A Randomised, Double-Blind, Placebo-Controlled, Exploratory Phase IIa Study to Assess the Safety And Efficacy of Orally Administered DS102 in NAFLD Patients

Protocol Number # DS102A-02

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Sponsor:

Afimmune,
Trintech Building,
South County Business Park,
Leopardstown,
Dublin 18,
Republic of Ireland.

CONTACT INFORMATION

Chief Investigator:	Prof. Philip Newsome Institute of Biomedical Research, Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.
Sponsor Medical Expert:	Dr. Markus Weissbach, Medical Director, Afimmune, Trintech Building, South County Business Park, Leopardstown, Dublin 18, Republic of Ireland. Tel: +353 1 293 3590
Pharmacovigilance/Medical Monitor:	Safety Physician, Product Life Ltd., The Jeffreys Building, St. John's Innovation Park, Cowley Road, Cambridge CB4 0DS, United Kingdom. Tel: +44 (0) 1223 402660 Email: safety@productlife-group.com

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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.

SPONSOR:

Signature: **Date:** 28 Aug, 2018

Dr. Markus Weissbach,
Medical Director
Afimmune

CHIEF INVESTIGATOR:

Signature: **Date:**

Prof. Philip Newsome
Director of Centre for Liver Research
Liver Unit - Consultant Hepatologist
University Hospitals Birmingham

STATISTICIAN:

Signature: **Date:** 29 Aug, 2018

Mr. Winfried Koch
Statistical Consultant
BDS Koch

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.

SPONSOR:

Signature: **Date:** 28 Aug, 2018

Dr. Markus Weissbach,
Medical Director
Afimmune

CHIEF INVESTIGATOR:

Signature: **Date:** 27 Aug 2018

Prof. Philip Newsome
Director of Centre for Liver Research
Liver Unit - Consultant Hepatologist
University Hospitals Birmingham

STATISTICIAN:

Signature: **Date:**

Mr. Winfried Koch
Statistical Consultant
BDS Koch

PRINCIPAL SITE INVESTIGATOR SIGNATURE PAGE

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 Harmonization (ICH) Good Clinical Practices Guidelines, 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, Exploratory Phase IIa Study To Assess The Safety And Efficacy Of Orally Administered DS102 In Patients with NAFLD
SHORT TITLE:	Safety And Efficacy Study Of Orally Administered DS102 In Patients With NAFLD
PHASE:	IIa
STUDY DURATION:	24 weeks (Treatment Duration: 16 weeks)
INVESTIGATIONAL PRODUCT:	DS102 Capsule Placebo (paraffin oil)
OBJECTIVES:	To assess the safety and efficacy of orally administered DS102 capsules versus placebo in the treatment of adult patients with Non-Alcoholic Fatty Liver Disease (NAFLD)
ENDPOINTS:	*Primary Endpoints* Efficacy • Change in serum ALT (alanine aminotransferase) from baseline to week 16 • Change in liver stiffness measurements by Transient Elastography from baseline to week 16 Safety • Number of Treatment Emergent Adverse Events (TEAEs) in each treatment group leading to treatment discontinuation *Secondary Endpoints* • Change in serum ALT (alanine aminotransferase) from baseline to weeks 2, 4, 8 and 12 • Change in AST (aspartate aminotransferase) from baseline to weeks 2, 4, 8, 12 and 16 • Change in AST:ALT ratio from baseline to weeks 2, 4, 8, 12 and 16 • Change in FIB-4 Index from baseline to week 16 • Change in NAFLD fibrosis score (NFS) from baseline to week 16 • Change in hepatic fat measured by CAP (controlled attenuation parameter) from baseline to week 16 • Change in ELF (Enhanced Liver Fibrosis score) from baseline to week 16 Change in HOMA-IR/Adipo-IR (Homeostatic model assessment Insulin Resistance / Adipose tissue Insulin Resistance) from baseline to weeks 2, 4, 8, 12 and 16

STUDY DESIGN:	This study will involve two dose levels of DS102 1000mg per day (500mg BD), 2000mg per day (1000mg BD) or placebo BD for 16 weeks using three treatment groups consisting of 32 patients each. The sample size may be increased up to a maximum of 150 patients based on the recommendation of the independent DSMB after interim analysis. Patients with diagnosed NAFLD (Non-Alcoholic Fatty Liver Disease) will be enrolled in the study. After assessment and documentation of the baseline disease characteristics by the investigator, the patient will be randomly assigned to one of the above mentioned treatment groups. The patient will be provided with study medication containing one of the assigned doses of DS102 or placebo according to the randomisation. During the 16 weeks of treatment patients will take one of the treatments twice daily with or after food (morning and evening). Evaluation of efficacy will be performed throughout the study. A follow-up visit will be performed 4 weeks after the last date of treatment to monitor the treatment effects in comparison to the end of treatment.
TOTAL NUMBER OF RANDOMISED PATIENTS:	96 patients total. This may be increased up to a maximum of 150 patients based on interim analysis.
STUDY POPULATION:	
Inclusion criteria:	1. Patients diagnosed with NAFLD by the presence of hepatic steatosis on imaging or histology in the absence of any secondary causes. 2. Patients with an ALT ≥ 1.5 ULN and < 5 ULN on two occasions 7 or more days apart during screening. 3. Patients with historical liver biopsy showing NASH and/or ≥ F1 fibrosis OR NFS ≥ -1.455 OR FIB-4 ≥ 1.3 OR Fibroscan ≥8kPa within 3 months of screening. 4. Patients with a body mass index (BMI) between 25.0 and 40.0 kg/m² inclusive. Patients with a history of controlled obesity or controlled diabetes are allowed on the study. 5. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator. 6. Patients aged between 18 and 75 years inclusive. 7. Female patients and male patients with female partners of child bearing potential must use adequate contraception or have a sterilized partner for the duration of the study. Adequate contraception is defined as: systemic hormonal contraceptives,

	intrauterine device or barrier method of contraception; in conjunction with spermicide; or agree to sexual abstinence, defined as a patient refraining from heterosexual intercourse during the entire period of risk associated with the study treatments and in line with their preferred and usual lifestyle. Hormonal contraceptives must be on a stable dose for at least one month before baseline 8. Patients who are able to communicate well with the Investigator, to understand and comply with the requirements of the study, and understand and sign the written informed consent.
Exclusion criteria:	1. Patients with an unstable metabolic condition such as weight change > 5% in the 3 months prior to inclusion. 2. Patients with medical/surgical history of gastric bypass surgery, orthotopic liver transplant (OLT) or listed for OLT. 3. Patients with uncontrolled diabetes mellitus type 2, i.e. HbA1c ≥ 9% (75mmol/mol) at the time of screening. 4. Patients with decompensated or severe liver disease as evidenced by one or more of the following: confirmed cirrhosis or suspicion of cirrhosis, esophageal varices, ascites, suspicion of portal hypertension, hospitalization for liver disease within 60 days of screening, bilirubin ≥ 2 x ULN, or ALT or AST ≥ 5 x ULN. Patient's with Gilbert's syndrome are eligible if the conjugated bilirubin is ≤1.5 x ULN. 5. Patients with inflammatory bowel disease that is either active or requiring medical therapy. 6. Patients with diagnosed or suspected autoimmune diseases such as systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA). 7. Patients with a history of or active non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas). 8. Patients with significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal insufficiency, serious psychiatric disease, respiratory or hypertensive disease, as well as diabetes and arthritis that, in the opinion of the Investigator, would preclude the patient from participating in and completing the study.

	9. Patients requiring anti-diabetic treatment (including insulin sensitizing agents), and/or lipid lowering treatment, and who are not on a stable dose for at least 3 months prior to screening should be excluded. If patients are insulin dependent this treatment should have commenced at least 3 months prior to screening, however changes in dose are permitted. 10. Patients with known hypersensitivity to any ingredients of the study treatment. 11. Patients with a positive test for human immunodeficiency virus (HIV) antibodies, Hepatitis B surface antigen or Hepatitis C antibodies at screening. 12. Patients with liver disease of other aetiologies such as drug-induced, autoimmune hepatitis, PBC, PSC, haemochromatosis, A1AT deficiency or Wilson's disease. 13. Patients with a significant history of drug/solvent abuse, in the opinion of the investigator. 14. Patients with a history of alcohol abuse in the opinion of the Investigator, or who currently drinks in excess of 21 units per week (males) or 14 units per week (females), whereby a unit consists of 10ml or 8mg of pure alcohol. 15. Patients who have used dietary supplements rich in omega-3 or omega-6 fatty acids in the 4 weeks prior to baseline. 16. Patients who have participated in any other clinical study with an investigational drug within 3 months before the first day of administration of study treatment. 17. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in inclusion criterion 7) during the trial. 18. Patients, in the opinion of the Investigator, not suitable to participate in the study.
Dietary restrictions:	Patients should avoid ingesting food supplements rich in omega-3 or omega-6 fatty acids (e.g. cod liver oil capsules) both during the study and for 4 weeks prior to baseline.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:	DS102 will be provided in a capsule, containing 500mg of 15-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.

	This study will involve two dose levels for 16 weeks 1000 mg per day (500mg BD), 2000mg per day (1000mg BD) or placebo BD using three treatment groups consisting of 32 Patients each.
EVALUATION CRITERIA:	Efficacy: • ALT • AST • Hepatic Fat measurement by CAP • Liver stiffness measurement by Transient Elastography • ELF • FIB-4 • NFS • AST:ALT Ratio • HOMA-IR/Adipo-IR Safety: • Physical examination, including height and weight • 12-lead ECG • Vital signs, including blood pressure (BP), pulse and temperature. • Clinical laboratory tests (haematology, coagulation, biochemistry, lipid profile, virology and urinalysis) • Pregnancy test for females of child bearing potential • Adverse Events (AEs) • Concomitant medications
PHARMACOKINETICS	Plasma concentrations of DS102: Predose C_{trough} levels taken at Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week 16 and Follow up Visit 11/Week 20.
EXPLORATORY	Blood will be collected throughout the study (at the timepoints specified in the Study Flow Chart [Appendix 1]) and will be stored for potential biomarker analysis. Blood will also be collected and stored for potential exploratory gene array analysis or additional testing at a later date.
STATISTICS	Sample Size: Assuming a 20% delta in the percentage response between active drug and placebo arms, a standard deviation of 25% and a drop out rate of 20%, this results in 32 patients per group with 5% level of significance, and 80% power. The sample size may be re-estimated at an interim analysis based on recommendation from an unblinded, independent DSMB. The sample size may be increased up to a maximum of 150 patients in total to achieve a conditional power of 80% for the primary endpoint.

	Methods: The active treatment groups will be compared against placebo via an analysis of variance (ANOVA) model. The comparisons against placebo will be done according to Dunnett's multiple testing procedure. A clinically meaningful response is defined as a mean or median difference of the active treatment groups to placebo of either 20% for ALT or Liver Stiffness or a difference of 10% for both ALT and Liver Stiffness
SPONSOR:	Afimmune

LIST OF ABBREVIATIONS

15(S)-HEPE EE	15(S)-Hydroxy-Eicosapentaenoic Acid Ethyl Ester
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CAP	Controlled Attenuation Parameter
CRF	Case Report Form
DOA	Drugs of Abuse
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ELF	Enhanced Liver Fibrosis Score
EPA	Eicosapentanoic Acid
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
ISF	Investigator Site File
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
NOAEL	No Observed Adverse Effect Levels
OTC	Over the Counter
PBMC	Peripheral Blood Mononuclear Cells
PIS	Patient Information Sheet
PK	Pharmacokinetic
PV CRO	Pharmacovigilance Contract Research Organisation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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

1 INTRODUCTION

1.1 Therapeutic Area and Disease Background

Non-alcoholic fatty liver disease (NAFLD) is a form of chronic liver damage that affects a wide range of individuals. It is estimated that up to 31% of adults in the United States and 33% of adults in Europe are affected and that the prevalence will continue to increase. The most commonly documented comorbidities that have been associated with NAFLD include obesity, impaired insulin sensitivity and dyslipidemia. NAFLD exists as a spectrum and is best characterised histologically. Important features include steatosis, inflammation, hepatocellular ballooning and fibrosis. NAFLD can be classified as non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). In NAFL there is an accumulation of fat in the liver but hepatocellular injury is absent, whereas NASH involves the presence of steatosis and inflammation with hepatocyte damage, with or without fibrosis. Once present, these specific changes mediate the risk of future disease progression (Malhotra and Beaton et al. 2015). About 20-40% of patients with NASH have some degree of fibrosis in their initial biopsy. Data on progression to cirrhosis is sparse but patients with NASH cirrhosis and cryptogenic cirrhosis account for 10-12% of liver transplants (Adams et al. 2005). Hepatocellular carcinoma occurs in 2-4% of patients with NASH cirrhosis but occasionally patients with NASH cirrhosis present with hepatocellular carcinoma also (Bullock et al. 2004).

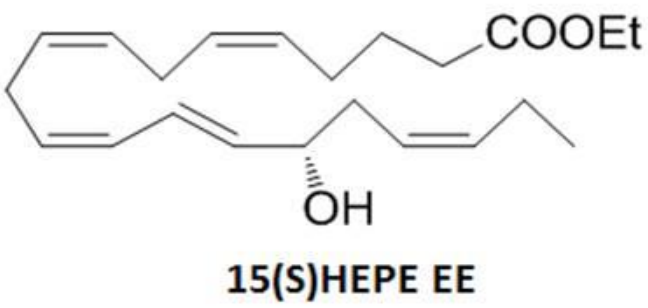
1.2 Standard Treatment

There are currently no approved drugs for NAFLD. The current standards of care include lifestyle management with a goal of sustained weight loss, treating associated features of the metabolic syndrome to reduce cardiovascular risk and in some cases transplantation. The off-label use of oral hypoglycemic agents and vitamin E has not been proven. Developing bariatric surgical techniques are promising, but additional studies with long-term follow up are needed before they can be widely recommended. Finally, liver transplantation is an increasingly frequent consideration once complications of end-stage disease have developed (Malhotra and Beaton et al. 2015). There is an obvious unmet need for advanced treatment in this disease area.

1.3 Drug Class

DS102 is an endogenously occurring essential 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, 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 LPS induced inflammation in Peripheral Blood Mononuclear cells (PBMCs) showing a significant decrease in Tumour Necrosis Factor-alpha (TNF-alpha), IL-6, IL-8 and IL-23. Anti-fibrotic effects of DS102 were observed in Transforming Growth Factor-beta (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 NASH.

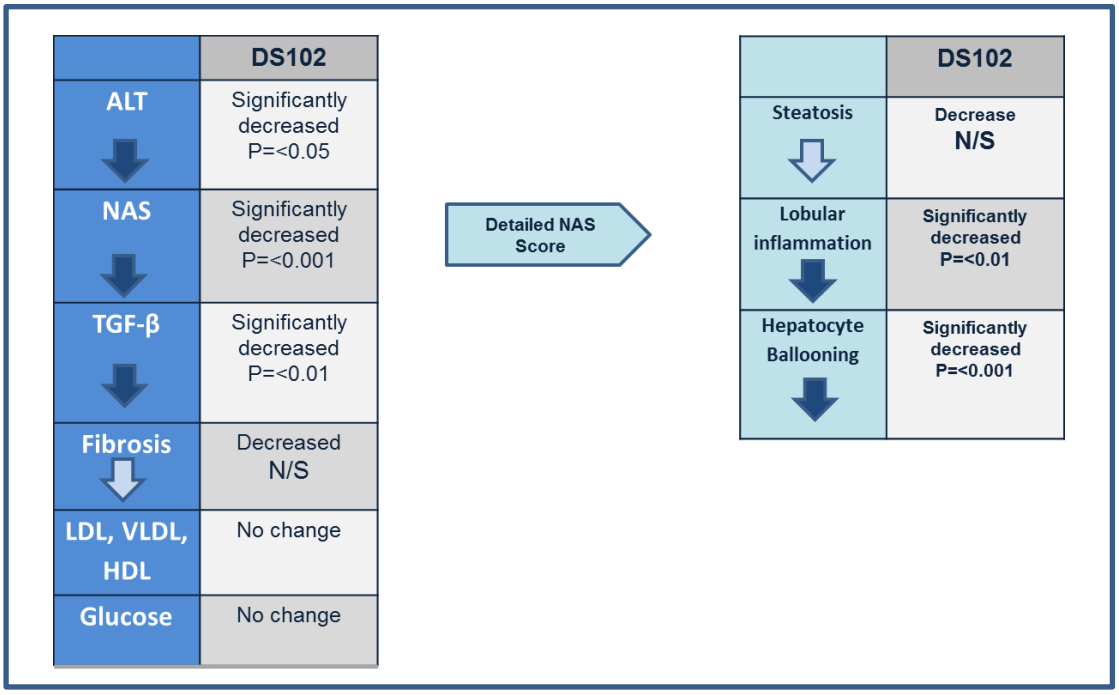
Table 1: DS102 Mechanism of Action Summary

#	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.

A subcutaneous injection of streptozotocin was administered to newborn mice followed by a high fat diet from 4 weeks of age. Results presented represent overall outcomes from 4 studies performed. NAS score is separated into three components: steatosis, lobular inflammation and hepatocyte ballooning. Light arrows signify a decrease. Dark arrows signify a significant decrease.

Figure 2: Schematic summarising the results of 4 in vivo studies performed using the STAM™ Model (DS-PC-26, DS-PC-27, DS-PC-28, DS-PC-29).



Treatment with DS102 at 500 mg/kg significantly decreased plasma ALT, a liver injury marker, and plasma TGF-beta, 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 it's 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 findings are important, because reduction of NAS is one of the major clinical endpoints for assessing the drug efficacy in NASH patients (Sanyal AJ. et al., 2011). Thus, the results suggested that DS102 has potential hepatoprotective and anti-inflammatory effects against steatohepatitis. Perisinusoidal fibrosis around the central vein is predominantly observed in human NASH (Brunt EM et al.1999) and reported to be associated with poor prognosis of NASH (Brunt EM et al. 2005). Therefore perisinusoidal collagen deposition is an important factor to estimate the disease condition of NASH. The reduction of fibrosis area suggests that DS102 treatment could contribute to achieve better prognosis in NASH.

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 NASH.

1.5 Toxicology

A number of 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 2000 mg/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 have

sponsored a 9 month dog and 6 month rat study that are currently ongoing. An interim 18 week report on the 9 month dog study concluded that DS102 well tolerated and safe with no haematology, coagulation or clinical chemistry changes or any urinary composition change attributed to treatment with DS102.

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

The company sponsored a phase I study, DS102A-01 (EudraCT 2015-001153-33, MHRA Ref No. 41175/0002/001-0001), 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 3 males and 3 females per cohort) in each cohort. One of the cohorts (500mg QD for 28 days) enrolled 9 subjects to compensate for discontinued subjects. 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 half-life of approximately 2hrs and a T_{max} of approximately 4-8hrs. Results across dose levels studied showed high variability in the single and multiple dose cohorts and do 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 SAEs reported.

2 RISK BENEFIT ASSESSMENT

The company have shown the therapeutic effects of DS102 in a number of preclinical mechanistic studies with clinically relevant endpoints in NASH, namely ALT, the histological NAFLD activity score and fibrosis. Toxicological safety studies to date demonstrate safety of the drug substance up to 2000mg/kg in two species and safety up to 18 weeks has been shown in an interim report of a 9 month dog study. The phase I study conducted in healthy volunteers demonstrated DS102 to be safe and well tolerated with no SAEs reported over 28 day dosing.

Based on the summary above of both the favourable safety profile and the therapeutic potential of DS102 in a disease that currently lacks effective therapies, it can be concluded that there is a positive risk-benefit ratio for the continued investigation of oral DS102**.**

3 RATIONALE FOR THE STUDY

There is a clear rationale for the development of DS102 as a treatment for patients with NAFLD**.** Preclincially, DS102 has been shown to have significant effects on clinically relevant endpoints, including serum ALT and both NAFLD activity score and fibrosis in a STAM™ model of non-alcoholic steatohepatitis (DS-PC-26, DS-PC-27, DS-PC-28, DS-PC-29).

Based on the positive safety results of the first-in-man phase I trial in healthy volunteers, DS102 showed that up to 2000mg once daily in healthy patients was safe and well tolerated.

The rationale for this study is therefore to examine the safety and efficacy of DS102 up to 2000mg per day for 16 weeks given in divided doses in non-alcoholic fatty liver disease patients (NAFLD).

4 STUDY OBJECTIVES

The objective of the study is to assess the safety and efficacy of orally administered DS102 capsules versus placebo in the treatment of adult patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Efficacy

- Change in serum ALT (alanine aminotransferase) from baseline to week 16
- Change in liver stiffness measurements by Transient Elastography from baseline to week 16

Safety

- Number of Treatment Emergent Adverse Events (TEAEs) in each treatment group leading to treatment discontinuation

5.2 Secondary Endpoints

- Change in serum ALT (alanine aminotransferase) from baseline to weeks 2, 4, 8 and 12
- Change in AST (aspartate aminotransferase) from baseline to weeks 2, 4, 8, 12 and 16
- Change in AST:ALT ratio from baseline to weeks 2, 4, 8, 12 and 16
- Change in FIB-4 Index from baseline to week 16
- Change in NAFLD fibrosis score (NFS) from baseline to week 16
- Change in hepatic fat measured by CAP (controlled attenuation parameter) from baseline to week 16
- Change in ELF (Enhanced Liver Fibrosis score) from baseline to week 16
- Change in HOMA-IR/Adipo-IR (Homeostatic model assessment Insulin Resistance / Adipose tissue Insulin Resistance) from baseline to weeks 2, 4, 8, 12 and 16

6 STUDY DESIGN

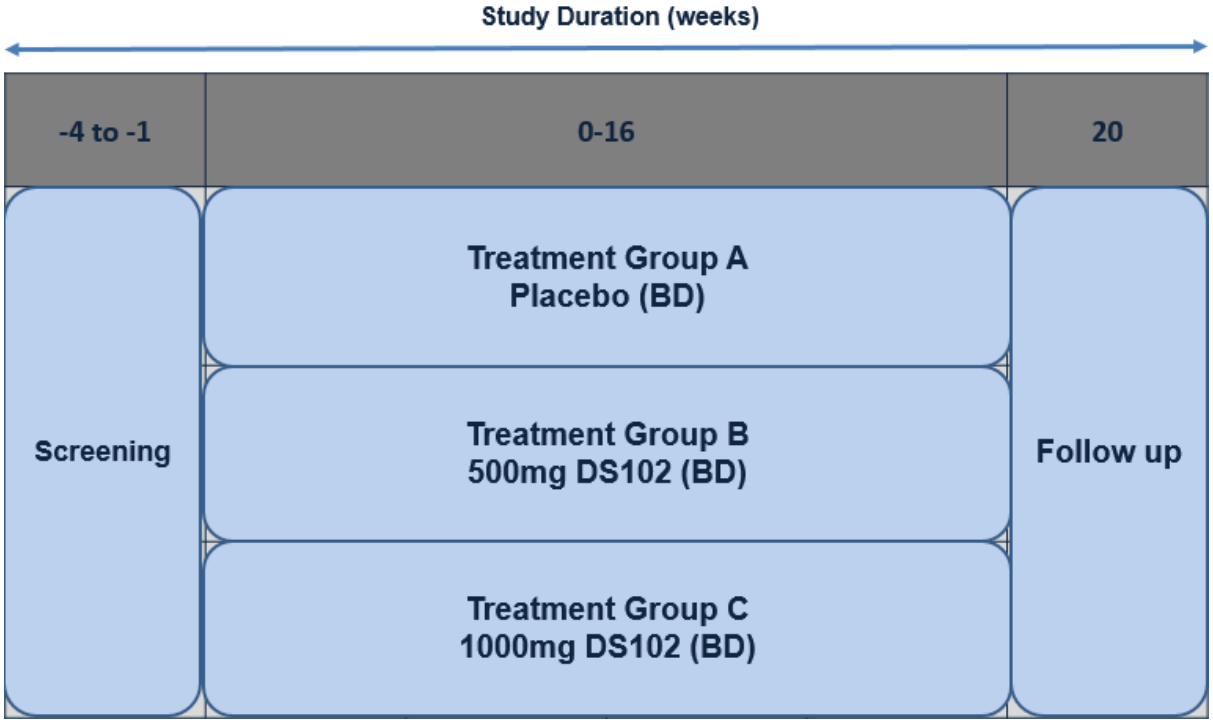
6.1 General

This is a randomised, placebo-controlled, double-blind, parallel group, multi-centre exploratory phase IIa study to investigate the safety and efficacy of orally administered DS102 capsules and the dose-response relationship between two doses of DS102 and placebo in NAFLD patients aged 18 to 75 years inclusive. Three parallel groups of patients with confirmed NAFLD will be investigated in this study to compare two different doses of DS102 with placebo over a 16 week treatment period. It is planned that 96 evaluable patients, 32 patients per treatment group will be randomized. The sample size may be re-estimated at an interim analysis based on at least 50% of the patients.

The study consists of a screening period of 28 days, a 16 week treatment period and a 4 week follow up period. At the screening visit, after giving informed consent to participate, patients will be assessed using the screening examinations. Patients who meet the inclusion criteria and who do not meet the exclusion criteria will be enrolled.

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

Figure 3: Study Outline



Once patients are enrolled on the study they will be restricted from using any other treatment for NAFLD. Any medication (prescription as well as over the counter (OTC) drugs) 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 unless they are included in the list of 'Concomitant Medications' (Section 9.2.11).

Before the comparative treatment period can commence, patients will return to the site for a baseline assessment of their disease and eligible patients will be randomly allocated to one of the three parallel group treatment regimens in a 1:1:1 randomization:

- Treatment group A: 2 x Placebo 500mg capsules orally administered twice a day (4 capsules daily) for 16 weeks
- Treatment group B: 1 x DS102 500mg capsule & 1 x Placebo 500mg capsule orally administered twice a day (4 capsules daily) for 16 weeks
- Treatment group C: 2 x DS102 500mg capsules orally administered twice a day (4 capsules daily) for 16 weeks

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.

The study consists of a treatment period of 16 weeks and was designed in order to assess the safety and efficacy of dosing of DS102 BD (total daily doses of 1000mg and 2000mg) in NAFLD patients.

Studies in rats and dogs treated for up to four weeks have demonstrated 15-HEPE EE did not indicate any limiting toxicity and resulted in a NOAEL of 2000 mg/kg/day in both species (CRL-527943, 527959). 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. The dose selection in this trial is therefore based on the phase I trial and the intention to characterize the safety and efficacy of up to 2000mg per day given in divided doses with or after food to NAFLD patients.

7 PATIENTS AND SCREENING

In order to participate in this study the patients must meet all of the following inclusion criteria and must not meet any of the following 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).

7.1 Source of Patients

The study population will consist of NAFLD male and female patients aged between 18 and 75 years inclusive.

7.2 Inclusion Criteria

1. Patients diagnosed with NAFLD by the presence of hepatic steatosis on imaging or histology in the absence of any secondary causes.
2. Patients with an ALT ≥ 1.5 ULN and < 5 ULN on two occasions 7 or more days apart during screening.
3. Patients with historical liver biopsy showing NASH and/or ≥ F1 fibrosis OR NFS ≥ -1.455 OR Fib-4 ≥ 1.3 OR Fibroscan ≥8kPa within 3 months of screening.
4. Patients with a body mass index (BMI) between 25.0 and 40.0 kg/m² inclusive. Patients with a history of controlled obesity or controlled diabetes are allowed on the study.
5. Patients whose pre-study clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator.
6. Patients aged between 18 and 75 years inclusive.
7. Female patients and male patients with female partners of child bearing potential must use adequate contraception or have a sterilized partner for the duration of the study. Adequate contraception is defined as: systemic hormonal contraceptives; intrauterine device or barrier method of contraception in conjunction with spermicide; or agree to sexual abstinence, defined as a patient refraining from heterosexual intercourse during the entire period of risk associated with the study treatments and in line with their preferred and usual lifestyle. Hormonal contraceptives must be on a stable dose for at least one month before baseline.
8. Patients who are able to communicate well with the Investigator, to understand and comply with the requirements of the study, and understand and sign the written informed consent.

7.3 Exclusion Criteria

1. Patients with an unstable metabolic condition such as weight change > 5% in the 3 months prior to inclusion.
2. Patients with medical/surgical history of gastric bypass surgery, orthotopic liver transplant (OLT) or listed for OLT.

3. Patients with uncontrolled diabetes mellitus type 2, i.e. HbA1c ≥ 9% (75mmol/mol) at the time of screening.

4. Patients with decompensated or severe liver disease as evidenced by one or more of the following: confirmed cirrhosis or suspicion of cirrhosis, esophageal varices, ascites, suspicion of portal hypertension, hospitalization for liver disease within 60 days of screening, bilirubin ≥ 2 x ULN, or ALT or AST ≥ 5 x ULN. Patients with Gilbert's syndrome are eligible if the conjugated bilirubin is ≤ 1.5 x ULN.

5. Patients with inflammatory bowel disease that is either active or requiring medical therapy.

6. Patients with diagnosed or suspected autoimmune diseases such as systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA).

7. Patients with a history of or active non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas).

8. Patients with a significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal insufficiency, serious psychiatric disease, respiratory or hypertensive disease, as well as diabetes and arthritis that, in the opinion of the Investigator, would preclude the patient from participating in and completing the study.

9. Patients requiring anti-diabetic treatment (including insulin sensitizing agents), and/or lipid lowering treatment, and who are not on a stable dose for at least 3 months prior to screening should be excluded. If patients are insulin dependent this treatment should have commenced at least 3 months prior to screening, however changes in dose are permitted.

10. Patients with known hypersensitivity to any ingredients of the study treatment.

11. Patients with a positive test for human immunodeficiency virus (HIV) antibodies, Hepatitis B surface antigen or Hepatitis C antibodies at screening.

12. Patients with liver disease of other aetiologies such as drug-induced, autoimmune hepatitis, PBC, PSC, haemochromatosis, A1AT deficiency or Wilson's disease.

13. Patients with a significant history of drug/solvent abuse, in the opinion of the investigator.

14. Patients with a history of alcohol abuse in the opinion of the Investigator, or who currently drinks in excess of 21 units per week (males) or 14 units per week (females), whereby a unit consists of 10ml or 8mg of pure alcohol.

15. Patients who have used dietary supplements rich in omega-3 or omega-6 fatty acids in the 4 weeks prior to baseline.

16. Patients who have participated in any other clinical study with an investigational drug within 3 months before the first day of administration of study treatment.

17. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in criterion 7) during the trial.

18. Patients, in the opinion of the Investigator, not suitable to participate in the study.

7.4 Screening and 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. Patients will be given the opportunity to ask questions to the investigational team. It must also be explained to the patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. The patient will be given sufficient time to consider participation in the study. If, after this, the patient agrees to participate, they will be asked to sign and date one original copy of the written informed consent form (ICF). The patients will then receive a copy of the signed and dated patient information sheet (PIS)/informed consent form (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 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 Board/Institutional Review Board. 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. Any written information given to potential patients will be submitted to, and approved by, the respective Ethics Committee(s) (EC) prior to implementation.

The Investigator will maintain a Patient Screening Log to collect information on all patients who sign an 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.

7.5 Withdrawal of Patients

Patients have the right to withdraw from the study at any time for any reason without penalty. 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.

The investigator or one of his or her staff members should 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 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 or an abnormal laboratory test result, the principal specific event or test will be recorded. Patients who discontinue the study before week 16 visit will be asked to come for an early termination visit as soon as possible and have the assessments listed at week 16 performed. They will also be asked to return two weeks later for the safety assessments listed at week 20.

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:

- Patients 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 adverse events
- Patient request
- Investigator's discretion
- Intercurrent illness
- Pregnancy

7.6 Patient Replacement

Patients who are withdrawn from the study due to an adverse event or lack of efficacy will not be replaced. Patients who are withdrawn for other reasons (such as lost to follow up) may be replaced.

7.7 Protocol Violations

All protocol violations 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.

8 STUDY CONDUCT

8.1 Study Schedule

During the study, ten visits to the clinic are scheduled after the screening visit: one at the start of the comparative treatment period/baseline (Day 0/Visit 2) and eight in the comparative treatment period (Week2/Visit 3, Week 4/Visit 4, Week 6/Visit 5, Week 8/Visit 6, Week 10/Visit 7, Week 12/Visit 8, Week 14/Visit 9, Week 16/Visit 10). A final safety follow-up visit (Visit 11) will be conducted four weeks after Visit 10 or two weeks after the final visit attended if the patient does not complete the study.

Patients who discontinue the study early will be asked to attend the investigative site as soon as possible so that assessments scheduled for Visit 10 can be conducted.

8.2 Clinic Visits

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

8.2.1 Screening Visit (Visit 1)

The patient must sign and date the ICF before any study-specific procedures are conducted.

Once informed consent has been obtained, the investigator will assign a Patient Screening Number. Ideally the patient should be fasted. 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)
- Physical examination (as detailed in Section 9.2.2)
- 12-lead ECG (as detailed in Section 9.2.3)
- Vital signs (blood pressures, 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)
- Virology (as detailed in Section 9.2.6)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (ALT to be measured on two occasions during screening as detailed in Section 9.1.1)
- Concomitant medication assessment (as detailed in Section 9.2.11)

Unscheduled visits may occur when a patient needs to make a visit in between the scheduled visit dates due to an adverse event (AE), difficulty complying with the study protocol requirements, or a significant change in their disease state. All procedures that are medically necessary should be followed. If qualified, before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.2 Treatment Period

Following completion of a successful screening visit, patients will begin the comparative treatment period (16 weeks).

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

Patients will take the allocated IMP (DS102 capsule or placebo capsule) twice-daily throughout the comparative treatment period. Each self-administration of IMP will be recorded in a patient diary card.

Patients will be instructed to take DS102 in the morning and in the evening with or after food (except on the mornings of clinic visits 3, 4, 6, 8 and 10 when patients will be instructed to abstain from taking DS102 prior to the visit and to take DS102 as soon as possible after the clinic visit).

Unscheduled visits may occur when a patient needs to make a visit in between the scheduled visit dates due to an adverse event (AE), difficulty complying with the study protocol requirements, or a significant change in their disease state. All procedures that are medically necessary should be followed.

Patients who discontinue the study early will have all study procedures scheduled for Visit 10 (see Section 9.2.11) performed as soon as possible after patient withdrawal so that all study-related information can be recorded.

At the discretion of investigator, urine DOA and alcohol breath test can be performed at any time during the conduct of the trial, as detailed in section 9.2.9.

8.2.3 Baseline (Visit 2)

Patients will attend the investigational site at Visit 2 when the following assessments/sample collections will be performed. The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Blood sampling will be the first assessment carried out. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast):

- Verification of inclusion/exclusion criteria (Sections 7.2 & 7.3)
- Medical history (as detailed in Section 9.2.1)
- Physical examination (as detailed in Section 9.2.2)
- 12-lead ECG (as detailed in Section 9.2.3)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Lipid Profile (as detailed in Section 9.2.5)
- Urinalysis (as detailed in Section 9.2.5)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- ELF (as detailed in Section 9.1.3)
- Liver stiffness and CAP (as detailed in Section 9.1.4)
- FIB-4 (as detailed in Section 9.1.5)
- NFS [including BMI] (as detailed in Section 9.1.6)

- Biomarkers blood sample (as detailed in Section 9.2.8.3)
- Exploratory blood sample (as detailed in Section 9.2.8.2)
- Patient Randomisation (as detailed in Section 12.2)
- Study drug/Placebo Administration
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

If all study entry criteria are satisfied the investigator will randomize 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.

Patients will be given a patient diary card. Clinical staff will explain to the patient how to use the diary card to document IMP administration compliance.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 3 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 3). Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.4 Week 2 (Visit 3)

Patients will return to the investigational site at Visit 3. Patients should not take IMP or placebo on the morning of Visit 3.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 2. Patients will be required to provide the patient diary card for confirmation of compliance. The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast).

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, heart rate and body temperature), as detailed in Section 9.2.4)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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 capsules will continue to be administered twice-daily. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 4 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 4). Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.5 Week 4 (Visit 4)

Patients will return to the investigational site at Visit 4. Patients should not take IMP or placebo on the morning of Visit 4.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 3. Patients will be required to provide the patient diary card for confirmation of compliance. The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast).

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 5 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 5).

8.2.6 Week 6 (Visit 5)

Patients will return to the investigational site at Visit 5.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 4. Patients will be required to provide the patient diary card for confirmation of compliance.

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 6 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 6). Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.7 Week 8 (Visit 6)

Patients will return to the investigational site at Visit 6. Patients should not take IMP or placebo on the morning of Visit 6.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 5. Patients will be required to provide the patient diary card for confirmation of compliance.

The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Blood sampling will be the first assessment carried out. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast):

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Lipid Profile (as detailed in Section 9.2.5)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- Biomarker blood samples (as detailed in Section 9.2.8.3)
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 7 and to bring with them the unused IMP/placebo blister packs,

the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 7).

8.2.8 Week 10 (Visit 7)

Patients will return to the investigational site at Visit 7.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 6. Patients will be required to provide the patient diary card for confirmation of compliance.

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 8 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 8). Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.9 Week 12 (Visit 8)

Patients will return to the investigational site at Visit 8. Patients should not take IMP or placebo on the morning of Visit 8.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 7. The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast). Patients will be required to provide the patient diary card for confirmation of compliance.

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 9 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 9).

8.2.10 Week 14 (Visit 9)

Patients will return to the investigational site at Visit 9.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 8. Patients will be required to provide the patient diary card for confirmation of compliance.

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

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. The patient diary card will be provided to the patient who will be instructed to complete this as before.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 10 and to bring with them the unused IMP/placebo blister packs, the used IMP/placebo blister packs, and the patient diary card. Patients should not take IMP or placebo on the morning of their return site visit (Visit 10). Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.11 Week 16 (Visit 10) or Early Withdrawal

Patients will return to the investigational site at Visit 10. Patients should not take IMP or placebo on the morning of Visit 10.

For accountability purposes, patients will be required to bring both the used and unused IMP/placebo blister packs supplied at Visit 9. Patients will be required to provide the patient diary card for confirmation of compliance.

The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration

of the fasting period. Blood sampling will be the first assessment carried out. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast):

The following assessments will be performed:

- Physical examination (as detailed in Section 9.2.2)
- 12-lead ECG (as detailed in Section 9.2.3)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Urinalysis (as detailed in Section 9.2.5)
- Lipid Profile (as detailed in Section 9.2.5)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)
- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- ELF (as detailed in Section 9.1.3)
- Liver stiffness and CAP (as detailed in Section 9.1.4)
- FIB-4 (as detailed in Section 9.1.5)
- NFS [including BMI] (as detailed in Section 9.1.6)
- Biomarker blood samples (as detailed in Section 9.2.8.3)
- Exploratory blood sample (as detailed in Section 9.2.8.2)
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

The IMP or placebo will be returned. No further IMP or placebo blister packs or patient diary cards will be issued. Following completion of the study assessments at this visit, there will be continued study restrictions in line with those described in section 9.2.11 and section 9.2.14.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in four weeks at Visit 11 to assess any AEs since this visit, and conduct safety and efficacy assessments. Before leaving the clinic the patient will be instructed not to have any breakfast before the next visit to allow a minimum fasting period of 8 hours.

8.2.12 Follow up Visit (Week 20/Visit 11)

Four weeks after Visit 10 (or 2 weeks after early withdrawal visit), patients will return to the investigational site. The patient will be asked if they have fasted for a minimum of 8hrs prior to visit. If this is not the case, the duration of fasting period will be documented and the patient will be reinstructed about the duration of the fasting period. Following this the patient will be provided with a light breakfast (e.g. tea or orange juice and toast). The following assessments will be carried out:

- Physical examination (as detailed in Section 9.2.2)
- Pharmacokinetic Sampling (as detailed in Section 9.2.8.1)
- Vital signs (blood pressures, 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)
- Pregnancy test (for female patients of child-bearing potential, as detailed in Section 9.2.7)
- ALT, AST tests (as detailed in Section 9.1.1)

- HOMA-IR/Adipo-IR (as detailed in Section 9.1.2)
- Biomarkers (as detailed in Section 9.2.8.3);
- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.11)

9 ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 ALT, AST, ALT:AST Ratio

Increased liver enzymes (ALT and AST) are a marker of liver injury and will be assessed at Visit 1/Screening (On two occasions during screening 7 or more days apart), Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week16 and Follow up Visit 11/Week 20.

9.1.2 HOMA-IR/Adipo-IR

HOMA-IR/Adipo-IR, measuring insulin resistance. HOMA-IR is calculated multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), then dividing by the constant 405. Adipo-IR is calculated by multiplying fasting non-esterified fatty acids (NEFA) × fasting insulin. Blood samples will be taken to assess HOMA-IR and Adipo-IR at Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week16 and Follow up Visit 11/Week 20. All subjects must be fasted for a minimum of 8hrs prior to blood sampling. If subjects have not fasted for a minimum of 8 hrs, the duration of fasting time should be recorded and subjects encouraged to fast appropriately for the next clinical visit.

9.1.3 ELF

Enhance Liver Fibrosis score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA). Blood samples will be taken to perform this assessment at baseline (Visit 2) and week 16 (Visit 10).

9.1.4 Liver Stiffness and CAP

Liver stiffness and Controlled attenuation parameter will be assessed using transient elastography (FibroScan® 502 Touch model or equivalent). Patients should be fasted and should be scanned at the same time of the day, if possible, for baseline (week 0) and Visit 10 (week 16).

1. Patient must be lying in dorsal decubitus position with the right arm in maximal abduction behind the head, in a similar position to that used for LB (Liver Biopsy).
2. The tip of the transducer must be placed on the skin between the ribs over the right lobe of the liver. The physician will take the measurements with the probe placed in the intercostal space.
3. During the FibroScan® examination the choice of M+ or XL+ probe will be determined by the Automatic Probe Selection tool (APS). If, the APS tool advises to use the "XL+ probe" or "switch" continuously between "M+ and XL+ probe", only the XL+ probe must be used.
4. The operator, assisted by an ultrasonic time motion image, will locate a portion of the liver which is free of large vascular structures. The depth of measurement will be between 35-75 mm for the XL+ probe and 25-65 mm for the M+ probe and the explored volume will be 3 cm^3.

   Once all the conditions mentioned above are met, the operator will be able to trigger a measurement.

5. For each patient, the operator will perform an examination including at least 10 valid measurements or a maximum of 20 attempts, with the XL+ or M+ probe, at the same spot. The entire examination should last no more than 10-15 minutes.
6. The final stiffness and CAP values will be recorded as median values of valid measurements.

9.1.5 FIB-4 Index

This index is based on age, platelet count, ALT level, and AST level and will be assessed at Baseline (Visit 2) and week 16 (Visit 10).

$$FIB4 = \frac{\text{Age (years) x AST (U/L)}}{\text{Platelet count } (10^9/L) \text{ x } \sqrt{\text{ALT (U/L)}}}$$

9.1.6 NFS

The NFS is based on age, hyperglycemia, BMI, platelet count, albumin level, and AST/ALT ratio. NAFLD fibrosis score = $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ IFG/diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/l) $- 0.66 \times$ albumin (g/dl). NFS will be assessed at Baseline (Visit 2) and week 16 (Visit 10).

http://nafldscore.com/

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 Screening visit (Visit 1) and Baseline (Visit 2) 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.

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) at Visit 1/Screening, Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week16 and Follow up Visit 11/Week 20 in accordance with local practices. This examination will be completed in full at baseline and symptom-directed thereafter, 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 ECG

Electrocardiogram Recording

A 12-lead 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 5 minutes before the ECG is taken. Recordings will be made on the days indicated in Study Flow Chart (Appendix 1) at Visit 1/Screening, Visit 2/Baseline and Visit 10/Week 16.

9.2.4 Vital Signs

Vital signs measurements will be performed as per the Study Flow Chart (Appendix 1) at Visit 1/Screening, Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week16 and Follow up Visit 11/Week 20. Measurements to be taken include:

- Blood pressure: will be performed as supine (after at least 5 minutes of rest) systolic and diastolic blood pressure (in mmHg)
- 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, Coagulation, Lipid Profile, and Urinalysis

Blood and urine samples will be taken as per the Study Flow Chart (Appendix 1) for routine haematology, serum biochemistry, coagulation and urinalysis tests, along with a Lipid Profile (as per Study Flow Chart [Appendix 1]). All samples will be analysed in the central laboratory. All subjects must be fasted for a minimum of 8hrs prior to blood sampling. If subjects have not fasted for a minimum of 8 hrs, the duration of fasting time should be recorded and subjects encouraged to fast appropriately for the next clinical visit.

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), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALT/AST ratio, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), albumin, total protein, cholesterol, triglycerides, glucose, C-reactive protein (CRP).
Coagulation:	PT (prothrombin time), INR (international normalized ratio) and APTT (activated partial prothrombin time)

Lipid Profile: LDL (Low Density Lipoprotein) HDL (High density), VLDL (very low density),

Urinalysis: pH, protein, glucose, blood, ketones, leukocytes, leukocyte esterase, bilirubin, specific gravity, urobilinogen and nitrate. Reflex micro if blood, protein, leukocyte esterase or nitrate/nitrite are present.

9.2.6 Virology

A blood sample will be taken to perform virology tests including HIV, Hep C and Hep B as detailed in Study Flow Chart (Appendix 1).

9.2.7 Pregnancy Test

For female patients of childbearing potential, a pregnancy test will be carried out as per the Study Flow Chart (Appendix 1) at Visit 1/Screening, Visit 2/Baseline, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week 16 and Visit 11/Week 20.

9.2.8 Blood Sampling

Details of the volume of blood or urine 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 PK analysis will be collected via direct venepuncture as per the Study Flow Chart (Appendix 1) at Visit 2/Baseline, Visit 3/Week 2, Visit 4/Week 4, Visit 6/Week 8, Visit 8/Week 12, Visit 10/Week16 and Follow up Visit 11/Week 20.

A 1 mL blood sample will be taken at each timepoint. Following centrifugation, plasma samples will be split in two and a back-up sample will be kept at the central laboratory until bioanalytical assays have been completed.

9.2.8.2 Exploratory Blood Collection

Blood will be collected as per the Study Flow Chart (Appendix 1) at baseline (Week 0) and Visit 10/Week 16 and stored for potential gene array analysis or additional exploratory testing at a later date.

9.2.8.3 Biomarker Blood Collection

Blood will be collected as per the Study Flow Chart (Appendix 1) at baseline (Week 0), Visit 6/Week 8, Visit 10/Week 16 and Follow up Visit 11/Week 20 and will be stored for potential biomarker analysis.

9.2.9 Urine DOA and Alcohol Breath Test

As clinically appropriate at the discretion of the investigator, an alcohol breath test will be performed and a urine sample will be taken from patients at any time during the conduct of the trial and testing will be done to detect the following: amphetamine, barbiturate, benzodiazepine, cocaine, cannabinoids, and opiates.

9.2.10 Adverse Event Assessment

See section 11.

9.2.11 Concomitant Medication

Patients must be on a stable dose of any concomitant medications for at least 3 months prior to screening and that dose should remain stable for the entire study duration. If patients are insulin dependent this treatment should have commenced at least 3 months prior to screening, however changes in dose are permitted.

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 Restrictions

Diet

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).

Alcohol

Patient should avoid alcohol consumption in excess of 21 units per week (males) or 14 units per week (females), whereby a unit consists of 10ml or 8mg of pure alcohol.

Caffeine

There are no restrictions on caffeine intake prior to or during the study.

Physical Activity

Patients should avoid exercise and strenuous physical activity for at least 3 to 4 hours before the safety laboratory test (biochemistry).

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 cabinet 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

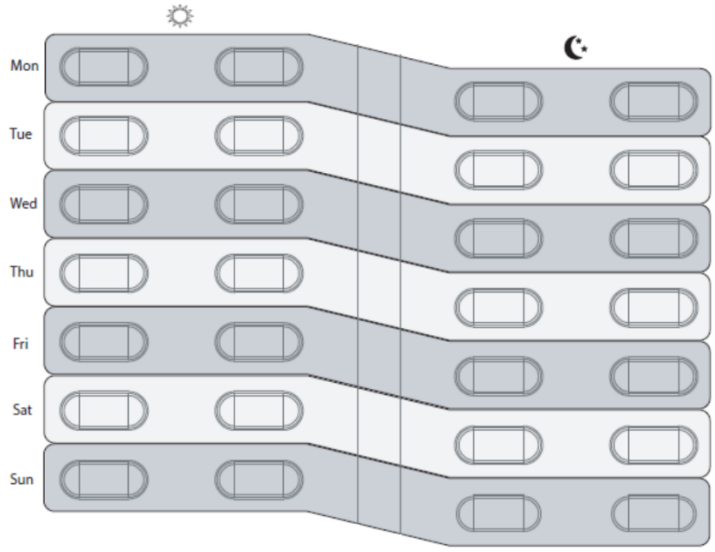
10.2 Dosage and Administration

Patients who fulfil all the inclusion and none of the exclusion criteria may be accepted in the study. Each patient must read and sign an informed consent form (ICF) prior to any screening procedures being performed. This study involves a comparison of DS102 with placebo, administered orally twice daily for a total duration of 16 weeks. The last study drug administration should occur on the day preceding week 16 visit / Early Termination (ET) visit. Patients will be randomized to one of the three treatment groups in a 1:1:1 ratio:

- Treatment group A: 2 x Placebo 500mg capsules twice a day (4 capsules daily)
- Treatment group B: 1 x DS102 500mg capsule & 1 x Placebo 500mg capsule twice a day (4 capsules daily)
- Treatment Group C: 2 x DS102 500mg capsules twice a day (4 capsules daily)

Patients will be required to take the capsules with or after food. Medication(s) for other conditions that are permitted in the study can be taken as usual.

Walleted blister packs will consist of 7 days of 4 capsules. Patients will be instructed to take the 2 capsules **from left to right**, on the relevant day, as shown below:



10.3 Duration of Treatment

Patients will take assigned medication for 16 consecutive weeks.

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 and the medication destroyed or returned to the Sponsor or designee. All study drug accountability forms and treatment logs must be retained in the Investigator's study file. 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 be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Seriousness

Adverse Events (AE):

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 investigational IMP(s). All Adverse Events (AEs) must be recorded in the case report form, 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 serious adverse event after the first dose of the study drug, the event will be recorded as a serious adverse event.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- 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 hospitalization but may jeopardize 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 hospitalization, or development of drug dependency or drug abuse.

Unexpected Adverse Event (UAE):

An experience not previously reported in the Investigator's Brochure 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 adverse event is transient and easily tolerated.
- Moderate: The adverse event causes the patient discomfort and interrupts the patient's usual activities.
- Severe: The adverse event 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 case report form, defining relationship to IMP and severity.

As soon as the Investigator is aware of a potential Serious Adverse Event (SAE), he/she should contact the Pharmacovigilance (PV) 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 Investigator Site File.

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 PV CRO at the number provided in the Investigator Site File. The faxed SAE reporting form should be received to the PV CRO within 24 hours after 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 PV CRO within 5 days after the initial report. Where appropriate, hospitalisation or autopsy reports should be made available. All Serious Adverse Events will be followed up until resolution (i.e., asymptomatic, stabilisation or death).

AE's should be reported for the entire study duration 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 Drug-induced Liver Injury

1. Severe drug-induced liver injury

Irrespective of perceived causation, in the event of severe drug-induced liver injury 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 rechallenged with the drug.

Severe drug-induced liver injury stipulates evidence of hepatic impairment as demonstrated by a total bilirubin >2× ULN or INR >1.5. 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.

2. Patients with abnormal baseline liver biochemistry

A fold increase should be calculated against baseline levels instead of using the ULN. Thus a figure of 3× baseline ALT or AST (or >200 IU/L) should be followed by repeat testing within 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.

11.3 Serious Adverse Reactions and Unexpected Adverse Reactions

11.3.1 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 adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised investigational product or similar product information sheet such as the Summary of Products Characteristics (SPC).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

Any serious adverse reaction that might be related to the IMP and are unexpected according to the definition above.

11.3.2 Reporting of suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) will be reported by PV CRO according to appropriate Competent Authority and Ethics Committee requirements. SUSARs will be reported to Investigators according to ICH Good Clinical Practice and to local regulations. SUSAR reporting to the Competent Authorities and Ethics Committees 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 PV CRO as soon as possible to the Competent Authorities and Ethics Committees according to local regulations, and in any case no later than seven calendar days, after knowledge by 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 concerned and to the Ethics Committee concerned according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by PV CRO.

11.4 Pregnancy Reporting

If a patient or a patient's partner becomes pregnant during the study, the patient should inform the study site as soon as possible. Upon confirmation of the pregnancy, the patient must be withdrawn from 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 is not itself 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 randomized, double-blind, placebo-controlled parallel group design. 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 evaluation of safety and efficacy. The use of placebo as 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 possible long-term irreversible damage that may be the result of placebo treatment. A full description of the study design is presented in Section 6 above.

12.2 Randomisation

Approximately 96 patients will be randomized into double-blind treatment groups in a 1:1:1 ratio as follows:

- Treatment group A: 2 x Placebo 500mg capsules twice a day (4 capsules daily)
- Treatment group B: 1 x DS102 500mg capsule & 1 x Placebo 500mg capsule twice a day (4 capsules daily)
- Treatment Group C: 2 x DS102 500mg capsules twice a day (4 capsules daily)

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.

The treatment assignment procedure will use blocks of sufficient size to maintain a blind and balance across treatment arms. Unique randomization numbers, generated according to the randomization specifications will be assigned and will determine the drug supply given to each patient. The Investigator will assign the lowest randomization number available at their site to the first patient randomized and proceed in increasing sequential order as patients are qualified for the study. A complete randomisation list containing details of all randomization numbers will be stored in an access-restricted folder at the CRO and accessible only to assigned CRO personnel not involved in the conduct of the study.

12.3 Estimation of Sample Size

Assuming a 20% delta in the percentage response between active drug and placebo arms, a standard deviation of 25% and a drop out rate of 20%, this results in a requirement of 32 patients per group for a statistical test with 5% level of significance, and 80% power.

The sample size may be re-estimated at an interim analysis based on recommendation from an unblinded, independent DSMB. The sample size may be increased up to a maximum of 150 patients in total to achieve a conditional power of 80% for the primary endpoint.

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 authorized 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.

Site will be provided with emergency code-break cards for all patients. The cards must not be opened for any other reason than a medical emergency. If a code break card is opened, the Investigator must note the date, time and reason for opening it and retain this information with the study documentation. The site monitor will check the integrity of the code-break cards at the site during routine monitoring visits.

12.5 Interim Analysis and Data Monitoring

An independent DSMB will monitor safety aspects of the study and perform an interim analysis for the primary and co-primary endpoints as well as the secondary endpoints. The procedures for performing the interim analysis by the DSMB are described in its charter.

Under the direction of the DSMB, the interim analysis will be carried out to estimate the conditional power when at least 50% of the patients have completed their Week 16 visit. The interim analysis will be based on data collected for the primary and co-primary efficacy endpoints as well as the secondary endpoints and will be used to estimate the conditional power to achieve the primary study objective, to potentially re-estimate the sample size and to potentially drop the less effective treatment arm.

The specific details regarding the DSMB organization and procedures will be outlined in the DSMB Charter and a statistical analysis plan (SAP) will be produced before the interim analysis covering the analysis required.

For further details regarding the DSMB, refer to Section 13.1.

12.6 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 SAP.

12.7 Clinically Meaningful Response

A clinically meaningful treatment difference is defined as follows:

- Higher mean or median reduction of at least 20% of ALT or Liver Stiffness compared to placebo
- Higher mean or median reduction of at least 10% of both ALT and Liver Stiffness compared to placebo

12.8 Analysis Sets

The **Enrolled Set** includes all patients who signed the informed consent form.
Screen failures are patients from the Enrolled Population who do not meet the eligibility requirements and are withdrawn from the study prior to randomisation.

The **Full Analysis Set** (FAS) includes all randomised patients who received at least one administration of study treatment and have at least one post-baseline measurement. Patients will be analysed according to the treatment they were assigned to at randomisation, irrespective of what treatment they actually received.

The **Per-Protocol Set** (PPS) will be a subset of the Full Analysis Set consisting of those patients of FAS who had no major protocol violations.

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock, and major deviations considered as having a serious impact on the efficacy results will lead to the relevant patient being excluded from the PPS.

The **Safety Analysis Set** (SAF) consists of all patients who take at least one administration of study treatment. Patients will be analysed according to the treatment actually taken.

The **Pharmacokinetic (PK) Set** will consist of those patients in the SAF who have at least one DS102 PK concentration. Patients will be analysed according to the treatment actually received.

12.9 Safety Analysis

Demographic, 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). AEs will be tabulated and summarised by treatment, relationship to treatment, seriousness and severity.

Clinical laboratory values (haematology, biochemistry, and urinalysis) 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.

Alcohol breath test and DOA test results will be listed for each patient.

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

12-lead 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, 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.

12.10 Statistical Analysis Plan

In addition to the summarised analysis plan outlined below, a separate document, Statistical Analysis Plan (SAP) for DS102A-02 will detail all analysis to be performed.

12.10.1 Pharmacokinetic Analysis

Plasma concentrations of 15(S)-HEPE will be tabulated and summarised descriptively. Individual and mean plasma concentration-time profiles of 15(S)-HEPE will be presented graphically.

12.10.2 Primary variables

The primary efficacy variable will be the change from baseline in serum ALT at week 16 (Visit 10). The active treatment groups will be compared against placebo via an analysis of covariance (ANCOVA) model, including the corresponding baseline value as covariate. The comparisons against placebo will be done according to Dunnett's multiple testing procedure. For missing week 16 values the last value available will be carried forward (LOCF). Similar methods will be applied for Liver Stiffness. For ALT, longitudinal modelling will be considered in addition.

The increase of sample size at interim will only be considered if promising (promising zone approach). This does not require alpha adjustment.

12.10.3 Secondary variables

The secondary efficacy variables and their changes from baseline to week 16 (Visit 10) will be summarized with descriptive statistics per treatment group and visit. This applies to the AST, AST:ALT ratio, hepatic fat measured by CAP, liver stiffness measurements by transient elastography, FIB-4, NFS, ELF and HOMA-IR/Adipo-IR. The change from baseline for the active treatment groups will be compared against placebo via an analysis of variance (ANOVA) model, including a term for centre effects. The 5% level of significance will be used for all treatment comparisons.

12.11 Data Collection / Case Report Forms

Data will be collected using a validated electronic data capture (EDC) solution. Electronic Case report forms (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 CRF 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 CRA respectively. Queries shall be resolved in a timely manner by a trained member of the site staff.

12.12 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 the CRO Standard Operating Procedures (SOP). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

12.13 Protocol Deviations

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

13 REGULATORY AND ADMINISTRATIVE PROCEDURES

13.1 Data and Safety Monitoring Board

An independent DSMB will be formed to review ongoing safety and efficacy data. Members of the DSMB will not be allowed to participate as Investigators in this study and will not be affiliated in any way with the sponsor. The DSMB will consist of at least two physicians and a statistician. A DSMB charter will provide full guidance on the function and practices to be followed by the DSMB.

13.2 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 Patient Information Sheet / Informed Consent Form will be approved by the relevant Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements before commencement. 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 Ethics Committees and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before 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 Ethics Committees according to local regulations.

13.3 GCP

The study will be managed and conducted according to the latest International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (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 Investigator Site File (ISF).

13.4 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 Ethics Committee. A complete list of essential GCP documents can be found in the Investigator Site File.

13.5 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 CRFs, 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 International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Trial Agreement (CTA), whichever is longest.

13.6 Monitoring / Quality Control

Monitoring visits will be conducted during the study at regular intervals. The 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 CRFs 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 is reviewed and signed by the PI.

13.7 Quality Assurance

The site may be audited during or after the study is completed by the 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.

13.8 Insurance and Liability

Insurance and liability for the study is the responsibility of the sponsor, Afimmune.

13.9 End of Trial

The end of the trial is defined as the date when the data for the final analysis are locked. The Competent Authorities and the Ethics Committees, as applicable, will be notified about the end of the trial.

13.10 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.

13.11 Report and Publication

Production of a clinical study report in accordance with the ICH guidelines will be the responsibility of 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: Study Flow-Chart

	Screening/ Visit 1	**Baseline/ Visit 2**	**Visit 3/ Week 2**	**Visit 4/ Week 4**	**Visit 5/ Week 6**	**Visit 6/ Week 8**	**Visit 7/ Week 10**	**Visit 8/ Week 12**	**Visit 9/ Week 14**	**EOT/ Visit 10 / Week 16**	**Follow Up/ Visit 11 / Week 20**
Study Procedure	**Day -28 to -1**	**Day 0**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 70**	**Day 84**	**Day 98**	**Day 112**	**Day 140**
Visit Window			+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-2 days	+/-4 days
Informed consent	**X**										
Inclusion Exclusion	**X**	**X**									
Demography	**X**										
Medical history	**X**	**X**									
Physical examination	**X**	**X**	**X**	**X**		**X**		**X**		**X**	**X**
12-lead ECG	**X**	**X**								**X**	
Plasma PK sampling[1]		**X**	**X**	**X**		**X**		**X**		**X**	**X**
Vital signs	**X**	**X**	**X**	**X**		**X**		**X**		**X**	**X**
Clinical laboratory tests [2]	**X**	**X**		**X**		**X**		**X**		**X**	**X**
Lipid Profile [3]		**X**				**X**				**X**	
Urinalysis		**X**								**X**	
Virology	**X**										
Pregnancy test [4]	**X**	**X**		**X**		**X**		**X**		**X**	**X**
ALT, AST [5]	**XX**	**X**	**X**	**X**		**X**		**X**		**X**	**X**
HOMA-IR/Adipo-IR		**X**	**X**	**X**		**X**		**X**		**X**	**X**
ELF		**X**								**X**	
Liver stiffness and CAP		**X**								**X**	
FIB-4		**X**								**X**	
NFS [including BMI]		**X**								**X**	
Biomarkers Blood Sample		**X**				**X**				**X**	**X**
Exploratory Blood Sample		**X**								**X**	
Patient Randomisation		**X**									
IMP/Placebo Dispensing		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Study drug/placebo administration		**X**----------**X**									
IMP Accountability/Diary Card review		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
AE assessment		**X**----------**X**									
Concomitant medication assessment	**X**	**X**----------**X**									

[1] Pharmacokinetics C_{trough} only. Sample will be taken pre-dose.
[2] Includes biochemistry, haematology and coagulation tests. This will be taken fasting (Minimum of 8hrs).
[3] Lipid Profile will be taken fasting (Minimum of 8hrs).
[4] Female Patients of child bearing potential only.
[5] ALT to be assessed on two occasions during screening 7 or more days apart.