efficacy.

Intention to publish date

Individual participant data (IPD) sharing plan

Individual patient data (de-identified) will be made available to bona fide investigators on request after publication from Mark Thursz (m.thursz@imperial.ac.uk).

Data available:

1. Patient demographics
2. Disease classification
3. Underlying aetiology
4. Severity scores
5. Clinical outcomes
6. Primary outcome
7. Secondary outcomes

Availability: from December 2026
Patient consent has been obtained
Data will be de-identified

IPD sharing plan summary

Stored in non-publicly available repository, Available on request