IL-1 Signal Inhibition in Alcoholic Hepatitis (Isaiah)

CLINICAL TRIAL PROTOCOL

Sponsor:	Imperial College, London
EudraCT Number:	2017-003724-79
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Development Phase:	II
Indications:	Severe Alcoholic Hepatitis
Sponsor Protocol Number:	17SM4152
Protocol Version:	5.0
Protocol Date	03.09.2020
Study Product:	Canakinumab (ACZ885) 150 mg / 1 mL solution for injection

ISAIAH

ISAIAH

CONTACT LIST

ROLE	NAME	ADDRESS	CONTACT DETAILS
CHIEF INVESTIGATOR	Prof Mark Thursz	Digestive Diseases Division, Imperial College, Norfolk Place, London W2 1NY	PA: Dawn Campbell Tel: 020 3312 6454 Fax: 020 7706 9161 Email: m.thursz@imperial.ac.uk Email: d.campbell@imperial.ac.uk
SPONSOR	Imperial College, London	Room 221, Medical School Building, St Marys Campus, Norfolk Place, London W2 1PG	Contact: Mr Gary Roper E-mail: jrco.ctimp.team@imperial.ac.uk Tel: 020 7594 1872
FUNDER	Novartis Pharmaceuticals UK Limited	200 Frimley Business Park, Surrey, Frimley, Camberley GU16 7SR	Tel. 01276 692255
TRIAL MANAGER	Justyna Czyzewska-Khan	Imperial Clinical Trials Unit, Stadium House, 68 Wood Lane, London, W12 7RH	E-mail: isaiah@imperial.ac.uk Tel: 020 7594 1687 / 07517 551851
SENIOR STATISTICIAN	Dr Francesca Fiorentino	Imperial Clinical Trials Unit & Department of Surgery and Cancer, 1091, 10th Floor, Queen Elizabeth and Queen Mary Building, St Mary's Hospital, W2 1NY	E-mail: f.fiorentino@imperial.ac.uk Tel: 02033123761 or 02075941739

LABORATORIES

LABORATORY	ADDRESS	CONTACT	CONTACT PERSONNEL
IMPERIAL COLLEGE HISTOPATHOLOGY	Histopathology Department, St Mary's Hospital, Norfolk Place, London. W2 1NY	Tel: 020 3312 1305 Fax: 020 3312 6775 Email: r.goldin@imperial.ac.uk	Prof Rob Goldin
Digestive Disease Laboratory	10th Floor QEQM Wing, St Mary's Hospital, London W2 1NY	Tel: 0203312 6454 Email: n.vergis@imperial.ac.uk / m.thursz@imperial.ac.uk	Dr Nikhil Vergis / Prof Mark Thursz
SGS CEPHAC EUROPE (subcontracted to undertake PK/PD analyses)	90 Avenue des Hauts de la Chaume, B.P. 28, 86281 Saint-Benoît Cedex, France	Tel: +33 (0)5 49 57 04 04 Fax: +33 (0)5 49 57 22 39 Email: fr.cephac.echantillons@sgs.com	Clinical Research Sample Coordinator
INSTITUTE OF HEPATOLOGY	Foundation for Liver Research, 111 Coldharbour Lane, London SE5 9NT	Tel: 020 3299 3713 Email: vishal.patel@researchinliver.org.uk	Dr Vish Patel

This protocol describes the Isaiah trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Manager. This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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ABBREVIATIONS

AE	Adverse Event
AH	Alcoholic Hepatitis
AHHS	Alcoholic Hepatitis Histological Score
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BM	Biomarkers
BP	Blood Pressure
CAPS	Cryopyrin-Associated Periodic Syndromes
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
CXR	Chest X-ray
DMEC	Data Monitoring and Ethical Committee
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FMF	Familial Mediterranean fever
GAHS	Glasgow Alcoholic Hepatitis Score
GCP	Good Clinical Practice
HIDS	Hyperimmunoglobulin D Syndrome
HIV	Human Immunodeficiency Virus
GI	Gastrointestinal
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IUD	Intrauterine Device
IUS	Intrauterine System
IMP	Investigational Medicinal Product
i.v.	Intravenous

LDH	Lactate Dehydrogenase
MA	Marketing Authorisation
mDF	Maddrey's discriminant function
MELD	Model for End stage Liver Disease
MHRA	Medicines and Healthcare Products Regulatory Agency
MSU	Mid-stream urine
NAS	Nonalcoholic fatty liver disease activity score
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SIRS	Systemic Inflammatory Response Syndrome
SJIA	Systemic Juvenile Idiopathic Arthritis
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMF	Trial Master File
TMG	Trial Management Group
TRAPS	Tumour necrosis factor receptor associated periodic syndrome
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
UNOS	United Network of Organ Sharing
UTI	Urinary Tract Infection
WHO	World Health Organisation

1 Protocol Summary

1.1 Objectives

To explore the potential benefits of the IL-1β antibody, Canakinumab, in the treatment of alcoholic hepatitis.

1.2 Primary End Point

Histological improvement of alcoholic hepatitis on liver biopsy after 28 days of treatment compared to baseline (See Section 7.6.5).

1.3. Secondary End Points

- Improvement of individual components of alcoholic hepatitis on liver histology from baseline to Day 28
- Changes in the components of Alcoholic Hepatitis Histological Score (AHHS) (1) from baseline to Day 28
- Changes in the components of Non-alcoholic fatty liver disease activity score (NAS) score from baseline to Day 28
- Changes in the hepatic venous pressure gradient (HVPG) between baseline and day 28.
- Changes in serum CK18-M30/M65 from baseline to Day 7, 14, 21, 28, 42 and 90
- Change in serum bilirubin from baseline to Day 7, 14, 28, 21, 42 and 90
- Change in MELD score at from baseline to Day 7, 14, 21, 28, 42 and 90
- Change in Glasgow alcoholic hepatitis score (GAHS) from baseline to Day 7, 14, 21, 28, 42 and 90
- Change in mDF score from baseline to Day 7, 14, 21, 28, 42 and 90
- Lille score at Day 7
- Resolution of systemic inflammatory response syndrome (SIRS) at Day 7, 14, 21, 28, 42 and 90 in patients with SIRS at baseline
- Incidence of SIRS at Day 7, 14, 21, 28, 42 and 90 in patients without SIRS at baseline
- Mortality rate at Day 90
- Incidence of infection and sepsis over 90 days
- Incidence of acute kidney injury over 90 days
- Incidence of variceal haemorrhage, ascites or encephalopathy over 90 days
- safety and tolerability of canakinumab
- Changes in CRP over time
- Length of hospital stay
- Serum and plasma biomarkers of hepatic function and inflammation including cytokine profiles which may indicate the degree of response to IL-1b inhibition.

1.4. Design

Multicentre, double blind, randomized (1:1), placebo controlled trial. The trial will follow patients up for 90 days and will be conducted in up to 18 centres in the United Kingdom. Twenty-six patients will be recruited to each arm of the trial: total 52 patients.

1.5. Trial Phase

Phase II – Exploring the benefits of IL-1 inhibition in alcoholic hepatitis

1.6 Main Eligibility Criteria

(Full eligibility criteria listed in Section 4.4)

Inclusion criteria

- Male and female patients aged 18 years or older at screening
- Clinical diagnosis of alcoholic hepatitis at screening:
  - Serum bilirubin > 80µmol/L
  - History of excess alcohol (> 80g/day male, > 60g/day female) to within 6 weeks before screening visit
  - Less than 4 weeks since admission to hospital at baseline visit
- mDF* ≥ 32 and MELD ≤ 27 at baseline visit
- Informed consent
- Women of child-bearing potential have to use an effective contraception method (as specified in section 9.6).

Exclusion criteria

- Alcohol abstinence of >6 weeks prior to randomization/baseline visit
- Duration of clinically apparent jaundice > 3 months before baseline visit
- Other causes of liver disease including:
  - Evidence of chronic viral hepatitis (Hepatitis B or C)
  - Biliary obstruction
  - Hepatocellular carcinoma
- Evidence of current malignancy (except non-melanotic skin cancer)
- Previous entry into the study, or use of either prednisolone or any systemic steroids (equivalent to a dose of systemic prednisolone >20mg) within 6 weeks of screening.
- AST >500 U/L or ALT >300 U/L (not compatible with alcoholic hepatitis)
- Patients with a serum creatinine >220 µmol/L (2.5 mg / dL) or requiring renal support (see below)
- Patients dependent upon inotropic support (adrenaline or noradrenaline). Terlipressin is allowed
- Variceal haemorrhage on this admission
- Untreated sepsis (see 4.4.2 Exclusion Criteria)

1.7 Treatment, formulation, route of administration and dose

Consenting eligible patients will be included, randomized and treated before the histology result is available because histology results usually come back within 5 to 7 days depending on the hospital. If the histology is negative then the patient will be discontinued from the study, will not undergo any further treatment or the second biopsy and will not be included into the efficacy analysis but will be followed up for safety assessment. For each patient with a negative histology, another patient will be recruited to ensure that the sample of positive histology patients is 52. Additionally, recruitment will be continued until both biopsies (at Baseline and Day28) from 48 patients will be collected.

A single dose of 3 mg/kg canakinumab or identical placebo will be administered intravenously at baseline (Day 1). Canakinumab will be made up by dilution in 100 ml 5% Dextrose by an unblinded research personnel at each site.
Patients with AST >2 x ULN on Day 28 will receive a second dose of 3 mg/kg study drug administered i.v. on Day 28:

- Patients who received placebo on baseline will receive placebo.
- Patients who received canakinumab on baseline will receive canakinumab.

2 Background and rationale

Alcohol consumption causes a spectrum of liver abnormalities and leads to over 2 million deaths per year (1). Alcoholic hepatitis (AH) is a florid presentation of alcoholic liver disease characterized by liver failure (jaundice and coagulopathy) in the context of recent and heavy alcohol consumption (2). The condition carries a high fatality risk; patients with severe AH have a 30% mortality rate at 90 days after presentation. Moderate AH carries a mortality rate of 6-10% at 90 days. Currently there are no effective treatments for alcoholic hepatitis although clinical guidelines currently recommend prednisolone(3). Prednisolone therapy improves survival in patients with severe AH up to 28 days but beyond this timepoint a higher incidence of infection results in no survival advantage at 90 days compared to placebo treatment (4-6)

Alcoholic hepatitis is a clinical syndrome associated with steatohepatitis on liver histology. Severity of the disease is classified according to Maddrey's discriminant function (mDF) (based on bilirubin and prothrombin time), Glasgow alcoholic hepatitis score (based on age, white blood cell count, urea, prothrombin time and bilirubin) or Model for End Stage Liver Disease (MELD) score (based on creatinine, bilirubin and INR)(2, 6). Alcoholic hepatitis is classified as severe when the mDF is ≥ 32. In the recent STOPAH trial we identified a group of patients with DF≥ 32and MELD < 25, representing 60% of the trial population in whom the 90 day mortality rate was 18%. In patients with mDF≥32 and MELD≤27 the 90 day mortality was marginally higher at 22%. This group of patients was less susceptible to infection even when treated with prednisolone (6).

2.1 Rationale for IL-1b inhibition

IL-1 levels are significantly increased in both serum and liver in patients with alcoholic hepatitis as well as in animal models of the disease. Patients with alcoholic hepatitis have serum levels almost 10 times higher than found in healthy controls(7). IL-1 is thought to be responsible for many of the clinical and metabolic characteristics of alcoholic hepatitis including fever, neutrophilia, monocyte activation, anorexia and muscle catabolism (8). In animal models, inhibition of IL-1 signaling considerably attenuates disease severity (9, 10)

IL-1 inhibition using Canakinumab is currently licensed therapy for cryopyrin-associated periodic syndromes, TRAPS, HIDS, systemic juvenile idiopathic arthritis, FMF and gouty arthritis. Canakinumab has demonstrated a favorable risk-benefit profile in patients with these diseases. Previous studies with anti-cytokine therapy in alcoholic hepatitis, targeting the TNFα system, have failed to show a survival benefit due to the increased risk of infection and possibly due to the removal of a regenerative signal provided by TNFα (11, 12). The current protocol will stratify the risk of infection and use prophylactic antibiotics to reduce the risk of sepsis (13).

The current protocol seeks to explore the potential use of Canakinumab in the treatment of AH. AH is a complex disorder in which liver dysfunction results from inflammatory liver injury and cirrhosis and the patient outcome is also determined by susceptibility to infection or the development of acute

kidney injury. In the first instance, it is therefore essential to establish the efficacy of Canakinumab in a proof-of-principle Phase II) study in alcoholic hepatitis. This is best achieved by demonstrating improvement of the hepatic tissue injury histologically.

There is a considerable unmet clinical need in alcoholic hepatitis. At present there is no treatment for patients with this condition which influences mortality rates at 90 days (5). A severe patient population defined by a DF ≥ 32 and MELD ≤27 is an ideal group in which to evaluate a new modality of treatment as this group of patients are less susceptible to infection and acute kidney injury could complicate the analysis of a treatment response.

Treatment of alcoholic hepatitis is usually delivered for a 4 week period. Assessment of clinical response can be made after 7 days and is demonstrated by a reduction in the serum bilirubin or the Lille score (14).

2.2 Rationale for dose/regimen, route of administration:

Canakinumab has been administered in clinical trials as an intravenous (i.v.) infusion and subcutaneous (s.c.) injection. The doses administered i.v. ranged from 0.03 mg/kg to 10 mg/kg or a fixed dose of 600 mg. The safety, tolerability and efficacy data of canakinumab administered i.v. in completed Novartis sponsored interventional studies are available from more than 800 male or female subjects. Data from completed clinical studies demonstrate strong efficacy as well as a good safety profile. In acute alcoholic hepatitis, immediate disease control is important to decrease the risk for acute kidney injury and other disease related complications. Therefore, canakinumab will be administered intravenously at a dose regimen of 3 mg/kg at Baseline to rapidly reach Cmax.

2.4 Rationale for this Study

Currently there is no effective treatment for severe alcoholic hepatitis. Based on our current understanding of the disease pathogenesis IL-1β is a key mediator of hepatic inflammation responsible for metabolic disturbances, fibrogenesis stellate cell activation and consequently portal hypertension. Canakinumab is a licensed monoclonal antibody inhibitor of IL-1β and may consequently reverse the adverse effects of the cytokine in patients with this disorder.

2.5 Rationale for the study population

Patients with severe alcoholic hepatitis defined by a discriminant function ≥32 have a mortality rate of around 30% at 90 days after admission. In the recent STOPAH trial we found that patients with a MELD ≤27 had 90 day mortality around 22% but had significantly less complications. In particular the incidence of on-treatment infection in patients with a MELD score < 27 was substantially lower in this group of patients. As it is possible that Canakinumab will increase the risk of infection we have chosen to investigate the potential benefit of IL-1b inhibition in patients with less risk of this complication.

2.6 Rationale for 16S-DNA measurement and prophylactic antibiotics

The overall risk of infection in alcoholic hepatitis is 20-30% but this is increased 3 – 4 fold in patients treated with immunosuppressive drugs such as prednisolone when the pre-treatment bacterial 16S ribosomal DNA (16S-DNA) in blood is > 18.5 pg/ml(13). In order to reduce the risk of infection we will place all patients on prophylactic antibiotics for 14 days from baseline and measure 16S DNA changes throughout the study.

3 Study Design

3.1. Objectives

To explore the potential benefits of the IL-1β antibody, Canakinumab, in the treatment of alcoholic hepatitis.

3.2. Primary End Point

Histological improvement of alcoholic hepatitis on liver biopsy after 28 days of treatment compared to baseline. (See Section 7.6.5). Histological improvement is defined as a reduction in lobular inflammation (regardless of cell type).

3.3. Secondary End Points

- Improvement of individual components (polymorphonuclear cell infiltrate, ballooned hepatocytes and steatosis) of alcoholic hepatitis on liver histology from baseline to Day 28.
- Changes in the components of Alcoholic Hepatitis Histological Score (AHHS) (1) from baseline to Day 28
- Changes in the components of Nonalcoholic fatty liver disease activity score (NAS) score from baseline to Day 28
- Changes in hepatic venous pressure gradient (HVPG) between baseline and day 28
- Changes in serum CK18-M30/M65 from baseline to Day 7, 14, 21, 28, 42 and 90
- Change in serum bilirubin from baseline to Day 7, 14, 28, 21, 42 and 90
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- Change in Glasgow alcoholic hepatitis score (GAHS) from baseline to Day 7, 14, 21, 28, 42 and 90
- Change in mDF score from baseline to Day 7, 14, 21, 28, 42 and 90
- Lille score at Day 7
- Resolution of systemic inflammatory response syndrome (SIRS) at Day 7, 14, 21, 28, 42 and 90 in patients with SIRS at baseline
- Incidence of SIRS at Day 7, 14, 21, 28, 42 and 90 in patients without SIRS at baseline
- Mortality rate at Day 90
- Incidence of infection and sepsis over 90 days
- Incidence of acute kidney injury over 90 days
- Incidence of variceal haemorrhage, ascites or encephalopathy over 90 days
- safety and tolerability of canakinumab
- Serum and plasma biomarkers of hepatic function and inflammation including cytokine profiles which may indicate the degree of response to IL-1b inhibition.
- Changes in CRP over time
- Length of hospital stay

3.4. Exploratory End Points

- Changes in monocyte oxidative burst function over time
- Changes in circulating monocyte phenotype over time
- Changes in circulating bacterial DNA over time
- Changes in transient elastography (Fibroscan) scores from baseline at Day 28 and Day 90
- Canakinumab PK/PD profile

- Changes in tissue gene expression from baseline to Day 28
- Immunohistochemistry
- Gene variant interaction of PNPLA3 with treatment outcome

3.5. Design

Multicentre, double blind, randomized (1:1), placebo controlled trial. The trial will follow patients up for 90 days and will be conducted in centres across the United Kingdom. Twenty-six patients will be recruited to each arm of the trial: total 52 patients.

3.6. Treatment

Patients will be included and randomized and treated before histology result is available. If the histology is negative then patient will be withdrawn.

A single dose of 3 mg/kg Canakinumab or identical placebo will be administered intravenously at baseline (Day 1). Canakinumab will be made up by dilution in 100 ml 5% Dextrose by an unblinded research personnel at each site. The drug or placebo (5% Dextrose alone) will be labelled by the designated unblinded team member.

Patients with moderate to severe ascites should undergo large volume paracentesis prior to administration of Canakinumab.

Patients with AST >2 x ULN on Day 28 will receive a second dose of 3 mg/kg study drug administered i.v. on Day 28:

- Patients who received placebo on baseline will receive placebo.
- Patients who received canakinumab on baseline will receive canakinumab.

The second dose of study drug (or placebo) should not be administered if the patient experienced an incident of infection during the prior 28 days, MELD >27 or in cases where the PI is concerned about the patient's condition deteriorating.

Randomisation will be via the trial InForm database which will enable the unblinded research team to ensure the right dosing and drug preparation in respect of the AST assessment on D28.

4. Patient population

The trial will be conducted in patients with severe alcoholic hepatitis (mDF* ≥ 32 and MELD ≤27) with treatment initiated during an index hospital admission with the condition.

4.1 Patient selection

Potential patients will be identified after admission for treatment of severe alcoholic hepatitis and the details of the study explained to them. Patients will receive a written explanation (Patient Information Sheet and Informed Consent Form) of the study and must freely give their informed consent in writing. Following consent, patients will be screened for eligibility for the trial and must fulfil the inclusion and exclusion criteria in order to be randomised into the trial, receive study drug and followed-up for further evaluations as per schedule of assessments (see Table 1).

4.2 Informed Consent

First approach will be made by the direct care team. Following referral and identification, the potential patients will be told about the study by the local PI and his/her team, and will have the opportunity to ask questions. They will be given a Patient Information Sheet (PIS) and will be given 24 hours to consider the study (or less if the patient feels that they do not need this long to decide whether or not to participate), prior to giving their informed consent. Patients will be given a copy of the signed Informed Consent Form.

4.3 Incapacitated Patients

Potential patients for the trial who present with hepatic encephalopathy may be unable to consent for themselves, but are not excluded from the trial. Special arrangements are in place to ensure that the interests of such patients are protected. Such patients should be considered for the trial as a patient group likely to receive maximum benefit from the trial interventions, if received soon after confirmation of eligibility.

When considering a patient who is unable to consent for themselves for suitability for the trial, the decision on whether to consent to, or refuse, participation in a trial will be taken by a "legal representative" who is independent of the research team and should act on the basis of the person's presumed wishes. The type and hierarchy of legal representative who should be approached to give informed consent on behalf of an incapacitated adult, prior to inclusion of the subject in the trial, is given following:

Personal legal representative

- A person not connected with the conduct of the trial who is:
(a) suitable to act as the legal representative by virtue of their relationship with the adult, *and*
(b) available and willing to do so.

Professional legal representative

A person not connected with the conduct of the trial who is:
(a) the doctor primarily responsible for the adult's medical treatment, or
(b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board).

A professional legal representative may be approached if no suitable personal legal representative is available.
The appropriate legal representative will be provided with the approved Legal Representative Information Sheet and Legal Representative Informed Consent Form, to document the consent process.
The consent given by the legal representative remains valid in law until such time as the as the patient recovers capacity. At this point, the patient will be informed about the trial and asked to decide whether or not they want to continue in the trial, and consent to continue will be sought from the patient themselves.

4.4 Eligibility Criteria

4.4.1 Inclusion criteria

- Male and female patients aged 18 years or older at screening
- Clinical diagnosis of alcoholic hepatitis at screening:
  - Serum bilirubin > 80µmol/L
  - History of excess alcohol (> 80g/day male, > 60g/day female) to within 6 weeks before screening visit
  - Less than 4 weeks since admission to hospital at baseline visit
- mDF* ≥ 32 and MELD ≤ 27 at baseline visit
- Informed consent
- Women of child-bearing potential have to use an effective contraception method (as specified in section 9.6).

4.4.2 Exclusion criteria

- Alcohol abstinence of >6 weeks prior to randomization/baseline visit
- Duration of clinically apparent jaundice > 3 months before baseline visit
- Other causes of liver disease including:
  - Evidence of chronic viral hepatitis (Hepatitis B or C)
  - Biliary obstruction
  - Hepatocellular carcinoma
- Evidence of current malignancy (except non-melanotic skin cancer)
- Previous entry into the study, or use of either prednisolone or any systemic steroids (equivalent to a dose of systemic prednisolone >20mg) within 6 weeks of screening.
- AST >500 U/L or ALT >300 U/L (not compatible with alcoholic hepatitis)
- Patients with a serum creatinine >220 µmol/L (2.5 mg / dL) or requiring renal support (see below)
- Patients dependent upon inotropic support (adrenaline or noradrenaline). Terlipressin is allowed
- Variceal haemorrhage on this admission
- Untreated sepsis (see below)
- Patients with known hypersensitivity or contraindications to Canakinumab
- Patients with cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction (within the last 6 weeks) or severe cardiac arrhythmias (not including atrial fibrillation)
- Pregnant or lactating women

- Patients treated with other IL-1 inhibitors and biologics or any other immunosuppressants within 3 months of study participation.
- Known infection with HIV at screening or randomization
- History or evidence of tuberculosis (TB) (active or latent) infection
- Active ongoing inflammatory diseases other than AAH that might confound the evaluation of the benefit of canakinumab therapy
- Underlying metabolic, hematologic, renal, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, including neutropenia (ANC <1.5) and leukopenia, which in the opinion of the investigator immune-compromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
- Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes
- Vaccination with a live vaccine within 3 month before baseline

Sepsis:

As per standard of care all patients will be screened for infection prior to randomization. Diagnosis of infection is based on the criteria outlined by Bajaj and colleagues and will involve chest radiography, urinalysis (mid-stream urine (MSU) culture if urinalysis positive), ascitic tap (if ascites present) and blood cultures if pyrexial. Positive culture and initiation of antibiotics with clinical or radiological signs of infection, as well as clinical suspicion, will be recorded as sepsis.

Blood culture negative pyrexia and a leucocytosis will not be regarded as signs of active sepsis on their own, as these are often co-existent findings with alcoholic hepatitis. Patients with evidence of sepsis will be treated for a minimum of 2 days with appropriate antibiotics before re-screening. Once the local Principal Investigator (PI) considers that the sepsis is under control, the patient may be re-screened and randomised if eligible. All patients will be treated with prophylactic antibiotics (e.g. co-trimoxazole, co-amoxyclav,ciprofloxacin) for the first 14 days treatment irrespective of whether they are randomized to Canakinumab or placebo. Details of the prescribed prophylactic antibiotics must be noted in the Concomitant Medication form in eCRF.

Patients to have screening for infection at baseline and on a weekly basis until the patient is discharged from hospital.

Renal Impairment:

Patients who are oligo-anuric, have a creatinine >220 uM/L (2.5 mg/dL) or who require renal support, will be given appropriate resuscitation therapy for up to 1 week. These patients may then be re-screened and considered for randomisation, once they meet eligibility criteria.

5. Patient Registration, Randomisation and Data Collection

The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the InForm database. Data is entered into the EDC system via site personnel. All source data recorded in the electronic case report form (eCRF) will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a signature and date. Specific instructions and further details will be outlined in the eCRF manual.

5.1 Account Creation

Each local user at the study sites must complete user training (appropriate to their role in the trial) for InForm after which an account will be created for them on the ISAIAH InForm database.

5.2 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the study Monitoring Plan.

5.3 Patient Registration

After informed consent has been obtained each patient must be registered for the study via the ISAIAH InForm database. Registered patients will be allocated a unique Subject ID number. Each patient will retain this number for the duration of the study. The unique Subject ID number and patients' age will be the patient identifiers in the study data.

5.4 Patient Randomisation

After the patient is registered, the screening assessments will take place; please refer to the assessment schedule in section 7 for detailed description of screening assessments.
If eligible for the study, the patient will be electronically randomised via the ISAIAH InForm database to a study treatment group, but this will be blinded to the site staff (with the exception of designated unblinded study personnel) and the patient, by means of a unique code. If the patient is not eligible for the study, they are deemed a 'screening failure', and will receive treatment as per local standard care.

5.5 eCRF

Data will be collected through the electronic case report forms (eCRF) on the ISAIAH InForm database at each patient visit as scheduled below in Section 7. Details of procedures for eCRF completion will be provided in a study manual.

5.6 Procedure for breaking treatment code

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the local principal investigators will have access to a mechanism that permits rapid un-blinding should they feel this is necessary and are unable to contact the study team. Local SOPs describing the emergency unblinding procedure will be in place. The chief investigator recommends, but does not require, that the investigator contact him before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject

emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained.

6. Concurrent Medication and Treatment

Many additional medications may be required. Concomitant medication may be given as medically indicated. Forbidden treatments are listed under section 6.4.

6.1 Alcohol withdrawal

Alcohol withdrawal therapy as required is allowed.

6.2 Infection / Sepsis

Patients who have infection or sepsis at screening or at any time during the study should be treated with antibiotics. Patients presenting with infection at screening visit will be eligible for randomization once the infection is under control. Antibiotics should be continued/given for the first two weeks after initiation in all patients. See Section 4.4 for further details.

Regular surveillance for infection or sepsis should be conducted throughout the study. Infection screening will be performed at every study visit.

6.3 Nutrition

All patients will receive supportive nutritional therapy. Patients will be offered nutritional supplements in the first instance. If they are unable to take these, they will be offered enteral nutrition via a nasogastric tube. An attempt should be made to provide 35-40 kcal/kg/day non-protein energy with 1.5g/kg/day protein. The responsible clinician will decide upon the use of other treatments such as terlipressin, for patients who are developing hepatorenal failure, acid suppression for prophylaxis against gastro-intestinal haemorrhage, antibiotics and vitamin supplementation.

6.4 Other treatments for Alcoholic Hepatitis

N-acetyl cysteine should not be used.

Patients must NOT be prescribed pentoxifylline or prednisolone during the treatment period of the study.

Other immunosuppressive treatments must not be used.

7. Investigations & Procedures

Please also refer to the tabulated Schedule of Assessments (Table 1) and the summary of treatment plan in appendix 1.

All patients must have freely given their informed consent before any trial-related procedures can be conducted.

Procedures marked '' written in italics are part of routine clinical practice and are listed only to denote that the data will be collected in the CRF

7.1 Screening

- Informed consent from patient/legal representative
- Demographic details
- Inclusion and Exclusion criteria
- HIV test
- **Hep B & Hep C screening*
- Genetic sequencing for gene variant PNPL3
- Pregnancy test^ (serum)
- **Alcohol consumption*
- Urinary ethyl glucuronide
- **Liver ultrasound (USS)*
- Past medical history including general history using the Charlson Index, liver-specific history (history of jaundice in past 3 months) and smoking history
- Prior/Concomitant medication
- **Complete physical examination, including height, weight, WHO performance status*
- **Vital signs (Temperature, systolic and diastolic blood pressure (BP), pulse rate)*
- **Laboratory tests: haematology, clinical chemistry (including electrolytes, creatinine, eGFR, LFTs [must include AST and GGT]), CRP and prothrombin time*
- **Disease scores: mDF, MELD, GAHS*
- **Evidence of GI bleed or sepsis in previous 7 days*
- **Acute kidney injury*
- **Infection/ sepsis/ SIRS screening including*
    - *Chest X-ray (CXR)*
    - *Blood cultures*
    - *Hepatic encephalopathy*
    - *Ascitic tap (in case required)*
    - *MSU*
    - *Urine culture*
- EDTA sample for host & bacterial DNA (16S)

^ Not required in post-menopausal females.

7.2 Baseline (pre-randomisation)

- Inclusion and Exclusion criteria
- Urinary ethyl glucuronide
- Concomitant medication
- **Dietary calorie and protein consumption*
- **Complete physical examination including WHO performance status*
- **Vital signs (Temperature, systolic and diastolic blood pressure (BP), pulse rate)*
- **Laboratory tests: haematology, clinical chemistry (including electrolytes, creatinine, eGFR, LFTs), CRP and prothrombin time*
- **Disease scores: mDF, MELD, GAHS*
- **Evidence of GI bleed or sepsis in previous 7 days*
- **Acute kidney injury*
- **Infection/ sepsis/ SIRS screening including*
    - *Chest X-ray (CXR)*
    - *Blood cultures (in case of fever)*
    - *Hepatic encephalopathy*
    - *Ascitic tap (in case required)*
    - *MSU*
    - *Urine culture (in case required)*
- EDTA sample for host & bacterial DNA (16S)
- Heparinised sample for PBMC (Monocyte oxidative burst + Monocyte phenotype)
- Serum CK18-M30/M65
- *Liver Biopsy at screening/pre-randomisation is Standard of Care*
- *HVPG measurement during trans-jugular biopsy procedure*
- Gene expression tissue sample
- Fibroscan
- PK/PD
- Exploratory/inflammatory BM serum
- Duration since admission to hospital
- Adverse events
- Stool and saliva sample

<u>See Schedule of Assessments and Footnote Table for timeframe allowances and full notes relating to sample collection.</u>

7.3 Evaluations During and After Treatment

Treatment Day 7, 14, 21, 28 and 42 Assessments.

- Alcohol consumption on Day 28 and 42
- Urinary ethyl glucuronide on Day 28 and 42
- Concomitant medication
- **Dietary calorie and protein consumption*

- **Complete physical examination including WHO performance (and weight on day of discharge)*
- **Vital signs (Temperature, systolic and diastolic blood pressure (BP), pulse rate)*
- **Laboratory tests: haematology, clinical chemistry (including electrolytes, creatinine, eGFR, LFTs), CRP and prothrombin time*
- **Disease scores: mDF, MELD, GAHS*
- **Lille score at Day 7*
- **Evidence of GI bleed or sepsis in previous 7 days*
- **Acute kidney injury*
- **Infection/ sepsis/ SIRS screening including*
    - *Chest X-ray (CXR)*
    - *Blood cultures (in case of fever)*
    - *Hepatic encephalopathy*
    - *Ascitic tap (in case required)*
    - *MSU*
    - *Urine culture (in case required)*
- EDTA sample for host & bacterial DNA (16S)[+]
- Heparinised sample for PBMC (Monocyte oxidative burst + Monocyte phenotype)[#]
- Serum CK18-M30/M65
- Liver Biopsy at Day 28 (incl. HVPG measurement during trans-jugular biopsy)
- Gene expression tissue sample at Day 28
- Fibroscan at Day 28
- PK/PD
- Exploratory/inflammatory BM serum
- Administration of study drug for patients presenting with AST > 2 x ULN at Day 28
- Duration of hospital stay on day of discharge
- Adverse events
- Stool and saliva sample[#]

[#] PBMC sample not required at on day 21 and 42 or at discharge.
[+] 16S DNA sample not required on day 42 or at discharge.
[#] Stool and saliva collected at (baseline and) day 14, 28 and 90.

<u>See Schedule of Assessments and Footnote Table for timeframe allowances and full notes relating to sample collection.</u>

7.4 Day 90

- **Alcohol consumption*
- Urinary ethyl glucuronide
- Pregnancy test^ (urinary)
- Concomitant medication
- Dietary calorie and protein consumption
- **Complete physical examination including weight, WHO performance status*
- **Vital signs (Temperature, systolic and diastolic blood pressure (BP), pulse rate)*

- **Laboratory tests: haematology, clinical chemistry (including electrolytes, creatinine, eGFR, LFTs), CRP and prothrombin time*
- *Disease scores: mDF, MELD, GAHS*
- **Evidence of GI bleed or sepsis in previous 7 days*
- **Acute kidney injury*
- **Infection/ sepsis/ SIRS screening including*
    - *Chest X-ray (CXR)*
    - *Blood cultures (in case of fever)*
    - *Hepatic encephalopathy*
    - *Ascitic tap (in case required)*
    - *MSU*
    - *Urine culture (in case required)*
- EDTA sample for host & bacterial DNA
- Heparinised sample for PBMC (Monocyte oxidative burst + Monocyte phenotype)
- Serum CK18-M30/M65
- Fibroscan
- PK/PD
- Exploratory/inflammatory BM serum
- Adverse events
- Stool and saliva sample

^ Not required in post-menopausal females.

See Schedule of Assessments and Footnote Table for timeframe allowances and full notes relating to sample collection.

7.5 Schedule of Assessments

Table 1 lists all of the assessments and indicates with an 'x' at which visits the assessments are performed. Patients should be seen for all visits on the designated day, or as close to it as possible – the visit window/tolerance for each visit is given below the table. At a minimum, patients will be contacted for safety evaluations during the 90 days following randomisation to the study. At this final visit the adverse event and concomitant medications should be reconciled on the CRF. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 1: Assessment schedule

	Screening	Baseline [6, 9, 11]	Day 7[4]	Day 14[4]	Day 21[4]	Day 28 [2, 11]	Day 42 [1,4]	On Discharge [10]	Day 90[3]	Unsche-duled
Informed Consent	X									
Demographic data	X									
Inclusion/Exclusion criteria	X	X								
HIV test^	X									
Pregnancy test[+]	X[5]								X	
*Hepatitis B & C serology^*	X									
Genetic sequencing (PNPLA3)	X									
Urinary ethyl glucuronide	X	X				X	X		X	
Alcohol consumption	X					X	X		X	
Duration since admission to hospital		X						X		
Medical history	X									
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	
Weight	X					X[1]		X	X	
Height	X									
Calorie and protein intake		X	X	X	X	X	X	X	X	
Randomisation		X								
IMP / placebo administration		X				X				
Prothrombin time	X	X	X	X	X	X	X	X	X	
Haematology[%]	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[%]	X	X	X	X	X	X	X	X	X	X
Serum CK18-M30/M65 sample		X	X	X	X	X	X	X	X	
DF, MELD, GAHS scores	X	X	X	X	X	X	X	X	X	
Lille score			X							
Overt GI Haemorrhage assessment[$]	X	X	X	X	X	X	X	X	X	
Acute kidney injury assessment[$]	X	X	X	X	X	X	X	X	X	
EDTA sample for DNA (16S)	X	X	X	X	X	X			X	
PBMC sample~		X	X	X		X			X	
Infection/ Sepsis/ SIRS screen	X	X	X	X	X	X	X	X	X	X
USS Liver assessment[$]	X									
Fibroscan measurement[$]		X				X			X	
Gene expression sample		X				X				
Liver biopsy (incl. HVPG measurement)*[8]		X				X				
Adverse events		X	X	X	X	X	X	X	X	
PK/PD samples in blood and ascites fluid #		X	X	X	X	X	X	X	X	
Biomarker serum		X	X	X	X	X	X	X	X	
Stool & saliva sample		X		X		X			X	

Footnotes to Schedule of Assessments

[1]	Day 42 visit	Required for patients who received second dose study drug at Day 28
[2]	Day 28 visit	A Day 28 assessment/follow up treatment/biopsy can be performed between Day 25 and Day 35
[3]	Day 90 visit	A Day 90 assessment can be performed 14 days either side of the target date
[4]	Day 7, 14, 21, 42 visits	For Day 7, 14, 21 and 42 assessments a tolerance of 48 hrs in time window either way is accepted
[5]	Screening pregnancy test	Needs to be performed as serum test
[6]	Screening and baseline samples	If baseline visit is performed within 72 hours since screening, then screening samples which repeat at baseline may be accepted on baseline date.
[7]	Screening and Baseline visit	The maximum time between screening and date baseline is 7 days
[8]	Baseline liver biopsy acceptance window	The maximum timeframe for a baseline biopsy to be accepted into the trial is 7 days before baseline visit (day of Randomisation and study drug administration).
[9]	Baseline visit	Allowance of -1 day is accepted to allow for blood results to come through for re-confirmation of eligibility before randomisation and IMP/Placebo administration. Baseline date of visit should always be the date of randomisation and IMP administration.
[10]	Discharge	Patients who are discharged during the follow-up period are not required to attend further weekly visits other than on Day 28 (when the potential second IMP dose and second biopsy is taking place), Day 42 (if second Imp dose was administered) and Day 90, which is the end of study visit. Patients due to be discharged will have the samples collected on discharge, as specified in the schedule of assessments below
[11]	Baseline; Day 28	Sample collection is pre-IMP administration.
#	Pharmacokinetic and pharmacodynamics samples - blood and ascitic fluid	In case of ascites, ascites fluid sample needs to be collected only once, at the time when patient is having ascites tapped for clinical purposes.
*	TJ liver biopsy	HVPG measurement should be collected in all TJ liver biopsies.
^	Virology screening	Results within 6 months of screening may be accepted without the need to repeat
[+]	Screening and Day 90 pregnancy tests	Pregnancy test required only for females of reproductive age only
[~]	PMBC	PBMC, which are to be sent to a central lab immediately after collection, should not be collected on Friday or Saturday in order to avoid loss of sample due to a weekend staff cover at the central laboratory. When PMBCs are posted out, an email notification must be sent, as per study Lab Manual.
[%]	Haematology & Biochemistry	± 1 day of screening date
[$]	Overt GI haemorrhage assessment, AKI assessment; Fibroscan, USS	From day of admission onwards

7.6 Assessments

7.6.1 Patient demographics/other baseline characteristics:

Patient demographic and baseline characteristic data to be collected on all patients include: age, gender, ethnicity, source of patient referral, relevant medical history/ current medical condition present before signing informed consent. Where possible diagnoses but not symptoms will be recorded.

Detailed information on the patient's vaccination status (to be recorded as part of prior medication), disease diagnosis and disease related prior medications, surgical and medical procedures that occurred before signing informed consent will also be collected.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

7.6.2 Physical exam:

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Weight and height will be measured as per the visit schedule. Physical exam includes WHO performance status.

7.6.3 WHO Performance Status

0	Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in a chair or in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair)
5	Death

7.6.4 Vital signs

Vital signs will include blood pressure (BP), pulse and body temperature measurements. Systolic and diastolic BP and radial pulse rate will be assessed after the patient has rested in the supine position for at least 3 minutes. Blood pressure should be assessed on the same arm each time measurements are taken. Body temperature should be measured by validated thermometers as commonly used by sites in the respective patient population. The same type of thermometer should be used throughout the study.

7.6.5 Liver biopsy

A liver biopsy is required at baseline visit prior to randomization and on day 28. This may be obtained via a transcutaneous or transjugular route depending on the patient's coagulation status and local expertise. Additionally, where a transjugular liver biopsy is performed, HVPG measurements will also be obtained. The liver biopsy is performed under local anaesthetic and requires the use of X-rays to guide the position of the needle that is inserted to take samples. Two biopsy specimens will be obtained with each liver biopsy; one for histology and one, snap frozen, for gene expression analysis.

All histology samples will be read and scored locally as per usual routine, as well as centrally by Prof Goldin at Imperial. Sites should use the widest gauge needle available for biopsy collection. Depending on the size of the needle, up to six passes may be performed; aggregate length of greater than 3cms is necessary and preferably (but not necessarily) obtained in one pass. The sample is to be used for:

a) Local histology assessment to confirm AH eligibility at baseline and for day 28 comparisons

b) At the time of liver sample collection, at least 3 and preferably 6 unstained slides (or block) should be prepared for central histology assessment for calculation of primary/secondary outcomes

c) Snap-frozen sample for gene expression analysis, which is to be prepared from the remaining sample and with at least one or two cores present. The snap-frozen sample should be stored frozen in liquid nitrogen (or at -80) in local sites until batch shipment is arranged at the end of the study.

The prepared unstained slides, together with residual formalin fixed paraffin embedded block should be sent to the central laboratory at Imperial College for central histology assessment. When samples are posted, a notification should be sent to Isaiah@imperial.ac.uk and Prof Goldin – please refer to the laboratory manual for more information.

There should be an H and E (hematoxylin and eosin) and Sirius Red stained sample to enable the local pathologist to confirm the presence of steatohepatitis and 3-6 unstained slides for central lab analysis, which will stained and digitalized and either returned to the referring sites (if requested by local pathology lab) or stored centrally at Imperial's Tissue Bank. Any remaining material will be used for biomarker analysis.

Biopsies will be assessed initially to confirm that all features of alcoholic hepatitis are present (based on locally histology). The primary endpoint, histological improvement will be measured in the central laboratory and is defined as a reduction in lobular inflammation (regardless of cell type). It will be read by one pathologist, who is blinded with regard to histology slide chronology, type of therapy, and patient clinical status. In addition a sensitivity analysis will be employed by having the histology slide read independently by 2 readers, who are blinded with regard to histology slide chronology, type of therapy, and patient clinical status. Histological improvement will be assessed by direct comparison of pre and post treatment biopsies and recorded as a binary answer, either there is less inflammation present in the biopsy or not. This method of blind biopsy comparison has been used previously (15). Secondary endpoints - AHHS and NAS score- will be measured and compared between active treatment and placebo treatment groups. Further the specimens will be stained and immunohistological findings will be assessed and compared between treatment groups.

7.6.6 Laboratory tests

The **haematology** panel will include: Hemoglobin, white blood cell count with differential including lymphocytes, monocytes, neutrophils and platelet count will be measured. Absolute Neutrophil Count (ANC) will be determined by the laboratory. Prothrombin time will be assessed as well.
The **clinical chemistry** panel will include: alkaline phosphatase, total bilirubin, total cholesterol, LDLC, HDL-C, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, sodium, potassium, lactate dehydrogenase (LDH), triglycerides, transferrin and CRP; The estimated creatinine clearance will be calculated using the Cockcroft-Gault equation for each creatinine measurement. This will require the information on patient's age, sex, weight, height and serum creatinine levels.
Urine samples will be assessed: Urinalysis (MSU) + assessment for urinary tract infection (UTI); urine white blood cell count with either positive urine gram stain or culture. Urinary ethyl glucuronide will be assessed to control patients' abstinence.

Standard laboratory assessments will be used to determine:

Maddrey Discriminant function (mDF)

mDF = 4.6 x (Prothrombin time ($PT_{PATIENT}$ – $PT_{CONTROL}$) + Serum Bilirubin (µmol/l) / 17.1
($PT_{CONTROL}$ is defined as the mean value at each site; this mean value may be updated on a weekly or monthly basis).

Model for End-Stage Liver Disease (MELD)

MELD Score = 10 * ((0.957 * ln(Creatinine)) + (0.378 * ln(Bilirubin)) + (1.12 * ln(INR))) + 6.43
MELD scores should be UNOS-modified (United Network of Organ Sharing). It is recommended that mdcalc.com (MELD Score - Original, Pre-2016, Model for End-Stage Liver Disease) is used to calculate scores. The Pre-2016 UNOS modification is as follows:

- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0 mg/dL
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8 a value of 1.0 is used) to prevent subtraction from any of the three factors, since the natural logarithm of a positive number below 1 (greater than 0 and less than 1) yields a negative value.

NOTE: Pre-2016 MELD does not include serum sodium level. Values used for MELD calculations must be noted in eCRF.

GAHS score

Will be calculated after Forrest et al., 2007

Score given	1	2	3
Age	<50	⩾50	–
WCC (10^9/l)	<15	⩾15	–
Urea (mmol/l)	<5	⩾5	–
PT ratio or INR	<1.5	1.5–2.0	>2.0
Bilirubin (µmol/l)	<125	125–250	>250

Lille score

Lille score is calculated as Exp(-R)/[1+exp(-R)]
where
R = [3.19 - (0.101*age in years)] + (1.47*albumin at baseline in g/dL) + [0.28215* (bilirubin at baseline - bilirubin at Day 7 in mg/dL)] - [0.206 * (if creatinine>=1.3 mg/dL at baseline)] - [0.11115*bilirubin baseline in mg/dL] - (0.0096*Prothrombin Time in seconds at baseline)

Change in bilirubin after 7 days

A fall of > 25% will be taken to be a clinically significant fall

Incidence of acute kidney injury

Defined as

- Rise in blood creatinine by 26 micromoles per liter or more within 48 hours
- Rise in blood creatinine over time by 50% or more within the past 7 days
- Urine output less than 0.5ml per kg per hour for more than 6 hours

SIRS

Recommendations of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference; Presence of 2 or more criteria out of following:

- **Temperature** < 36 ºC or > 38 ºC
- **Heart rate** > 90 beats/minute
- **Respiratory rate** > 20 breaths/minute or venous pCO2 <32 mmHg
- **Leukocyte count** > 12,000/mm3 or < 4,000/mm3 or band forms > 10%

7.6.7 Infection screening

Diagnosis of infection is based on the criteria outlined by Bajaj and colleagues:
1) spontaneous bacteremia: positive blood cultures without a source of infection; 2) SBP: ascitic fluid polymorphonuclear cells >250/µL; 3) lower respiratory tract infections: new pulmonary infiltrate in the presence of: i) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain) with ii) at least one finding on auscultation (rales or crepitation) or one sign of infection (core body temperature >38°C or less than 36°C, shivering, or leukocyte count >10,000/mm3 or <4,000/mm3) in the absence of antibiotics; 4) *Clostridium difficile* Infection: diarrhea with a positive *C. difficile* assay; 5) bacterial entero-colitis: diarrhea or dysentery with a positive stool culture for *Salmonella, Shigella, Yersinia, Campylobacter*, or pathogenic *E. coli;* 6) soft-tissue/skin Infection: fever with cellulitis; 7) urinary tract infection (UTI): urine white blood cell >15/high-power field with either positive urine gram stain or culture; 8) intra-abdominal infections: diverticulitis, appendicitis, cholangitis, etc.; 9) other infections not covered above; and 10) fungal infections as a separate category. Infection screening will involve chest radiography, urinalysis (mid-stream urine (MSU) culture if urinalysis positive), ascitic tap (if ascites present) and blood cultures if pyrexial.

7.6.8 Monocyte oxidative burst

Monocyte oxidative burst is assessed *ex vivo* using the Phagoburst™ kit according to the manufacturers' instructions (Glycotrope, Germany). 100µl whole blood is incubated with $2x10^7$ *E. coli* for 20 minutes at both 37°C (test condition) and on ice (control condition). 20µl 1,2,3-dihydrorhodamine (1,2,3DHR) is then added for a further 20 minutes at 37°C and the oxidation to rhodamine within $CD14^+$ monocytes is measured by flow cytometry.

7.6.9 Changes in plasma bacterial DNA

DNA extraction is performed on 400µl of blood using Qiagen (Hilden, Germany) QIAamp DNA Mini kits under aseptic conditions. The quantity of 16S ribosomal bacterial DNA (bDNA) is determined and measured by real-time polymerase chain reaction (qPCR). Primers directed against the V7-V9 variable region of the 16S gene (forward: RW01; 5'->3' sequence AACTGGAGGAAGGTGGGGAT, reverse: DG74.R; 5'->3' sequence AGGAGGTGATCCAACCGCA) are combined with a custom fluorescent probe (6-FAM- TACAAGGCCCGGGAACGTATTCACCG-TAMRA; Life Technologies, Carlsbad, USA) at final concentrations of 0.5 µM and 0.25µM, respectively. This is combined with 10ul of Taqman Gene Expression mix (Applied Biosceiences, Foster City, USA), 4ul of extracted DNA and PCR-grade water to give a final reaction volume of 20ul. PCR is performed on a StepOne Plus PCR machine (Applied Biosciences, Foster City, USA) with hot-start activation (2 minutes at 50°C, 10 minutes at 95°C) and 40 reaction cycles (15 seconds at 95°C, 30 seconds at 60°C and 60 seconds at 72°C to collect fluorescence). Serial 10-fold dilutions of *E.coli* DNA (0.08 ng/µl to 0.000008 ng/µl) and a negative control are run to generate a standard curve.

7.6.10 Changes in transient elastography scores

Fibroscan will be used to obtain elastography scores at baseline, Day 28 and Day 90. Changes in scores from baseline will be compared between the two treatment groups.

7.6.11 Canakinumab sample collection

Blood samples (1 mL) will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 rpm for 10 minutes. Serum samples will be split into 2 aliquots (polypropylene tubes) and then stored (within 30 min of preparation) at -20°C or -70°C (approximately) prior to shipment. Canakinumab is stable in serum samples for 12 months at -20°C or at -70°C. All samples will be given a unique sample number. The actual sample collection date and time will be entered on the PK blood collection page of the CRF. Sampling problems will be commented in the CRFs.

7.6.12 Pharmacodynamic assessments

1. Total IL-1β assessment: Pharmacodynamic assessments (IL-1β concentrations) will be assessed in serum as per the Assessment Schedule, pre-dose (trough levels).
2. Pharmacodynamic sample collection and processing: Blood samples (1.5 mL) will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 rpm for 10 minutes. Serum samples will be split into 2 aliquots (polypropylene tubes) and then stored (within 30 min. of preparation) at -20°C or -70°C (approximately) prior to shipment. IL-1β is stable in serum samples for 12 months at -20°C or -70°C.

7.6.13 Other assessments

1. HIV test: An HIV test will be performed at screening (HIV test conducted within 6 months of screening may be accepted). Patients with a known infection with HIV at screening or randomisation will be excluded from participating in the trial.
2. Pregnancy Test (in females of reproductive age): A pregnancy test will be performed as a serum test at screening and pregnant patients excluded from participation. A urinary pregnancy test will be performed at day 90. If a subject or his partner becomes pregnant whilst taking part in the trial they will be followed up according to Section 9.6.
3. Hepatitis B & C Serology: Serology will be undertaken at screening (Hep B/C result performed within 6 months of screening may be accepted) and evidence of chronic viral hepatitis (B or C) will exclude the patient from participation.
4. Genetic sequencing: Genetic sequencing will be carried out at screening.
5. Alcohol consumption: Details on alcohol consumption will be collected at screening, day 28, day 42 and day 90.
6. Calorie and protein intake: Details on calorie and protein intake will be collected at all visits apart from screening.
7. Liver ultrasound (USS): A liver ultrasound will take place at screening only and is part of Standard of Care for the patients.
8. Stool and saliva samples will be collected at baseline and days 14, 28 and 90.
9. Exploratory BM serum to be collected (2 x 500ul) at baseline and all subsequent visits.

8 Statistical Considerations

8.1 Power calculation

It is estimated that improvement of histological alcoholic steatohepatitis will occur in 40% of patients treated with placebo and 80% of patients treated with Canakinumab. A trial with 80% power to detect a difference at the $P < 0.05$ threshold would require 23 patients in each arm, 46 in total. Assuming a drop-out rate of 10%, we will recruit 52 patients in total (26 patients per group). Patients will be included and randomized and treated before histology result is available. If the histology is negative, then patient will be withdrawn and another patient recruited. Additionally, to meet the study power we will continue recruitment until we have paired biopsies in 48 patients.

8.2 Statistical Analysis Plan

A statistical analysis plan will be drafted prior to the first data extraction.

The primary analysis will estimate the difference between the groups in proportion of patients with improvement of the disease using a chi square test. Logistic regression, adjusted for histology baseline values, will investigate the relationship between disease histological improvement and other independent variables including the baseline severity (MELD score), age and gender. All statistical tests will be two-tailed with a 5% significance level. Further details of the planned analysis of the

secondary outcomes and methods for dealing with missing data will be given in the Statistical Analysis Plan.

There is no planned interim or subgroup analyses. Any deviations from the statistical analysis plan will be dealt with in accordance with Imperial Clinical Trial Unit's statistical Standard Operating Procedures.

9. Assessment of Safety

9.1 Definitions of Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 (UK), as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE):
Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR):
Any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions.

Serious Adverse Event (SAE):
Any adverse event that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Is medically significant

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Hospitalisation means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
The term 'medically significant' is defined as an event that jeopardises the patient or may require medical or surgical intervention.

Serious Adverse Reaction (SAR)
A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject or withdrawn from the subject.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) i.e. is unexpected as per Appendix 2.

9.2 Recording Adverse Events

The Imperial Clinical Trials Unit (ICTU) has been delegated by the Sponsor to undertake all sponsor duties relating to pharmacovigilance.
All non-serious AR/AEs, whether expected or not, should be recorded in the adverse event section of the relevant Case Report Form. All new SAEs regardless of causality, occurring after the patient has signed informed consent and until the last patient visit must be reported to ICTU within 24 hours of learning of its occurrence and must also be recorded on Adverse Event Case Report Form (AE CRF) within the InForm database

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted according to the study specific reporting procedures.
An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.
At each contact with the subject during the treatment period, the Investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information elicited should be recorded immediately in the source document, and the AE CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document using the event terms and grading given in the relevant eCRF pages.
The clinical course of each event should be followed until resolution or stabilisation.

9.2.1 Exclusions to Adverse Event Recording Requirements

Many clinical events are likely to occur which would ordinarily need recording as adverse events. However, events that are recognised and expected complications of the condition (listed in Appendix 1) are exempt from the normal recording procedures, unless they become 'serious' by definition (section 9.1).

9.3 Pre-existing Conditions

A pre-existing condition should not be reported as an AE unless the condition worsens during the trial. The condition, however, must be reported in the Medical History Form.

9.4 Reporting of Serious Adverse Events (SAEs, SARs and SUSARs)

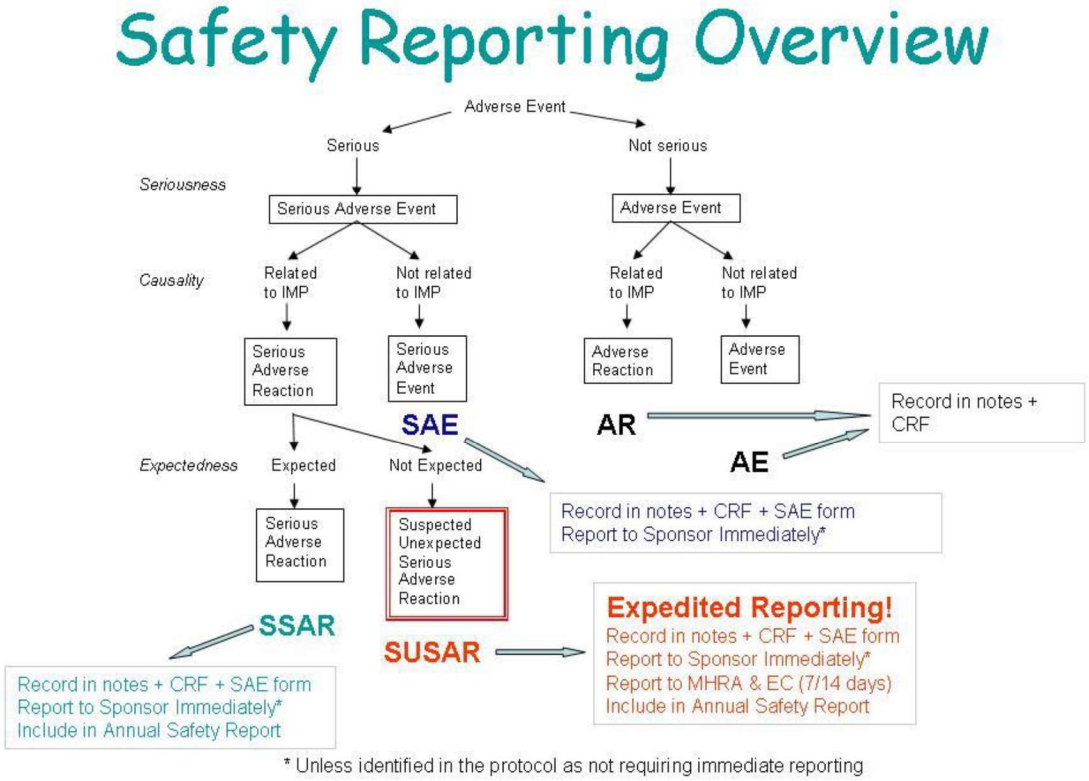
All serious adverse events and reactions must be reported immediately by the Principal Investigator or delegate to the ICTU. In turn, ICTU will inform the Sponsor (within 24hrs of becoming aware of the event) and the Funder (as soon as becoming aware and not more than 15 calendar days).

Summary of product characteristics (SmPC) should be used as the Reference Safety Information. Serious adverse events expected to occur with Canakinumab should be recorded on an SAE/SUSAR Report Form on InForm and the ICTU/Sponsor informed within 24 hours. A submitted SAE form on InForm will automatically send alert emails to the Chief Investigator, the Project Manager and the Sponsor. Adverse Events considered to be expected for Reporting purposes are detailed in Appendix

2. These reports should be followed by further detailed SAE/SUSAR Report Forms until resolution of the event.

N.B. The SAE/SUSAR Report Form should be completed as though the patients were taking active form of IMP, even though all parties are blinded.

Study specific SAE reporting instructions will be available and provide full detail on reporting requirements. An overview of the Safety Reporting Process is detailed in the diagram below.



Contact details for reporting SAEs and SUSARs
Follow the study specific procedure for reporting SAEs and SUSARs and complete an SAE form & submit to the Study Coordination Centre (ICTU) as soon as possible (within 24 hrs). SAE forms are available on the InForm eCRF system.

ICTU Trial Manager: isaiah@imperial.ac.uk

Sponsor's contact: jrco.ctimp.team@imperial.ac.uk (contact only by ICTU)
Funder's contact: ct_processing.gbfr@novartis.com (contact only by ICTU)

9.5 Post-treatment SAEs & Follow-Up

The reporting requirement for SAEs affecting subjects applies for all events occurring up to the patients last study visit.

All unresolved adverse events (serious and non-serious) should be followed up by the Investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the Investigator should document any ongoing AEs/SAEs, and these should be managed as per local practice.

The Investigator should notify the ICTU of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

9.6 Pregnancy

If a subject or his partner becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP, the Investigator must ensure that the subject and the subject's healthcare professional are aware that follow-up information is required on the outcome of the pregnancy. If the subject leaves the area, their new healthcare professional should also be informed. Each pregnancy occurring while the patient is on study treatment must be reported to ICTU within 24 hours of learning of its occurrence. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment.

Study treatment for pregnant participants must be discontinued immediately.

Contraception

The following methods of contraception are accepted:

(i) Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

(ii) Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

(iii) Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.

(iv) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.

(v) Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Reliable contraception should be maintained throughout the study.

9.7 Evaluation of SAEs

The Principal Investigator should ensure that each SAE is identified and assessed for the likelihood of the event being a response to an IMP. Once reported to the ICTU, the event will also undergo a review of the evaluation of seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed and those that are SUSARs, identified and reported to the UK regulatory authority (MHRA).
In the event of a possible SUSAR, the Clinical Reviewer may contact the local PI to discuss the causality assessment.

9.7.1 Causality of AEs

The relationship of an AE to the IMP should be graded by the investigator responsible for the care of the participant as follows:

Definitely related:

- Starts a reasonable time after the study drug administration;
- Stops/improves when the study drug has been stopped;
- Can reasonably be explained by known characteristics of the study drug.

Probably related:

- Starts a reasonable time after the study drug administration;
- Stops/improves when the study drug has been stopped;
- Cannot be reasonably explained by known characteristics of the patient's clinical state.

Possibly related:

- Starts a reasonable time after the study drug administration but could have been produced by the subject's clinical state or other modes of therapy administered to the patient.

Unlikely to be related:

- The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.

Unrelated:

- The AE is definitely not associated with the study drug administered.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.
In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

9.8 Expedited Reporting

The ICTU will report SUSARs to the regulatory authorities (MHRA and the relevant ethics committees) as follows:

- SUSARs which are fatal or life-threatening will be reported within 7 calendar days of the CTU first becoming aware of the reaction. Any additional relevant information must be reported within a further 8 days (i.e. by day 15).
- SUSARs that are not fatal or life-threatening will be reported within 15 days of the CTU first becoming aware of the reaction.

9.9 Annual reporting of Serious Adverse Events

Annual Safety reports will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with regulatory requirements.
Novartis Pharmaceuticals UK Limited will be responsible for submission of the Development Safety Update Report (DSUR). The Sponsor (via ICTU) will provide information required by Novartis to include the study in the Novartis DSUR in an integrated manner. Novartis will provide a copy of the submitted DSUR to ICTU for filing in the study TMF.

9.10 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

10. Patient Loss from Study Post-Randomisation

The PI will make every reasonable effort to keep each patient on study.

10.1 Patients lost

The following 3 sub-sections describe patients that will be regarded as having been lost from the study, i.e. no further follow-up visits will take place and no further data will be collected;

10.1.1 Withdrawn

Patients who withdraw their consent at any point in the study fall into one of two categories. Site staff should ascertain which category a patient wishes to be in at the point of withdrawal;

a) Those who allow their data (collected up to the point of withdrawal) to be used

OR

b) Those who do not allow the use of any of their data collected prior to withdrawal.

10.1.2 Lost to follow-up

These are patients who do not attend a follow-up assessment after site staff have attempted to contact the patient at least twice, e.g. by telephone.
As these patients have not withdrawn their consent, the data already collected for them may be used and therefore needs returning in the usual manner.

10.1.3 Patients that have died

These patients have not withdrawn their consent and therefore the data already collected for them may be used.

10.2 Patients not lost

Patients that fall into one or more of the following categories, which are indications for treatment discontinuation, are not considered as withdrawn or lost from the study. <u>They should continue to attend all follow-up study assessments as per protocol</u>, unless they subsequently fall into one of the categories listed in Section 10.1;

- Patients who ask to stop study treatment
- Pregnancy
- Steroid psychosis or persisting psychotic symptoms for more than 7 days, that cannot be explained by alcohol withdrawal
- Any event which in the judgement of the PI makes further study treatment inadvisable
- SAE requiring discontinuation of treatment.

Stopping treatment or having a prolonged/numerous treatment gaps, for whatever reason, does not mean the patients are withdrawn or lost from the study, they should still continue to attend <u>all</u> follow-up assessments. If the screening biopsy histology is negative then the patient will be discontinued from the study, will not undergo any further treatment or the second biopsy but will be followed-up for safety assessment for 28 days, as per assessment schedule.

11. END OF THE CLINICAL TRIAL

The recruitment period of the trial will be stopped when:

- The stated number of patients to be recruited and randomised is reached, or the trial is stopped for another reason, e.g. by the funding body or the regulatory authority.

The active treatment phase will be completed:

- 28 days after start of treatment of the last patient randomised.

The end of the trial is defined as:

- The end of the trial will occur when the final participant has completed the last study visit and all study data have been captured on the study database.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor and the Investigators will ensure that adequate consideration is given to the protection of the patient's interests.

12 REGULATORY, ETHICAL AND LEGAL ISSUES

12.1 Treatment

12.1.1 Investigational Medicinal Product Details

Drug Name	Dosage	Description
Canakinumab	3mg Canakinumab per kg.	Canakinumab will be made up by dilution in 100ml 5% dextrose and administered intravenously
Placebo	100ml 5% Dextrose	Dextrose alone will be administered intravenously

12.1.2 Labelling, storage and dispensing

IMP (Canakinumab) is manufactured by Novartis according to Good Manufacturing Practices (GMP) and will be packaged/stored/transported as per requirements specified in SmPC. IMP (Canakinumab) will be provided by Novartis for the trial. Labelling, storage and distribution of drug to sites will be carried out by a company independent of the funder and Sponsor. They will be contracted by Imperial College to receive the study drug from Novartis, to label and repackage the drug for clinical trial use, for final QP release and to distribute the drugs to sites as requested by the trial team.

A single dose of 3 mg/kg Canakinumab or identical placebo will be administered intravenously at baseline (Day 1). Canakinumab will be made up by dilution in 100 ml 5% Dextrose by an unblinded research personnel at each site.

The trial team at each site will randomise each new patient on the study eCRF/InForm database. This will provide a code to the trial team for that patient (that does not identify the treatment allocation) and the code will be used by the site pharmacy to identify if the patient will have active drug or placebo based on a pre specified randomisation list that pharmacy will be provided with. This will be double checked by a second pharmacist against the code on InForm and the code on the randomisation list to reduce the risk of error. The pharmacist will then either prepare the i.v. infusion bag at trial pharmacy or dispense the IMP+Placebo/Placebo-only to a designated unblinded research member who will then make up the i.v. infusion bag and label it with this code – this will be double checked by another unblinded member of the research team before administration by a blinded nurse/doctor.
Patients with moderate to severe ascites should undergo large volume paracentesis prior to administration of Canakinumab.
Patients with AST >2 x ULN on Day 28 will receive a second dose of 3 mg/kg study drug administered i.v. on Day 28:

- Patients who received placebo on baseline will receive placebo.
- Patients who received canakinumab on baseline will receive canakinumab.

Overdose of IMP should be reported immediately and recorded as a protocol deviation and AE on the InForm database and the patient followed up. Reported experience with overdose of IMP is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

12.1.3 Accountability

Hospital pharmacies will be responsible for recording study drugs dispensed. Preparation of all drug solution for injection will be recorded on the study drug accountability logs, and drug administration in the patient's medical file. The study drug stores will include a sheet recording the use of each vial of active drug. Used vials will be checked for reconciliation by the Trial Monitor at monitoring visits before destruction. At the end of the study any remaining unused vials of drug will be destroyed.

12.2 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

12.3 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 R2 guidelines).

12.4 Independent Ethics Committee Approval

(vi) Initial Approval

Prior to the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form and any other written information that will be provided to the subjects.

(vii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

(iii) Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements.

(iv) Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

12.5 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) will be obtained prior to the start of the study. In addition, the MHRA will approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

12.6 HRA Approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.
The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

12.7 Insurance and Indemnity

Imperial College London, the Sponsor of the trial has civil liability insurance, which covers this study in all participating centres. Imperial College London also holds negligent harm and non-negligent harm insurance policies which apply to this study.

12.8 Trial Registration

The study will be registered on a trial database (clinicaltrials.gov and/or ISRCTN) in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

12.9 Informed Consent

Informed consent will be obtained from all participants or their legal representative. Further details are given in Section 4.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

12.10 Non-compliance and serious breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.
A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

12.11 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Patient Information Sheet and Informed Consent. A copy of the letter should be filed in research record for the patient at sites.

12.12 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and RECs.

12.13 Data Protection

All personnel involved in the study will observe or work within the confines of the local data protection guidelines.

12.14 End of Trial

The end of the trial is defined in Section 11.

12.15 Study Documentation and Data Storage

The investigator will retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Patient files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) will be retained. Documents will be stored in such a way that they can be accessed/data retrieved at a later date.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

13 STUDY MANAGEMENT STRUCTURE

13.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, 2 independent clinicians, a lay representative (also independent), the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress. A TSC Charter will be devised to list the roles and responsibilities of the TSC members. Frequency of meetings will be defined in the Charter. The first TSC meeting to take place following the start of recruitment will be after the first 10 patients have been randomised to the study and thereafter frequency of meetings will be determined by the DMEC and TSC based on this initial data.

13.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues including recruitment and other practical aspects of the trial.
The day-to-day management of the trial will be co-ordinated through the Imperial Clinical Trials Unit and the Chief Investigator.

13.3 Data Monitoring Committee

An independent Data Monitoring and Ethical Committee (DMEC) will be set up to monitor progress, patient safety and any ethical issues involved in this trial. They will review trial progress, recruitment rates, event rates and safety data. A separate charter will be drawn up defining their exact remit and criteria for reporting to the trial steering committee. Frequency of meetings will be defined in the Charter. The first DMEC meeting to take place following the start of recruitment will be after the first 10 patients have been randomised to the study and thereafter frequency of meetings will be determined by the DMEC and TSC based on this initial data.

13.4 Early Discontinuation of the Study

If, in the opinion of the Chief Investigator, clinical events indicate that it is not justifiable to continue the trial, the Trial Steering Committee may terminate the trial following consultation with the Sponsor.

13.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager/Operations Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study. The risk assessment will also provide guidance for risk reduction activities so where risks are identified prior to the start of the study they can be managed and identified early on and measures put in place to reduce the risk.

13.6 Monitoring

The study will be monitored periodically by a trial monitor to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.
A monitoring plan will be devised based on risk analysis and described in detail in the monitoring manual. A Trial Monitor will visit all sites and facilities where the trial will take place to ensure compliance with the protocol, GCP and local regulatory compliance.
Initiation visits will be completed at all trial sites prior to the recruitment of participants, and will consist of review of protocol and trial documents, training with respect to trial procedures (informed consent, SAE reporting, inclusion and exclusion criteria), review of recruitment strategy, review of site facilities and equipment, essential document receipt, collection and filing, and archiving and inspection.
The investigators will allow the monitors to:

- inspect the site, the facilities, IMP management and materials used for the trial
- meet all members of the team involved in the trial, and ensure all staff working on the trial are experienced and appropriately trained, and have access to review all of the documents relevant to the trial
- have access to the electronic case record forms and source data
- discuss with the investigator and site staff trial progress and any issues on a regular basis

The monitor will ensure that;

- all participant records will be inspected for confirmation of existence, eligibility and informed consent
- there is adherence to the protocol, including consistency with inclusion/exclusion criteria
- there is GCP and regulatory compliance
- Trial Documentation is complete and up to date (e.g. correct versions of documents being used, source data captured) and relevant documents are collected for the Trial Master File (TMF)
- The eCRFs have been completed correctly and accurately, and all entries correspond to data captured in source documents

At the end of the trial, close out visits will be performed by the monitor after the final participant visit has been completed.
Each investigator will also be notified that an audit or inspection may be carried out - by the sponsor, sponsor's representatives or the host institution, or regulatory authorities - at any time, before, during or after the end of the trial. The investigator must allow the representatives of the audit or inspection team:

- to inspect the site, facilities and material used for the trial,
- to meet all members of his/her team involved in the trial,

to have direct access to trial data and source documents, to consult all of the documents relevant to the trial. If an Investigator is informed of an impending audit or inspection, the trial coordination centre should be notified immediately.

13.7 Quality Control and Quality Assurance

Quality Control will be performed according to Imperial Clinical Trials Unit internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

13.8 Disclosure of Data and Publication

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results before any presentations or publications are produced.
All publications and presentations relating to the study will be authorised by the Trial Management Group. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

Novartis, as study funder, will be informed of study publications as per the contract between Novartis and Imperial College.

13.9 Patient and Public Involvement (PPI)

At least one PPI representative will sit on the Trial Steering Committee and will provide input from a patient perspective at trial meetings. Representatives have reviewed and provided feedback on all of the project documents prior to the ethics and regulatory submissions and their comments have been incorporated.

13.10 Peer review

The trial has undergone peer review as part of the funding application to Novartis. The trial has also been reviewed by senior members of ICTU as part of the Collaborations process.

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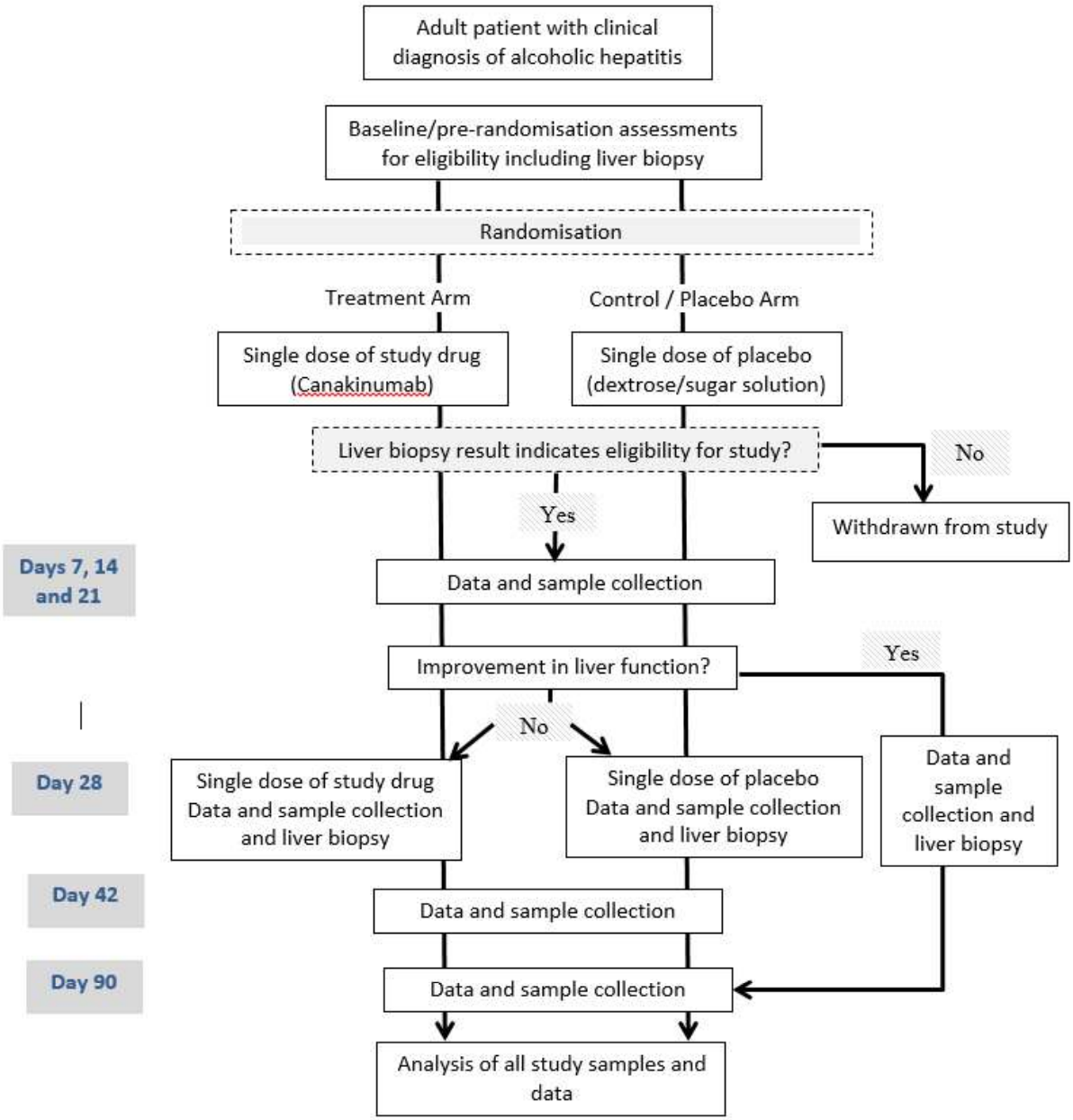
APPENDIX 1
Summary of treatment plan for the Isaiah study



APPENDIX 2
Protocol Exempt Adverse Events

Neurological
- Fits or seizures
- Confusion
- Wernicke's encephalopathy
- Korsakoff's dementia
- Coma
- Peripheral neuropathy
- Proximal myopathy
- Delirium tremens
- Tremor

Cardiac
- Arrhythmias
- Hypotension
- Hypertension
- Cardiac failure
- Tachycardia
- Peripheral Oedema

Respiratory
- Hydrothorax
- ARDS

Renal
- Acute renal failure
- Hypomagnesaemia
- Hypophosphataemia
- Hyponatraemia
- Hypokalaemia
- Hypoglycaemia

Gastrointestinal
- Vomiting
- Haematemesis
- Melaena
- Chronic pancreatitis

Dermatological
- Bruising
- Psoriasis

Haematological
- Anaemia
- Acanthocytosis
- Coagulopathy

Gynaecological
- Menstrual irregularity
- Amenorrhea
- Menorrhagia

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: (**Isaiah**) IL-1 Signal Inhibition in Alcoholic Hepatitis

Protocol Number: Protocol number: 17SM4152

Signed: _____

Mark Thursz
Professor of Hepatology
Imperial College, London.
9th September 2020

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: (**Isaiah**) IL-1 Signal Inhibition in Alcoholic Hepatitis

Protocol Number: Protocol number: 17SM4152

Signed: Keith Boland Digitally signed by Keith Boland Date: 2020.09.14 11:27:44 +01'00'

_____
Joint Research Compliance Office
Imperial College, London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: (**Isaiah**) IL-1 Signal Inhibition in Alcoholic Hepatitis

Protocol Number: Protocol number: 17SM4152

Signed: Francesca Fiorentino Digitally signed by Francesca Fiorentino Date: 2020.09.14 16:48:18 +01'00'

Dr Francesca Fiorentino
Senior Statistician
Imperial College, London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: (**Isaiah**) IL-1 Signal Inhibition in Alcoholic Hepatitis

Protocol Number: Protocol number: 17SM4152

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____