A Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis.

Protocol Number # DS102A-05-AH1

Version 6.0
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Sponsor:

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SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to local legal and regulatory requirements, applicable country regulations, the International Conference on Harmonization (ICH) Good Clinical Practices Guidelines and the Declaration of Helsinki.

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Germany

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Dr Markus Weissbach
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CHIEF INVESTIGATOR:

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Investigator name: _____

Signature: _____ **Date:** _____

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Independent Ethics Committee (IEC) procedures, instructions from Afimmune representatives, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practices Guidelines (GCP), and national/local regulations governing the conduct of clinical studies.

The signature also confirms that the Investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigators name, address, qualifications and extent of involvement.

PROTOCOL SYNOPSIS

STUDY TITLE:	A Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis.
SHORT TITLE:	Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis.
PHASE:	II
STUDY DURATION:	90 days (treatment duration: 28 days)
INVESTIGATIONAL PRODUCT:	DS102 Capsule Placebo (paraffin oil)
OBJECTIVES:	*Efficacy Objective:* • To compare the efficacy of orally administered DS102 capsules versus placebo, in the treatment of adult patients with severe acute decompensated Alcoholic Hepatitis (AH). *Safety Objective:* • To compare the safety of orally administered DS102 capsules versus placebo, in the treatment of adult patients with severe acute decompensated AH. *Pharmacokinetic Objective:* • To evaluate the pharmacokinetics (PK) of 15(S)-HEPE following orally administered DS102 capsules, in six adult patients with AH in the initial pilot phase of the study, followed by trough level assessment of 15(S)-HEPE in all study participants.
ENDPOINTS:	*Primary Endpoint* • % Change in MELD score from baseline to Day 28 *Secondary Endpoints* • Change in total bilirubin from baseline to Day 7, 14, 21 and 28 • Proportion of patients showing a 25% reduction of bilirubin at day 7, 14, 21, and 28. • Change in serum cytokeratin 18-M30/M65 from baseline to Day 7, 14, 21 and 28 • Change in AST levels from Baseline to Day 7, 14, 21 and 28 • Change in AST:ALT ratio from Baseline to Day 7, 14, 21, 28 • Change in MDF score from baseline to Day 7, 14, 21 and 28. • Proportion of patients showing a 25% reduction in MELD score from baseline to Day 7, 14, 21 and 28 • Change in MELD score from baseline to Day 7, 14 and 21 • Change in modified Sequential Organ Failure Assessment (m-SOFA) from baseline to Day 7, 14, 21 and 28 • Proportion of patients with a 2-point worsening of m-SOFA

	from baseline to Day 7, 14, 21 and 28. • Change in hepatic encephalopathy as assessed by West Haven criteria, from baseline at Day 7, 14, 21 and 28 • Incidence of acute kidney injury over 28 days (defined by requiring medicinal or mechanical support) • Incidence of variceal haemorrhage, ascites or hepatic encephalopathy over 28 days *Exploratory Endpoints* • Survival at day 7, 14, 21, 28 and 90 using Kaplan-Meier Plot • Change in Gamma Glutamyl Transferase (GT) from Baseline to Day 7, 14, 21 and 28 • Change in ALT from Baseline to Day 7, 14, 21 and 28. • Change in Child Pugh score from baseline to Day 7, 14, 21 and 28 • Change in APACHE-II score from baseline to Day 7, 14 and 28 • Change in Lille score from baseline to Day 7, 14 and 28 *Safety Endpoints* • Treatment emergent (S)AE and SUSARs
STUDY DESIGN:	This is a multicentre, double blind, placebo controlled, 2-arm parallel group comparison (Phase 2) study, preceded by an open label pilot phase, in which six patients will receive open label treatment with DS102 1000mg twice daily within 30 minutes after a meal for 28 days. After the pilot phase, all patients will either receive 2000mg DS102 (1000mg BD) or placebo (BD), in addition to standard of care therapy, within 30 minutes after a meal for 28 days in the two treatment groups of 60 patients each. Before randomisation each patient will undergo a screening period of up to five days after signing informed consent.
TOTAL NUMBER OF RANDOMISED PATIENTS:	Approximately 126 male or female patients, aged 18 years or older, with evident severe acute decompensated AH will be included in this study.
STUDY POPULATION:	
INCLUSION CRITERIA:	1. Male or female patients aged 18 years and older 2. Total bilirubin of ≥ 5 mg/dl (85µmol/l) 3. Patients with definite or probable AH 4. MELD ≥18 at baseline visit 5. Maddrey DF ≥32 at baseline visit 6. Aspartate aminotransferase (AST) >50 U/L 7. Aspartate aminotransferase/alanine aminotransferase (AST:ALT) ratio > 1.5

	8. Female patients, or female partners of male patients, of child bearing potential must use highly effective birth control methods or have a sterilised partner for the duration of the study. Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include intrauterine device or sexual abstinence. Note: A woman is considered of child bearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Note: Hormonal contraceptives are contraindicated in patients with severe hepatic diseases and are not acceptable as a birth control method in this study. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject 9. Patient and/or legally authorised representative must provide Informed consent 10. Able to swallow the provided study medication 11. Not eligible for liver transplant during this hospitalisation

EXCLUSION CRITERIA:	1. Pregnant or lactating females. 2. Spontaneous liver function improvement defined by decrease of bilirubin level and MDF of >10% within 5 days of hospital admission 3. Grade 4 hepatic encephalopathy (West Haven Criteria) 4. Type 1 hepatorenal syndrome (HRS) or a serum creatinine >2 x ULN or requirement for haemodialysis 5. History of hypersensitivity to any substance in DS102 capsules or placebo capsules. 6. Alcohol abstinence of >6 weeks prior to screening 7. Duration of clinically apparent jaundice >3 months prior to baseline 8. Other causes of liver disease including: a. Evidence of chronic viral hepatitis (Hepatitis B DNA positive or HCV RNA positive) b. Biliary obstruction c. Hepatocellular carcinoma d. Wilsons disease e. Budd Chiari Syndrome f. Non-alcoholic fatty liver disease 9. History of or active non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas). 10. Previous entry into the study 11. AST >400 U/L or ALT >270 U/L 12. Treatment with any experimental drug within 30 days prior to Day 0 visit (Baseline), or 5 half-lives (whichever is longer). 13. Patients who have used dietary supplements rich in omega-3 or omega-6 fatty acids in the four weeks prior to baseline 14. Patients dependent on inotropic support (adrenaline or noradrenaline), including Terlipressin 15. Active variceal haemorrhage on this admission requiring more than 2 units of blood to maintain hemoglobin level within 48 h 16. Untreated or unresolved sepsis 17. Presence of refractory ascites 18. Patients with known cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction (within last 6 weeks)

	or severe cardiac arrhythmias (not including atrial fibrillation) 19. Known infection with HIV at screening 20. Significant systemic or major illnesses other than liver disease that, in the opinion of the investigator, would preclude or interfere with treatment with DS102 and/or adequate follow up 21. Previous liver transplantation
CONCOMITANT MEDICATION	Patients requiring the need for treatment due to a comorbidity during the trial will be treated using the standards of care for that indication e.g. diabetes, cholesterol, infection management, etc.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:	DS102 will be provided in a capsule, containing 500mg of 15(S)-HEPE EE with 5% w/w of colloidal silicon dioxide as viscosity modifier. Placebo (liquid paraffin) will be provided in a capsule containing equivalent fill weight of liquid paraffin. In the open label pilot phase 2000mg (1000mg BD) will be orally administered within 30 minutes after a meal for 28 days. In the double-blind phase of the study either 2000mg (1000mg BD) or placebo (BD) will be orally administered, in addition to standard of care therapy, within 30 minutes after a meal for 28 days.
SAFETY	A Data and Safety Monitoring Board (DSMB) will be established and will meet regularly to monitor on-going safety.
EVALUATION CRITERIA:	<u>Efficacy:</u> • Total bilirubin • MELD • MDF • Cytokeratin (CK) 18-M30/M65 • m-SOFA • APACHE-II • ALT • AST • AST:ALT ratio • Gamma GT • Child Pugh Score • West Haven score (hepatic encephalopathy) • Lille score <u>Safety:</u> • Physical examination, including height and weight • ECG (6-lead or 12-lead) • Vital signs, including blood pressure (BP), pulse and temperature • Clinical laboratory tests (haematology, coagulation, biochemistry, plasma caeruloplasmin and virology)

	• Pregnancy test for females of child bearing potential • Adverse events (AEs) • Concomitant medications <u>Pharmacokinetic:</u> <u>Pilot Phase:</u> • C_{max} – maximum observed concentration • T_{max} - time of maximum observed concentration • AUC_t – Area under the concentration-time curve to time t • AUC_{tau} - Area under the concentration-time curve to the end of the dosage interval • AUC_{inf} - Area under the concentration-time curve extrapolated to infinite time • %Extrap – Percentage of AUCinf obtained by extrapolation • Kel – Apparent first-order terminal elimination rate constant • $T_{1/2}$ – Apparent first-order terminal elimination half-life • Flucp – Fluctuation at pharmacokinetic steady-state • R_{ac} – Accumulation ratio at pharmacokinetic steady-state • T_{ss} – Time to achieve pharmacokinetic steady-state <u>Double-Blind Phase:</u> • R_{ac} – Accumulation ratio at pharmacokinetic steady-state • T~~ss~~ – Time to achieve pharmacokinetic steady-state
EXPLORATORY	Blood samples will be collected at Baseline/Visit 2, Day 14/Visit 6 and Day 28/Visit 8 for the potential analysis of Severe Alcoholic Hepatitis biomarkers
STATISTICS	See Chapter 12
SPONSOR:	Afimmune Ltd

LIST OF ABBREVIATIONS

15(S)-HEPE EE	15(S)-Hydroxy-Eicosapentaenoic Acid Ethyl Ester
AH	Alcoholic Hepatitis
ASH	Alcoholic Steatohepatitis
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAP	Controlled Attenuation Parameter
CK	Cytokeratin
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELF	Enhanced Liver Fibrosis Score
EPA	Eicosapentanoic Acid
Gamma GT	Gamma Glutamyl Transferase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-	Interleukin-
IPF	Idiopathic Pulmonary Fibrosis
INR	International Normalised Ratio
ISF	Investigator Site File
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LPS	Lipopolysaccharide
LSLV	Last Subject Last Visit
MCP-1	Monocyte Chemoattractant Protein-1
MDF	Maddrey's Discriminant Function
MedDRA	Medical Dictionary for Regulatory Activities

MELD	Model End-stage Liver Disease
MHRA	Medicines and Healthcare products Regulatory Agency
m-SOFA	Modified Sequential Organ Failure Assessment
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Non-Alcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
NOAEL	No Observed Adverse Effect Levels
OTC	Over the Counter
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetic
PV CRO	Pharmacovigilance Contract Research Organisation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SIRS	Systemic Inflammatory Response Syndrome
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGF-β	Transforming Growth Factor – Beta
TNF-α	Tumour Necrosis Factor – Alpha
WOCBP	Women of Child Bearing Potential

1 INTRODUCTION

1.1 Therapeutic Area and Disease Background

Alcoholic hepatitis (AH) is a clinical condition characterised by jaundice accompanied by elevated levels of serum aspartate transaminase (AST). Excessive alcohol consumption is a precursor to the condition (Crabb et al. 2016). AH is a major cause of hospitalisation due to liver-related conditions in those with a history of heavy alcohol intake, also a condition prominently associated with repeated hospitalisations (Sanyal & Gao. 2015). Excessive consumption of alcohol is the third leading preventable cause of death in the United States. Regular alcohol consumption can lead to hepatic steatosis, which eventually progresses to steatohepatitis, fibrosis and cirrhosis. In up to 40% of patients, severe acute alcoholic hepatitis has a mortality rate of six months (Lavallard et al. 2011). AH or alcoholic steatohepatitis (ASH) as its histological equivalent occurs in up to 35% of excessive alcohol consumers and is often a precursor of cirrhosis (Menachery & Duseja 2011). However, the severe acute form of AH - as evaluated in this study - is a rare, acute liver disease characterised by self-sustained inflammation of the liver, often leading to multi organ failure with a mortality exceeding 30% (Mark Thursz et al, STOPAH Trial, 2015)

AH is diagnosed by patient history and anamnesis, observation of rapid onset of high bilirubin values, AST>ALT (and both <500) and may be histologically confirmed by liver biopsy (ASH). The condition is always accompanied by different degrees of fibrosis of the liver. Severe acute decompensated AH may also include such hallmarks as macrovesicular steatosis together with neutrophil infiltration, hepatocyte injury and Mallory-Denk bodies. The presence of megamitochondria, satellitosis and cholestasis is also often observed (Crabb et al. 2016). If left untreated, severe acute decompensated AH can progress to multiorgan failure, sepsis and death.

1.2 Standard Treatment

The current standard-of-care treatment for AH includes prednisolone, a corticosteroid which works by altering the balance of cytokines, reducing pro-inflammatory cytokines, e.g. tumour necrosis factor-α (TNF-α), and increasing anti-inflammatory cytokines such as interleukin-10 (IL-10) (Saberi et al. 2016). However, prednisolone is of limited efficacy and has numerous side effects (Crabb et al. 2016); in the presence of infection, steroids are contraindicated (Sanyal & Gao. 2015) and is often replaced by pentoxyphilline. This and other treatments for severe AH have not consistently shown a survival benefit (Crabb et al. 2016).

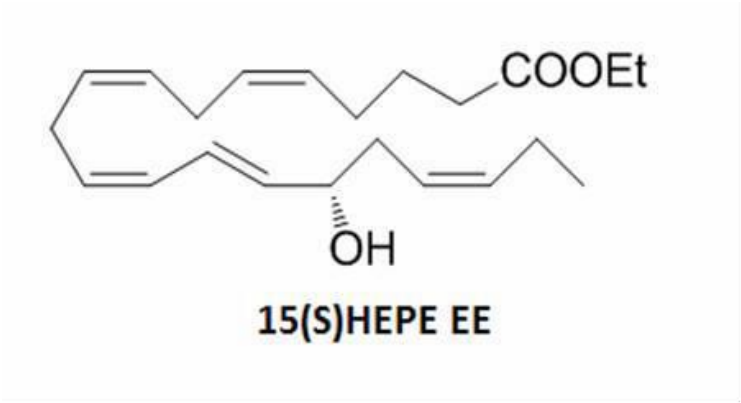
Patients suffering with severe acute decompensated AH often present as malnourished. Nutritional supplementation is also provided as a primary treatment for AH and, in some studies, has been seen to facilitate equal, if not better, survival compared to treatment with corticosteroids (Morgan. 2007).

There is an obvious unmet need for advanced treatment in this life threatening indication.

1.3 Drug Class

DS102 is an endogenously occurring fatty acid 15-hydroxy-eicosapentaenoic acid ethyl ester (15-HEPE EE).

Figure 1. Structure of 15(S)-HEPE EE (DS102)



1.4 Preclinical Pharmacology

A number of *in vitro* and *in vivo* mechanistic studies were performed by the company to elucidate the pharmacology of DS102 (DS-PC-17, DS-PC-18, DS-PC-21, DS-PC-22, DS-PC-23, DS-PC-26, DS-PC- 27, DS-PC-28, DS-PC-29, and DS-PC-32).

DS102 has been shown (Table 1) to be significantly anti-apoptotic in a staurosporin model of apoptosis. The anti-inflammatory effects of DS102 were illustrated in a model of lipopolysaccharide (LPS) induced inflammation in peripheral blood mononuclear cells (PBMCs) showing a significant decrease in tumour necrosis factor-α (TNF-α), IL-6, IL-8 and IL-23. Anti-fibrotic effects of DS102 were observed in TGF-β treated fibroblasts isolated from idiopathic pulmonary fibrosis (IPF) patients, reducing the production of fibrotic markers collagen and α–smooth muscle actin (α-SMA). DS102 also showed varying degrees of peroxisome proliferator-activated receptor (PPAR) activation in human PPAR reporter cells. DS102 has therefore been shown to have a pleiotropic mechanism of action including key anti-inflammatory and anti-fibrotic mechanisms involved in the pathogenesis of AH.

Table 1: DS102 Mechanism of Action Summary

#	Type	Model	Objective	Result
1.	*In vivo*	Tissue Distribution Study	Rats dosed for 7 days with DS102 and tissues levels assessed	DS102 was sequestered in, but not exclusively to, the liver, lung, heart, spleen and kidney tissues.
2.	*In vivo*	Whole genome screen of rat genome	Rats Dosed for 4 days with DS102 and genome array performed	Increases in cell proliferation markers (e.g . cyclins), hepatoprotective cytokines (IL-11) and fatty metabolism receptors.
3	*In vitro*	TGF-beta Induced Fibrotic Markers	DS102 anti-fibrotic properties	DS102 inhibited TGF-beta induced collagen and alpha-SMA (Smooth Muscle Actin)
4.	*In vitro*	LPS induced Inflammation	DS102 anti-inflammatory properties	DS102 inhibited TNF-alpha, IL-6, IL-8 and IL-23
5.	*In vitro*	Screening of PPAR family in Human PPAR reporter cells	Investigate the mechanism of action for DS102 via the PPAR family signalling pathway	DS102 moderately activated PPAR-alpha and mildly activated delta and gamma
6.	*In vitro*	Staurosporine induced Caspase Activity	To investigate the Caspase 3 inhibition potential of DS102	DS102 showed to be a potent caspase inhibitor in response to staurosporine induced cell death

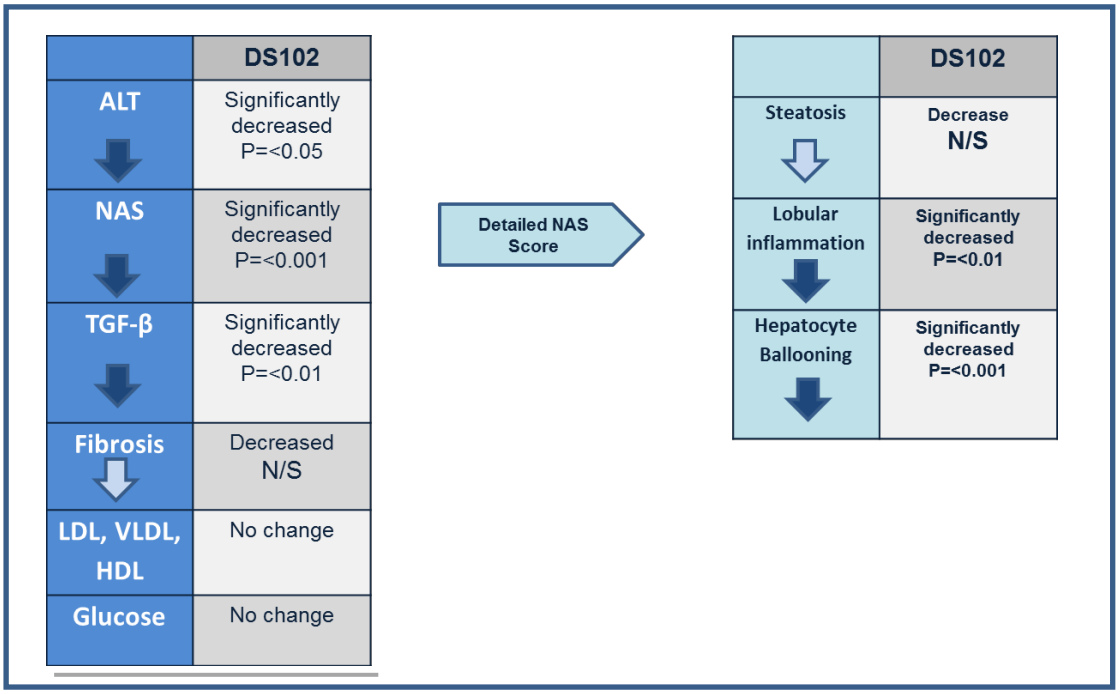
Investigation of DS102 in the pathological progression of non-alcoholic steatohepatitis (NASH) was performed in an established NASH preclinical model (STAM™) sponsored by the company. As

it is postulated that pathophysiologically AH is in principle an accelerated form of NASH, it can be

assumed that results from this study can also be used to expand upon knowledge of DS102 in the pathological progression of AH.

A subcutaneous injection of streptozotocin was administered to newborn mice followed by a high fat diet from four weeks of age. Results presented below represent overall outcomes from four studies performed. NAS score (NAFLD Activity Score**) is separated into three components: steatosis, lobular inflammation and hepatocyte ballooning. Light arrows signify a decrease. Dark arrows signify a statistically significant difference in the extent of decrease.**

Figure 2: Schematic summarising the results of four in vivo studies performed using the STAM™ Model (DS-PC-26, DS-PC-27, DS-PC-28, and DS-PC-29).



Treatment with DS102 at 500mg/kg significantly decreased plasma ALT, a liver injury marker, and plasma TGF-β, a marker of fibrosis progression. Histological analysis showed DS102 also significantly decrease NAFLD activity score (NAS). The improvement of NAS was attributable to the reduction in the lobular inflammation and hepatocellular ballooning scores. It also showed its efficacy in liver fibrosis of STAM™ mice. The treatment reduced the pathological deposition of collagen (perisinusoidal fibrosis) in the liver as demonstrated by Sirius red staining.

The above results suggest that DS102 has potential hepatoprotective and anti-inflammatory effects against steatohepatitis. Recent research has linked fibrosis, as well as bilirubinostasis, with a poor outcome of AH (Sanyal & Gao. 2015). The reduction of fibrosis area suggests that DS102 treatment could contribute to achieve a better prognosis in AH.

The *in vitro* and *in vivo* studies performed to date illustrate the hepatoprotective, anti-inflammatory and anti-fibrotic mechanisms of DS102 and supports its development as a compound to treat AH.

1.5 Toxicology

A number of good laboratory practice (GLP) toxicology studies were performed by the company to assess the safety of DS102 (CRL-527943, 527959, 529139, 529123). Daily administration of DS102 up to 2000mg/kg/day for four weeks to rats and dogs was deemed well tolerated and safe. The no observed adverse effects levels (NOAEL) for repeated dosing over four weeks in both species was 2000 mg/kg/day. The company recently completed a nine month dog and six month rat study; both studies concluded that administration of DS102 was well-tolerated with a NOAEL of 1000mg/kg/day.

1.6 Previous Clinical Safety Studies with 15(S)-HEPE

The company sponsored a phase I study, DS102A-01 (EudraCT 2015-001153-33), a first in man study conducted in healthy volunteers, to assess the safety, pharmacokinetics and effect of food on orally administered DS102. DS102 (15(S)-HEPE EE) was administered to healthy volunteers in the following regimens: a single dose of 100mg, 500mg, 1000mg, or 2000mg under fasted conditions; a single 500mg dose under two fed conditions (standard diet and high fat diet); and as multiple doses of 500mg, 1000mg or 2000mg taken once daily for 28 consecutive days in a fasted state. In this study, 57 subjects (male and female) aged 18 to 45 years were enrolled with eight subjects (at least three males and three females per cohort) in each cohort. Subjects in each cohort were randomised in a ratio of 3:1 to receive either DS102 or placebo. Cohorts were commenced in a sequential manner starting with the 100mg, 500mg and 1000mg single dose cohorts in parallel and progressing to higher doses and multiple doses following evaluation by a safety monitoring committee (SMC).

This first in man study showed that DS102 overall had an excellent safety profile, a short elimination half-life of approximately two hours and a T_{max} of approximately four to eight hours. Results across dose levels studied showed high variability in the single and multiple dose cohorts and did not show a linear correlation between increasing dose and that of systemic exposure. The study demonstrated that administration with food increased the bioavailability of 15(S)-HEPE, as mean plasma concentrations of 15(S)-HEPE were higher under fed conditions compared to fasted conditions. There was no difference in bioavailability between normal and high fat diet fed conditions. DS102 was safe and well-tolerated in healthy subjects in this study with no serious adverse events (SAEs) reported.

The company is currently recruiting patients for two phase II studies, DS102A-02 (EudraCT 2016-000311-33), to assess the safety and efficacy of orally administered DS102 in NAFLD patients at doses of 1000mg or 2000mg per day, with placebo as a comparator and DS102A-03 (EudraCT 2016-002853-39), to assess the safety and efficacy of orally administered DS102 in COPD patients at doses of 1000mg or 2000mg per day, with placebo as a comparator. To date, DS102 has been well-tolerated with no related SAEs reported.

2 RISK BENEFIT ASSESSMENT

The company has shown potentially beneficial effects of DS102 in clinical endpoints relevant for the treatment of AH, namely reduction of ALT and fibrosis in a number of preclinical mechanistic studies. To date, toxicological studies demonstrate good tolerability of the drug substance in

doses of up to 2000mg/kg in two species. The phase I study conducted in healthy volunteers demonstrated DS102 to be safe and well-tolerated with no SAEs reported over a 28 day dosing period, as has the ongoing phase II study in which DS102 is administered for a 16 week treatment period (blinded data).

Based on the data summarised above a favourable safety profile may be postulated which, in combination with the potential therapeutic effect of DS102 in a disease that currently lacks effective therapies, gives a positive risk-benefit ratio for the conduct of a Proof of Concept Study with DS102 in patients suffering from severe acute decompensated AH**.**

The burden for patients in this study is minimised by ensuring standard of care is delivered to all patients and supportive care including nutritional support is available.

The target population of the study are at high risk of mortality and significant morbitity. Without experimental treatments that offer an opportunity to improve outcomes, patients with severe AH have a very poor prognosis.

3 RATIONALE FOR THE STUDY

The postulated mode of action of DS102 covering all relevant pathophysiological features of severe acute decompensated AH together with a preclinically and clinically clean safety profile of the compound makes DS102 an ideal candidate to evaluate clinically the effects of DS102 in this life threatening disease, for which no established treatment is available.

4 STUDY OBJECTIVES

Efficacy Objective:

• To compare the efficacy of orally administered DS102 versus placebo, in the treatment of adult patients with severe acute decompensated AH.

Safety Objective:

• To compare the safety of orally administered DS102 in the treatment of adult patients with severe acute decompensated AH.

Pharmacokinetic Objective:

• To evaluate the PK of 15(S)-HEPE following orally administered DS102 capsules, in six adult patients with severe acute decompensated AH in an initial pilot phase of the study, followed by trough level assessment of 15(S)-HEPE in all study participants.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Percentage change in MELD score from baseline to Day 28

5.2 Secondary Endpoints

- Change in total bilirubin from baseline to Day 7, 14, 21 and 28
- Proportion of patients showing a 25% reduction of bilirubin at day 7, 14, 21, and 28.
- Change in serum Cytokeratin18-M30/M65 from baseline to Day 7, 14, 21 and 28
- Change in AST levels from Baseline to Day 7, 14, 21 and 28
- Change in AST:ALT ratio from Baseline to Day 7, 14, 21, 28
- Change in MDF score from baseline to Day 7, 14, 21 and 28.
- Proportion of patients showing a 25% reduction in MELD score from baseline to Day 7, 14 and 21
- Change in m-SOFA from baseline to Day 7, 14, 21 and 28
- Proportion of patients with a 2-point worsening of m-SOFA from baseline at Day 7, 14, 21 and 28
- Change in hepatic encephalopathy as assessed by West Haven criteria, from baseline at Day 7, 14, 21 and 28 from baseline to Day 28
- Incidence of acute kidney injury over 28 days (defined by requiring medicinal or mechanical support)
- Incidence of variceal haemorrhage, ascites or hepatic encephalopathy over 28 days

5.3 Exploratory Endpoints

- Survival at day 7, 14, 21, 28 and 90 using Kaplan-Meier Plot
- Change in GT from baseline to Day 7, 14, 21 and 28
- Change in ALT from baseline to Day 7, 14, 21 and 28.
- Change in Child Pugh score from baseline to Day 7, 14, 21 and 28
- Change in APACHE-II score from baseline to Day 7, 14 and 28
- Change in Lille score from baseline to Day 7, 14 and 28

5.4 Safety Endpoints

- Treatment emergent (S)AEs and SUSARs

6 STUDY DESIGN

6.1 General

This is a randomised, placebo-controlled, double-blind, parallel group, multicentre, exploratory phase II study preceded by an open label pilot phase to investigate the efficacy and safety of orally administered DS102 capsules in patients with acute decompensated AH aged over 18 years.

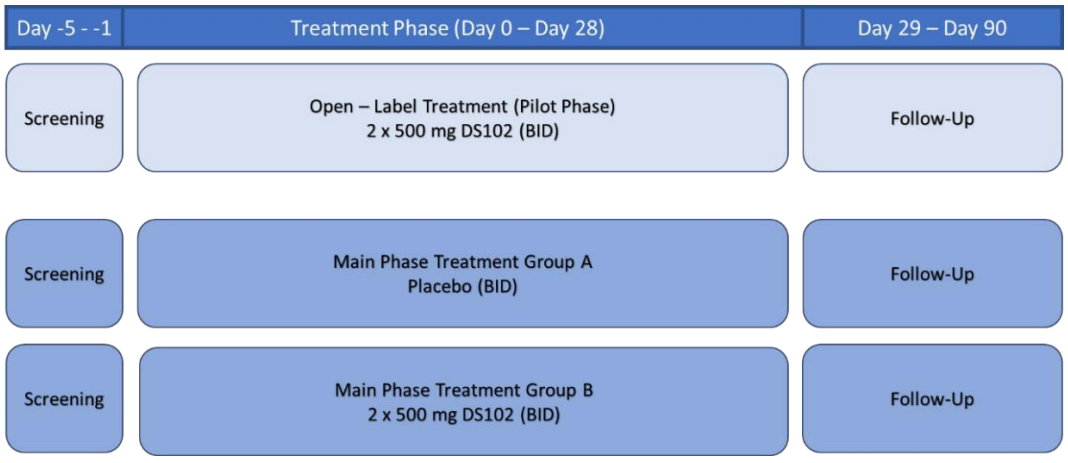
After the completion of the open-label phase of the study the DSMB will evaluate the safety and pharmacokinetic data and might recommend a dose adjustment for the double blind randomised phase of the study

After the open-label pilot phase of the study during which six patients will be enrolled, two parallel groups of patients will be enrolled into the randomised double-blind phase of the study to compare one dose of DS102 with placebo over a 28 day treatment period. Patients will receive standard of care therapy in addition to their assigned IMP throughout the treatment period of the study. It is planned that 120 evaluable patients, 60 per treatment group, will be randomised.

Both parts of the study, the open label phase and the double blind phase of the study consist of a screening period of up to five days (at the discretion of the investigator), a 28 day treatment period and a follow up period until day 90 after start of treatment. Screening is to commence upon admission to hospital; at the screening visit, after giving informed consent to participate, patients will be assessed using the screening examinations.

A schematic diagram of the overall timeframe of the study is given in Figure 3.

Figure 3: Study Outline



Any medication or therapeutic intervention deemed necessary for the patient, and which, in the opinion of the Investigator, do not interfere with the safety and efficacy evaluations, may be continued.

Before the comparative treatment period can commence, patients will complete a baseline assessment of their disease and eligible patients will be randomly allocated to one of the two parallel group treatment regimens in a 1:1 randomisation ratio:

- Treatment group A: 2 x placebo 500mg capsules orally administered twice a day (BD) (four capsules daily) for 28 days
- Treatment group B: 2 x DS102 500mg capsules orally administered BD (four capsules daily) for 28 days

To maintain the double-blind conditions, the DS102 capsule and placebo capsule will be identical in appearance.

6.2 Rationale for Study Design and Dose Selection

The study is randomised, placebo-controlled, and double-blinded to minimise bias during the safety and efficacy assessments, preceded by an open label pilot treatment phase to gather pharmacokinetic information in severely impacted patients.

The study consists of a treatment period of 28 days and was designed in order to assess the safety and efficacy of dosing of DS102 BD (total daily dose of 2000mg) in patients with acute decompensated AH.

Studies in rats and dogs treated for up to 26 weeks and 39 weeks respectively have demonstrated 15-HEPE EE did not indicate any significant toxicity and resulted in a NOAEL of 1000 mg/kg/day in both species (CRL-529123, 529139). This information along with the FDA and EMA guidance on first in man study dose calculation and pre-clinical studies formed the basis for the dose selection in the phase I trial.

Doses of up to 2000mg were administered QD for 28 days in the phase I trial to healthy volunteers. The results from the phase I trial indicate that DS102 was safe and well tolerated. The pharmacokinetic profile of the DS102 seen in the phase I trial indicated that administration with food increased the bioavailability of 15(S)-HEPE. An ongoing phase II study includes dosing of up to 2000mg per day with or after food and so far, has shown DS102 to be safe and well tolerated with no related SAEs. The dose selection in this trial is therefore based on the phase I trial and ongoing phase II trial and the intention to characterise the safety and efficacy of up to 2000mg per day given in divided doses with or after food to patients with acute decompensated AH. A dose adjustment may be decided based on the pharmacokinetic and safety data deriving from the open label phase of the study.

7 PATIENTS AND SCREENING

In order to participate in this study the patients must meet all inclusion criteria and must not meet any of the exclusion criteria. Inclusion in the trial starts with the informed consent signature. The inclusion and exclusion criteria are to be verified at the screening visit (Visit 1) and at the start of treatment/baseline visit (Visit 2). Patient history of alcohol abuse for at least six months must be documented at enrolment.

7.1 Source of Patients

The study population will consist of male and female patients diagnosed with severe acute decompensated AH aged 18 years and over.

7.2 Inclusion Criteria

1. Male or female patients aged 18 years and older
2. Total bilirubin of ≥ 5 mg/dl (85µmol/l)
3. Patients with definite or probable AH
4. MELD ≥18 at baseline visit
5. MDF ≥32 at baseline visit
6. AST >50 U/L
7. AST`:ALT ratio > 1.5
8. Female patients, or female partners of male patients, of child bearing potential must use highly effective birth control methods or have a sterilised partner for the duration of the study. Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include intrauterine device or sexual abstinence.

   Note: A woman is considered of child bearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy

   Note: Hormonal contraceptives are contraindicated in patients with severe hepatic diseases and are not acceptable as a birth control method in this study

   Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject
9. Patient and/or legally authorised representative must provide informed consent
10. Able to swallow the provided study medication
11. Not eligible for liver transplant during this hospitalisation

7.3 Exclusion Criteria

1. Pregnant or lactating females.
2. Spontaneous liver function improvement defined by decrease of bilirubin level and MDF of >10% within 5 days of hospital admission
3. Grade 4 hepatic encephalopathy (West Haven Criteria)
4. Type 1 hepatorenal syndrome (HRS) or a serum creatinine >2 x ULN or the requirement for haemodialysis
5. History of hypersensitivity to any substance in DS102 capsules or placebo capsules.
6. Alcohol abstinence of >6 weeks prior to screening
7. Duration of clinically apparent jaundice >3 months prior to baseline
8. Other causes of liver disease including:
    a. Evidence of chronic viral hepatitis (Hepatitis B DNA positive or HCV RNA positive)
    b. Biliary obstruction
    c. Hepatocellular carcinoma
    d. Wilsons disease
    e. Budd Chiari Syndrome
    f. Non-alcoholic fatty liver disease
9. History of or active non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas).
10. Previous entry into the study
11. AST >400 U/L or ALT >270 U/L
12. Treatment with any experimental drug within 30 days prior to Day 0 visit (Baseline), or 5 half-lives (whichever is longer).
13. Patients who have used dietary supplements rich in omega-3 oromega-6 fatty acids in the four weeks prior to baseline.
14. Patients dependent on inotropic support (adrenaline or noradrenaline), including Terlipressin
15. Active variceal haemorrhage on this admission requiring more than 2 units of blood to maintain haemoglobin level within 48 hours
16. Presence of refractory ascites
17. Untreated or unresolved sepsis
18. Patients with cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction (within last 6 weeks) or severe cardiac arrhythmias (not including atrial fibrillation)
19. Known infection with HIV at screening.
20. Significant systemic or major illnesses other than liver disease that, in the opinion of the investigator, would preclude or interfere with treatment with DS102 and/or adequate follow up.
21. Previous liver transplantation

7.4 Screening and Consent

The Investigator will maintain a Patient Screening Log to collect information on all patients who sign an Informed Consent Form (ICF) regardless of whether or not they meet the study eligibility criteria following completion of the screening evaluations. After completion of screening, all patients deemed eligible to take part in this study will be entered onto an enrolment log.

For information on the consent process, refer to Section 13.2

7.5 Withdrawal of Patients

Patients have the right to withdraw from the study at any time for any reason, without repercussion. The Investigator must explain this to the patient and that this will in no way prejudice their future treatment. The investigator also has the right to withdraw patients from the study if she/he feels it is in the best interest of the patient or if the patient is uncooperative or non-compliant. It is understood by all concerned that an excessive rate of withdrawal can render the study un-interpretable, therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations, particularly the follow-up examination, as thoroughly as possible.

In the event of patient withdrawal, the Investigator or one of his or her staff members should talk to the patient or in case of hospital discharge contact the patient either by telephone or through a personal visit to determine as completely as possible the reason for the withdrawal, and record the reason in patient's source document and case report form (CRF). A complete final early termination evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient is an adverse event (AE) or an abnormal laboratory test result, the principal specific event or test will be recorded.

Please note: the patient is allowed not to give a reason for withdrawal. If this is the case this must be recorded as well.

Patients who discontinue the study before Day 28 visit and are discharged from the hospital will be asked to come for an early termination visit as soon as possible and have the assessments listed at Day 28 performed. Mortality will be assessed throughout to Day 90.

There will be two main categories for withdrawals from the study: "complete withdrawal" and "withdrawals from investigational product".

7.5.1 Complete Withdrawal

Discontinuation of investigational product and all efficacy and safety evaluations. Standard reasons for withdrawing from further participation in the study and from the follow-up visits may be:

- Patient's decision (withdrawal of consent to participate)
- Patient lost to follow-up

7.5.2 Withdrawals from Investigational Product

Discontinuation of investigational product, but continued follow-up visits, including efficacy and safety evaluations. Standard reasons for withdrawing from taking further investigational product, but continuing follow-up visits and safety evaluations may be:

- Unacceptable AEs
- Patient request
- Investigator's discretion
- Intercurrent illness
- Pregnancy

Patients who develop Grade 3 or higher National Cancer Institute Common Terminology Criteria or Adverse Events (NCI-CTCAE), or who experience a 2-point worsening of m-SOFA criteria, that is determined to be possibly or probably attributable to the study drug will be discontinued.

7.6 Patient Replacement

Patients who are withdrawn from the study due to AE or lack of efficacy will not be replaced. Patients who are withdrawn for lost to follow up may be replaced.

7.7 Protocol Deviations

All protocol deviations will be reviewed by the medical monitor as and when each violation is detected. Based on this review, a decision on the patient's continuation in the trial will be reached and this decision will be documented as appropriate. Notification will be made to the relevant authorities as required.

If a patient fails eligibility criteria or meets treatment withdrawal criteria then the treatment must be withdrawn.

7.8 Stopping Criteria

Trial will be stopped if more than one patient has a grade 3 or higher AE on the CTCAE scale in any one category that is determined to be possibly or probably attributable to study drug (exclusion evaluation of liver function).

8 STUDY CONDUCT

8.1 Study Schedule

During the study, 8 visits to the clinic are scheduled after the screening visit (Visit 1): one at the start of the comparative treatment period (Baseline/Visit 2) and six in the comparative treatment period (Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28 or Early Termination).

A final safety follow-up visit (Visit 9/Day 90) will be conducted on Day 90.

For patients who discontinue the study early, for whatever reason, the Early Termination visit (Visit 8) will be performed. Patients who discontinue the study before Day 28 and are already discharged from the hospital will be asked to attend the investigative site as soon as possible that assessments scheduled for Visit 8 can be conducted. These patients will be asked also to attend a final safety follow-up visit (Visit 9/Day 90).

8.2 Clinic Visits

A tabulated flow chart of the study is presented in Appendix 1 and 2.

8.2.1 Screening Visit (Visit 1)

The patient must sign and date the informed consent form (ICF) before any study-specific procedures are conducted.

Once informed consent has been obtained, the Investigator will assign a patient screening number. The following screening assessments/sample collections will be performed:

- Verification of inclusion/exclusion criteria (Sections 7.2 & 7.3)
- Demographic data
- Medical history (as detailed in Section 9.2.1)
- History of alcohol abuse for at least six months documented
- Physical examination (as detailed in Section 9.2.2)
- Liver ultrasound (as detailed in Section 9.2.11)
- Vital signs (blood pressure, heart rate and body temperature)(as detailed in Section 9.2.4)
- Electrocardiogram (ECG) (as detailed in Section 9.2.3)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, coagulation tests and plasma caeruloplasmin as detailed in Section 9.2.5)
- Virology (as detailed in Section 9.2.6)
- Urinalysis (as detailed in Section 9.2.15)

- Pregnancy test (as detailed in Section 9.2.7)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- West Haven criteria assessment (as detailed in Section 9.1.11)
-)
- Total bilirubin (as detailed in Section 9.1.2)
- AST:ALT (as detailed in Section 9.1.3)
- Concomitant medication assessment (as detailed in Section 9.2.10)

All procedures that are medically necessary should be followed.

8.2.2 Treatment Period

Following completion of a successful screening visit, patients will begin the comparative treatment period (28 days).

At the start of the comparative treatment period, after confirmation of continued eligibility, patients will be randomly assigned to one of the two treatment regimens.

Patients will take the allocated investigational medicinal product (IMP) to which he/she is allocated twice-daily, in the morning and in the evening, within 30 minutes after a meal, throughout the comparative treatment period. Each administration of IMP will be recorded in the eCRF/hospital records or in a patient diary card, if discharged before day 28 of the study.

Patients who discontinue the study early will have all study procedures scheduled for Visit 8 (see Section 8.2.9) performed as soon as possible after patient withdrawal so that all study-related information can be recorded.

Counselling on alcohol consumption should be performed during the study. In-study and post-discharge referral and intervention will be provided as needed.

8.2.3 Baseline (Visit 2)

The following assessments/sample collections will be performed at Baseline/Visit 2:

- Verification of inclusion/exclusion criteria (as detailed in Sections 7.2 & 7.3)
- Medical history (as detailed in Section 9.2.1)
- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature)(as detailed in Section 9.2.4)
- ECG (as detailed in Section 9.2.3)
- Pregnancy test(as detailed in Section 9.2.7)
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Exploratory blood sampling (as detailed in Section 9.2.8.2)

- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score(as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
- West Haven criteria assessment (as detailed in Section 9.1.11)
- Lille score assessment (as detailed in Section 9.1.10)
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)

Biomarker (as detailed in Section 9.2.8.3)

In addition, the following assessments of nutritional status will also be performed, with nutritional interventions provided where required:

- BMI
- Bedside Subjective Global Assessment (SGA) score (0, 1, 2, and 3). Patients will be classified into the following categories:
    - Well nourished (0)
    - Mild malnutrition (1)
    - Moderate malnutrition (2)
    - Severe malnutrition (3)

If all study entry criteria are satisfied the Investigator will randomise the patient and provide the patient with the designated IMP or placebo from one of the patient treatment packs available at the site.

The first dose of IMP or placebo will be administered at site once all baseline assessments have been completed. The patient will take their second dose of IMP or placebo in the evening of Day 0. The capsules will then be administered twice-daily.

8.2.4 Visit 3/Day 3

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4)

- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)
- Biomarker (as detailed in Section 9.2.8.3)
- Lille Score (as detailed in Section 9.1.10)
- West Haven criteria assessment (as detailed in Section 9.1.11)

8.2.5 Visit 4/Day 5

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4)
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
- AE assessment (as detailed in Section 11)
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- Concomitant medication assessment (as detailed in Section 9.2.10)
- West Haven criteria assessment (as detailed in Section 9.1.11)

- Biomarker (as detailed in Section 9.2.8.3)
- Lille Score (as detailed in Section 9.1.10)

8.2.6 Visit 5/Day 7

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4)
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
- West Haven criteria assessment (as detailed in Section 9.1.11)
- Lille score assessment (as detailed in Section 9.1.10)
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)
- Biomarker (as detailed in Section 9.2.8.3)

8.2.7 Visit 6/Day 14

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4)
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Exploratory blood sampling (as detailed in Section 9.2.8.2)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score(as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)

- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
- West Haven criteria assessment (as detailed in Section 9.1.11)
- Lille score assessment (as detailed in Section 9.1.10)
- Total bilirubin (as detailed in Section 9.1.2)

Pregnancy Test (as detailed in Section 9.2.7)

- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)
- Biomarker (as detailed in Section 9.2.8.3)

For discharged patients, the IMP or placebo will be returned and further IMP or placebo will be supplied to the patient. The patient should take their next dose of IMP or placebo as soon as all visit assessments have been completed. The capsule will continue to be administered twice-daily.

In addition, the following assessments of nutritional status will also be performed, with nutritional interventions provided where required:

- BMI
- Bedside Subjective Global Assessment (SGA) score (0, 1, 2, and 3). Patients will be classified into the following categories:
    - Well nourished (0)
    - Mild malnutrition (1)
    - Moderate malnutrition (2)
    - Severe malnutrition (3)

8.2.8 Visit 7/Day 21

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4);
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)

- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)
-
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)
- Biomarker (as detailed in Section 9.2.8.3)
- Lille score assessment (as detailed in Section 9.1.10)
- West Haven criteria assessment (as detailed in Section 9.1.11)

For discharged patients, the IMP or placebo will be returned and further IMP or placebo will be supplied to the patient. The patient should take their next dose of IMP or placebo as soon as all visit assessments have been completed. The capsule will continue to be administered twice-daily.

8.2.9 Visit 8/Day 28/Early Termination

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4);
- ECG (as detailed in Section 9.2.3)
- Pharmacokinetic sampling (as detailed in Section 9.2.8.1)
- Exploratory blood sampling (as detailed in Section 9.2.8.2)
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- Pregnancy test (as detailed in Section 9.2.7)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)
- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)

- Gamma GT (as detailed in Section 9.1.4)
- Biomarker (as detailed in Section 9.2.8.3)
- West Haven criteria assessment (as detailed in Section 9.1.11)
- Lille score assessment (as detailed in Section 9.1.10)
- Collection of acute kidney injury, ascites and variceal haemorrhage data
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.10)

In addition, the following assessments of nutritional status will also be performed, with nutritional interventions provided where required:

- BMI
- Bedside Subjective Global Assessment (SGA) score (0, 1, 2, and 3). Patients will be classified into the following categories:
    - Well nourished (0)
    - Mild malnutrition (1)
    - Moderate malnutrition (2)
    - Severe malnutrition (3)

The IMP or placebo will be returned. Further IMP or placebo will not be supplied to the patient.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in 62 days at Visit 9 for final assessment.

8.2.10 Visit 9/Day 90/Follow Up

In case of the patient's survival the following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Vital signs (blood pressure, heart rate and body temperature), as detailed in Section 9.2.4);
- Samples for clinical laboratory safety tests (haematology, serum biochemistry, and coagulation tests as detailed in Section 9.2.5)
- MELD (as detailed in Section 9.1.1)
- MDF (as detailed in Section 9.1.7)
- m-SOFA (as detailed in Section 9.1.8)
- West Haven criteria assessment (as detailed in Section 9.1.11)
- Lille score assessment (as detailed in Section 9.1.10)
- APACHE II score (as detailed in Section 9.1.9)
- Total bilirubin (as detailed in Section 9.1.2)
- CK-18 (as detailed in Section 9.1.6)

- AST:ALT (as detailed in Section 9.1.3)
- Child pugh score (as detailed in Section 9.1.5)
- Gamma GT (as detailed in Section 9.1.4)

9 ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 Model for End-Stage Liver Disease

The model for end-stage liver disease (MELD) is employed in the evaluation of hepatic function and the assessment of prognosis. MELD is calculated based on variables including the international normalised ratio (INR), serum creatinine, and serum bilirubin.

A MELD score ≥18 (within 24 hours of presentation) is considered a good predictor of 90 day mortality in patients with AH.

MELD will be assessed at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.2 Total Bilirubin

Total bilirubin concentration is a marker of hepatic function.

Blood samples will be taken to assess total bilirubin at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.3 ALT, AST, AST:ALT Ratio

Increased liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) are a marker of liver injury and will be assessed at all time points.

Blood sample will be taken to assess ALT, AST, and AST:ALT ratio at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.4 Gamma Glutamyl Transferase

Gamma glutamyl transferase (GGT) is a liver enzyme indicative of liver dysfunction and alcohol intake.

Gamma GT levels will be assessed as part of serum biochemistry at Visit 2/Baseline, Visit 3/Day 3, Visit 4/ Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.5 Child-Pugh Score

The Child-Pugh score is a means of assessing the severity of chronic liver disease, including cirrhosis, based on five clinical parameters, each of which is allocated a score; total score indicates the severity and prognosis of chronic liver disease.

Table 1: Child-Pugh Score (Jackson & Gleeson 2010)

Factor	1 point	2 points	3 points
Bilirubin (µmol litre−1)	< 34	34–50	< 50
Albumin (g litre−1)	> 35	28 – 35	< 28
INR	< 1.7	1.7 – 2.2	> 2.2
Ascites	None	Controlled	Refractory
Hepatic encephalopathy	None	I – II or controlled	III – IV or refractory

Blood samples will be taken to assess the Child-Pugh score at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.6 Cytokeratin-18 M30/M65

Cytokeratin(CK)-18 M30 and M65 are biomarkers of hepatocyte apoptosis and total cell death, respectively, and are employed in the detection of fibrosis and steatosis.

Blood samples will be taken to perform this assessment at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.7 Maddrey Discriminant Function

The Maddrey discriminant function (MDF) is a measure of liver dysfunction and a method of assessing disease severity.

MDF is calculated as follows:

MDF = 4.6 (patient's PT − control PT) + total bilirubin (mg/dl)

MDF will be assessed at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.8 Modified Sequential Organ Failure Assessment

The m-SOFA score is used in the assessment of disease severity, as well as in predicting outcome and is classified as follows:

Organ System	0	1	2	3	4
Respiratory SpO2/FiO2	>400	≤400	≤315	≤235	≤150
Liver	No scleral icterus or jaundice			Scleral icterus or jaundice	
Cardiovascular, hypotension	No hypo-tension	MAP <70 mm Hg	dopamine≤5 or dobutamine any dose	dopamine>5 epinephrine≤0.1 norepinephrine≤0.1	dopamine>15 epinephrine>0.1 norepinephrine>0.1
CNS, Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal, Creatinine mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0

m-SOFA will be assessed at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.9 Acute Physiologic and Chronic Health Evaluation II

The acute physiologic and chronic health evaluation (APACHE) II score (see appendix 15.3) will assess patients for the presence of multiple organ dysfunction and predict mortality by generating a point score ranging from 0 to 71 based on twelve physiologic variables, age and underlying health.

APACHE II will be assessed at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.10 Lille Score

The Lille score is a composite score which predicts mortality in patients with AH who are not responding to steroid therapy. It is based on age, albumin, bilirubin (initial), bilirubin (day 7), creatinine and PT; a score of >0.45 identifies 75% of deaths, a score of >0.45 predicts a 6-month survival of 25%, and a score of <0.45 predicts survival of 85%.

Lille score will be assessed at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.1.11 West Haven Criteria

The West Haven Criteria is used to classify the severity of hepatic encephalopathy with a grading of 1 – 4, Grade 1 being the least serious with the patient having a trivial lack of awareness to Grade 4 in which the patient is in a state of unconsciousness.

Grade	Criteria
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
2	Lethargy or apathy Minimal disorientation of time or place Subtle personality changes Inappropriate behaviour
3	Somnolence to semi-stupor but responsive to verbal stimuli Confusion Gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

(Ferenci et al. 1998)

West Haven criteria will be assessed at Visit 1/Screening , Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

9.2 Safety Assessments

9.2.1 Medical History

A complete review of the patient's medical history will be undertaken by the Investigator or designee at the Visit 1/Screening and Visit 2/Baseline) to ensure that no exclusion criteria have been met.

Any concomitant disease, whether considered relevant for the study or not by the Investigator, must be reported in the CRF. The date of diagnosis or duration of the condition should be noted where possible. A history of alcohol abuse for > 6 months is key to qualify for the study.

9.2.2 Physical Examination

A physical examination, including height and weight, will be performed by the Investigator as per the Study Flow Chart (Appendix 1 and 2) at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up, in accordance with local practices.

A complete physical examination will be conducted at Visit 2/Baseline. At subsequent visits, the examination will be directed by patient symptoms and clinical features i.e., a standard panel of body systems will not be assessed unless indicated by patient. For example should the patient report to the investigator the presence of 'rash' then the skin would be evaluated. It is not required that additional body systems are assessed unless clinically warranted. Any abnormal results should be recorded in the CRF. Changes in findings of the physical examination compared with the baseline examination should be recorded as an AE.

9.2.3 Electrocardiogram

A 6-lead electrocardiogram (ECG) 10 mm/1 mV, 25 mm/s with a 10 second lead II rhythm strip will be recorded at each time point. ECGs will be recorded using the GE Mac 1200 or equivalent model. Patients will be rested quietly in a fully supine position for five minutes before the ECG is taken. Recordings will be made at Visit 1/Screening, Visit 2/Baseline and Visit 8/Day 28/Early Termination.

Use of a 12-lead ECG is acceptable if no 6-lead ECG is available.

9.2.4 Vital Signs

Vital signs measurements will be performed as per the Study Flow Chart (Appendix 1 and 2) at Visit 1/Screening, Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and Visit 9/Day 90/Follow up.

Measurements to be taken include:

- Blood pressure: will be performed as supine (after at least five minutes of rest); systolic and diastolic blood pressure (in mmHg) will be recorded.
- Heart rate: taken at rest (in bpm).
- Temperature: will be taken as per clinic practice. Temperature and route will be recorded in the CRF.

Vital signs measurements will be performed before any blood samples are taken. All new findings or changes to previous findings considered clinically significant will be recorded in the CRF as an AE if the finding is made after the patient has signed the ICF.

9.2.5 Clinical Laboratory Safety Tests: Haematology, Serum Biochemistry, and Coagulation

Blood and urine samples will be taken as per the Study Flow Chart (Appendix 1 and 2) for routine haematology, serum biochemistry, coagulation. All samples will be analysed in a central laboratory.

Haematology:	Full blood count to include red cell count, haemoglobin, haematocrit, white cell count, differential white cell count, platelet count and reticulocyte count.
Serum biochemistry:	Urea (blood urea nitrogen (BUN)), creatinine, uric acid, total bilirubin, indirect and direct bilirubin, sodium, bicarbonate potassium, phosphorus, calcium chloride, alkaline phosphatase (ALP), AST, ALT, AST:ALT ratio, gamma GT, albumin, total protein, total cholesterol, triglycerides, glucose, C-reactive protein (CRP), plasma caeruloplasmin (screening only).
Coagulation:	PT (prothrombin time), INR and APTT (activated partial prothrombin time)

9.2.6 Virology

A blood sample will be taken to perform virology tests including human immunodeficiency virus (HIV), Hepatitis C and Hepatitis B as detailed in Study Flow Chart (Appendix 1 and 2)

9.2.7 Pregnancy Test

For female patients of childbearing potential only, a pregnancy test will be carried out as per the Study Flow Chart (Appendix 1 and 2) at Visit 1/Screening, Visit 2/Baseline, Visit 6/Day 14 and Visit 8/Day 28/Early Termination.

9.2.8 Exploratory Blood Sampling

Details of the volume of blood to be taken, sample preparation and handling are contained in a separate laboratory procedures manual.

Laboratory results will be reviewed for clinically significant values by each investigator following sample analysis and verification. The report must be signed and dated by the investigator before insertion in the eCRF.

Additional blood may be required for repeats of safety laboratory test.

9.2.8.1 Pharmacokinetic sampling

Blood samples for pharmacokinetic (PK) analysis will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1 and 2) at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, and Visit 8/Day 28/Early Termination.

Trough plasma samples will be obtained from all patients (pilot and double blind phases) prior to first daily dose on the indicated days. Additional post-dose serial plasma samples will be obtained from the six patients on Days 0 and 7 of the preceding pilot phase for full PK characterisation at 0.5, 1, 2, 3, 4, 6, 7, 8, 10, and 12 (before next dose) hours post-dose.

A 1 mL blood sample will be taken at each time point. Following centrifugation, plasma samples will be split in two and a back-up sample will be handled as specified in Section 9.2.12 and described in the laboratory manual.

9.2.8.2 Exploratory Blood Collection

Blood for genomic DNA will be collected as per the Study Flow Chart (Appendix 1 and 2) at Visit 2/Baseline and Visit 6/Day 14 and Visit 8/Day 28/Early Termination and stored for potential gene array analysis or additional exploratory testing at a later date.

Blood for essential lipid analysis will be collected as per Study Flow Chart (Appendix 1 and 2) atVisit 2/Baseline, Visit 6/Day 14 and Visit 8/Day 28/Early Termination and analysed at a later date.

9.2.8.3 Biomarker Blood Collection

Blood for biomarkers will be collected as per the Study Flow Chart (Appendix 1 and 2) at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28/Early Termination and will be stored for later biomarker analysis.

9.2.9 Adverse Event Assessment

See Section 11.

9.2.10 Concomitant Medication

All administered concomitant medications should be recorded throughout the study.

Patients should avoid both during the study and for 4 weeks prior to baseline, ingesting food supplements rich in omega-3 or omega-6 fatty acids (e.g., cod liver oil capsules).

9.2.11 Liver Ultrasound

A liver ultrasound will be conducted at screening which, in conjunction with patient history and clinical examination, will eliminate other causes of liver disease including biliary obstruction, hepatocellular carcinoma and Budd Chiari syndrome.

9.2.12 Bioanalysis

Human plasma levels of 15(S)-HEPE will be determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods and conducted at Charles River Laboratories Edinburgh Ltd.

9.2.13 Sample Storage, Handling and Shipping

Sample storage, handling and shipping will be done as per standard operating procedures and as specified in the laboratory procedures manual.

9.2.14 Liver Histopathology

For patients who have liver biopsies as part of their clinical care before and/or during the study, liver histopathology results will be reported in the eCRF

9.2.15 Urinalysis

pH, protein, glucose, blood, ketones, leukocytes, leukocyte esterase, bilirubin, specific gravity, urobilinogen and nitrate will be assessed. Reflex micro to be done locally if blood, protein, leukocyte esterase or nitrate/nitrite are present.

Note: Urinalysis assessment will be conducted at screening only.

10 INVESTIGATIONAL PRODUCT/INVESTIGATIONAL DRUG

The following medication supplies will be used in the study:

DS102 Capsule:

Description:

White, opaque hard-shelled capsule (size 0) containing 500mg of 15-HEPE EE with 5% w/w of colloidal silicon dioxide as viscosity modifier.

DS102 Placebo (Paraffin Oil):

Description:

White, opaque hard-shelled capsule (size 0) containing equivalent fill weight of liquid paraffin with 1% w/w of colloidal silicon dioxide as viscosity modifier.

10.1 Supply, Packaging, Labelling, Handling and Storage

The study treatment is capsules of 15-HEPE EE or placebo. DS102 (15(S)-HEPE EE) will be provided by Afimmune.

DS102 and Placebo capsules will be stored at 2 – 8°C in a secure area (e.g., a locked refrigerator or drug storage room), protected from unintended use.

The test materials will be identified by the batch numbers and expiry date.

Labelling, packaging and release will be in accordance with the Clinical Trials Directive 2001/20/EC and GMP Directive 2003/94/EC as for Investigational Medicinal Products and Annex 13 of the GMP Guide. Labels will be blinded to the dose and contain the randomisation number. In addition, DS102 (15(S)-HEPE EE) and placebo capsules will be labelled with information according to local regulations.

10.2 Dosage and Administration

Patients who fulfil all inclusion and no exclusion criteria may be accepted in the study. Each patient must read and sign an ICF prior to any screening procedures being performed. This study involves a comparison of DS102 with placebo, administered orally within 30 minutes after a meal twice daily for a total duration of 28 days. Patients will also receive standard of care therapy in addition to their assigned IMP throughout the treatment period of the study. The last study drug administration should occur on the day preceding Visit 6/Day 28/Early Termination.

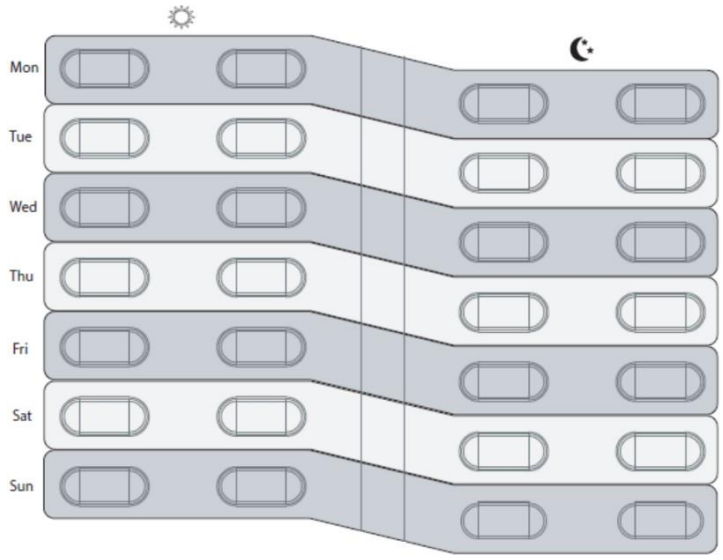
Patients will be randomised to one of the two treatment groups in a 1:1 ratio:

- Treatment group A: 2 x placebo 500mg capsules orally administered BD (four capsules daily) for 28 days

- Treatment group B: 2 x DS102 500mg capsules orally administered BD (four capsules daily) for 28 days

Patients will be required to take the capsules within 30 minutes after a meal. Medication(s) for other conditions that are permitted in the study can be taken as usual.

Walleted blister packs will consist of seven days of four capsules. Patients will be instructed to take the two capsules **from left to right**, on the relevant day, as shown below:



10.3 Duration of Treatment

Patients will take assigned medication for 28 consecutive days.

10.4 Drug Accountability

The Investigator is responsible for maintaining accurate records of the study medication received initially, the study drug dispensed/used, the returned medication by patients (in the case of patients discharged prior to 28 days) and the medication returned to the Sponsor or designee for destruction. All study drug accountability forms and treatment logs must be retained in the ISF. These records must be available for inspection by the Sponsor, its designees or by regulatory agencies at any time.

Used drug boxes/blister packs will be stored safely until destruction and must be accounted for by the Investigator. The study monitor will perform drug accountability for all study drug at the site and assist in returning study drug, including used and unused study drug, to the Sponsor or designee. After verification of the drug accountability by the Sponsor, the Investigator will ensure proper destruction or return of the remaining study product.

Any study medication accidentally or deliberately destroyed will need to be accounted for. Any discrepancies between amounts dispensed and returned will need to be explained.

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Seriousness

Adverse Events (AE):

An AE is defined as any undesirable experience occurring to a patient that has signed the ICF and who has taken their first dose of the study drug, whether or not considered related to the IMP(s). All AEs must be recorded in the eCRF, defining relationship to IMP and severity. AEs should also be recorded by the Investigator in the patient file/notes.

Serious Adverse Events (SAE):

If a patient experiences a SAE after the first dose of the study drug, the event will be recorded as a SAE.

A SAE (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Unexpected Adverse Event (UAE):

A UAE is defined as an experience not previously reported in the Investigator's Brochure (IB) or similar product information sheet such as the Summary of Products Characteristics (SPC).

11.1.2 Severity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience. The following definitions are to be used to rate the severity of an AE:

- Mild: the AE is transient and easily tolerated.
- Moderate: the AE causes the patient discomfort and interrupts the patient's usual activities.
- Severe: the AE causes considerable interference with the patient's usual activities, and may be incapacitating or life-threatening.

11.1.3 Relationship to IMP

The Investigator will establish causality of the AE to experimental treatment. The Investigator should take into account the patient's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: temporal relationship of the onset of the AE, relative to the experimental treatment is not reasonable or another cause can explain the occurrence of the AE.
- Related: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

11.1.4 Reporting of AEs and SAEs

All AEs must be recorded in the eCRF, defining relationship to IMP and severity.

As soon as the Investigator is aware of a potential SAE, he/she should contact the pharmacovigilance (PV) contract research organisation (CRO) monitor by phone, fax or e-mail, and, in any case, no later than 24 hours after the knowledge of such a case. The contact information is provided in the ISF.

At the time of the call, the Investigator must provide, as a minimum requirement, the patient number, birth date, nature of the SAE and a preliminary assessment of causality. The Investigator should follow-up the initial notification of the potential SAE by faxing a copy of the SAE reporting form to the PV CRO at the number provided in the ISF. The faxed SAE reporting form should be sent to the PV CRO within 24 hours of knowledge of such a case.

Follow-up information on an existing SAE that is fatal or life-threatening should be reported by the Investigator to the PV CRO within five days after the initial report. Where appropriate, hospitalisation or autopsy reports should be made available. All SAEs will be followed up until resolution (i.e., asymptomatic, stabilization or death).

AEs should be reported from the first dose of study drug up to and including the follow up period. Following completion of the study, if the Investigator becomes aware of any AE that is potentially related to the IMP the Sponsor should be notified.

11.2 Serious Adverse Reactions and Unexpected Adverse Reactions

11.2.1 Definitions

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

For marketed medicinal products, an adverse reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Unexpected Adverse Reaction:

An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorised IMP or similar product information sheet such as the SPC).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

A SUSAR is defined as any serious adverse reaction that might be related to the IMP and is unexpected according to the definition above.

11.2.2 Reporting of suspected unexpected serious adverse reactions

SUSARs will be reported by the PV CRO according to appropriate competent authority and EC requirements. SUSARs will be reported to Investigators according to ICH GCP and to local regulations. SUSAR reporting to competent authorities and ECs will be performed according to local regulations in an unblinded manner. The competent authorities will be notified of all SUSARs through the EudraVigilance database.

Fatal and life-threatening SUSARs should be reported by the PV CRO as soon as possible to the competent authorities and ECs according to local regulations, and, in any case, no later than seven calendar days after knowledge by the PV CRO of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the competent authorities and ECs according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by the PV CRO.

11.3 Drug Induced Liver Injury (DILI)

11.3.1 Severe drug-induced liver injury

Irrespective of perceived causation, in the event of severe drug-induced liver injury (DILI) then the investigational drug should be discontinued until the episode is deemed to have resolved. In the event the investigational drug is deemed to be the cause of the liver injury then the patient should not be re-challenged with the drug.

Potential severe DILI in the study population (severe acute decompensated AH patients with impaired baseline liver biochemistry) stipulates evidence of hepatic impairment as demonstrated by:

- Total bilirubin >2x baseline and ALT and/or AST >3x baseline (confirmed by immediate repeat testing)
- Total bilirubin >3x baseline (confirmed by immediate repeat testing)
- ALT and/or AST >5x baseline (confirmed by immediate repeat testing)
- ALT and/or AST >500 U/L (confirmed by immediate repeat testing)
- Alkaline Phosphatase ≥5x baseline
- An increase in MELD score > 10
- Lille score > 0.85

Prompt (within 24 hours) adjudication of events of possible DILI or treatment failure, as listed above, will be performed by an independent expert in AH and DILI with recommendations for or against drug discontinuation.

Other causal factors should be considered and if found they must be discussed with the sponsor before investigational product is restarted.

Even if patients discontinue the investigational drug they should still be encouraged to attend study visits for continued study data collection.

11.3.2 Monitoring of patients with impaired liver biochemistry

Abnormalities of liver biochemistry indicating evidence of hepatic impairment as listed above should be followed by repeat testing within 48-72 hours to confirm/determine if the biochemical changes are improving or worsening. AE information should be collected alongside a thorough physical examination. A liver aetiology screen and/or other appropriate testing should be undertaken. In the event of liver dysfunction then the patient should be managed as a severe drug-induced liver injury (see above). Pausing of drug treatment should be considered if any of the criteria in the previous section occur.

11.4 Pregnancy Reporting

If a patient or a patient's partner becomes pregnant during the study, study staff must be

informed as soon as possible. Upon confirmation of the pregnancy, the patient must be withdrawn from the study drug but may continue study participation. The Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to the Sponsor within 24 hours of confirmation of the pregnancy.

Post-treatment follow-up should be done to ensure patient safety. Pregnancy itself is not an AE or SAE, however maternal/foetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor of the outcome as a follow up to the initial pregnancy form.

12 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

12.1 Study Design

This clinical trial employs a randomised, double-blind, placebo-controlled 2-arm parallel group design preceded by an open-label pilot phase. Randomisation is used to minimise assignment bias and to increase the likelihood that known and unknown patient attributes (e.g. demographic characteristics) are evenly balanced across the treatment groups. Blinding is used to reduce potential bias during data collection and the evaluation of safety and efficacy. The use of placebo as a comparator is justified as a reasonable design to assess safety and efficacy in patients based on the brevity of the study duration and the absence of any real established standard of care for alcoholic hepatitis. A full description of the study design is presented in Section 6 above.

12.2 Randomisation

For the open label pharmacokinetic pilot phase, six patients will be enrolled and treated with study drug (2 x DS102 500mg capsules orally administered BD (four capsules daily)), for 28 days. Results of this pilot phase will be assessed by a DSMB for safety and if dose adjustments for the main study are needed.

For the main, double-blind phase, approximately 120 patients will be randomised into double-blind treatment groups in a 1:1 ratio as follows:

- Treatment group A: 2 x placebo 500mg capsules orally administered BD (four capsules daily) for 28 days
- Treatment group B: 2 x DS102 500mg capsules orally administered BD (four capsules daily) for 28 days

At the investigational site, each patient will be assigned a patient screening number during screening that will be used on all patient documentation. The patient screening number will contain the site number and the patient number assigned in numerical order at the screening visit (e.g.: 02-010 for the tenth patient screened at the site #02). Numbers will be assigned in ascending order starting with 001.

A randomisation list, permuted blocks and stratified by site, will be generated by Afimmune or its designee. The randomisation schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the interactive web response system (IWRS) team responsible for implementing the schedule. The IWRS will assign medication kit numbers to each patient, as required, at visits and the contents will be based on the randomisation code.

12.3 Estimation of Sample Size

Two-Sample T-Tests using Effect Size

Numeric Results for Two-Sample T-Test
Alternative Hypothesis: H1: d ≠ 0

Target Power	Actual Power	N1	N2	N	Effect Size d	Alpha
0.80	0.8036	100	100	200	0.40	0.050
0.80	0.8002	90	90	180	0.42	0.050
0.80	0.8045	83	83	166	0.44	0.050
0.80	0.8044	76	76	152	0.46	0.050
0.80	0.8051	70	70	140	0.48	0.050
0.80	0.8015	64	64	128	0.50	0.050
0.80	0.8065	60	60	120	0.52	0.050
0.80	0.8014	55	55	110	0.54	0.050
0.80	0.8074	52	52	104	0.56	0.050
0.80	0.8030	48	48	96	0.58	0.050
0.80	0.8037	45	45	90	0.60	0.050

To discover an effect size of 0.54 (=Difference in means/standard deviation) in MELD change from baseline with 80% power, 55 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided).

To take deviations from ideal parametric conditions and drop-outs into account randomisation of 60 patients per group is recommended.

12.4 Blinding and Code Breaking Instructions

All study site personnel, as well as the personnel involved in the monitoring or conduct of the study, will be blinded to the individual patient treatment assignments. Randomisation details will be kept strictly confidential, accessible only in an emergency to authorised persons, until the time of formal unblinding. The blinded code for the trial will be broken only after all patient data has been recorded and verified and the database locked.

Emergency unblinding will be performed via the IWRS, with relevant site personnel and PV monitors provided with the required system access to carry out unblinding.

12.5 Data Analysis

Data analysis will be performed at the CRO. All computations will be completed using SAS® version 9.1.3 or later. Graphical summaries will be produced using SAS®. A detailed description of the analyses to be performed will be provided in the Statistical Analysis Plan (SAP).

12.6 Analysis Populations

Full Analysis Set (FAS):

Patients will be included in the FAS for analysis of efficacy if they are randomised to the study and received at least one dose of study medication. The specific criteria for the FAS will be detailed in a separate SAP. Analysis will be done according to treatment as randomised.

Safety Analysis Set (SAS)

The SAS consists of all patients who received at least one dose of the medication. SAS is the analysis population for all safety endpoints. Analysis will be done according to the actual treatment patients received.

Pharmacokinetic Population

The PK population consists of all patients who received at least one dose of study medication.

Per Protocol Set:

In order to qualify for the Per Protocol Set (PPS), the patients must have followed the study protocol without any major protocol deviation. Protocol violations will be assessed for each patient in a blinded fashion prior to database lock at a Blind Data Review Meeting (BDRM), and the PPS will also be finalised during this meeting. PPS is a supportive analysis population for the primary efficacy endpoint. Analysis will be done according to the treatment that patients were randomised to.

Total population:

Any patient who withdraws from the randomised phase of the study will be included in the safety analysis (AEs and laboratory parameters). Data for all patients will be listed, and a list of withdrawn patients, with all reasons for withdrawal, will be given.

Total population also includes data for those patients who, after having consented to participate, underwent screening examinations required for inclusion into the study but who, because a criterion for exclusion was met or for other reasons, were not included in the study.

12.7 Safety Analysis

Demographic information, medical history and physical examination data will be listed for each patient and summarised descriptively.

All AEs recorded during the study will be coded to system organ class and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-

emergent AEs will be tabulated and summarised by treatment, relationship to treatment, seriousness and severity. Non-treatment emergent AEs will be listed separately.

Clinical laboratory values (haematology, biochemistry, and coagulation) will be listed for each patient by treatment and day. Values outside the laboratory normal ranges will be listed separately with associated comments as to their clinical significance, with potentially clinically significant abnormalities highlighted and summarised by treatment. Clinical laboratory values obtained prior to dosing will be defined as baseline values.

Individual values of vital signs will be listed and summarised descriptively for each treatment and day.

ECG assessments will be listed for each patient with all associated comments and summarised by treatment and day.

Concomitant medications (if any), categorised by medication group and subgroup according to the latest version of the World Health Organisation drug dictionary (WHODD), will be listed and summarised by treatment.

In general, appropriate descriptive statistics, according to the nature of the variable, will be applied. Categorical variables will be presented using counts and percentage, whilst continuous variables will be presented using mean, standard deviation, median, minimum, maximum, coefficient of variation and number of patients.

12.8 Statistical Analysis Plan

In addition to the summarised analysis outlined below, a separate document, SAP for DS102A-05-AH1, will detail all analysis to be performed.

12.8.1 Pharmacokinetic Analysis

PK will be analysed using the following parameters:

<u>Pilot Phase:</u>

- C_{max} – maximum observed concentration
- T_{max} - time of maximum observed concentration
- AUC_t – Area under the concentration-time curve to time t
- AUC_{tau} - Area under the concentration-time curve to the end of the dosage interval
- AUC_{inf} - Area under the concentration-time curve extrapolated to infinite time
- %Extrap – Percentage of AUCinf obtained by extrapolation
- Kel – Apparent first-order terminal elimination rate constant
- $T_{1/2}$ – Apparent first-order terminal elimination half-life

- Flucp – Fluctuation at pharmacokinetic steady-state
- R_{ac} – Accumulation ratio at pharmacokinetic steady-state
- T_{ss} – Time to achieve pharmacokinetic steady-state

Double-Blind Phase:

- R_{ac} – Accumulation ratio at pharmacokinetic steady-state
- T~~ss~~ – Time to achieve pharmacokinetic steady-state

12.8.2 Primary Variables

The primary efficacy variable will be change in MELD score from baseline to Day 28. This change in MELD score and its difference between treatment groups will be estimated using a General Linear Repeated Measures Model with treatment arm, baseline MELD value, visit and treatment arm by visit interaction as factors. The primary analysis will be based on the FAS and repeated for the PPS as a supportive analysis.

12.8.3 Secondary variables

The secondary and exploratory efficacy variables will be summarised with descriptive statistics per treatment group and visit. The change from baseline to Day 28 (and other visits) for the active treatment group will be compared against placebo either via logistic regression or analysis of covariance taking the baseline level as covariate into account. Survival time will be analysed using the Cox Proportional Hazards model including treatment group and MELD score at baseline as covariate. The 5% level of significance will be used for all treatment comparisons of secondary and exploratory endpoints without adjustment for multiplicity.

A new secondary efficacy variable will be a 5-level ordinal variable combining change of MELD score from baseline, premature treatment terminations and mortality as follows; each patient will be allocated to the first level that occurs

- level 1: death within 28 days,
- level 2: death within 90 days,
- level 3: early treatment termination because of safety issues or lack of efficacy,
- level 4: no improvement in Meld Score at day 28 compared to baseline,
- level 5: improvement in Meld Score at day 28 compared to baseline

Patients with lost to follow up within 28 days will be allocated to level 4 or 5 according to their imputed result at day 28 based on the model in 12.9.2 as for these patients the MAR assumption seems appropriate.

This ordinal variable will be analysed using ordinal logistic regression with MELD score as baseline covariate (alpha=0.05 two-sided). An odds ratio including 95%-confidence limits will be calculated as measure of effect size for this variable.

12.9 Data Collection/Electronic Case Report Forms

Data will be collected using a validated electronic data capture (EDC) solution. eCRFs will be utilised for recording data from each patient meeting the eligibility criteria and being randomised in the study, and a limited amount of data will be completed for patients who fail to meet eligibility criteria (i.e. screen failures). Electronic access to the eCRF will be available to all investigator sites. All study staff responsible for entering data into the eCRF system will be trained prior to the start-up of the study. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained.

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator of the clinical site. It is the responsibility of the Investigator to ensure that the eCRFs are properly completed. The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data-protection regulations.

Captured data will be monitored electronically and source data verification (SDV) will take place at the site where all information will be verified against the individual patient records. Any inconsistencies will be presented as queries, either as automatically generated queries if raised by the logical data checks of the eCRF system, or by manually generated queries if raised by the data validation checks or the SDV performed by the data manager (DM) or the clinical research associate (CRA), respectively. Queries shall be resolved in a timely manner by a trained member of the site staff.

12.10 Data Management

Data will be transmitted electronically into the web based EDC system. Data will be coded according to pre-specified dictionaries and in accordance with CRO SOPs. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

12.11 Protocol Deviations

Protocol deviations will be captured through site self-reporting, CRA SDV and data management edit checks, and will be recorded by the CRA throughout the study in both monitoring visit reports and in a centralised log.

13 REGULATORY AND ADMINISTRATIVE PROCEDURES

13.1 Institutional Review

Investigators will agree that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state and local laws or regulations.

The protocol and the PIS/ICF will be approved by the relevant competent authorities and ECs, and possibly other public bodies according to local requirements, before commencement of the study. If a protocol amendment is necessary, this will be prepared with the agreement of the national co-ordinating Investigator and signed by the relevant parties. If the amendment is considered to be substantial, it will be submitted to the competent authorities and ECs, and possibly other public bodies according to local requirements, for review and approval. The protocol amendment will not be implemented before such approvals are obtained, if required. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) do not need to be submitted to competent authorities

SUSAR reports and periodic safety reports will be sent to competent authorities and ECs, according to local regulations.

13.2 Informed Consent and Inclusion of Subjects Incapable of Providing Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable to local regulation), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. If the patient is incapacitated, e.g. in the case of Grade II or Grade III hepatic encephalopathy, a relative (with the exception of certain countries) or legal representative will be responsible for giving informed consent on behalf of the patient in accordance with the Declaration of Helsinki.

Additional requirements for representatives giving informed consent for an incapacitated patient may apply in certain countries. Investigators in these countries will be notified accordingly in a protocol clarification memo and the patient information sheet and informed consent will be adapted.

Clinical trials are essential to improve the outcomes of subjects with critical illness, such as the target population of this study. However, individuals with Severe Acute Alcoholic Hepatitis comprise a critically ill patient population in which it may be difficult to obtain robust informed consent. The value and generalisability of study results is contingent upon recruitment of a representative sample of patients, ensuring that consenting participants and non-consenting participants are not systematically different. As a result, it may be necessary that persons who are incapable of giving informed consent are included in this study.

Robust measures are in place to ensure that in such situations informed consent is obtained

from an appropriate relative or legal representative. A separate ICF will be used in such cases. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the recruiting physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent must be respected.

The patient, or a relative/legal representative, if applicable, will be given the opportunity to ask questions to the investigational team. It must also be explained that they are completely free to refuse permission to enter the study or to withdraw from it at any time for any reason. Sufficient time will be given to consider participation in the study. If, after this, permission is given to enter the study, the patient, or relative/legal representative, if applicable, will be asked to sign and date one original copy of the written informed consent form (ICF). The patient, or relative/legal representative, if applicable, will then receive a copy of the signed and dated patient information sheet (PIS)/ICF. The original signed ICF will be filed in the Investigator Site File (ISF). The PIS will contain site contact information in case of any questions or medical emergency.

If, at a later stage, a previously incapacitated patient becomes able to give consent to the study, the Investigator, or delegate, must obtain informed consent from the patient for them to continue in the study.

The investigator will constantly assess the level of burden to the patients, and if new safety information results in significant changes in the risk/benefit assessment or any new information presents that may affect willingness to continue to participate, the consent form should be updated and approved, if necessary, by the Research Ethics Committee (REC)/Institutional Review Board (IRB). All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study. In the case of patients who remain unable to give consent, a relative/legal representative will receive the updated information and be asked to give consent for the patient to continue in the study. Any written information given to potential patients or relatives/legal representatives will be submitted to, and approved by, the respective Ethics Committee(s) (EC) prior to implementation.

13.3 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be in place, composed of independent experts, to monitor the safety and scientific integrity of the study. The DSMB will periodically review accumulated patient data for safety, study conduct and progress and efficacy, and assess the potential benefits and risks to the patient. The DSMB also can provide recommendations to the sponsor related to the continuation, modification or termination of the study. Details of the roles and responsibilities of the DSMB members are regulated in the DSMB charter.

13.4 Good Clinical Practice

The study will be managed and conducted according to the latest ICH GCP and applicable regulatory requirement(s) (specifically the principles of GCP in ICH topic E6, as laid down by the Commission Directive 2005/28/EC and in accordance with applicable local laws and guidelines). A copy of the ICH guidelines can be found in the ISF.

13.5 Essential Documents

The ICH guideline for GCP lists a number of essential GCP documents required prior to, during, and after the conduct of the study. It is the responsibility of the monitor to ensure that the Investigator is always provided with a copy of such documents prepared by the study management, and it is likewise the responsibility of the Investigator to provide the monitor with essential documents prepared by the Investigator or the local EC. A complete list of essential GCP documents can be found in the ISF.

13.6 Record Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These records include, but are not limited to, the identity of all participating patients, all original signed informed consent documents, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition and adequate documentation of relevant correspondence.

The records should be retained by the Investigator according to ICH, local regulations, or as specified in the clinical trial agreement (CTA), whichever is longest.

13.7 Monitoring/Quality Control

Monitoring visits will be conducted during the study at regular intervals. Monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries in the eCRF, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities.

Incorrect or missing entries in the eCRFs will be queried and will be corrected appropriately.

All clinical data will undergo quality control checks prior to clinical database lock. Edit checks will then be performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Each eCRF will be reviewed and signed by the PI.

13.8 Quality Assurance

Investigational sites may be audited during or after the study is completed by Sponsor representatives, or regulatory authorities may conduct an inspection. The Investigator(s) will be expected to cooperate with such a visit and to provide assistance and documentation (including all study documentation, and patient source data), as requested.

13.9 Insurance and Liability

Insurance and liability for the study is the responsibility of the sponsor, Afimmune. Patient insurance is taken out for study participants in accordance with legal requirements.

13.10 End of Trial

The end of trial is defined as ‘last patient last visit (LPLV)’. LPLV is defined as the date the Investigator reviews the last subject’s safety data and determines that no further evaluation is required for the subject to complete the trial.

The study will be prematurely terminated should more than one patient experience a Grade 3 or higher AE on the CTCAE scale in any one category that is determined to be possibly or probably attributable to study drug (excluding evaluation of liver function), or a 2-point worsening of modified m-SOFA score if possibly or probably attributable to study drug.

13.11 Confidentiality

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and is included in the ICF signed by the patient. The study data shall not be disclosed to a third party without the written consent of the Sponsor.

13.12 Report and Publication

Production of a clinical study report (CSR) in accordance with the ICH guidelines will be the responsibility of the CRO. No information from the study will be published without the prior written consent of the Sponsor.

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15 APPENDICES

15.1 Appendix 1: Flow Chart – Pilot Phase

Visit	Screening/ Visit 1	Baseline/ Visit 2	Day 3/ Visit 3	Day 5/ Visit 4	Day 7/ Visit 5	Day 14/ Visit 6	Day 21/ Visit 7	Day 28/Visit 8/ Early Termination	Day 90/Visit 9/ Follow Up
Day		**0**	**3**	**5**	**7**	**14**	**21**	**28**	**90**
Visit Window	**N/A**	±0 day	±0 day	±0 day	±2 day	±2 day	±2 day	±1 day	±10 days
Informed Consent[3]	X								
Inclusion/Exclusion	X	X							
Demographics	X								
Patient Randomisation		X							
Medical History	X	X							
Physical Examination	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
ECG (6-lead or 12-lead)	X	X						X	
Pharmacokinetic Sampling[4]		X	X	X	X	X	X	X	
Exploratory Blood Sample		X				X		X	
Clinical Laboratory Tests[1]	X	X	X	X	X	X	X	X	X
Virology	X								
Urinalysis	X								
Liver ultrasound	X								
Pregnancy Test[2]	X	X				X		X	
MELD	X	X	X	X	X	X	X	X	X
MDF	X	X	X	X	X	X	X	X	X
m-SOFA		X	X	X	X	X	X	X	X
West Haven Criteria	X	X	X	X	X	X	X	X	X
APACHE II		X	X	X	X	X	X	X	X
Lille score		X	X	X	X	X	X	X	X
Total Bilirubin	X	X	X	X	X	X	X	X	X
CK-18		X	X	X	X	X	X	X	X
ALT, AST	X	X	X	X	X	X	X	X	X
Child Pugh Score		X	X	X	X	X	X	X	X
Gamma GT		X	X	X	X	X	X	X	X
Assessment of nutritional status		X				X		X	
Collection of acute kidney injury, ascites and variceal haemorrhage data		X	X	X	X	X	X	X	
Biomarker		**x**	**x**	**x**	**x**	**x**	**x**	**x**	

Visit	Screening/ Visit 1	Baseline/ Visit 2	Day 3/ Visit 3	Day 5/ Visit 4	Day 7/ Visit 5	Day 14/ Visit 6	Day 21/ Visit 7	Day 28/Visit 8/ Early Termination	Day 90/Visit 9/ Follow Up
Mortality			X	X	X	X	X	X	X
IMP/Placebo Administration		X ----------X							
AE Assessment		X	X	X	X	X	X	X	
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	

[1] Includes biochemistry, haematology,and coagulation tests. Caeruloplasmin will be collected at screening only

[2] Female Patients of child bearing potential only.

[3] Patient may be required to reconsent after Visit 1 if new information is made available.

[4]PK sampling for pilot phase will be conducted at the following timepoints on Day 0 and Day 7: 0.5hours, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 7 hours, 8 hours, 10 hours and 12 hours (before next dose). Trough plasma samples will also be obtained prior to the first daily dose on the indicated days.

15. 2 Appendix 2: Study Flowchart – Double-Blind Phase

Visit	Screening/ Visit 1	Baseline/ Visit 2	Day 3/ Visit 3	Day 5/ Visit 4	Day 7/ Visit 5	Day 14/ Visit 6	Day 21/ Visit 7	Day 28/Visit 8/ Early Termination	Day 90/Visit 9/ Follow Up
Day		**0**	**3**	**5**	**7**	**14**	**21**	**28**	**90**
Visit Window	**N/A**	±0 day	±0 day	±0 day	±2 day	±2 day	±2 day	±1 day	±10 days
Informed Consent[3]	X								
Inclusion/Exclusion	X	X							
Demographics	X								
Patient Randomisation		X							
Medical History	X	X							
Physical Examination	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
ECG (6-lead or 12-lead)	X	X						X	
Pharmacokinetic Sampling [4]		X	X	X	X	X	X	X	
Exploratory Blood Sample		X				X		X	
Clinical Laboratory Tests[1]	X	X	X	X	X	X	X	X	X
Virology	X								
Urinalysis	x								
Liver ultrasound	X								
Pregnancy Test[2]	X	X				X		X	
MELD	X	X	X	X	X	X	X	X	X
MDF	X	X	X	X	X	X	X	X	X
m-SOFA		X	X	X	X	X	X	X	X
West Haven Criteria	X	X	X	X	X	X	X	X	X
APACHE II		X	X	X	X	X	X	X	X
Lille score		X	X	X	X	X	X	X	X
Total Bilirubin	X	X	X	X	X	X	X	X	X
CK-18		X	X	X	X	X	X	X	X
ALT, AST	X	X	X	X	X	X	X	X	X
Child Pugh Score		X	X	X	X	X	X	X	X
Gamma GT		X	X	X	X	X	X	X	X
Assessment of nutritional status		X				X		X	
Collection of acute kidney injury, ascites and variceal haemorrhage data		X	X	X	X	X	X	X	
Biomarker		**x**	**x**	**x**	**x**	**x**	**x**	**x**	

Visit	Screening/ Visit 1	Baseline/ Visit 2	Day 3/ Visit 3	Day 5/ Visit 4	Day 7/ Visit 5	Day 14/ Visit 6	Day 21/ Visit 7	Day 28/Visit 8/ Early Termination	Day 90/Visit 9/ Follow Up
Mortality			X	X	X	X	X	X	X
IMP/Placebo Administration		X ----------					----------X		
AE Assessment		X	X	X	X	X	X	X	
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	

[1] Includes biochemistry, haematology, and coagulation tests. Caeruloplasmin will be collected at screening only

[2] Female Patients of child bearing potential only.

[3] Patient may be required to reconsent after Visit 1 if new information is made available.

[4] Trough plasma PK samples will also be obtained prior to the first daily dose on the indicated days.

15.2 Appendix 3: Acute Physiologic and Chronic Health Evaluation II

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**	**Points**
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	>160	130 to 159	110 to 129		70 to 109		50 to 69		<49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO_2 **or**PaO_2 (mm Hg) a. FIO_2 ≥0.5 record A-aDO2 b. FIO_2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) <44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; >75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:

5 points for nonoperative or emergency postoperative patients
2 points for elective postoperative patients

***Definitions*:** organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

- **Liver** – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
- **Cardiovascular** – New York Heart Association Class IV.
- **Respiratory** – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.
- **Renal** – receiving chronic dialysis.
- **Immunocompromised** – the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukaemia, lymphoma, AIDS).