A Randomised, Double-Blind, Placebo-Controlled, Dose Finding Phase IIb Study to Assess the Efficacy and Safety of Orally Administered Epeleuton in Patients with Hypertriglyceridemia and Type 2 Diabetes.

Short Title

TRIglyceride **A**nd **G**lucose control with **E**peleuton in Metabolic Syndrome Patients
(TRIAGE)

Protocol Number # DS102A-07-CV1

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Sponsor:

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SIGNATURE PAGE

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

SPONSOR:

Signature: _____ **Date:** February 17, 2022

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Signature: _____ **Date:** February 17, 2022

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Investigator name: _____

Signature: _____ **Date:** _____

Institution Name: _____

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

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

PROTOCOL SYNOPSIS

STUDY TITLE:	A Randomised, Double-Blind, Placebo-Controlled, Dose Finding Phase IIb Study to Assess the Efficacy and Safety of Orally Administered Epeleuton in Patients with Hypertriglyceridemia and Type 2 Diabetes.
SHORT TITLE:	**TRI**glyceride lowering **A**nd **G**lycemic control with **E**peleuton in metabolic syndrome patients: **TRIAGE**
PHASE:	IIb
STUDY DURATION:	32 - 34 weeks (4 - 6 weeks lead-in, 26 weeks treatment, two weeks post-treatment follow-up)
INVESTIGATIONAL PRODUCT:	Epeleuton Capsules Placebo (light liquid paraffin)
OBJECTIVES:	*Efficacy Objective:* • To assess the efficacy of orally administered Epeleuton capsules versus placebo, in the treatment of adult patients with hypertriglyceridemia and type 2 diabetes. *Safety Objective:* • To assess the safety of orally administered Epeleuton capsules versus placebo, in the treatment of adult patients with hypertriglyceridemia and type 2 diabetes.
PRIMARY ENDPOINTS:	• Percent change in triglycerides from baseline to week 16. • Change in HbA1c from baseline to week 26. ***Note**:* • *Each of the independent primary endpoints will be analysed separately.*

SECONDARY ENDPOINTS:	• Percent change in triglycerides from baseline to weeks 4, 8, 12, 20 and 26. • Change in HbA1c from baseline to weeks 4, 8, 12, 16 and 20. • Proportion of patients achieving a HbA1c below 7.0% at weeks 4, 8, 12, 16, 20 and 26. • Percent change in very low-density lipoprotein cholesterol (VLDL-C) from baseline to weeks 4, 8, 12, 16, 20 and 26. • Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to weeks 4, 8, 12, 16, 20 and 26. • Percent change in total cholesterol from baseline to weeks 4, 8, 12, 16, 20 and 26. • Change in fasting plasma glucose from baseline to weeks 4, 8, 12, 16, 20 and 26. • Proportion of patients achieving a HbA1c below 6.5% at weeks 4, 8, 12, 16, 20 and 26. • Percent change in apolipoprotein B (ApoB) from baseline to weeks 16 and 26. • Percent change in remnant lipoprotein cholesterol (RLP-C) from baseline to weeks 8, 16 and 26. • Percent change in high-density lipoprotein cholesterol (HDL-C) from baseline to weeks 4, 8, 12, 16, 20 and 26. • Percent change in low-density lipoprotein cholesterol (LDL-C) (preparative ultracentrifugation) from baseline to weeks 16 and 26. • Change in body weight (kg) from baseline to weeks 4, 8, 12, 16, 20 and 26. • Change in high-sensitivity C-reactive protein (hsCRP) from baseline to weeks 8, 16 and 26. • Change in systolic blood pressure from baseline to weeks 4, 8, 12, 16, 20 and 26. • Change in diastolic blood pressure from baseline to weeks 4, 8, 12, 16, 20 and 26. • Change in urinary albumin-to-creatinine ratio (UACR) from baseline to week 26 in the sub-group of patients with microalbuminuria at baseline.

EXPLORATORY ENDPOINTS	• Change in waist circumference from baseline to weeks 8, 16 and 26. • Percent change in apolipoprotein CIII (ApoCIII) from baseline to weeks 16 and 26. • Percent change in apolipoprotein A1 (ApoA1) from baseline to weeks 16 and 26. • Percent change in lipoprotein (a) (Lp(a)) from baseline to weeks 16 and 26. • Percent change in high-density lipoprotein particle concentration (HDL-P) from baseline to weeks 16 and 26. • Percent change in small low-density lipoprotein particle concentration (Small LDL-P) from baseline to weeks 16 and 26. • Percent change in large low-density lipoprotein particle concentration (Large LDL-P) from baseline to weeks 16 and 26. • Percent change in low-density lipoprotein size (LDL size) from baseline to weeks 16 and 26. • Percent change in very low-density lipoprotein size (VLDL size) from baseline to weeks 16 and 26. • Percent change in high-density lipoprotein size (HDL size) from baseline to weeks 16 and 26. • Change in fasting plasma insulin from baseline to weeks 16 and 26. • Change in Homeostatic model assessment insulin resistance (HOMA-IR) from baseline to weeks 16 and 26. • Change in Homeostatic model assessment β-cell function (HOMA-β) from baseline to weeks 16 and 26. • Change in interleukin 6 (IL-6) from baseline to week 26. • Change in interleukin 1β (IL-1β) from baseline to week 26. • Change in plasminogen activator inhibitor 1 (PAI-1) from baseline to week 26. • Change in vascular cell adhesion molecule 1 (VCAM-1) from baseline to week 26. • Change in intercellular adhesion molecule 1 (ICAM-1) from baseline to week 26. • Change in monocyte chemoattractant protein 1 (MCP-1) from baseline to week 26.

	• Change in red cell distribution width (RDW) from baseline to weeks 16 and 26. • Change in haemoglobin from baseline to weeks 16 and 26. • Change in reticulocyte count from baseline to weeks 16 and 26. • Change in erythrocyte (red blood cell) count from baseline to weeks 16 and 26. • Trough plasma concentrations of total and unesterified 15-hydroxy eicosapentaenoic acid (15(S)-HEPE) in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8, Week 16 and Week 26. • Trough plasma concentrations of eicosapentaenoic acid (EPA) in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8, Week 16 and Week 26. • Determination of exploratory serum biomarkers in treated population compared to placebo population at Baseline and Week 26.
SAFETY VARIABLES	• Incidence of treatment-emergent level 2 and level 3 hypoglycaemic episodes ○ Level 2 – Glucose <54 mg/dL, with or without symptoms ○ Level 3 – A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia. • Adverse event (AE) and serious adverse event (SAE) frequency and severity. • Safety laboratory parameters (haematology, clinical chemistry, coagulation). • Urinalysis • Electrocardiograms (ECGs) • Vital signs (heart rate, temperature, blood pressure) • Physical examination. • Pregnancy
STUDY DESIGN:	This is a multi-centre, double blind, placebo controlled, 3-arm, phase IIb study consisting of 26 weeks of active treatment and a 2 week follow up period. The screening period will consist of up to 6-weeks lead-in during which all

	patients will undergo diet and lifestyle stabilisation, washout of disallowed medications and optimisation of statins. Lipid qualification criteria include a fasting triglyceride level ≥200 mg/dL and <750mg/dL (inclusion #3) and LDL cholesterol<130mg/dL (inclusion #6). Triglycerides and LDL cholesterol will be checked at Screening #1 and a second qualifying visit (Screening #2). which will take place one week before randomisation at the baseline visit. Patients who meet the inclusion criteria at both screening visits will be eligible to participate in the study. Eligible patients will be randomised one week after Screening #2 at the baseline visit. Patients will be randomised (1:1:1) at baseline visit to either receive Epeleuton 4g/day (2g twice daily), Epeleuton 2g/day (1g twice daily) or placebo twice daily for 26 weeks.
TOTAL NUMBER OF RANDOMISED PATIENTS:	Approximately 240 male or female patients, aged 18 years or older; i.e. 80 patients per treatment group
STUDY POPULATION:	
INCLUSION CRITERIA:	1. Patients diagnosed with type 2 diabetes mellitus at least 90 days prior to the first screening visit. 2. Patients with a HbA1C (glycosylated haemoglobin) between 7.0 - 10.0% (53-86mmol/mol) (both inclusive) 3. Patients with a fasting triglyceride level ≥200 mg/dL (2.26 mmol/L) and <750 mg/dL (8.46 mmol/L) at both screening visits. ***Note:*** *If the triglyceride level is outside the required range at the second screening visit, an additional measurement can be obtained 1 week later, to confirm eligibility.* ***Note:*** *If a large difference in triglyceride level (>15%) is observed between Screening 1 and Screening 2, an additional measurement may be requested or patient may be deemed not eligible.* 4. Patients who have been educated regarding diet and exercise at or before visit 1 (screening 1) and are willing to maintain and not alter a stable diet and activity routine throughout the study. 5. Patients who have been on a stable statin therapy at doses that are likely to achieve optimal LDL cholesterol and who are willing to continue this treatment throughout the study. ***Note:*** *Stable statin therapy may consist of a statin with or without ezetimibe*. 6. Patients with an LDL cholesterol level <130mg/dL (3.34 mmol/L) at both screening visits. 7. Patients who have a body mass index (BMI) ≥ 25kg/m^2 and <50kg/m^2.

	8. Patients who have been on a stable daily dose of metformin (at least 1500mg or maximum tolerated dose for metformin monotherapy as documented in the subject medical record) and/or a sulfonylurea and/or a dipeptidyl peptidase-4 (DPP-4) inhibitor and/or a sodium-glucose transport protein 2 inhibitor (SGLT2i) and/or a glucagon-like peptide 1 receptor agonist (GLP1-RA) and/or basal insulin for at least 90 days prior to the day of first screening visit. ***Note:*** *Dose of GLP1-RA must be stable for 6 months prior to baseline with no weight change >2kg for 3 months prior to baseline.* ***Note:*** *Dose of basal insulin must be stable for 4 months prior to baseline. All types of basal insulin are permitted, including insulin glargine, insulin degludec, insulin detemir, NPH insulin and pre-mixed insulin* 9. Female patients and male patients with female partners of childbearing potential must use highly effective contraceptive methods or have a sterilised partner for the duration of the study. Highly effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include hormonal contraception, intrauterine device or sexual abstinence. ***Note:*** *A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.* ***Note:*** *Hormonal contraceptives must be on a stable dose for at least one month before baseline*. ***Note:*** *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.* 10. Patients whose pre-study or screening clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator, and do not violate any inclusion or exclusion criteria 11. Male or female patients aged 18 years and older on the day of signing the informed consent form (ICF). 12. 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 prior to initiation

	of any study specific activities or procedures.
EXCLUSION CRITERIA:	1. Patients who have a history of intolerance or hypersensitivity to any substance in epeleuton capsules, placebo capsules or statins. 2. Patients with uncontrolled hypertension defined as a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥100mmHg. 3. Patients who have a body mass index (BMI) <25kg/m^2 or ≥ 50kg/m^2. 4. Patients who have a weight change >2kg from the first screening visit to the baseline visit. 5. Patients who have type 1 diabetes mellitus. 6. Patients who have thyroid stimulating hormone (TSH) levels >1.5 times the upper limit of normal. 7. Patients with known familial lipoprotein lipase deficiency (Fredriksen type I), apolipoprotein C-II deficiency or familial dysbetaliproteinemia (Fredriksen type III). 8. Patients with significant liver disease or liver function impairment defined as any of the following; cirrhosis, hepatitis, biliary obstruction with hyperbilirubinemia (total bilirubin >2 times the upper limit of normal) and aspartate aminotransferase (AST) or alanine aminotransferase levels (ALT) >3 times the upper limit of normal. 9. Patients with renal impairment defined as an estimated glomerular filtration rate <50mL/min/1.73m2 as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. 10. Patients with a history of malignancies within the past 5 years other than curatively treated non-melanoma skin cancer (basal cell or squamous cell carcinomas). 11. Patients who have been treated with any investigational product within 60 days prior to visit 1 (Screening 1), or 5 half-lives (whichever is longer). Patients cannot participate in any other investigational medication or medical device trial while participating in this study.

	12. Patients who have used dietary supplements or prescription products rich in omega-3 or omega-6 fatty acids in the four weeks prior to baseline. 13. Patients who have been treated with any medication for diabetes or obesity in the four weeks before the baseline visit, except for metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, basal insulin, GLP1-RAs (must be on a stable dose for at least 6 months) and short-term insulin treatment for acute illness for a total of below or equal to 14 days. 14. Patients who have been treated with fibrates, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants, niacin, niacin analogues or dietary supplements for the purpose of lowering triglycerides or cholesterol in the six weeks prior to baseline. 15. Patients who have a family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinomas. 16. Patients who have a history of acute or chronic pancreatitis. 17. Patients who have a history of major surgical procedures involving the stomach potentially affecting absorption of investigational medicinal product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery) 18. Patients who have planned major surgical procedures, coronary intervention (such as stent placement or heart bypass), carotid or peripheral revascularisation. 19. Patients who have a history of myocardial infarction, stroke, coronary revascularisation or hospitalisation for unstable angina in the 3 months prior to screening. 20. Patients with creatine kinase concentrations > 10 times the upper limit of normal or creatine kinase elevation due to known muscle disease at visit 1 (screening 1) 21. Patients who are classified as being in New York Heart Association (NYHA) Class IV heart failure. 22. Patients who have a history of diabetic ketoacidosis. 23. Patients with known proliferative retinopathy or maculopathy requiring acute treatment. 24. Patients with significant systemic or major illnesses that, in the opinion of the Investigator, would preclude or interfere with treatment with Epeleuton, adequate follow up and/or compliance with the protocol.

	25. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in Inclusion Criterion 9) during the trial. 26. Patients with active infectious diseases or chronic infectious disease (e.g. human immunodeficiency virus or tuberculosis). 27. Patients who have recently received a vaccination or for whom a vaccination is planned (apart from flu, SARS-COV2 and pneumococcal vaccines which are permitted at any time). 28. Patients who have previously been randomised into the study. 29. Patients, in the opinion of the Investigator, not suitable to participate in the study.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:	Epeleuton will be provided as a capsule, containing 500mg of 15(S)-HEPE EE with 2.5% w/w of colloidal silicon dioxide as viscosity modifier. Placebo (light liquid paraffin) will be provided in a capsule containing equivalent fill weight of light liquid paraffin. This study will involve 2 dose levels of Epeleuton administered for 26 weeks; 4g/day (2g BID = 4 Epeleuton capsules BID), 2g/day (1g BID = 2 Epeleuton capsules and 2 placebo capsules BID) or placebo (4 placebo capsules BID). Investigational Medicinal Product (IMP) will be administered with or after food at the same time each day.
SAFETY EVALUATION CRITERIA	• Physical examination • ECG (12-lead) • Vital signs, including blood pressure (BP), heart rate and temperature • Clinical laboratory tests (haematology, coagulation, and biochemistry) • Urinalysis • Pregnancy test for females of child-bearing potential • Adverse events (AEs) • Concomitant medications (CMs) • Self-monitoring of blood glucose (SMBG)

SAMPLE SIZE	The sample size was estimated based on results of *post hoc* analyses of triglycerides and HbA1C from a phase II trial of Epeleuton in patients with non-alcoholic fatty liver disease (NAFLD). Changes in triglycerides and HbA1C at the highest tested dose (2g/day) at week 16 (end-of-treatment) were used to estimate relative effect sizes (Cohen's D). To discover a conservative relative effect size (Cohen's d) between each epeleuton group and placebo of 0.6 in triglyceride change from baseline with 80% power, 45 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided). To discover a conservative relative effect size (Cohen's d) between each epeleuton group and placebo of 0.48 in HbA1C change from baseline with 80% power, 70 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided). To power the study for both primary endpoints and take deviations from ideal parametric conditions and drop-outs into account 80 patients per group will be randomised.
STATISTICS	The primary analysis will be conducted in the full analysis set (FAS) population which will be a modified intention-to-treat (mITT) population consisting of all randomised patients who received at least one dose of the study drug and have one post-baseline measurement. For continuous variables, descriptive statistics will include: the number of patients reflected in the calculation (n), mean, median, standard deviation, interquartile range, minimum, and maximum. For categorical data, frequencies and percentages will be displayed for each category. Analysis of changes and percentage changes of triglycerides will be performed using a Wilcoxon rank sum test with the Hodges Lehmann median and 95% confidence intervals estimates. For analysis of triglycerides, baseline will be defined as the mean of the Baseline (Visit 3) and Screening 2/Week -1 (Visit 2) measurements. Changes from baseline of HbA1c at each visit will be analysed using mixed model analysis of covariance (ANCOVA) with baseline value as a covariate. Secondary and exploratory endpoints will be analysed by either an ANCOVA mixed model if the data for that endpoint are normally distributed, or a Wilcoxon-rank-sum test if the data are not normally distributed. Logistic regression with baseline HbA1C as a covariate will be used to analyse the percentage of patients with HbA1c < 7.0% and the percentage of patients with HbA1c < 6.5% at week 16. Exploratory analyses pooling the two doses vs. placebo for all pre-

	specified endpoints will be performed. Missing data will be accounted for using a multiple imputation approach. Sensitivity analyses will be conducted for the primary endpoints using a last observation carried forward (LOCF) missing data handling approach. A two-sided p-value less than 0.05 is considered statistically significant for all comparisons.
SPONSOR	Afimmune Ltd.

LIST OF ABBREVIATIONS/ DEFINITIONS

15(S)-HEPE	15-Hydroxy-Eicosapentaenoic Acid
15(S)-HEPE EE	15-Hydroxy-Eicosapentaenoic Acid Ethyl Ester, Epeleuton
AE	Adverse Event
AH	Alcoholic Hepatitis
AHA	American Heart Association
ANCOVA	Analysis of Covariance
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BDRM	Blind Data Review Meeting
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Observed Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF / eCRF	Case Report Form / Electronic Case Report Form
CRO	Clinical Research Organisation
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CV	Cardiovascular
CVD	Cardiovascular Disease
DHA	Docosahexaenoic Acid
DM	Data Manager
DPP4	Dipeptidyl Peptidase 4
DPP4i	Dipeptidyl Peptidase 4 Inhibitors
EC	Ethics Committee
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EDC	Electronic Data Capture
EMA	European Medicines Agency
EPA	Eicosapentanoic Acid
Eudravigilance database	EMA system for managing and analysing suspected adverse reactions to medicines and investigational medicinal products in clinical trials in the European Economic Area (EEA)
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLP	Good Laboratory Practice
GLP-1 RA	Glucagon-like Peptide 1 Receptor Agonists
GMP	Good Manufacturing Practice
HDL-C	High Density Lipoprotein Cholesterol

HDL-P	High Density Lipoprotein Particle Concentration
HDL Size	High Density Lipoprotein Size
HOMA-β	Homeostatic Model Assessment of β-cell Function
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hsCRP	High-Sensitivity C-Reactive Protein
IB	Investigator's Brochure
ICAM-1	Intercellular Adhesion Molecule 1
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL-	Interleukin-
IND	Investigational New Drug
INR	International Normalised Ratio
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
IWRS	Interactive Web Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LDL-P	Low-Density Lipoprotein Particle Concentration
LDL Size	Low-Density Lipoprotein Size
LOCF	Last Observation Carried Forward
Lp(a)	Lipoprotein (a)
LPLV	Last Patient Last Visit
MCP-1	Monocyte Chemoattractant Protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
nMR	Nuclear Magnetic Resonance
NOAEL	No Observed Adverse Effect Levels
Non-HDL-C	Non-High-Density Lipoprotein Cholesterol
NYHA	New York Heart Association
PAI-1	Plasminogen Activator Inhibitor 1
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Prothrombin Time
RDW	Red Cell Distribution Width
REC	Research Ethics Committee
RLP	Remnant Lipoprotein Cholesterol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SDV	Source Data Verification
SGLT2	Sodium Glucose Co-transporter 2
SGLT2i	Sodium Glucose Co-transporter 2 Inhibitors
SMBG	Self-monitoring of Blood Glucose
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

$T_{1/2}$	Apparent first-order terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time of maximum observed concentration
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinediones
UACR	Urinary albumin-to-creatinine ratio
UAE	Unexpected Adverse Event
VCAM-1	Vascular Cell Adhesion Molecule 1
VLDL	Very Low-Density Lipoprotein
VLDL-C	Very Low-Density Lipoprotein Cholesterol
VLDL Size	Very Low-Density Lipoprotein Size
WBC	White Blood Cells
WHODD	World Health Organisation Drug Dictionary
WOCBP	Women of Child-Bearing Potential

1 INTRODUCTION

1.1 Therapeutic Area and Disease Background

Type 2 diabetes mellitus is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is heterogeneous involving environmental, lifestyle and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver. Type 2 diabetes is associated with multiple comorbidities including hypertriglyceridemia and non-alcoholic fatty liver disease (NAFLD), and ultimately microvascular and macrovascular complications (American Diabetes Association 2019a).

Type 2 diabetes is large and increasing public health challenge, estimated to affect 9.4% (30.3 million people) of the US population with 1.5 million cases diagnosed every year, with similar prevalence reported globally. Among people aged 65 years and older prevalence is even higher, at 25.2% or 12.0 million. It is was reported to be the seventh leading cause of death in the United States in 2015 and its prevalence is increasing. In 2015, 84.1 million Americans aged 18 and older were prediabetic (American Diabetes Association, 2019b).

Hypertriglyceridemia and its many comorbidities affect a large and increasing segment of many populations. It is estimated that approximately 30% of the US population may have elevated triglyceride levels which are associated with increased cardiovascular risk (Toth *et al.* 2018. A small proportion of patients with hypertriglyceridemia have severe hypertriglyceridemia (>500 mg/dL) which is associated with acute pancreatitis, a potentially fatal complication (Grundy *et al*. 2018).

Atherosclerotic cardiovascular disease remains a leading cause of morbidity and mortality globally with persistently high rates of ischemic events reported especially in at risk populations such as individuals with diabetes or hypertriglyceridemia. It is estimated that $37.3 billion per year in cardiovascular-related spending alone is associated with diabetes. Additionally, despite the advent of statins, ischemic heart disease remains the leading cause of premature adult mortality globally (American Diabetes Association 2019a).

1.2 Standard Treatment

Optimal glycaemic control is the treatment goal in patients with type 2 diabetes, in order to prevent long term complications associated with chronic hyperglycaemia including microvascular and macrovascular complications. Ongoing patient self-management, education and support are critical to preventing acute complications and reducing the risk of long-term complications (American Diabetes Association 2019c).

Current pharmacological standard of care treatment is based on a patient-centred approach which includes consideration of efficacy and patient-specific factors. Commonly recommended treatments include metformin as first-line therapy, sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide 1 receptor agonists (GLP-1RA), sodium glucose co-transporter 2 inhibitors (SGLT2i) and thiazolidinediones (TZD) (American Diabetes Association 2019d).

However, despite the availability of several anti-hyperglycaemic drugs, a significant proportion of patients with type 2 diabetes do not achieve the recommended targets for glycaemic control.

Current standard of care for hypertriglyceridemia typically consists of lifestyle modification. However, emergence of data from the REDUCE-IT cardiovascular (CV) outcomes study of icosapent ethyl, the ester of the omega 3 fatty acid eicosapentaenoic acid (EPA) suggests that EPA-axis therapy reduces cardiovascular risk in patients with hypertriglyceridemia (Bhatt *et al.* 2019). In contrast, EPA/DHA mixtures are not associated with a cardiovascular benefit as evidenced by the lack of benefit reported in a recent large CV outcome study (STRENGTH) of Epanova (omega 3 carboxylic acids - EPA/DHA).

There is a persistent unmet need for patients with type 2 diabetes and patients with hypertriglyceridemia for additional treatments that improve biochemical parameters and ultimately improve clinical outcomes.

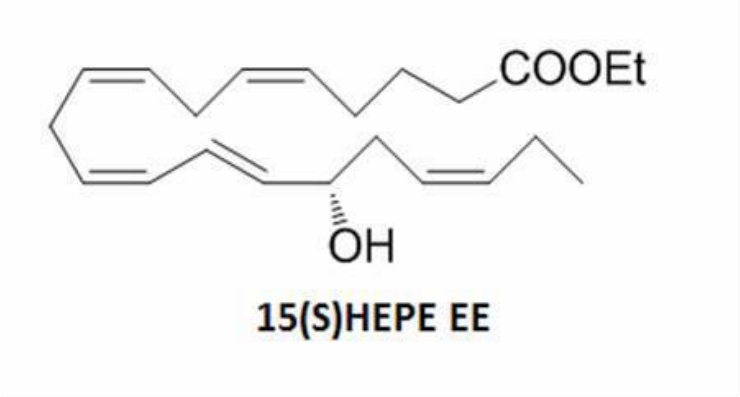
1.3 Drug Class

Epeleuton is 15-hydroxy eicosapentaenoic acid (15(S)-HEPE) ethyl ester (15(S)-HEPE EE), a highly-purified, semi-synthetic omega-3 fatty acid derivative of EPA.

15(S)-HEPE, at much lower concentrations, is an endogenous downstream 15-lipoxygenase metabolite of EPA.

Epeleuton has been associated with potent triglyceride lowering, anti-hyperglycaemic, anti-inflammatory and anti-fibrotic effects in clinical and non-clinical studies.

Figure 1: Structure of 15(S)-HEPE EE (Epeleuton)



1.4 Preclinical Pharmacology

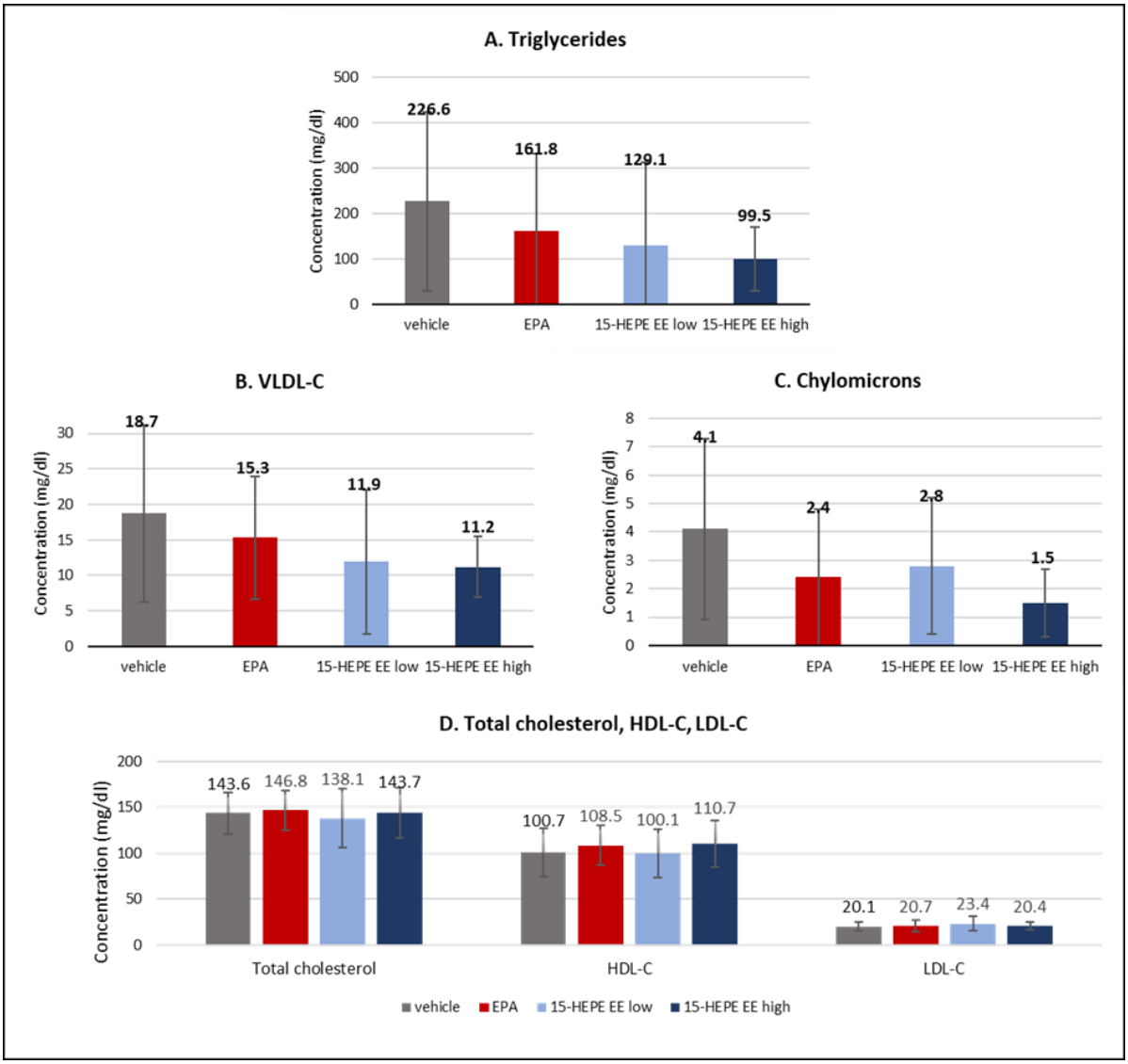
Similar to other omega-3 polyunsaturated fatty acids and their metabolites, Epeleuton is postulated to exert its therapeutic effects through pleiotropic mechanisms which include:

- Incorporation into and re-ordering of cell membranes
- Modulation of the expression and function of certain cell surface receptors, leading to regulation of cell signalling and alteration of the production of mediators including cytokines, leukotrienes and prostaglandins
- Acting as an endogenous ligand for certain G-protein coupled receptors.
- Further conversion by lipoxygenase enzymes into its downstream metabolites Lipoxin A5 and Lipoxin B5.

The mechanism of action of the triglyceride lowering and antihyperglycemic effect of Epeleuton has not been fully elucidated. It is thought to be partially mediated through free fatty acid degradation leading to decreased very-low-density lipoprotein (VLDL) and increased clearance of diglycerides and triglycerides, in addition to other pleotropic mechanisms as described above.

Epeleuton has been shown to decrease plasma triglycerides, total cholesterol, VLDL cholesterol and chylomicrons in non-clinical species. Administration of Epeleuton to streptozocin and high fat diet model mice (SMCN013-1411-8) produced dose-dependent reductions in triglycerides which notably exceeded the triglyceride reduction produced by the EPA positive control when administered at the same dose **(Figure 2).** Triglyceride levels were mirrored by dose-dependent decreases of VLDL cholesterol and chylomicron concentrations in serum.

Figure 2. Streptozocin and High Fat Diet Mouse Study - Concentrations of Serum Triglycerides and Cholesterol at End of Treatment



EPA - 500 mg/kg, 15-HEPE EE low – 50 mg/kg, 15-HEPE EE high – 500 mg/kg

Nonclinical toxicology studies with Epeleuton in normolipidemic rats also showed dose-dependent decreases in triglycerides and total cholesterol. In a 28-day repeat dose rat study (CRL 527943), dose-related decreases in triglycerides were observed in both sexes and were significant in males. A significant decrease in total cholesterol was also observed in females at 2g/kg/day. In a 26-week repeat dose rat study (CRL 529123), dose-related decreases in triglycerides and total cholesterol were observed in both sexes at week 13 and week 26 and were significant in males at 1g/kg/day at both time points. In a further 26-week repeat dose rat study (CRL509554), significant dose-related decreases in triglycerides and total cholesterol were observed at both tested doses, 2g/kg/day and 3g/kg/day.

Additionally, Epeleuton delayed and prevented the progression of end-organ effects in multiple animal models including mouse models of chronic kidney disease, liver fibrosis and lung fibrosis. In a unilateral ureteral obstruction model of tubulointerstitial nephritis and chronic kidney disease, Epeleuton decreased fibrosis area and collagen deposition (SLMC062-1805-5). In a streptozocin and high fat diet mouse model of dyslipidemia and non-alcoholic steatohepatitis (NASH), Epeleuton decreased urinary microalbuminuria in addition to delaying and preventing the progression of renal fibrosis, hepatic fibrosis and hepatic steatosis (SMCN013-1411-8). Similarly, in a bile duct ligation model of liver fibrosis (SLMN063-1805-6), Epeleuton delayed the progression of liver fibrosis. In a bleomycin induced pulmonary fibrosis mouse model, treatment with Epeleuton decreased inflammatory cell influx in broncheoalveolar fluid and ultimately decreased lung fibrosis (DS-PC-30).

1.5 Toxicology

A number of good laboratory practice (GLP) toxicology studies have been conducted by the company to assess the safety of Epeleuton in rats (CRL-527545, CRL-527943, CRL-529123, CRL509554) and dogs (CRL-527550, CRL-527959, CRL-529139).

Repeated dose, once-daily oral administration of Epeleuton in chronic toxicity studies in rats (4 and 26 week duration at doses up to 2000 and 1000mg/kg/day, respectively) and dogs (4 and 39 weeks duration at doses up to 2000 and 1000mg/kg/day, respectively) was well tolerated and showed no adverse, treatment-related effects. The no observed adverse effect levels (NOAEL) for repeated dosing over four weeks in both species was the highest tested dose 2000mg/kg/day. The NOAEL for the 26-week rat and 39-week dog study was also the highest tested dose of 1000mg/kg/day. In addition, a 26-week study in rats has recently been completed and is currently being analysed, with the aim to evaluate the safety and toxicity of oral administration of Epeleuton at higher doses.

1.6 Previous Clinical Safety Studies with Epeleuton

Safety of Epeleuton was assessed in:

- three completed Phase I studies in healthy subjects (DS102A-01, DS102A-04 and DS102A-06-HV3),
- two completed Phase II studies in patients with NAFLD (DS102A-02) and patients with chronic obstructive pulmonary disease (COPD) (DS102A-03) and,
- in the pilot phase of a Phase II study in patients with severe acute decompensated alcoholic hepatitis (AH) (DS102A-05-AH1).

Overall, Epeleuton capsules at doses of up to 4 grams per day were well tolerated in studies of up to 16 weeks treatment duration, with a safety profile similar to placebo.

DS102A-01

This Phase I first in man study was conducted in healthy volunteers, to assess the safety, pharmacokinetics (PK) and effect of food on orally administered Epeleuton. The study was conducted in a total of 57 healthy volunteers (27 female and 30 male subjects). Epeleuton capsules were administered to healthy volunteers in the following regimens: a single dose of 100mg, 500mg, 1000mg, or 2000mg under fasted conditions; a single dose of 500mg under fed conditions (standard diet and high fat diet); and as multiple doses of 500mg, 1000mg or 2000mg doses taken once daily for 28 consecutive days.

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

There were no deaths, serious adverse events (SAEs) or subject discontinuations due to adverse events (AEs) reported in this study. The majority of reported treatment emergent adverse events (TEAEs) were considered to be mild in intensity and not related to study treatment. The events of dysgeusia and eructation (following Epeleuton treatment), diarrhoea (following Epeleuton and placebo treatment), and nausea (following placebo) were considered related to the study treatment. Overall, Epeleuton was considered safe and well-tolerated with no SAEs reported.

DS102A-02

This was a randomised, double-blind, placebo-controlled, exploratory Phase IIa study assessing the safety and efficacy of orally administered Epeleuton capsules versus placebo in the treatment of adult patients with NAFLD, over a 16-week treatment period.

In total, 52 patients experienced 146 non-serious AEs while participating in the DS102A-02 trial. The most common AEs reported were diarrhoea (n=8), headache (n=8), increased CPK (n=6), upper respiratory tract infection (n=5), fatigue (n=4), nausea (n=4) and dyspepsia (n=4). Out of all AEs, seven events (preferred terms dysgeusia (n=3), eructation (n=1), dyspepsia (n=1), abdominal pain upper (n=1), and abdominal discomfort (n=1)) were considered related to Epeleuton capsules, thus most of the related TEAEs (i.e. all except dysgeusia) belong to the gastrointestinal disorders. All events related to Epeleuton capsules were mild in severity except one event of abdominal pain upper which was moderate. Two SAEs were reported during the study, schizophrenia in the epeleuton 2g/day group and pilonidal cyst in the placebo group, both of which were considered unrelated to study treatment. No deaths were observed during the study.

DS102A-03

This was a randomised, double-blind, placebo-controlled, exploratory Phase IIa study assessing the

safety and efficacy of orally administered Epeleuton capsules versus placebo in the treatment of adult patients with COPD, over a 12-week treatment duration.

Overall, a total of 78 TEAEs were reported by 33 patients. The most common TEAEs reported were headache (n=7), nasopharyngitis (n=6), productive cough (n=5), nocturnal dyspnoea (n=4), chronic obstructive pulmonary disease (n=4) and lower respiratory tract infection (n=4). None of the TEAEs were considered related to Epeleuton (or placebo). All TEAEs were of mild or moderate severity except one event of CRP increase (Epeleuton 2g/day group), which was considered severe and not related to study drug. The event self-resolved without intervention and no additional laboratory results were reported for this patient. No SAEs and no deaths were observed during the study.

DS102A-04

This was a Phase I study in 11 healthy volunteers per treatment arm to assess the effect of a high fat meal on the PK of Epeleuton following single dose or twice daily oral administration of 1000mg Epeleuton.

No serious AEs, and no AEs leading to death were reported in this study. There were no AEs considered as related to the study drug.

Overall, no clinically significant changes in any of the blood chemistry or urinalysis parameters, physical examination, vital signs or electrocardiogram (ECG) findings were detected during the study. Overall, safety findings observed in this study were unremarkable.

DS102A-05-AH1

This was a randomised, double-blind Phase II study assessing the safety and efficacy of Epeleuton in the treatment of adult patients with AH. An open-label pilot phase was conducted prior to a randomised double-blind phase to assess the PK of Epeleuton in patients with severe acute decompensated AH.

Seven patients experienced 30 non-serious AEs while participating in the open-label pilot phase of the DS102A-05-AH1 trial. All AEs were experienced by 1 patient only except for the AEs abdominal distension (n=2), aspartate aminotransferase increased (n=2) and fall (n=2). The majority of the AEs were of mild and moderate severity. Four out of the 30 AEs were assessed as severe. None of the non-serious AEs were considered related to Epeleuton capsules.

In total eight SAEs were reported. One SAE, pulmonary edema initially reported as respiratory distress, was assessed as possibly related to study treatment. Due to the temporal relationship to study treatment, the causal role of study medication was considered as possible, although the event may have been caused by other reasons including excess alcohol consumption. There were in total 5 SAEs with fatal outcome, all of which were deemed unrelated to study medication, and all were considered most likely related to the natural course of the underlying severe acute AH. Two additional SAEs were reported, renal failure and mental status changes. Neither of these SAEs were considered related to study medication. Overall the observed AE profile was consistent with the underlying disease of the study population.

DS102A-06-HV3

This Phase I study was conducted in 24 healthy volunteers, to assess the safety and PK of Epeleuton. Epeleuton capsules were administered to healthy volunteers in the following regimens: a single dose of 1000mg or 2000mg under fed conditions; and as multiple doses of 2000mg per day (1000mg BID) or 4000mg per day (2000mg BID) for 14 consecutive days.

There were no deaths, SAEs or subject discontinuations due to AEs reported in this study. The majority of reported TEAEs were considered to be mild or moderate in severity. The events of abdominal discomfort (Epeleuton 2000mg), nausea (Epeleuton 4000mg), vomiting (placebo) and increased white blood cells (WBC) (placebo) were considered possibly related to the study treatment. Overall, Epeleuton was well-tolerated, with a safety profile similar to placebo.

2 RISK BENEFIT ASSESSMENT

Recent advances in primary and secondary prevention of cardiovascular events provide hope that new therapies targeting various cardiovascular risk factors including elevated triglycerides, hyperglycaemia and inflammation will produce additional benefits to LDL cholesterol management with statins and other prevention strategies. Therapies that target multiple factors associated with residual cardiovascular risk may further improve patient outcomes (American Diabetes Association 2019a).

Afimmune has conducted three Phase I studies in healthy subjects, two Phase II studies in patients with NAFLD and COPD, and a safety and PK pilot study in patients with severe acute AH.

Studies conducted to date have demonstrated a very favourable safety profile for Epeleuton. Single ascending doses of 100mg, 500mg, 1000mg, and 2000mg Epeleuton, and multiple ascending doses of 500mg, 1000mg, 2000mg and 4000mg were well tolerated with similar safety to placebo in healthy subjects under fasted and fed conditions.

Afimmune conducted a Phase IIa study in patients with NAFLD. Due to the overlap between NAFLD, dyslipidemia and type II diabetes, a *post hoc* analysis was undertaken to compare the lipid lowering, antihyperglycemic and anti-inflammatory effects of Epeleuton 2g/day and Epeleuton 1g/day with placebo. We hypothesised that Epeleuton may exert superior triglyceride lowering and anti-inflammatory effects to its endogenous precursor EPA.

The *post hoc* analyses revealed that treatment with Epeleuton for 16 weeks resulted in significant dose-dependent decreases of triglycerides, atherogenic lipids and lipoproteins, HbA1C, fasting glucose, insulin resistance indices and multiple markers of inflammation and endothelial dysfunction with no evidence of a plateau in treatment effect. The results of this study, while *post hoc*, have identified Epeleuton's unique potential to synergistically address multiple axes of cardiovascular risk and several disease indications associated with cardiometabolic dysfunction, suggesting that Epeleuton may have substantial therapeutic potential for cardiovascular risk reduction by simultaneously targeting hypertriglyceridemia, hyperglycaemia and inflammation.

Due to the unique triad of therapeutic effects demonstrated by Epeleuton and the safety profile demonstrated to date in GLP toxicology studies, Phase I studies in healthy volunteers and Phase II studies in patients with various disease indications, the company intends to perform this Phase II study (TRIAGE) in patients with concomitant hypertriglyceridemia and type 2 diabetes mellitus. The proposed Phase IIb dose-ranging study aims to prospectively assess the previously demonstrated antihyperglycemic, triglyceride lowering and anti-inflammatory effects of Epeleuton at 2g and 4g daily doses.

3 RATIONALE FOR THE STUDY

The proposed study aims to investigate the triglyceride lowering, antihyperglycemic, and anti-inflammatory effects of Epeleuton as surrogate markers of its potential to improve diabetic control and cardiovascular outcomes.

4 STUDY OBJECTIVES

Efficacy Objective:

• To assess the efficacy of orally administered Epeleuton capsules versus placebo, in the treatment of adult patients with hypertriglyceridemia and type 2 diabetes.

Safety Objective:

• To assess the safety of orally administered Epeleuton capsules versus placebo, in the treatment of adult patients with hypertriglyceridemia and type 2 diabetes.

5 STUDY ENDPOINTS

5.1 Primary Endpoints

- Percent change in triglycerides from baseline to week 16.
- Change in HbA1c from baseline to week 26.

Note:

- *Each of the independent primary endpoints will be analysed separately.*

5.2 Secondary Endpoints

- Percent change in triglycerides from baseline to weeks 4, 8, 12, 20 and 26.
- Change in HbA1c from baseline to weeks 4, 8, 12, 16 and 20.
- Proportion of patients achieving a HbA1c below 7.0% at weeks 4, 8, 12, 16, 20 and 26.
- Percent change in very low-density lipoprotein cholesterol (VLDL-C) from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Percent change in total cholesterol from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Change in fasting plasma glucose from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Proportion of patients achieving a HbA1c below 6.5% at weeks 4, 8, 12, 16, 20 and 26.
- Percent change in apolipoprotein B (ApoB) from baseline to weeks 16 and 26.
- Percent change in remnant lipoprotein cholesterol (RLP-C) from baseline to weeks 8, 16 and 26.
- Percent change in high-density lipoprotein cholesterol (HDL-C) from baseline to weeks 4, 8,

12, 16, 20 and 26.

- Percent change in low-density lipoprotein cholesterol (LDL-C) (preparative ultracentrifugation) from baseline to weeks 16 and 26.
- Change in body weight (kg) from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Change in high-sensitivity C-reactive protein (hsCRP) from baseline to weeks 8, 16 and 26.
- Change in systolic blood pressure from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Change in diastolic blood pressure from baseline to weeks 4, 8, 12, 16, 20 and 26.
- Change in urinary albumin-to-creatinine ratio (UACR) from baseline to week 26 in the sub-group of patients with microalbuminuria at baseline.

5.3 Exploratory Endpoints

- Change in waist circumference from baseline to weeks 8, 16 and 26.
- Percent change in apolipoprotein CIII (ApoCIII) from baseline to weeks 16 and 26.
- Percent change in apolipoprotein A1 (ApoA1) from baseline to weeks 16 and 26.
- Percent change in lipoprotein (a) (Lp(a)) from baseline to weeks 16 and 26.
- Percent change in high-density lipoprotein particle concentration (HDL-P) from baseline to weeks 16 and 26.
- Percent change in small low-density lipoprotein particle concentration (Small LDL-P) from baseline to weeks 16 and 26.
- Percent change in large low-density lipoprotein particle concentration (Large LDL-P) from baseline to weeks 16 and 26.
- Percent change in low-density lipoprotein size (LDL size) from baseline to weeks 16 and 26.
- Percent change in very low-density lipoprotein size (VLDL size) from baseline to weeks 16 and 26.

- Percent change in high-density lipoprotein size (HDL size) from baseline to weeks 16 and 26.
- Change in fasting plasma insulin from baseline to weeks 16 and 26.
- Change in Homeostatic model assessment insulin resistance (HOMA-IR) from baseline to weeks 16 and 26.
- Change in Homeostatic model assessment β-cell function (HOMA-β) from baseline to weeks 16 and 26.
- Change in interleukin 6 (IL-6) from baseline to week 26.
- Change in interleukin 1β (IL-1β) from baseline to week 26.
- Change in plasminogen activator inhibitor 1 (PAI-1) from baseline to week 26.
- Change in vascular cell adhesion molecule 1 (VCAM-1) from baseline to week 26.
- Change in intercellular adhesion molecule 1 (ICAM-1) from baseline to week 26.
- Change in monocyte chemoattractant protein 1 (MCP-1) from baseline to week 26.
- Change in red cell distribution width (RDW) from baseline to weeks 16 and 26.
- Change in haemoglobin from baseline to weeks 16 and 26.
- Change in reticulocyte count from baseline to weeks 16 and 26.
- Change in erythrocyte (red blood cell) count from baseline to weeks 16 and 26.
- Trough plasma concentrations of total and unesterified 15-hydroxy eicosapentaenoic acid (15(S)-HEPE) in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8, Week 16 and Week 26.
- Trough plasma concentrations of EPA in treated population compared to placebo population at Baseline/Day 0, Week 4, Week 8, Week 16 and Week 26.
- Determination of exploratory serum biomarkers in treated population compared to placebo population at Baseline and Week 26.

5.4 Safety Variables

- Incidence of treatment-emergent level 2 and level 3 hypoglycaemic episodes
    - Level 2 – Glucose <54 mg/dL (3.0 mmol/L), with or without symptoms
    - Level 3 – A severe event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia.
- AE and SAE frequency and severity.
- Safety laboratory parameters (haematology, clinical chemistry, coagulation).
- Urinalysis
- ECGs
- Vital signs (heart rate, temperature, blood pressure)
- Physical examination
- Pregnancy

6 STUDY DESIGN

6.1 General

This is a randomised, double-blind, placebo controlled, 3-arm, multi-centre Phase IIb study consisting of 26 weeks of active treatment and a 2-week post-treatment follow up period in adult patients with hypertriglyceridemia and concomitant type 2 diabetes.

The screening period will consist of up to 6-weeks lead-in during which all patients will undergo diet and lifestyle stabilisation, washout of disallowed medications and optimisation of statins.

Lipid eligibility criteria include a fasting triglyceride level ≥200 mg/dL (2.26 mmol/L) and <750mg/dL (8.46 mmol/L) (inclusion #3) and LDL cholesterol <130mg/dL (3.34 mmol/L) (inclusion #6). Triglycerides and LDL cholesterol will be checked at Screening #1 and a second qualifying visit (Screening #2) which will take place one week before randomisation at the baseline visit. Patients who meet the inclusion criteria at both screening visits will be eligible to participate in the study. Eligible patients will be randomised one week after Screening #2 at the baseline visit.

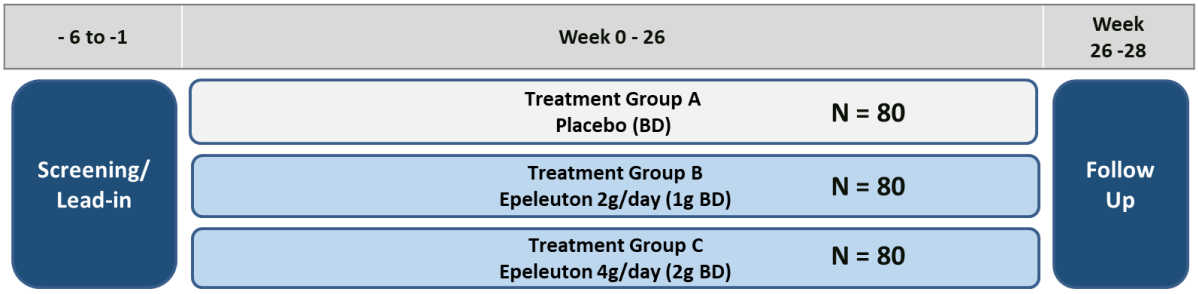
Patients will be randomised (1:1:1) at the baseline visit into the following treatment groups:

- Treatment Group A (placebo): four placebo capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks.
- Treatment Group B (Epeleuton 2g): two Epeleuton 500mg capsules and two placebo capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks.
- Treatment Group C (Epeleuton 4g): four Epeleuton 500mg capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks.

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

A schematic diagram of the study is presented in Figure 3.

Figure 3: Study Outline



6.2 Rationale for Study Design and Dose Selection

This 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 26 weeks after a lead-in phase of four to six weeks and was designed in order to assess the efficacy and safety of two doses of Epeleuton (2 gram daily dose and 4 gram daily dose) in patients with hypertriglyceridemia and type 2 diabetes.

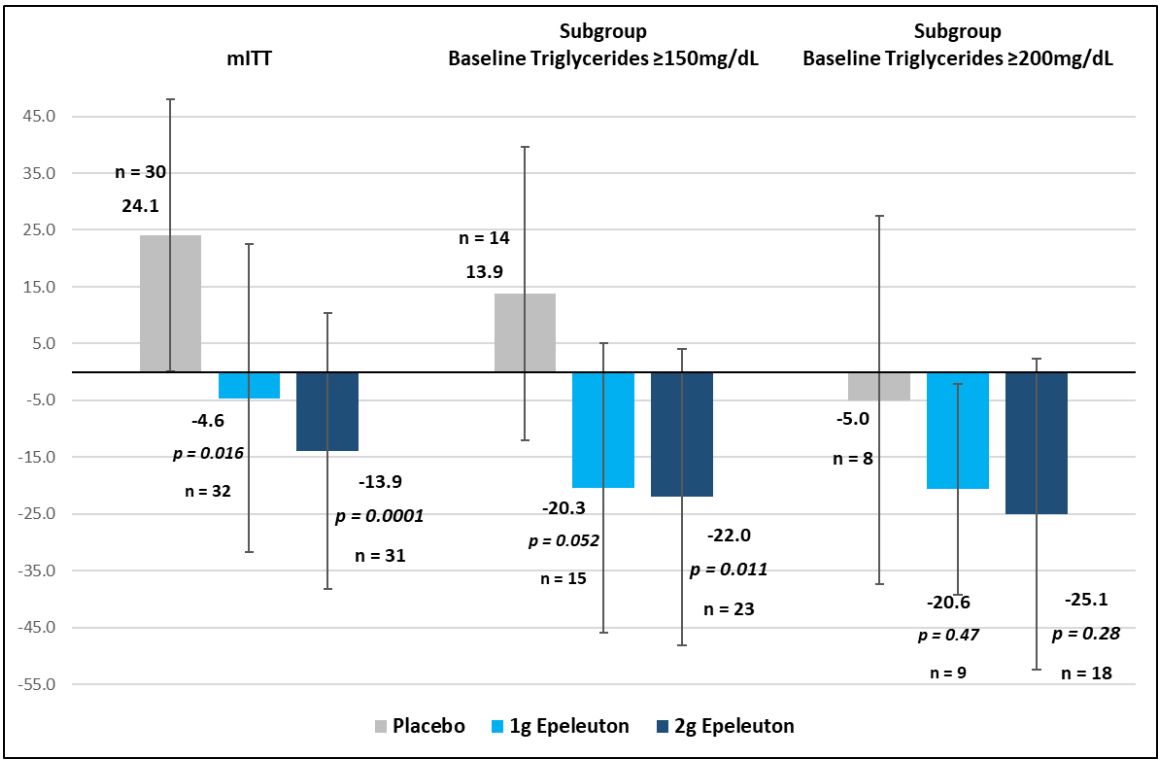
Studies in rats and dogs treated for up to 26 weeks and 39 weeks respectively have demonstrated that Epeleuton did not indicate any significant toxicity and resulted in a NOAEL of 1000mg/kg/day in both species (CRL-529123, 529139). This information along with the Food and Drug Administration (FDA) and European Medicines Agency (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.

Epeleuton at daily doses of 2000mg and 4000mg were administered to healthy volunteers for up to 28 days and 14 days respectively in Phase I studies, and at a daily dose of 2000mg for up to 16 weeks in Phase II studies in patients with NAFLD and COPD. The results from the studies conducted to date indicate that Epeleuton is well tolerated, with a similar safety profile to placebo.

The PK profile of Epeleuton seen in Phase I trials indicated that administration with food increased the bioavailability of Epeleuton, and its active moiety 15(S)-HEPE.

In a Phase IIa trial in patients with NAFLD, Epeleuton produced significant decreases of triglycerides, total cholesterol and multiple atherogenic lipids without raising LDL cholesterol. Notably, decreases were greater in the higher dose group; and greater at both 1g and 2g daily doses in sub-groups with elevated triglycerides at baseline, suggesting that further decreases may be seen in prospectively designed studies in patients with hypertriglyceridemia and at a higher daily dose.

Figure 4. DS102A-02 study – Median change in triglycerides in patients receiving Epeleuton 2g/day or Epeleuton 1g/day

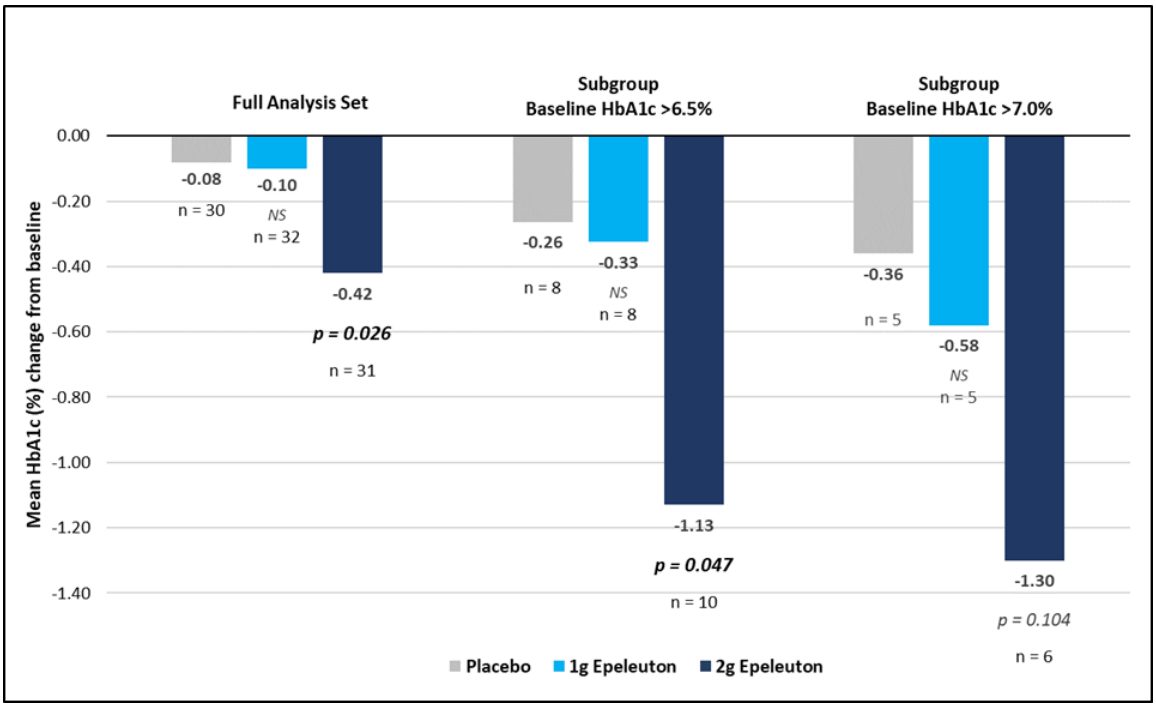


P-values for between group comparisons of epeleuton vs placebo, Wilcoxon Rank Sum test with Hodges Lehmann estimates. mITT – modified intention-to-treat (n=93), Error bars – interquartile range

Additionally, Epeleuton significantly decreased HbA1c. Notably, at week 16 (end-of-treatment) HbA1C was decreased by >1.0% in sub-groups with elevated HbA1C at baseline, at least comparable to most common antihyperglycemic agents after 26 to 52 weeks treatment. Additionally, HbA1C lowering was dose-dependent with no evidence of a plateau in treatment at week 16 suggesting that further decreases may be observed at a higher dose and over a longer treatment duration. Similar, dose-dependent decreases were observed for fasting plasma glucose, insulin resistance indices and markers of inflammation and endothelial dysfunction.

These data suggest Epeleuton may have substantial therapeutic potential for cardiovascular risk reduction by simultaneously targeting hypertriglyceridemia, hyperglycaemia and inflammation.

Figure 5. DS102A-02 study - Mean Change in HbA1C from Baseline to Week 16 (End-of-treatment)



NS denotes non-significant p-values (>0.05) compared to placebo.

The dose selection in this trial is based on the safety, PK and efficacy data from Phase I and Phase II trials and the intention to characterise the safety and efficacy of Epeleuton at up to 4000mg per day given in divided doses (BID) with or after food to patients with hypertriglyceridemia and concomitant type 2 diabetes.

7 PATIENTS AND SCREENING

In order to participate in this study, patients must meet all inclusion criteria and must not meet any of the exclusion criteria. Inclusion in the trial starts with the informed consent signature. The inclusion and exclusion criteria are to be verified at the first Screening Visit (Visit #1), confirmed at the second Screening Visit (Visit #2) and again at Baseline (visit #3).

7.1 Source of Patients

The study population will consist of male and female patients diagnosed with hypertriglyceridemia and type 2 diabetes, aged 18 years and over.

7.2 Inclusion Criteria

1. Patients diagnosed with type 2 diabetes mellitus at least 90 days prior to the first screening visit.

2. Patients with a HbA1C (glycosylated haemoglobin) between 7.0 - 10.0% (53-86 mmol/mol) (both inclusive)

3. Patients with a fasting triglyceride level ≥200 mg/dL (2.26 mmol/L) and <750mg/dL (8.46 mmol/L) at both screening visits.

   Note: If the triglyceride level is outside the required range at the second screening visit, an additional measurement can be obtained 1 week later, to confirm eligibility.

   Note: *If a large difference in triglyceride level (>15%) is observed between screening 1 and screening 2, an additional measurement may be requested or patient may be deemed not eligible.*

4. Patients who have been educated regarding diet and exercise at or before visit 1 (screening 1) and are willing to maintain and not alter a stable diet and activity routine throughout the study.

5. Patients who have been on a stable statin therapy at doses that are likely to achieve optimal LDL cholesterol and who are willing to continue this treatment throughout the study.

   Note: Stable statin therapy may consist of a statin with or without ezetimibe.

6. Patients with an LDL cholesterol level <130mg/dL (3.34 mmol/L) at both screening visits.

7. Patients who have a body mass index (BMI) ≥ 25kg/m2 and <50kg/m2.

8. Patients who have been on a stable daily dose of metformin (at least 1500mg or maximum tolerated dose for metformin monotherapy as documented in the subject medical record) and/or a sulfonylurea and/or a dipeptidyl peptidase-4 (DPP-4) inhibitor and/or a sodium-glucose transport protein 2 inhibitor (SGLT2i) and/or a GLP1-RA and/or basal insulin for at least 90 days prior to the day of first screening visit.

Note: *Dose of GLP1-RA must be stable for 6 months prior to baseline with no weight change >2kg for 3 months prior to baseline.*

Note: *Dose of basal insulin must be stable for 4 months prior to baseline. All types of basal insulin are permitted, including insulin glargine, insulin degludec, insulin detemir, NPH insulin and pre-mixed insulin.*

9. Female patients and male patients with female partners of childbearing potential must use highly effective contraceptive methods or have a sterilised partner for the duration of the study. Highly effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include hormonal contraception, intrauterine device or sexual abstinence.

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

   Note: Hormonal contraceptives must be on a stable dose for at least one month before baseline.

   Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

10. Patients whose pre-study or screening clinical laboratory findings do not interfere with their participation in the study, in the opinion of the Investigator, and do not violate any inclusion or exclusion criteria

11. Male or female patients aged 18 years and older on the day of signing the informed consent form (ICF).

12. 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 prior to initiation of any study specific activities or procedures.

7.3 Exclusion Criteria

1. Patients who have a history of intolerance or hypersensitivity to any substance in epeleuton capsules, placebo capsules or statins.

2. Patients with uncontrolled hypertension defined as a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥100mmHg.

3. Patients who have a body mass index (BMI) <25kg/m2 or ≥ 50kg/m2.

4. Patients who have a weight change >2kg from the first screening visit to the baseline visit.

5. Patients who have type 1 diabetes mellitus.

6. Patients who have thyroid stimulating hormone (TSH) levels >1.5 times the upper limit of normal.

7. Patients with known familial lipoprotein lipase deficiency (Fredriksen type I), apolipoprotein C-II deficiency or familial dysbetaliproteinemia (Fredriksen type III).

8. Patients with significant liver disease or liver function impairment defined as any of the following; cirrhosis, hepatitis, biliary obstruction with hyperbilirubinemia (total bilirubin >2 times the upper limit of normal) and aspartate aminotransferase (AST) or alanine aminotransferase levels (ALT) >3 times the upper limit of normal.

9. Patients with renal impairment defined as an estimated glomerular filtration rate <50mL/min/1.73m^2 as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

10. Patients with a history of malignancies within the past 5 years other than curatively treated non-melanoma skin cancer (basal cell or squamous cell carcinomas).

11. Patients who have been treated with any investigational product within 60 days prior to visit 1 (Screening 1), or 5 half-lives (whichever is longer). Patients cannot participate in any other investigational medication or medical device trial while participating in this study.

12. Patients who have used dietary supplements or prescription products rich in omega-3 or omega-6 fatty acids in the four weeks prior to baseline.

13. Patients who have been treated with any medication for diabetes or obesity in the four weeks before the baseline visit, except for metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, basal insulin, GLP1-RAs (must be on a stable dose for at least 6 months) and short-term insulin treatment for acute illness for a total of below or equal to 14 days.

14. Patients who have been treated with fibrates, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants, niacin, niacin analogues or dietary supplements for the purpose of lowering triglycerides or cholesterol in the six weeks prior to baseline.

15. Patients who have a family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinomas.

16. Patients who have a history of acute or chronic pancreatitis.

17. Patients who have a history of major surgical procedures involving the stomach potentially affecting absorption of investigational medicinal product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery)

18. Patients who have planned major surgical procedures, coronary intervention (such as stent placement or heart bypass), carotid or peripheral revascularisation.

19. Patients who have a history of myocardial infarction, stroke, coronary revascularisation or hospitalisation for unstable angina in the 3 months prior to screening.

20. Patients with creatine kinase concentrations > 10 times the upper limit of normal or creatine kinase elevation due to known muscle disease at visit 1 (screening 1)

21. Patients who are classified as being in New York Heart Association (NYHA) Class IV heart failure.

22. Patients who have a history of diabetic ketoacidosis.

23. Patients with known proliferative retinopathy or maculopathy requiring acute treatment.

24. Patients with significant systemic or major illnesses that, in the opinion of the Investigator, would preclude or interfere with treatment with Epeleuton, adequate follow up and/or compliance with the protocol.

25. Patients who are pregnant, planning pregnancy, breastfeeding and/or are unwilling to use adequate contraception (as specified in Inclusion Criterion 9) during the trial.

26. Patients with active infectious diseases or chronic infectious disease (e.g. human immunodeficiency virus or tuberculosis).

27. Patients who have recently received a vaccination or for whom a vaccination is planned (apart from flu, SARS-COV2 and pneumococcal vaccines which are permitted at any time).

28. Patients who have previously been randomised into the study.

29. 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 risks/benefits 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 ICF. The patients will then receive a copy of the signed and dated patient information sheet (PIS)/ICF. The original signed ICF will be filed in the Investigator Site File (ISF). The PIS will contain site contact information in case of any questions or medical emergency.

If 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 repercussions. 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, every effort should be made to minimize the withdrawal of patients. Should a patient decide to withdraw, all efforts will be made to complete and report the observations from assessments conducted during study visits, particularly the follow-up examination, as thoroughly as possible.

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

Standard reasons for withdrawing from further participation in the study may be:

- Unacceptable AEs
- Patient's decision
- Investigator's discretion
- Intercurrent illness
- Pregnancy
- Patient lost to follow-up

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

Patients who discontinue the study treatment before week 26 (visit #9) will be asked to come for an early termination visit as soon as possible and have the assessments listed at week 26 (visit #9) performed.

7.6 Patient Replacement

Patients who are withdrawn from the study due to an AE or lack of efficacy will not be replaced.

Patients who do not meet the eligibility criteria or are withdrawn due to loss to follow up may be replaced.

7.7 Protocol Deviations

All protocol deviations will be reviewed by the medical monitor as and when each deviation 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, 10 visits to the clinic are scheduled: two Screening Visits (Visit 1 and Visit 2), one visit at the start of the comparative treatment period (Baseline/Visit 3), six visits in the comparative treatment period (Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20 and Visit 9/Week 26 or Early Termination) and one final safety follow-up visit (Visit 10/Week 28).

Patients who discontinue the study early before Week 26, for whatever reason, will be asked to attend the investigative site as soon as possible so that assessments scheduled for the early termination visit (Visit 9) will be performed.

8.2 Clinic Visits

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

8.2.1 Screening Visit 1 (Visit 1)

The patient must sign and date the ICF for inclusion in the screening phase before any study-specific procedures are conducted.

Once informed consent has been obtained, the Investigator will assign a patient number.

The following screening assessments/sample collections will be performed:

- Obtain Informed consent.
- Verification of inclusion/exclusion criteria (Sections 7.2 & 7.3)
- Serum pregnancy test (only female patients of childbearing potential) (as detailed in Section 9.2.1)
- Counselling on contraception (as detailed in Section 9.2.1)
- Demographic data
- Medical history (including history of diabetes, cardiovascular disease (CVD), liver disease and smoking) (as detailed in Section 9.2.3)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Physical examination (weight, height, BMI, waist circumference) (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Counselling on healthy lifestyle (see below)
- Blood sampling for laboratory tests #1 (clinical haematology, serum biochemistry, coagulation) (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (triglycerides, LDL-C (calculated), HbA1c) (as detailed in Section 9.1.3)

- Serum blood sample for TSH testing

All procedures that are medically necessary should be followed.

Counselling on healthy lifestyle should be performed during this visit according to step 6 of the National Cholesterol Education Program Adult Treatment Panel III guidelines (NIH Publication No. 01–3305). The assessment should include consultation on:

- Diet: saturated fat <7% of calories, cholesterol <200mg/day, increase soluble fibre intake (10-25g/day) and plants stanols/sterols (2g/day)
- Weight management
- Increased physical activity

8.2.2 Screening Visit 2 (Visit 2)

Screening visit 2 will be conducted one week prior to the baseline visit.

- Concomitant Medication Assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Review of inclusion/exclusion criteria (Sections 7.2 & 7.3)

8.2.3 Treatment Period

Following completion of a successful screening period, patients will begin the comparative treatment period (26 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 in a 1:1:1 ratio.

Patients will take the allocated investigational medicinal product (IMP) twice daily, in the morning and in the evening, with or after food (within 30 minutes after a meal), throughout the 26 weeks study treatment period. Patients will attend the study visits fasting but will receive their morning IMP dose (Epeleuton or placebo) at site with or after food (within 30 minutes after a meal) after blood samples have been collected.

Each administration of IMP will be recorded by the patient in an electronic diary. The record will include date, time and value. If the patient is unable to access the electronic diary, a paper diary back up will be provided and the data will be transcribed during the next site visit into the IRT by the Investigator or designee.

Patients who discontinue the study early will have all study procedures scheduled for Visit 9 (see Section 8.2.10) performed as soon as possible after patient withdrawal so that all study-related information can be recorded.

In-study and post- discharge referral and intervention will be provided as needed.

8.2.4 Baseline (Visit 3)

The following assessments/sample collections will be performed at Baseline/Visit 3:

- Verification of inclusion/exclusion criteria (as detailed in Sections 7.2 & 7.3)
- Serum and Urine Pregnancy test (as detailed in Section 9.2.1); female patients of childbearing potential only
- Counselling on contraception (as detailed in Section 9.2.1)
- Medical history (as detailed in Section 9.2.3)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- ECG (as detailed in Section 9.2.5)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Counselling on healthy lifestyle (see below)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- PK sampling (sample will be taken pre-dose) (as detailed in Section 9.3)
- Exploratory blood sampling (as detailed in Section 9.4)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (VLDL-C, non-HDL-C, total cholesterol, glucose, HDL-C, RLP-C) (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #4 (LDL-C (preparative ultracentrifugation), ApoA1, ApoB, ApoCIII, Lp(a), insulin, hsCRP, HOMA-IR, HOMA-β, nMR lipid profile) (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #5 (IL-6, IL-1β, PAI-1, VCAM-1, ICAM-1, MCP-1, serum biomarker) (as detailed in Section 9.1.3)
- Urinalysis (dipstick) (as detailed in Section 9.2.10)
- Urinary sample for urinary albumin-to-creatinine ratio (as detailed in Section 9.1.4)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- Patient randomisation (see below)
- IMP administration (see below)

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

Counselling on healthy lifestyle should be performed during this visit according to step 6 of the National Cholesterol Education Program Adult Treatment Panel III guidelines (NIH Publication No. 01–3305). The assessment should include consultation on:

- Diet: saturated fat <7% of calories, cholesterol <200mg/day, increase soluble fibre intake (10-25g/day) and plants stanols/sterols (2g/day)
- Weight management
- Increased physical activity

All patients will be instructed on how to use their blood glucose meter device and test strips, and educated regarding hypoglycaemia. SMBG profiles will be recorded daily from Baseline (Visit 3) to Week 4 (Visit 4).

The first dose of IMP (Epeleuton or placebo) will be administered at site only after all baseline assessments have been completed, with food or within 30 minutes after a meal. The patient will take their second dose of IMP in the evening of the day of the baseline visit (visit #3). Patients will be instructed how to store study medication (in the fridge) and to continue taking the capsules twice daily, starting with the next day. Patients will also be instructed to take medication with food, or within 30 minutes after a meal.

8.2.5 Week 2 Telephone Call

Patients will receive a telephone call from site staff at Week 2.

A review of SMBG (as detailed in Section 9.2.8) and assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1) will be conducted.

IMP compliance and administration will be discussed to ensure correct dosing. Patients will also be asked to discuss the patient logs for confirmation of compliance.

The following procedures/assessments will also occur:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)

8.2.6 Visit 4/Week 4

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- PK sampling (as detailed in Section 9.3)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- IMP reconciliation and supply of new IMP pack to patient

Patients will return their used IMP (Epeleuton or placebo) and further IMP will be supplied to the patient. The patient should take their next dose of IMP as soon as all visit assessments have been completed, with food or within 30 minutes after a meal. The IMP will continue to be taken twice-daily.

After Week 4 (Visit 4), at the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

8.2.7 Visit 5/Week 8

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- PK sampling (as detailed in Section 9.3)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- IMP reconciliation and supply of new IMP pack to patient

Patients will return their used IMP (Epeleuton or placebo) and further IMP will be supplied to the patient. The patient should take their next dose of IMP as soon as all visit assessments have been completed, with food or within 30 minutes after a meal. The IMP will continue to be taken twice-daily.

At the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

8.2.8 Visit 6/Week 12

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Urinary pregnancy test (as detailed in Section 9.2.1); female patients of childbearing potential only
- Counselling on contraception (as detailed in Section 9.2.1)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- IMP reconciliation and supply of new IMP pack to patient

Patients will return their used IMP (Epeleuton or placebo) and further IMP will be supplied to the

patient. The patient should take their next dose of IMP as soon as all visit assessments have been completed, with food or within 30 minutes after a meal. The IMP will continue to be taken twice-daily.

At the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

8.2.9 Visit 7/Week 16

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- PK sampling (as detailed in Section 9.3)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #4 (as detailed in Section 9.1.3)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- IMP reconciliation and administration of new IMP packs

Patients will return their used IMP (Epeleuton or placebo) and further IMP will be supplied to the patient. The patient should take their next dose of IMP as soon as all visit assessments have been completed, with food or within 30 minutes after a meal. The IMP will continue to be taken twice-daily.

At the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

8.2.10 Visit 8/Week 20

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Self-monitoring of blood glucose (SMBG) (as detailed in Section 9.2.8)
- IMP reconciliation and supply of new IMP packs to patient

Patients will return their used IMP (Epeleuton or placebo) and further IMP will be supplied to the patient. The patient should take their next dose of IMP as soon as all visit assessments have been completed, with food or within 30 minutes after a meal. The IMP will continue to be taken twice-daily.

At the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

8.2.11 Visit 9/Week 26/ Early Termination

The following assessments will be performed:

- AE assessment (as detailed in Section 11)
- Concomitant medication assessment (as detailed in Section 9.2.4)
- Serum pregnancy test (as detailed in Section 9.2.1); female patients of childbearing potential only
- Counselling on contraception (as detailed in Section 9.2.1)
- ECG (as detailed in Section 9.2.5)
- Physical examination (as detailed in Section 9.2.6)
- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- PK sampling (as detailed in Section 9.3)
- Exploratory blood sampling (as detailed in Section 9.4)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #4 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #5 (as detailed in Section 9.1.3)
- Urinalysis (dipstick) (as detailed in Section 9.2.10)
- Urinary sample for urinary albumin-to-creatinine ratio (as detailed in Section 9.1.4)
- IMP reconciliation

The IMP (Epeleuton or placebo) will be returned by the patient. Further IMP will not be supplied to the patient.

On completion of this visit, patients will be advised that they will be required to return to the investigational site in two weeks at Visit 10 for a final assessment.

8.2.12 Visit 10/Week 28/ Follow up

The following assessments will be performed:

- AE Assessment (as detailed in Section 11)
- Concomitant medication Assessment (as detailed in Section 9.2.4)
- Physical examination (as detailed in Section 9.2.6)

- Vital signs (blood pressure, heart rate and body temperature) (as detailed in Section 9.2.7)
- Assessment of hypoglycaemic episodes (as detailed in Section 9.2.8.1)
- Blood sampling for laboratory tests #1 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #2 (as detailed in Section 9.1.3)
- Blood sampling for laboratory tests #3 (as detailed in Section 9.1.3)

9 ASSESSMENTS

9.1 Efficacy Assessments

The efficacy assessments in this study consist of laboratory tests to assess the status of the underlying hypertriglyceridemia and type 2 diabetes and additional cardiovascular risk factors, as well as body weight, waist circumference and blood pressure.

For a list of all laboratory tests in this study see Section 15.2(Appendix 2).

9.1.1 Body weight, waist circumference, BMI

Body weight (kg), waist circumference (cm), and BMI are assessed as part of physical examination procedures at all visits (see Section 9.2.6.

9.1.2 Blood pressure

Systolic and diastolic blood pressure is taken as part of the vital sign assessments at all visits (see Section 9.2.7).

9.1.3 Blood samples

Blood samples will be collected according to the study flow chart (see Appendix 1) and will be analysed at the central laboratory to determine concentrations of the efficacy laboratory parameters.

All patients must be fasted for a minimum of eight hours prior to blood sampling. If patients have not fasted for a minimum of eight hours, the duration of fasting should be recorded, and patient encouraged to fast appropriately for the next clinical visit.

Different assessments will be organised in laboratory test panels as following:

- **Laboratory test panel 1** samples will be collected as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The test panel will include safety parameters (clinical haematology, biochemistry and coagulation, see Section 9.2.9).

- **Laboratory test panel 2** samples will be collected as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 2/Screening 2, Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The test panel will include the following efficacy laboratory parameters:
  triglycerides, LDL-C (calculated), HbA1C

- **Laboratory test panel 3** will be collected as per the study flow chart (Appendix 1) at Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The test panel will include the following efficacy laboratory parameters:
  VLDL-C, non-HDL-C, total cholesterol, glucose, HDL-C, RLP-C.

- **Laboratory test panel 4** will be collected as per the study flow chart (Appendix 1) at Visit 3/Baseline, Visit 7/Week 16 and Visit 9/Week 26/Early Termination.

  The test panel will include the following efficacy laboratory parameters:
  LDL-C (preparative ultracentrifugation), ApoA1, ApoB, ApoCIII, Lp(a), insulin, hsCRP, HOMA-IR, HOMA-β, nMR lipid profile.

  The nMR lipid profile will include measurement of lipoprotein particle concentration and size; HDL-P, small LDL-P, large LDL-P, LDL-size, VLDL-size, HDL-size.

- **Laboratory test panel 5** will be collected as per the study flow chart (Appendix 1) at Visit 3/Baseline and Visit 9/Week 26/Early Termination.

  The test panel will include the following efficacy laboratory parameters:
  IL-6, IL-1β, PAI-1, VCAM-1, ICAM-1, MCP-1, serum biomarker.

The following efficacy assessments will be calculated from laboratory test results:

- **LDL cholesterol (calculated)** will be calculated at Visit 1/Screening 1, Visit 2/Screening 2, Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The LDL-C (calculated) value will be obtained using the Friedewald calculation.

- **Non-HDL Cholesterol (non-HDL-C)** will be calculated at Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The non-HDL-C value will be obtained by subtracting the HLD-C value from the total cholesterol value.

- **RLP Cholesterol (RLP-C)** will be calculated at Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up.

  The RLP-C value will be obtained by subtracting LDL-C (calculated) from non-HDL-C.

- **HOMA-IR and HOMA-β.**
  HOMA-IR and homeostatic model assessment for ß-cell function (HOMA-ß) will be calculated

at Visit 3/Baseline, Visit7/Week 16 and Visit 9/Week 26/Early termination. HOMA-IR and HOMA-β are methods for assessing insulin resistance and β cell function from fasting glucose and insulin.

The calculations for HOMA-IR and HOMA-β will use the following formulas:

- **HOMA-IR** is calculated by multiplying fasting plasma insulin (µU/mL) by fasting plasma glucose (mg/dL), then dividing by the constant 405.

- **HOMA-ß** is calculated as follows: 360 x fasting plasma insulin (µU/mL) / (fasting plasma glucose (mg/dL) - 63).

9.1.4 Urinary albumin-to-creatinine ratio

Urinary samples will be collected according to the study flow chart (see Appendix 1) at Visit3/Baseline and Visit 9/Week 26/ Early Termination. They will be analysed at the central laboratory to determine albuminuria, assessed by urinary albumin-to-creatinine ratio (UACR) .

9.2 Safety Assessments

9.2.1 Pregnancy test and Contraception Counselling

For female patients of childbearing potential only, a pregnancy test will be carried out as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 3/Baseline, Visit 6/Week 12 and Visit 9/Week 26.

Female patients and male patients with female partners of childbearing potential must use highly effective contraceptive methods or have a sterilised partner for the duration of the study and this must be continued post study for at least 30 days for WOCBP and 90 days for men. This should be discussed with the patient as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 3/Baseline, Visit 6/Week 12 and Visit 9/Week 26.

Highly effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include hormonal contraception, intrauterine device or sexual abstinence.

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

Note: Hormonal contraceptives must be on a stable dose for at least one month before baseline.

Note: *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical*

trial and the preferred and usual lifestyle of the patient.

9.2.2 Adverse Events Assessment

See Section 11.

9.2.3 Medical History

A complete review of the patient's medical history will be undertaken by the Investigator or designee at the Visit 1/Screening 1 and Visit 3/Baseline to ensure that no exclusion criteria have been met.

Any concomitant disease, whether considered relevant for the study or not by the Investigator, must be reported in the eCRF. The date of diagnosis or duration of the condition should be noted where possible.

The following will be recorded in the eCRF at Visit 3/Baseline:

- **Diabetes history and complications**: date of diagnosis, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy
- **History of CVD:** ischaemic heart disease, myocardial infarction, heart failure, NYHA class, hypertension, atrial fibrillation, stroke, peripheral arterial disease
- **History of liver disease:** NAFLD, NASH, liver biopsy
- **Hypercholesterolaemia**
- **Smoking history:** including smoking status

9.2.4 Concomitant medication

All administered concomitant medications should be recorded throughout the study.

For the pre-trial background medications; antihyperglycemic (antidiabetic) medication, statins and ezetimibe, the following information must be collected at Visit 3/Baseline:

- Generic name
- Start date
- Total daily dose

The dose of pre-trial background medications should remain stable throughout the study.

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

Patients should also avoid:

- Any medication for diabetes or obesity (except for metformin, sulfonylureas, DPP-4

inhibitors, SGLT2 inhibitors, GLP1-RAs and short-term insulin treatment for acute illness), both during the study and for four weeks prior to baseline, as well as

- Fibrates, PCSK9 inhibitors, bile acid sequestrants, niacin, niacin analogues or dietary supplements for the purpose of lowering cholesterol, both during the study and for six weeks prior to baseline

9.2.5 Electrocardiogram

A 12-lead electrocardiogram (ECG) 10 mm/1 mV, 25 mm/s with a 10 second lead II rhythm strip will be recorded. Patients will be rested quietly in a fully supine position for five minutes before the ECG is taken. Recordings will be made at Visit 3/Baseline and at Visit 9/Week 26/Early Termination.

9.2.6 Physical Examination

A physical examination, including height (Visit 1/Screening 1 only), weight, BMI and waist circumference measurement, will be performed by the Investigator as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 2/Screening 2, Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up, in accordance with local practices.

BMI should be calculated according to the following formula: BMI (kg/m2) = body weight (kg)/(Height (m) x Height (m)) or (kg/m2 = [lb/in2 x 703]).

The **waist circumference** is the circumference located midway between the lower rib margin and the iliac crest. Waist circumference should be measured according to the following procedure:

- Waist circumference is measured in the horizontal plane and rounded up or down to the nearest 0.5 cm using non-stretchable measuring tape.
- The same measuring tape should be used throughout the study.
- The circumference should be measured when the patient is in a standing position, with an empty bladder, with feet together, arms down and waist accessible.
- The tape should touch the skin but not compress soft tissue.
- Twists in the tape should be avoided.

9.2.7 Vital Signs

Vital signs measurements will be performed as per the study flow chart (Appendix 1) at Visit 1/Screening 1, Visit 2/Screening 2, Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow up, in accordance with local practices.

Measurements to be taken include (see references for full guidelines):

- **BP** which will be assessed according to American Heart Association (AHA) guidelines (Whelton et al, 2018):
  - Make sure that the device is properly validated and calibrated.
  - Instruct the patient to avoid coffee, exercise and smoking 30 minutes before the

assessment.
  - The patient should be seated and resting for five minutes before the BP is measured.
  - Choose the correct cuff size and measure the BP by positioning it on the bare arm at the level of the right atrium.
  - Record systolic and diastolic BP (in mmHg) and use an average of two sequential readings obtained at least 5 minutes apart to estimate the patient's BP.
- **Heart rate**: taken at rest (in bpm).
- **Temperature**: will be taken as per clinic practice. Temperature and route will be recorded in the eCRF.

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 eCRF as an AE if made after the patient has received their first dose of IMP. Clinically significant findings made prior to the patient receiving the first dose if IMP will be recorded as medical history.

9.2.8 Self-monitoring of blood glucose (SMBG) and hypoglycaemia assessment

All patients will be instructed or re-educated on how to use their blood glucose meter device and test strips at the baseline visit. The instruction will be repeated as necessary during the trial.

SMBG profiles will be recorded daily from Visit 3/Baseline to Visit 4/Week 4. After Visit 4/Week, at the investigator's discretion, patients who have experienced hypoglycaemia may be asked to continue SMBG.

Patients will be asked to record SMBG daily before meals and before bedtime. Patients will also be asked to record SMBG before exercise and if they suspect low blood glucose, as described in Section 9.2.8.1 Hypoglycaemia assessment.

Patients will record the results of the SMBG values in an electronic diary. The record of each SMBG value will include date, time and value. Any SMBG values <70 mg/dL (3.9 mmol/L) entered into the electronic diary will be automatically alerted to the investigator and medical monitor for follow-up. If the patient is unable to access the electronic diary, a paper diary back up will be provided and the data will be transcribed during the next site visit into the IRT by the Investigator or designee.

9.2.8.1 Hypoglycaemia assessment

Assessment of hypoglycaemic episodes will be conducted as per the study flow chart (Appendix 1) at Visit 3/Baseline, Week 2 Telephone Call, Visit 4/ Week 4, Visit 5/Week 8, Visit 6/ Week 12, Visit 7/ Week 16, Visit 8/Week 20, Visit 9/Week 26/Early Termination and Visit 10/Week 28/Follow-up.

Hypoglycaemia is classified by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as outlined in Table 1.

Table 1. ADA/EASD classification of hypoglycaemia

Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L), with or without symptoms
Level 3	A severe event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia.

Level 2 hypoglycaemia with or without symptoms and Level 3 hypoglycaemia should be recorded and warrant further investigation.

Hypoglycaemic symptoms include hunger, headache, nausea, light-headedness, palpitations, sweating, confusion, drowsiness, speech difficulty and incoordination. Severe hypoglycaemia may lead to loss of consciousness (McAulay et al, 2001). Patients will be educated regarding hypoglycaemia at Baseline/Visit 3.

When a hypoglycaemic episode is suspected, plasma glucose should be self-measured and all values, hypoglycaemic symptoms and details of the event should be reported in the provided form (Section 15.3, Appendix 3) by the patient, according to the instructions. The patient is required to:

- Self-measure plasma glucose every 15 minutes until the value is > 3.9mmol/L (70mg/dL) or symptoms have been resolved. This will be considered as one hypoglycaemic episode.
- In a case of several low glucose values within the hypoglycaemic episode, the lowest value will be reported (the remaining values will be kept as source data).
- The start time of the episode will correspond to the first glucose measurement and or/ hypoglycaemic symptom.
- If the hypoglycaemic episode fulfils the criteria for an SAE, it must be reported as described in Section 11.

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

Blood samples will be taken as part of the laboratory test panel #1 (see Section 9.1.3), as per the study flow chart (Appendix 1). All samples will be analysed in the central laboratory.

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 tests.

Haematology: Full blood count to include red cell count, haemoglobin, haematocrit, white cell count, differential white cell count, platelet count, reticulocyte count and red cell distribution width (RDW).

Serum biochemistry: Urea (blood urea nitrogen (BUN)), creatinine, uric acid, total bilirubin, indirect and direct bilirubin, sodium, bicarbonate potassium,

	phosphorus, calcium chloride, alkaline phosphatase (ALP), AST, ALT, AST:ALT ratio, gamma-glutamyl transferase (GGT), albumin, total protein and TSH (screening only).
Coagulation:	PT (prothrombin time), International normalised ratio (INR) and APTT (activated partial prothrombin time)

9.2.10 Urinalysis

Urinalysis assessment will be conducted as per Flow Chart (Appendix 1) at Visit3/Baseline and Visit 9/Week 26/Early Termination.

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

9.3 Pharmacokinetic sampling

Plasma samples will be obtained prior to the first daily dose at Visit 3/Baseline, Visit 4/Week 4, Visit 5/Week 8, and Visit 7/Week 16 and Visit 9/Week 26/Early Termination for the measurement of trough plasma concentrations of total and unesterified 15-HEPE, and total EPA.

A 1mL blood sample will be taken at each time point. Following centrifugation, plasma samples will be split in two and a back-up sample will be handled as specified in Section 9.5 and described in the laboratory manual.

9.4 Exploratory Blood Sampling

Blood for exploratory biomarkers will be collected as per the Study Flow Chart (Appendix 1) at Visit 3/Baseline and Visit 9/Week 26/Early Termination and will be stored for later biomarker analysis.

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

9.5 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.

10 INVESTIGATIONAL PRODUCT/INVESTIGATIONAL DRUG

10.1 Investigational Medicinal Product (IMP)

The following medication supplies will be used in the study:

Epeleuton Capsule:
Description:
Green hard-shelled capsule (size 0) containing 500mg of 15(S)-HEPE EE with 2.5% w/w of colloidal silicon dioxide as viscosity modifier.

Epeleuton Placebo (Liquid Paraffin):
Description:
Green hard-shelled capsule (size 0) containing equivalent fill weight of liquid paraffin with 1% w/w of colloidal silicon dioxide as viscosity modifier.

Liquid paraffin is selected as placebo to mimic the colour and consistency of epeleuton (15(S)-HEPE EE). Liquid paraffin at high doses (15-30g/day) has been used as a laxative for over 100 years, in adults and children with good tolerability and limited AEs.

10.2 Supply, Packaging, Labelling, Handling and Storage

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

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

The study treatment will be identified by batch numbers and expiry date with each patient kit (sufficient for two weeks dosing) assigned a unique medication number.

Labelling, packaging and release will be in accordance with the Clinical Trials Directive 2001/20/EC and Good Manufacturing Practice (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 detail the unique medication number for each kit which is traceable back to the dose. In addition, Epeleuton (15(S)-HEPE EE) and placebo capsules will be labelled with information according to local regulations.

10.3 Dosage and Administration

Patients who fulfil all inclusion and no exclusion criteria may be accepted in the study. Each patient must read and sign an ICF prior to any screening procedures being performed. This study involves a comparison of Epeleuton with placebo, administered orally with or after food (within 30 minutes after a meal) twice daily for a total duration of 26 weeks. Patients will also receive standard of care therapy in addition to their assigned IMP throughout the treatment period of the study. The last study drug administration should occur on the day preceding Visit 9/Week

26/Early Termination.

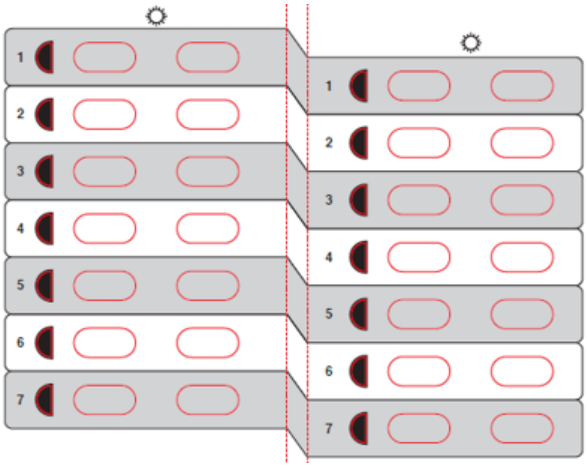
Patients will be randomised to one of the three treatment groups in a 1:1:1 ratio:

- Treatment Group A (placebo): Four x placebo 500mg capsules orally administered BID (eight capsules daily) for 26 weeks.
- Treatment Group B (Epeleuton 2g): Two x placebo 500 mg capsules + two x Epeleuton (DS102) 500mg capsules orally administered BID (eight capsules daily) for 26 weeks.
- Treatment Group C (Epeleuton 4g): four x Epeleuton (DS102) 500mg capsules orally administered BID (eight capsules daily) for 26 weeks.

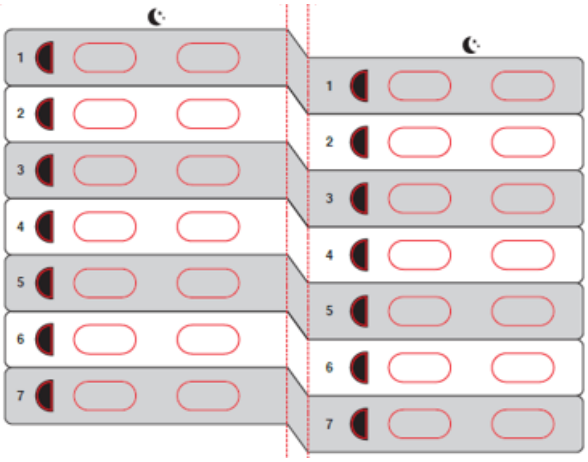
Patients will be required to take the capsules with or after food (within 30 minutes after a meal). Medication(s) for other conditions that are permitted in the study can be taken as usual.

Morning and Evening walleted blister packs will each consist of seven days of four capsules. Each patient kit containing four wallets, sufficient for two weeks dosing. Patients will be instructed to take the four capsules in the morning and four capsules in the evening **from Morning and Evening wallets**, on the relevant day, as shown below:

Figure 6: Walleted Blister Packs



(Morning walleted blister packs)



(Evening walleted blister packs)

10.4 Duration of Treatment

Patients will take assigned medication for 182 consecutive days (26 weeks).

10.5 Method for Assigning Patients to Treatment

Approximately 240 patients will be randomized into double-blind treatment groups in a 1:1:1 ratio by an Interactive Web Response System (IWRS) as follows:

- 4g Epeleuton: four x Epeleuton (DS102) 500mg capsules orally administered BID (eight capsules daily) for 26 weeks

- 2g Epeleuton: two x placebo 500mg capsules + two x Epeleuton (DS102) 500mg capsules orally administered BID (eight capsules daily) for 26 weeks

- Placebo: four x placebo 500mg capsules orally administered BID (eight capsules daily) for 26 weeks

A randomization list permuted by blocks and stratified by site will be generated by the Sponsor or its designee. The randomization schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the IWRS team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomization code.

At the investigational site, each patient will be assigned a patient identifier number during screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number assigned in numerical order at the screening visit (e.g.: 102-10 for the tenth patient screened at the site number 102). Patient numbers will be assigned in ascending order starting with 01.

10.6 Drug Accountability

The Investigator is responsible for maintaining accurate records of the study medication received initially, the study drug dispensed/used, the returned medication by patients (in the case of patients discharged prior to week 26) and the medication returned to the Sponsor or designee for destruction. All study drug accountability forms and treatment logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees or by regulatory agencies at any time.

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

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

11 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Definitions and Reporting of Adverse Events

11.1.1 Definitions

Adverse Event (AE):

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. All AEs must be recorded in the eCRF, defining relationship to IMP and severity. AEs should also be recorded by the Investigator in the patient file/notes.

Examples of AEs include one of the following or a combination of two or more of these factors:

- Any unfavourable and unintended sign, symptom, illness, or syndrome
- Abnormal laboratory values, if judged clinically significant in the opinion of the Investigator
- Worsening (change in nature, severity or frequency) of a concomitant or pre-existing illness
- An AE of the IMP, including comparator or concomitant medication
- Drug interactions
- An AE of an invasive procedure required by the protocol
- An accident or injury

Of note:

- Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.
- Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study.

In the latter case the condition should be reported as medical history.

Serious Adverse Event (SAE):

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

- results in death, or
- is life-threatening, or

  <u>*Note*</u>: “Life-threatening” means that the patient was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.

- requires in-patient hospitalisation or prolongation of existing hospitalisation, or

Note: This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the AE, or that they occurred as a consequence of the event.

Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalisation unless the event fulfils any other of the serious criteria.

- results in persistent or significant disability/incapacity, or

Note: "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.

- is a congenital anomaly/birth defect, or

- is an important medical event

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

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

Unexpected Adverse Event (UAE):

Expectedness will be determined by the Sponsor according to the designated Reference Safety Information. The Reference Safety Information for the IMP is contained in the Investigator's Brochure (IB).

Unexpected: An AE or suspected adverse reaction is considered unexpected if it is not listed in the Reference Safety Information or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.2 Severity

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

- Mild: the AE is transient and easily tolerated.
- Moderate: the AE causes the patient discomfort and interrupts the patient's usual activities.
- Severe: the AE causes considerable interference with the patient's usual activities and

may be incapacitating or life-threatening.

Clarification of the difference in meaning between "severe" and "serious":

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Causality

The term "causality" describes the degree of attributability (causality) between an IMP and an event.

Causality assessment of AEs is the structured and standardised assessment of individual patients/case reports for the likelihood of involvement of a suspected drug in causing a particular event in a given patient.

To assess whether there is a reasonable possibility that the AEs are associated with the IMP, temporal relationship between administration of the IMP and the event, de-challenge/re-challenge, association with underlying disease or concomitant medication, and the presence of a more likely cause and physiological/pathological plausibility are considered.

The Investigator should use medical judgment to determine whether he/she assumes a reasonable causal relationship, including into his/her evaluation all relevant factors and factual evidence such as

- temporal course and latency
- results from de-challenge or re-challenge
- pattern of the reaction
- known pharmacological properties of the product
- and alternative explanations (e.g. other drugs, medical history, concomitant diseases).

The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Assessment will be documented on the AE and SAE form.

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

- If reasonable causal relationship, either:
  - Definitely

- Probable
- Possible

- If no reasonable causal relationship, either:
- Unlikely
- Unrelated

11.1.4 Reporting of AEs and SAEs

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

Every SAE must be reported to the pharmacovigilance contract research organisation (spm²) by **e-mail or fax** within 24 hours of the investigator/site becoming aware of it. In case of questions regarding an SAE that will be reported, the Investigator or authorised study personnel can contact spm² by phone. The contact information is provided in the ISF.

At the time of the call, the Investigator must provide, as a minimum requirement, the patient number, birth year, nature of the SAE and a preliminary assessment of causality. The Investigator should follow-up the initial notification of the potential SAE by **faxing/e-mailing** a copy of the SAE reporting form to spm² at the number provided in the ISF. The **faxed/e-mailed** SAE reporting form should be sent to the spm² within 24 hours of knowledge of such a case.

Every attempt should be made to describe all AEs in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

The “initial SAE report” should be as complete as possible, including details of the current illness and (serious) adverse event, the reason why the event was considered serious, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with study medication.

Follow-up information on an existing SAE that is fatal or life-threatening should be reported by the Investigator to spm² within five days after the initial report. Upon request from spm², hospitalisation or autopsy reports should be made available.

The TEAE reporting period begins from signing of the consent form and continues until the end of the follow-up visit. 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.

All AEs that occur in the course of the study regardless of the causal relationship should be monitored and followed up until the outcome is known or it is evident that no further information can be obtained. There must be documented reasonable attempts to obtain follow-up information and outcome. It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

11.1.5 Follow-up of Missing Information/Response to Sponsor Queries

Information not available at the time of the initial SAE report (e.g. an end date for the AE or laboratory values received after the report) must be documented on a "Serious Adverse Event" form, with the box "Follow-up" checked under "Report type".

All patients who have AEs, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible.

The Sponsor or pharmacovigilance contract research organisation (CRO) (spm²) will identify missing information for each SAE report. Requests for follow-up will be sent to the Investigator until all queries are resolved or no further information can be reasonably expected. All responses to queries and supply of additional information by the Investigator should follow the same reporting route and timelines as the initial report.

11.2 Serious Adverse Reactions and Unexpected Adverse Reactions

11.2.1 Definitions

Adverse Reaction:

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

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

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

Unexpected Adverse Reaction:

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

Suspected Unexpected Serious Adverse Reaction (SUSAR):

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

11.2.2 Reporting of suspected unexpected serious adverse reactions (SUSARs)

The Sponsor will report all serious and unexpected AEs, which are judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship (suspected

unexpected serious adverse reaction - SUSAR), to the competent authorities and the concerned ethics committee (EC) according to applicable law.

SUSARs will be reported by spm² according to appropriate competent authority and EC requirements. SUSARs will be reported to Investigators according to ICH Good Clinical Practice (GCP) and to local regulations. SUSAR reporting to competent authorities and ECs will be performed according to local regulations in an unblinded manner. Competent Authorities within the EU will be notified of all SUSARs through the EudraVigilance database. An electronic common technical document (eCTD) submission will be performed by a local representative to the FDA.

Fatal and life-threatening SUSARs should be reported by spm² as soon as possible to the competent authorities and ECs according to local regulations, and, in any case, no later than seven calendar days after knowledge by spm² of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the competent authorities and ECs according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by the Sponsor.

11.3 Pregnancy Reporting

If a patient or a patient's partner becomes pregnant during the study, study staff must be informed as soon as possible. Upon confirmation of the pregnancy, the patient must be withdrawn from the study but closely followed-up during the entire course of the pregnancy and postpartum period. All recommendations described in the IB regarding pregnancy and lactation have to be carefully considered. 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.

Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Offspring should be followed up for at least eight weeks after delivery. Longer observation periods may be determined by the Sponsor if an adverse outcome of the pregnancy was observed. For documentation and follow-up, the Sponsor will collect all information on a specific pregnancy form which will be provided by spm².

11.4 Unblinding for Regulatory Reporting or Medical Necessity

The study medication blind shall not be broken by the Investigator unless information concerning the study medication is necessary for the medical treatment of the patient. If possible, the Sponsor should be notified before the study medication blind is broken. If a medical emergency requiring unblinding occurs, the Investigator (or designee) will break the blind immediately. In the event unblinding is necessary for a patient, the site must notify the Sponsor's medical monitor immediately after the unblinding. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

Note: If the unblinding is performed by the Investigator due to a medical requirement, the patient will discontinue trial participation.

The method of unblinding is specified in Section 12.4 of the protocol. **The study team will be kept**

blinded regarding treatment assignment.

11.4.1 Unblinding for studies conducted in the EU

If applicable and required, treatment codes will be unblinded prior to submission to authorities and concerned ECs, by the Sponsor's safety group, which is an independent entity within the Sponsor or by the pharmacovigilance CRO.

The Sponsor will also inform all Investigators in a blinded fashion (EU only), unless otherwise required by local regulations. Reporting obligations to the local EC of the Investigator will be fulfilled by the Investigator, unless otherwise specified.

11.4.2 Unblinding for studies conducted in the US

The blind will be broken for investigational new drug (IND) safety reports submitted to FDA and all participating Investigators.

12 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

12.1 Study Design

This clinical trial employs a randomised, double-blind, placebo-controlled, 3-arm, 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 the evaluation of safety and efficacy data. The use of placebo as a comparator is justified as a reasonable design to assess safety and efficacy in patients based on the fact that Epeleuton is administered as an add-on treatment to stable background treatment for hypertriglyceridemia and type 2 diabetes. A full description of the study design is presented in Section 6 above.

12.2 Randomisation

All patients will be screened, and the inclusion and exclusion criteria will be assessed during the screening period (Visit 1 and Visit 2).

At the baseline visit (Visit 3), approximately 240 Patients will be randomised (1:1:1) into the following treatment groups:

- Treatment Group A (placebo): Four x placebo capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks
- Treatment Group B (Epeleuton 2g): Two Epeleuton (DS102) 500mg capsules and two placebo capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks
- Treatment Group C (Epeleuton 4g): Four Epeleuton (DS102) 500mg capsules orally administered twice a day, i.e. eight capsules daily for 26 weeks

A randomisation list permuted by blocks and stratified by site and a corresponding medication number list linking each patient kit to dose group will be generated by the Sponsor or its designee. The randomisation schedule and medication number list will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the interactive web response system (IWRS) team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomisation code.

At the investigational site, each patient will be assigned a patient identifier number during screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number assigned in numerical order at the screening visit (e.g.: 102-10 for the tenth patient screened at the site number 02 in country designated by the number 1). Patient numbers will be assigned in ascending order starting with 01.

12.3 Estimation of Sample Size

Table 2. Sample size estimation using effect size (Cohen's d from -0.02 to -0.75)

d	Total Sample Size	Sample size per group
-0.2	1180.2	393.4
-0.25	756.5	252.2
-0.3	526.2	175.4
-0.35	387.3	129.1
-0.4	297.3	99.1
-0.45	235.5	78.5
-0.5	191.3	63.8
-0.55	158.6	52.9
-0.6	133.8	44.6
-0.65	114.5	38.2
-0.7	99.0	33.0
-0.75	86.7	28.9

The sample size was estimated based on results of a *post hoc* analysis of triglycerides and HbA1C from a Phase IIa trial of Epeleuton in patients with NAFLD. Changes in triglycerides and HbA1C at the highest tested dose (2g/day) at week 16 (end-of-treatment) were used to estimate relative effect sizes (Cohen's D). Cohen's D or the standardised relative effect size is the difference between the group means divided by the pooled standard deviation.

To discover a conservative relative effect size (Cohen's d) between epeleuton and placebo of 0.6 in triglyceride change from baseline with 80% power, 45 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided).

To discover a conservative relative effect size (Cohen's d) between epeleuton and placebo of 0.48 in HbA1C change from baseline with 80% power, 70 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided).

To power the study for both primary endpoints and take deviations from ideal parametric conditions and drop-outs into account, randomisation of 80 patients per group is recommended.

12.4 Blinding and Code Breaking Instructions

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

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

12.5 Data Analysis

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

12.6 Analysis Populations

Full Analysis Set (FAS):

Patients will be included in the FAS, a modified intention-to-treat population, if they are randomised to the study, received at least one dose of study medication and have at least one post-baseline measurement. Analysis will be done according to treatment as randomised.

Safety Analysis Set (SAS)

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

Per Protocol Set (PPS):

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

12.7 Safety Analysis

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

All AEs recorded during the study will be coded to system organ class and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be tabulated and summarised by treatment, relationship to treatment, seriousness and severity. Non-TEAEs will be listed separately.

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

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

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

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

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

12.8 Statistical Analysis Plan

In addition to the summarised analysis outlined below, a separate SAP will detail all analyses to be performed.

For continuous variables, descriptive statistics will include: the number of patients reflected in the calculation (n), mean, median, standard deviation, interquartile range, minimum, and maximum.

For categorical data, frequencies and percentages will be displayed for each category.

12.8.1 Primary Variables

The primary efficacy endpoints are:

- Percent change in triglycerides from baseline to week 16.

- Change in HbA1c from baseline to week 26.

Each of the independent primary endpoints will be analysed separately. Success in either of the primary endpoints will support a conclusion of effectiveness.

The primary analysis will be based on the FAS and repeated for the PPS as a supportive analysis.

Analysis of changes and percentage changes of triglycerides will be performed using a Wilcoxon rank sum test with the Hodges Lehmann median and 95% confidence intervals estimates. For analysis of triglycerides, baseline will be defined as the mean of the Baseline (Visit 3) and Screening 2/Week -1 (Visit 2) measurements.

Changes from baseline of HbA1c at each visit will be analysed using mixed model analysis of covariance (ANCOVA) with baseline value as a covariate.

12.8.2 Secondary variables

Secondary and exploratory endpoints will be analysed by either an ANCOVA mixed model, if the data for that endpoint are normally distributed, or a Wilcoxon-rank-sum test, if the data are not

normally distributed.

Logistic regression with baseline HbA1C as a covariate will be used to analyse the percentage of patients with HbA1c < 7.0% and the percentage of patients with HbA1c < 6.5% at week 16.

Exploratory analyses pooling the two doses vs. placebo for all pre-specified endpoints will be performed.

12.8.3 Missing data and sensitivity analyses

Missing data will be accounted for using a multiple imputation approach.

Sensitivity analyses will be conducted for the primary endpoints using a last observation carried forward (LOCF) missing data handling approach.

A two-sided p-value less than 0.05 is considered statistically significant for all comparisons.

12.9 Interim Analysis

An interim analysis may be conducted after at least 50% of planned enrolled patients have completed their Week 16 assessments or an early termination visit. The interim analysis will be conducted in accordance with sponsor standard operating procedure (SOP) “Interim Analysis of Clinical Studies”.

An unblinded interim analysis will be performed by an unblinded independent statistician. Interim data and the results of interim analyses will not be accessible by anyone other than the unblinded statistician and an Independent Data Monitoring Committee (IDMC).

The sponsor trial team will remain blinded with procedures in place to ensure the confidentiality of the interim data in accordance with sponsor SOP “Interim Analysis of Clinical Studies”.

The IDMC will make one of the following recommendations to the sponsor based upon the primary efficacy endpoints:

- Increase the sample size to a defined number
- Continue the study as originally planned
- Stop the study due to futility

The IDMC may also make further recommendations to the sponsor including changes to study design and conduct. Further interim analyses may be conducted if recommended by the IDMC.

Further details will be described in an interim statistical analysis plan.

12.10 Data Collection/Electronic Case Report Forms

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

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator (PI) 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 information will be verified against the individual patient records. Any inconsistencies will be presented as queries, either as automatically generated queries, if raised by the logical data checks of the eCRF system, or by manually generated queries if raised by the data validation checks or the SDV performed by the data manager (DM) or the clinical research associate (CRA), respectively. Queries shall be resolved in a timely manner by a trained member of the site staff.

12.11 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 data management CRO standard operating procedures (SOPs). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

12.12 Protocol Deviations

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

13 REGULATORY AND ADMINISTRATIVE PROCEDURES

13.1 Institutional Review

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

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

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

13.2 Good Clinical Practice

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

13.3 Essential Documents

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

13.4 Record Retention

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

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

13.5 Monitoring/Quality Control

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

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

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

13.6 Quality Assurance

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

13.7 Insurance and Liability

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

13.8 End of Trial

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

13.9 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.

13.10 Data Protection

All information collected for this study will be kept strictly confidential. The Sponsor undertakes to comply with applicable data protection regulations, which are further detailed in the written information provided to the patient. In case of data security breach, this will be reported to the relevant supervisory authority where the breach presents a risk to the affected individuals. This

will be reported within 72 hours of becoming aware of the breach. Where a breach is likely to result in a high risk to the affected individuals, the Sponsor will also inform those individuals without undue delay.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the regulatory agency(ies), and the IRB/IEC direct access to review the patient's original medical records for verification of study-related procedures and data. For further information, the Sponsor data protection officer can be contacted at dataprotection@afimmune.com.

13.11 Report and Publication

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

13.12 COVID-19 Contingency

Due to the unprecedented worldwide COVID-19 pandemic, the Sponsor is implementing measures to assure the safety of trial participants, to maintain compliance with GCP and to minimise risk to trial integrity.

Among these measures are modifications to the protocol to ensure that, if difficulties in adhering to protocol-specific procedures or protocol-mandated visits are encountered by patients, investigators or study sites, adequate and appropriate contingencies are in place.

COVID-19 contingency measures do not replace the existing protocol procedures and visit schedule.

The following contingencies and actions will be implemented in response to the evolving COVID-19 pandemic:

1. An interim analysis may be conducted after at least 50% of patients have completed their week 16 visits as described in Section 12.9 Interim Analysis. Due to the rapidly evolving COVID-19 situation at both a global and country level, a modification to the prospectively planned sample size may be necessary if patient recruitment is not feasible and must be stopped. The interim analysis will safeguard the integrity of the trial and inform whether further patient recruitment is required when conditions at participating sites are amenable to re-initiation of patient recruitment.

2. In a worst-case scenario where a patient is unable to attend the study site for protocol-mandated visits, due to patient considerations (such as COVID-19 infection or quarantine) or study site restrictions;

   A. The investigator will complete all possible assessments via phone for all impacted study visits as described in Appendix 4. COVID-19 Contingency Investigator Assessment Phone Visits.

   - Phone visit assessments must include assessment of adverse events, patient-reported endpoints and compliance.

- The patient will be reminded that IMP will continue to be administered with food or within 30 minutes after a meal at the same time twice daily and compliance should be recorded in the electronic diary or paper backup as appropriate.
- On completion of this visit, patients will be advised that they will be required to return to the investigational site at the next scheduled visit and to bring with them the used epeleuton/placebo patient packs, and the patient compliance log.

B. IMP will be couriered directly to the patient.

Investigators must make every effort possible to ensure that patients adhere to the protocol procedures and attend all scheduled visits. COVID-19 contingency measures regarding IMP delivery and phone visits must only be used if absolutely necessary and after every effort to follow the protocol visit schedule has been exhausted. Investigator responsibilities as prescribed by ICH GCP, including oversight of patient safety must continue to be observed in all cases whether or not contingency actions relating to COVID-19 are required.

This contingency will facilitate the conduct of appropriate safety monitoring and will preserve the investigational product supply chain.

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15 APPENDICES

15.1 Appendix 1. Flow Chart

Visit	Visit 1 Screening 1	Visit 2 Screening 2	Visit 3 Baseline	Phone call Week 2	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Visit 7 Week 16	Visit 8 Week 20	Visit 9 EoT Week 26	Visit 10 EoS Week 28
Day	-42	-7	0	14	28	56	84	112	140	182	196
Visit window	+28	±1 day	0	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days
Informed consent	X										
Inclusion/exclusion	X	X	X								
Urine pregnancy test[1]			X				X				
Serum pregnancy test[1]	X		X							X	
Contraception counselling	X		X				X			X	
Demographics	X										
AE assessment	X	X	X	X	X	X	X	X	X	X	X
Medical history	X		X								
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)			X							X	
Physical examination (incl. weight, BMI, waist circumference)	X	X	X		X	X	X	X	X	X	X
Physical examination (height)	X										
Vital signs (incl. heart rate, blood pressure, temperature)	X	X	X		X	X	X	X	X	X	X
Counselling	X		X								
Assessment of hypoglycaemic episodes			X	X	X	X	X	X	X	X	X
Plasma PK sampling (trough levels)[2]			X		X	X		X		X	
Exploratory blood sample			X							X	
Blood sampling for laboratory tests #1 (details below)	X		X		X	X	X	X	X	X	X
Blood sampling for laboratory tests #2 (details below)	X	X	X		X	X	X	X	X	X	X
Blood sampling for laboratory tests #3 (details below)			X		X	X	X	X	X	X	X
Blood sampling for laboratory tests #4 (details below)			X					X		X	
Blood sampling for laboratory tests #5 (details below)			X							X	
Urinary sampling for urinary albumin-to-creatinine ratio			X							X	
Urinalysis (dipstick)			X							X	
TSH sample	X										
Self-monitoring of blood glucose[3]			X.....			X[3].....					X
Patient randomisation			X								
IMP (Epeleuton/placebo) administration[4]			X.....		x.....	x.....	x.....	x.....	X		
IMP (Epeleuton/placebo) reconciliation					X	X	X	X	X	X	

[1] Female Patients of childbearing potential only

[2] Pharmacokinetics C_{trough} only. Sample will be taken pre-dose

[3] SMBG is at the investigator's discretion from visit 4/week 4

[4] To be taken with food at the same time each day

Laboratory test panel #1 includes: Clinical haematology, clinical chemistry, coagulation.
Laboratory test panel #2 includes: Triglycerides, LDL-C (calculated), HbA1c

Laboratory test panel #3 includes: VLDL-C, non-HDL-C, total cholesterol, glucose, HDL-C, RLP-C
Laboratory test panel #4 includes: LDL-C (preparative ultracentrifugation), ApoA1, ApoB, ApoCIII, Lp(a), insulin, hsCRP, HOMA-IR, HOMA-β, nMR lipid profile
Laboratory test panel #5 includes: IL-6, IL-1β, PAI-1, VCAM-1, ICAM-1, MCP-1, serum biomarker

15.2 Appendix 2. Table of Central Laboratory Assessments

Analyte/Test	Serum	Plasma	Urine	Other	Screening 1 Week -6 to -2	Screening 2 Week -1	Baseline Week 0	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12	Visit 7 Week 16	Visit 8 Week 20	Visit 9 EoT Week 26	Visit 10 EoS Week 28
Clinical haematology[1]					x		x	x	x	x	x	x	x	x
Serum biochemistry[2]	x				x		x	x	x	x	x	x	x	x
Coagulation[3]					x		x	x	x	x	x	x	x	x
Urinalysis[4]			x				x						x	
Triglycerides	x			fasting	x	x	x	x	x	x	x	x	x	x
LDL-C (calculated)	x			fasting	x	x	x	x	x	x	x	x	x	x
LDL-C (preparative ultracentrifugation)	x			fasting			x				x		x	
HbA1c		x		fasting	x	x	x	x	x	x	x	x	x	x
VLDL-C (calculated)	x			fasting	x	x	x	x	x	x	x	x	x	x
HDL-C	x			fasting	x	x	x	x	x	x	x	x	x	x
Non-HDL-C (calculated)	x			fasting	x	x	x	x	x	x	x	x	x	x
RLP-C (calculated)	x			fasting	x	x	x	x	x	x	x	x	x	x
Total cholesterol	x			fasting	x	x	x	x	x	x	x	x	x	x
Glucose		x		fasting			x	x	x	x	x	x	x	x
ApoA1	x			fasting			x				x		x	
ApoB	x			fasting			x				x		x	
ApoCIII	x			fasting			x				x		x	
Lp(a)	x			fasting			x				x		x	
Insulin		x		fasting			x				x		x	
hsCRP	x			fasting			x				x		x	
IL-6	x			fasting			x						x	
IL-1β	x			fasting			x						x	
PAI-1		x		fasting			x						x	
VCAM-1	x			fasting			x						x	
ICAM-1	x			fasting			x						x	
MCP-1 (CCL2)	x			fasting			x						x	
HOMA-IR (calculated)		x		fasting			x				x		x	
HOMA-β (calculated)		x		fasting			x				x		x	
nMR lipid profile[5]		x		fasting			x				x		x	
Urinary albumin-to-creatinine ratio			x				x						x	
Trough 15-HEPE (15-hydoxy-eicasopentaenoic acid)		x		fasting			x	x	x		x		x	
Trough EPA		x		fasting			x	x	x		x		x	
Serum biomarker sample	x			fasting			x						x	
TSH	x			fasting	x									

[1] Including: Full blood count including red cell count, haemoglobin, haematocrit, white cell count, differential white cell count, platelet count, reticulocyte count and RDW

[2] Including: BUN, creatinine, uric acid, total bilirubin, indirect and direct bilirubin, sodium, bicarbonate potassium, phosphorus, calcium chloride, ALP, AST, ALT, AST:ALT ratio, GGT, albumin, total protein

[3] Including: PT, INR and APTT

[4] Including: pH, protein, glucose, blood, ketones, leukocytes, leukocyte esterase, bilirubin, specific gravity, urobilinogen and nitrate

[5] Including: HDL-P, small LDL-P, Large LDL-P, LDL-size, VLDL size, HDL-size

15.3 Appendix 3: Hypoglycaemic Episode Form

Please record the following information regarding the hypoglycaemic episode:	Answer
Start date and time of the hypoglycaemic episode.	
Self-measured plasma glucose values	
Stop date and time of the hypoglycaemic episode (stop time is the first time the plasma glucose value is > 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved)[1]	
The plasma glucose level before treating the episode (if available) and any follow up measurements.	
Was the episode symptomatic? **(Yes/No)** [2]	
Date, time and dose of last study drug administration and other anti-diabetic treatments prior to the episode.	
Date and time of last main meal (not including snacks) prior to the episode.	
Did the episode occurred in relation to physical activity?	
Please report changes in any concomitant illness and any sign of fever or other acute disease	
Were you asleep when the episode occurred?	
Were you able to treat your-self alone **(Yes/No)**? If the answer is NO answer following questions[3]: **The following questions should be completed at the study site by the investigator.**	
a) Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person) b) Where the treatment was administered (in clinic/emergency room/ hospital or other). If in clinic/ emergency room/ hospital, was the patient transported in ambulance? c) Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other) d) Were symptoms alleviated after administration of treatment? e) Did the patient experience a seizure? f) Was the patient unconscious/comatose? g) Did the patient experience any of the following symptoms: • Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat) • Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement) • General malaise: headache or malaise (feeling discomfort/unease) • Other symptoms?	

[1] If a stop date and time is not reported a hypoglycaemic episode will cover a period of 60 minutes.

[2] A hypoglycaemic episode starting without symptoms should be updated to symptomatic if the patient experiences symptoms later during the episode.

[3] The answer should be NO, if during the episode the patient needed assistance of another person to administer carbohydrate, glucagon or take other corrective actions. Oral carbohydrates should not be given if the patient is unconscious.

15.4 Appendix 4: COVID-19 Contingency Investigator Assessment Phone Visits

Only to be used if a patient is unable to attend the Investigational Site due to COVID-19. Every effort should be made to complete the Study Visit at the Investigational Site.

Please conduct all of the following:

- Phone call to be completed by PI/Sub-Investigator
- Please complete all assessments as listed in the flowchart below
- Please document Phone Visit in Source Notes
- Data to be entered into eCRF

Visit	**Visit 4 Week 4**	**Visit 5 Week 8**	**Visit 6 Week 12**	**Visit 7 Week 16**	**Visit 8 Week 20**	**Visit 10 EoS Week 28**
Day	28	56	84	112	140	196
Visit window	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days
AE assessment	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Discuss hypoglycaemic episodes	X	X	X	X	X	X
Discuss IMP compliance and diary compliance	X	X	X	X	X	
Courier Study Drug	X	X	X	X	X	