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Restoring immune function in liver failure

Submission date 14/02/2025	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 19/02/2025	**Overall study status** Ongoing	
Last Edited 12/11/2025	**Condition category** Digestive System	

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 June 2026

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

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
313128

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
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

Study type(s)
Other

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

Phase
Phase 0

Drug/device/biological/vaccine name(s)
Nivolumab, pembrolizumab

Primary outcome(s)
HLA-DR expression on circulating monocytes measured using flow cytometry on day 15 compared to baseline

Key secondary outcome(s))
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

Completion date
30/06/2026

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

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

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
31/05/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
The Bays
St Marys Hospital
South Wharf Road
London
England
W2 1BL

Study participating centre
Kings College Hospital NHS Trust
Denmark Hill
London
England
SE5 9RS

Study participating centre
St George's Hospital NHS Trust
Blackshaw Road
London
England
SW17 0QT

Sponsor information

Organisation
Imperial College London

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

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

Available on request, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes