CONTRACT RESEARCH ORGANIZATION:

AMS Advanced Medical Services GmbH

Am Exerzierplatz 2

D-68167 Mannheim

Phone: +49 (0)621 / 70095 100

Fax: +49 (0)621 / 70095 140

SPONSOR:

Afimmune Ltd.

Trintech Building, South County Business Park, Leopardstown

Dublin 18, Republic of Ireland.

Statistical Analysis Plan

for Clinical Trial Protocol DS102A-07-CV1

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.
Test product	Epeleuton 2g and Epeleuton 4g
Type of Study	Randomised, double-blind, placebo controlled, 3-arm, multi-centre Phase IIb study
Objectives of Study	To assess the efficacy and safety of orally administered Epeleuton capsules versus placebo, in the treatment of adult patients with hypertriglyceridemia and type 2 diabetes.
Sponsor Study No.	DS102A-07-CV1
EudraCT-No.:	2020-000065-16
SAP Author	Sandra Roldan ***AMS*** Advanced Medical Services GmbH
Responsible Biostatistician	Florian Schelz ***AMS*** Advanced Medical Services GmbH
Date	June 09, 2022
Status of Document	Final Version 2.0
Pages	38

CONFIDENTIAL

Version history

Version	Date	Author	Description of changes
0.3	May 27, 2020	Frank Scherer	Third Draft Version
0.4	November 23, 2021	Florian Schelz	Fourth Draft Version
0.5	March 11, 2022	Florian Schelz	Fifth Draft Version according to protocol version 5.0
1.0	May 03, 2022	Florian Schelz	Final Version
2.0	June 09, 2022	Sandra Roldan	Final Version

I have thoroughly read and reviewed the Statistical Analysis Plan for the above mentioned study and approve its content:

Sponsor Signature(s)

Markus Weissbach — Date 15/06/22
(Chief Medical Officer, Afimmune)

Maud Hennion — Date
(Statistical Consultant, PharmaLex)

AMS Signature(s)

Sandra Roldan, Biostatistician — Date
(SAP Author)

Frank Scherer, Director Biostatistics — Date
(SAP Reviewer)

Version history

Version	Date	Author	Description of changes
0.3	May 27, 2020	Frank Scherer	Third Draft Version
0.4	November 23, 2021	Florian Schelz	Fourth Draft Version
0.5	March 11, 2022	Florian Schelz	Fifth Draft Version according to protocol version 5.0
1.0	May 03, 2022	Florian Schelz	Final Version
2.0	June 09, 2022	Sandra Roldan	Final Version

I have thoroughly read and reviewed the Statistical Analysis Plan for the above mentioned study and approve its content:

Sponsor Signature(s)

Markus Weissbach
(Chief Medical Officer, Afimmune) Date

Maud Hennion
(Signature)

Digitally signed by Maud Hennion
(Signature)
Date: 2022.06.14 08:34:49 +02'00'

Maud Hennion
(Statistical Consultant, PharmaLex) Date

AMS Signature(s)

Sandra Roldán 09 Jun 2022

Sandra Roldan, Biostatistician
(SAP Author) Date

Frank Scherer, Director Biostatistics
(SAP Reviewer) Date

Version history

Version	Date	Author	Description of changes
0.3	May 27, 2020	Frank Scherer	Third Draft Version
0.4	November 23, 2021	Florian Schelz	Fourth Draft Version
0.5	March 11, 2022	Florian Schelz	Fifth Draft Version according to protocol version 5.0
1.0	May 03, 2022	Florian Schelz	Final Version
2.0	June 09, 2022	Sandra Roldan	Final Version

I have thoroughly read and reviewed the Statistical Analysis Plan for the above mentioned study and approve its content:

Sponsor Signature(s)

Markus Weissbach
(Chief Medical Officer, Afimmune) Date

Maud Hennion
(Statistical Consultant, PharmaLex) Date

AMS Signature(s)

Sandra Roldán 09 Jun 2022

Sandra Roldan, Biostatistician
(SAP Author) Date

Frank Scherer, Director Biostatistics
(SAP Reviewer) Date

Version history

Version	Date	Author	Description of changes
0.3	May 27, 2020	Frank Scherer	Third Draft Version
0.4	November 23, 2021	Florian Schelz	Fourth Draft Version
0.5	March 11, 2022	Florian Schelz	Fifth Draft Version according to protocol version 5.0
1.0	May 03, 2022	Florian Schelz	Final Version
2.0	June 09, 2022	Sandra Roldan	Final Version

I have thoroughly read and reviewed the Statistical Analysis Plan for the above mentioned study and approve its content:

Sponsor Signature(s)

Markus Weissbach
(Chief Medical Officer, Afimmune) Date

Maud Hennion
(Statistical Consultant, PharmaLex) Date

AMS Signature(s)

Sandra Roldan, Biostatistician
(SAP Author) Date

Frank Scherer, Director Biostatistics
(SAP Reviewer) 13 Jun 2022 Date

Contents

List of Abbreviations and Definition of Terms

15(S)-HEPE	15-Hydroxy-Eicosapentaenoic Acid
15(S)-HEPE EE	15-Hydroxy-Eicosapentaenoic Acid Ethyl Ester, Epeleuton
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
AMS	Advanced Medical Services GmbH (CRO)
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
APTT	Activated Partial Prothrombin Time
AST	Aspartate transaminase
BDRM	Blind Data Review Meeting
BUN	Blood Urea Nitrogen
CRO	Clinical Research Organisation
ECG	Electrocardiography
eCRF	electronic Case Report Form
EPA	Eicosapentanoic Acid
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IND	Investigational new drug
IWRS	Interactive Web Response System

HDL-C	High Density Lipoprotein Cholesterol
HDL-P	High Density Lipoprotein Particle Concentration
HOMA-β	Homeostatic Model Assessment of β-cell Function
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hsCRP	High-Sensitivity C-Reactive Protein
ICAM-1	Intercellular Adhesion Molecule 1
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IL-	Interleukin-
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
LDL-C	Low-Density Lipoprotein Cholesterol
LDL-P	Low-Density Lipoprotein Particle Concentration
LOCF	Last observation carried forward
Lp(a)	Lipoprotein (a)
MCP-1	Monocyte Chemoattractant Protein 1
MedDRA	Medical dictionary for Drug Regulatory Affairs
nMR	Nuclear Magnetic Resonance
non-HDL-C	Non-High-Density Lipoprotein Cholesterol
PAI-1	Plasminogen Activator Inhibitor 1
PPS	Per-Protocol Set
PT	Prothrombin Time
RDW	Red Cell Distribution Width
RLP-C	remnant lipoprotein cholesterol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAS	Safety Analysis Set
SDV	Source data verification
SMBG	Self-monitoring of Blood Glucose
SOC	System Organ Class
SOP	Standard Operating Procedure
TSH	Thyroid Stimulating Hormone
UACR	Urinary Albumin-to-Creatinine Ratio
V	Visit
VCAM-1	Vascular Cell Adhesion Molecule 1
VLDL	Very Low-Density Lipoprotein
VLDL-C	Very Low-Density Lipoprotein Cholesterol
WHO	World Health Organisation

1 Introduction

This Statistical Analysis Plan (SAP) refers to trial protocol DS102A-07-CV1, version 5.0 dated February 14, 2022. The SAP will be finalised before any analysis will be conducted. The specifications included in this SAP provide more detail to the analysis descriptions in the study protocol and are focussed to statistical methodologies.

Additions or changes to the analysis planned in this SAP may be defined during the BDRM (Blind Data Review Meeting) and documented in the BDRM minutes which will be approved by the BDRM participants prior to database hard lock and unblinding.

The document is written in compliance with ICH Guideline E9 and ***AMS*** SOP ST-02.01 (Statistical Analysis Plan).

1.1 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.

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 details on primary/secondary efficacy endpoints and safety endpoints see section 7.

1.2 General Study Design

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. It is planned to perform this study in Germany, Switzerland, Latvia, Israel, US, UK and Georgia.

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

Blood samples 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 patients encouraged to fast appropriately for the next clinical visit. Safety laboratory parameters will be analysed at the central laboratory as well.

In a Phase IIa trial in patients with non-alcoholic fatty liver disease, 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.

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.

1.3 Study Population

The study population will consist of male and female patients diagnosed with hypertriglyceridemia and type 2 diabetes, aged 18 years and over. For a detailed list of the inclusion/exclusion criteria please refer to study protocol sections 7.2 and 7.3.

Approximately 240 male or female patients, i.e. 80 patients per treatment group will be randomised.

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.

1.4 Study Medication

The study treatment is capsules of Epeleuton (15(S)-HEPE EE) or placebo. Epeleuton and placebo will be provided by Afimmune. Epeleuton and corresponding placebo are provided as green hard-shelled capsules.

A patient kit contains four wallets (two “Morning” and two “Evening” walleted blister packs) is sufficient for two weeks dosing. Each wallet holding 4 capsules for each of seven days (cf. Figure 6 in study protocol section 10.3).

At the baseline visit, the first dose of IMP (Epeleuton or placebo) will be administered at site only after all baseline assessments have been completed. 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, throughout the 26 weeks study treatment period, starting with the next day. Patients will also be instructed to take medication with food, or within 30 minutes after a meal.

Patients will attend the study visits fasting but will receive their morning IMP dose (Epeleuton or placebo) at site after blood samples have been collected.

Each administration of IMP will be recorded by the patient in their eDiary or on a paper diary card which is then transcribed during the next site visit into the eDiary system by the Investigator or designee.

At Visit 4 and subsequent visits, 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.

From Visit 9 on, further IMP will not be supplied to the patient.

Patients will receive standard of care therapy in addition to their assigned IMP throughout the treatment period of the study.

1.5 Randomisation and Unblinding

A randomisation list permuted by blocks and stratified by site will be generated by the Sponsor or its designee. The randomisation schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the 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.

Patients will be randomised (1:1:1) at the baseline visit into the following treatment groups according to a computer-generated randomisation plan:

- 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.

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.

1.5.1 Emergency unblinding

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 subject. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

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

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.

The rest of the study team will be kept blinded regarding treatment assignment.

1.5.2 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.

1.5.3 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.

1.6 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.

1.7 Time Schedule / Study Duration

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).

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.

Patients who meet the inclusion criteria at both screening visits will be eligible to participate in the study. Eligible patients will be randomised at the baseline visit.

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.

The flowchart below details the timing of assessments up to Visit V10.

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,	X	X	X		X	X	X	X	X	X	X
Counselling	X		X								
Assessment of symptomatic 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								
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							
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: Clinical haematology, clinical chemistry, coagulation.
Laboratory test panel #2: Triglycerides, LDL-C (calculated), HbA1c
Laboratory test panel #3: VLDL-C, non-HDL-C, total cholesterol, glucose, HDL-C, RLP-C
Laboratory test panel #4: LDL-C (preparative ultracentrifugation), ApoA1, ApoB, ApoCIII, Lp(a), insulin, hsCRP, HOMA-IR, HOMA-β, nMR lipid profile
Laboratory test panel #5: IL-6, IL-1β, PAI-1, VCAM-1, ICAM-1, MCP-1, serum biomarker

For a full list of the laboratory tests to be performed please refer to Appendix 2. “Table of Central Laboratory Assessments” in the study protocol.

2 Sample Size

The primary efficacy endpoints are the percent change in triglycerides from baseline to week 16 and the change in HbA1c from baseline to week 26, which will be analysed separately. For details how the familywise error rate is preserved see section 6.1.

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 non-alcoholic fatty liver disease. 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.

3 Analysis Populations

The following population will be defined:

1. Enrolled Set (ES): All patients who provided informed consent will be included in the ES.
2. 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.
3. 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.
4. 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.

4 Blind Data Review Meeting

During the study conduct, protocol deviations will be captured through site self-reporting, source data verification (SDV) and data management edit checks, and will be recorded throughout the study in monitoring visit reports and in the eCRF.

A BDRM will be held prior to database hard lock/unblinding where ***AMS*** and Sponsor representatives will assess protocol deviations as major or minor with regard to their influence on any of the efficacy variables.

The ***AMS*** biostatistician will prepare blinded data review listings. Deviations not apparent in the clinical database (e.g. findings during monitoring of the investigational site) will be contributed by the clinical project leader. Additionally, data management may provide information to the discussions.

The following criteria might be considered as major protocol violations:

(1) Violation of inclusion or exclusion criteria

(2) Assignment to incorrect treatment (i.e. actual treatment taken differs from the randomised treatment scheduled)

(3) Non-adherence to the treatment schedule indicating insufficient treatment compliance

(4) Intake of prohibited concomitant therapies (medication for diabetes or obesity except for metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors and short-term insulin treatment for acute illness / Fibrates, PCSK9 inhibitors, bile acid sequestrants, niacin, niacin analogues or dietary supplements for the purpose of lowering cholesterol / food supplements rich in omega-3 or omega-6 fatty acids)

Listings for the criteria mentioned above and further listings relating to the following topics will be prepared for the discussion in the review meeting:

- Identification of patients randomised but not treated
- Eligibility of diary data including checks on the availability of diaries (especially regarding primary endpoint)
- Patients without efficacy data
- Patients where blind was broken prior to formal unblinding of the study
- Procedural deviations at the trial sites which are not reflected in the clinical database
- Premature patient discontinuations (reason and timing).
- Visit window deviations
- Further aspects deemed of interest

Further outputs may be prepared for data exploration purposes, e.g. to check distribution assumptions, to check for outliers.

The decision of findings being major or minor protocol deviations will be taken during the BDRM.

The patients allocated to the PPS and the reasons for exclusion of patients from the PPS will be documented prior to database hard lock and unblinding.

Full details on the reviews performed and the decisions made in the BDRM will be documented in writing in the BDRM protocol and will be approved by signature of the attendees. The decisions in the BDRM protocol may potentially amend/ overrule methodology/ analysis set definitions planned in this SAP. The BDRM protocol will be handled as an addendum to the SAP.

5 Data Handling

5.1 General

5.1.1 Data sources

Data will be collected using a validated, FDA CFR 21 Part 11compliant, 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).

Captured data will be monitored electronically and SDV will take place at the site, where information will be verified against the individual patient records. Details will be specified in a data validation plan, respectively monitoring plan.

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

SAEs will be reported to the pharmacovigilance contract research organisation (spm²). Prior to data base lock an SAE reconciliation between the pharmacovigilance database and the clinical database will be performed.

The biostatistical analysis will be based on the information recorded in the clinical database.

5.1.2 Coding

The process of coding will be performed according to the data management CRO standard operating procedures and will comply with applicable regulatory coding guidelines (e.g. ‘MedDRA Points to consider’ / ‘Best Practices for the use of the WHO Drug Dictionaries’).

Adverse events and medical history terms will be coded to system organ class and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

The current version of the WHO Drug Dictionary (WHO-DD) Global version B3 dictionary will be used for the coding of concomitant medications. Coding will be performed indication-specific, such that each medication is assigned the ATC code corresponding to its reason for administration.

5.1.3 Visits

In the analysis, visits and points in time will be presented under the visit number as documented in the database.

5.1.4 Baseline value

For analysis of triglycerides, baseline will be defined as the mean of the Baseline (Visit 3) and Screening 2/Week -1 (Visit 2) measurements.

For other parameters, the last non-missing value prior to first treatment will be referred to as baseline value and will be used for change from baseline calculations. Thus, depending on data availability, the baseline value could be a pre-dose value from Visit 3 (Baseline), a value from Visit 2 (Screening 2) or from Visit 1 (Screening 1).

5.1.5 Units for laboratory tests

All blood samples will be analysed at the central laboratory. In the biostatistical analysis, the laboratory tests will be displayed in the unit defined by the central laboratory.

5.2 Handling of missing values

Imputation of missing values will be performed for primary efficacy endpoints and secondary efficacy endpoints: A multiple imputation (MI) approach will be applied that uses the baseline value and all post-baseline values for a specific variable (e.g. triglycerides) as well as the treatment group.

For the primary endpoints, a last observation carried forward (LOCF) missing data handling approach will be conducted as an alternative imputation approach.

For exploratory endpoints, a last observation carried forward missing data handling approach will be conducted.

Where mentioned there also will be a complete-case analysis, i.e. a data presentation without imputation.

5.2.1 Handling of missing dates

Where a complete date is required for calculations but an incomplete date is documented only, the following rules will be applied:

If only the day is not known completely, for onset dates or start dates missing day information will be assumed as the 1st. If both day and month are missing, the 1st January will be used. For stop dates missing day information will be imputed as the last of the month, if both day and month are missing, the 31st December will be used.

However, if for adverse events it is not clear whether the event started prior to or in the treatment period, the onset at day of first treatment will be assumed.

Handling of incomplete stop dates for concomitant medications is described in section 5.3.6.

5.3 Algorithms for data calculations and modifications

5.3.1 Study Day

Consistent with the study flowchart, the Study Day of an assessment or event will be defined as

Study Day = Date of Assessment - Date of first treatment

For patients without treatment, study day will not be calculated.

5.3.2 Age

The age of patients at screening as documented in the eCRF will be analysed.

5.3.3 Time since diagnosis

The time since diagnosis of diabetes will be given in months and will be rounded to one decimal. Further analyses will use the rounded value. Time since diagnosis will be calculated as: Time since diagnosis = (date of informed consent – date of diagnosis)/(365.25/12)

If the date of diagnosis is incomplete it will be imputed assuming the first of the month or the first of January (cf. section 5.2.1).

5.3.4 BMI

If the Body Mass Index (BMI) is missing (e.g. weight not collected at a specific visit). BMI will be defined as weight [kg] / (height [cm]/100)^2 using a patient's last preceding non-missing weight value.

5.3.5 Treatment duration

The treatment duration of study medication [days] will be calculated as date of last dose administration minus the date of first dose (i.e. usually the baseline visit date Visit 3) plus one.

5.3.6 Previous vs. concomitant medication

Previous medications are those medications on the concomitant medication page that were stopped before the date of first study treatment of the patient. Concomitant medications are all other medications. In case of doubt (due to incomplete stop date) a medication will be assumed to be taken concomitantly.

For concomitant medication, if for indication "primary diagnosis" is ticked, the coding on the TSG-level will be used to decide, if it is a medication for Type II Diabetes or for Hypertriglyceridemia. It will be filtered for TSG= A10 Drugs used in diabetes and TSG= C10-Lipid modifying agents.

6 General Methodology

All analyses will be performed using SAS Version 9.1.3 or higher.

If not mentioned otherwise significance tests and confidence intervals will be two-sided using a Type I error rate of 0.05 / a confidence level of 95%. A two-sided p-value less than 0.05 is considered statistically significant for all comparisons.

If not mentioned otherwise, analyses will be stratified by treatment group displaying the following treatment groups (in this ordering): Epeleuton 4g, Epeleuton 2g, Epeleuton Total (where mentioned), Placebo, Total. Therefore treatment will not be mentioned explicitly as stratification variable usually.

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). This patient identifier number will be used in listings.

Usually listings will be sorted by treatment, patient number and (if applicable) visit/point in time.

All eCRF data will be listed, therefore listings may not be mentioned explicitly in section 7.

6.1 Primary Endpoint Evaluation

The primary efficacy endpoints are:

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

The primary analysis will be based on the FAS using values imputed via multiple-imputation.

Pairwise comparisons of both Epeleuton doses vs Placebo will be performed.

The primary analysis will be repeated for FAS using LOCF and for the PPS as supportive analyses.

Analysis of the percentage change of triglycerides will be performed using a Wilcoxon rank sum test with the Hodges Lehmann median and 95% confidence intervals estimates (Test 1 and Test 2).

Changes from baseline of HbA1c will be analysed using mixed model analysis of covariance (ANCOVA) with baseline value as a covariate, patient as random effect and treatment regime as fixed effect using type III sum of squares and calculating the least squares means for treatment and treatment contrast including corresponding 95% confidence intervals (Test 3 and Test 4).

6.2 Descriptive Analyses, Exploratory Tests

Categorical variables will be displayed by absolute and relative frequencies (percentages). Percentages for categorical variables will be based on all non-missing values (=100%). Percentages will be rounded to one decimal place and therefore, there may be occasions when the total of the percentages does not exactly equal 100%. The number of missing values will be displayed.

Continuous variables will be summarised with number of observations used, number of missing values, mean, standard deviation, median, minimum, maximum and the 25% and 75% quantiles.

If other statistical tests than those described in section 6.1 will be performed, these will have exploratory character only and will be carried out using a two-sided significance level of 5% without adjustment for multiplicity.

6.3 Subgroup analyses

Where conducted, subgroup analyses may use one or several of the following stratification variables:

- Gender (male, female)
- Age group (<65, ≥65 years)
- Country

Subgroup definitions may be amended during the BDRM and further subgroups may be defined during the BDRM.

7 Final analysis

The final analysis will be conducted after end of patient observation, i.e. after the last patient completed Visit 10 (Week 28) assessments.

The following sections summarise all analyses planned.

7.1 Demographic and other baseline data

All analyses described in this section will be performed as described in section 6.2 with the Safety Analysis Set.

The analysis will be presented overall. The following variables will be analysed:

- Age at Screening [years]
- Age group (<65, ≥65 years)
- Gender (male, female)
- Ethnic origin (Caucasian, Black, Asian, other)
- Smoking status (current smoker / ex-smoker / never smoked)

For medical history, the number/percentage of patients will be displayed by MedDRA primary SOC and Preferred Term.

Medical history data will be listed including its MedDRA coding information.

The time since diagnosis of diabetes will be summarised descriptively. Further analyses may be considered (at latest in the BDRM) for other data on diabetes history and complications (diabetic nephropathy, diabetic retinopathy, diabetic neuropathy).

7.2 Efficacy - Primary Endpoint Evaluation

The primary efficacy endpoints (i.e. Percent change in triglycerides from baseline to week 16 and Change in HbA1c from baseline to week 26) will be tested as described in section 6.1.

Triglyceride and HbA1c values and percentage change from baseline will be summarised descriptively (location and dispersion parameters) by visit as detailed in section 6.2 (displaying all visits).

Descriptive summary statistics for the two Epeleuton doses pooled will be given as well and exploratory inference tests for the two Epeleuton doses pooled vs Placebo will be performed for both primary endpoints.

Descriptive analyses for changes from baseline will generally include both absolute change and percentage change.

7.3 Efficacy - Secondary Endpoints Evaluation

The secondary efficacy endpoints are:

- 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.

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.

All other secondary efficacy endpoints will be analysed using 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. Significant departure from normality is defined as p-value of <0.01 for the Shapiro-Wilk test. The ANCOVA mixed model for each specific endpoint will use the baseline value of the specific endpoint variable as a covariate, patient as random effect and treatment regime as fixed effect, type III sum of squares and the least squares means for treatment and treatment contrast including corresponding 95% confidence intervals.

All statistical tests will be performed in an exploratory manner, without adjustment for multiplicity. All tests will be repeated for the pooled Epeleuton dose vs Placebo.

All analyses of secondary efficacy endpoints will be performed a) based on the FAS using values imputed via multiple-imputation b) using FAS with LOCF for endpoints related to triglycerides, change in HbA1c, and body weight. Endpoints related to Triglycerides and change in HbA1c will also be evaluated for PPS.

7.4 Exploratory Endpoints

Exploratory Endpoints are:

- 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.

All exploratory endpoints will be analysed using 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. Significant departure from normality is defined as p-value of <0.01 for the Shapiro-Wilk test. The ANCOVA mixed model for each specific endpoint will use the baseline value of the specific endpoint variable as a covariate, patient as random effect and treatment regime as fixed effect, type III sum of squares and the least squares means for treatment and treatment contrast including corresponding 95% confidence intervals.

All statistical tests will be performed in an exploratory manner, without adjustment for multiplicity. All significance tests will be repeated for the pooled Epeleuton dose vs Placebo.

All analyses of exploratory endpoints will be performed for FAS using LOCF imputation.

Further exploratory endpoints are:

- 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.

The analysis of these endpoints will be conducted by an independent pharmacokineticist. The analysis methods for these exploratory endpoints will be described in a separate document. The results and conclusions will be forwarded to the Medical Writer for incorporation into the Clinical Study Report.

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. The biostatistical evaluation therefore will be performed separately from the analyses described in this SAP. The sampling dates will be listed.

7.5 Safety Evaluation

Safety endpoints include

- 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

Analyses generally use the Safety Analysis Set.

7.5.1 Adverse Events

The degree of attributability (causality) between an IMP and an AE is documented as Definitely / Probable / Possible / Unlikely / Unrelated. A reasonable causal relationship is assumed if the causality is at least “possible”.

An AE will be considered “treatment emergent” if its onset is at or after the first dose of study drug at the baseline visit or if it worsened at or after the first dose of study drug.

The analyses of adverse events with onset on or after first administration of study medication (“treatment-emergent AEs”) will be based on the Safety Analysis Set.

Adverse events occurring before first application of study medication will be included in AE listings. Please note that Adverse Events with onset on study day of 0 or higher are treatment emergent AEs, while AEs with negative study day are those that occurred before first application of study medication.

The number and percentage of patients with specific adverse events during the treatment period will be displayed by MedDRA primary SOC, Preferred Term and worst severity. The counts in these analyses will reflect numbers of patients reporting one or more AE that map to the MedDRA system organ class/preferred term, displaying patients who reported several AEs of one Preferred Term with differing severities under the worst severity reported. E.g. one patient with two reported headaches (mild and moderate) will be analysed with moderate. The percentage is a crude incidence rate, i.e. the number of patients with a specific adverse event divided by the total number of patients in the analysis population.

The analysis of treatment-emergent adverse events will be repeated for the following AE categories:

- All adverse events
- Serious adverse events
- Adverse events related to the study medication
- Serious related adverse events
- Adverse events leading to permanent discontinuation of study drug

Furthermore, a summary table with the overall incidences of the above mentioned AEs will be created.

Listings will be based on the Enrolled Set and will include study day of AE onset and AE stop as well as MedDRA information (i.e. SOC, Preferred Term, and Lowest Level Term).

Listings will be created for the following topics:

- All adverse events
- Serious adverse events
- Adverse events related to the study medication

The number/percentage of patients with treatment-emergent adverse events will also be summarised by MedDRA primary SOC and Preferred Term for most frequent non-serious adverse events (incidence of preferred term ≥ 5%). In this table, the Totals overall or by SOC will consider only those preferred terms with an incidence >=5%.

7.5.2 Hypoglycaemia assessment

Assessment of symptomatic hypoglycaemic episodes will be conducted 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) into the following levels:

- 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 characterized 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.

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 Hypoglycaemic Episode Form (cf. study protocol section 15.3, Appendix 3) by the patient.

Based on a blinded medical review the episodes will be classified into Level 1 to Level 3.

Data on the Hypoglycaemic Episode Form will be listed.

The number/percentage of patients with events (overall and per level) will be summarised.

The number/percentage of events (with percentage based on the total number of events) will be summarised overall and per level.

7.5.3 Self-monitoring of blood glucose (SMBG)

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 7.5.2 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.

The information if self-monitoring of blood glucose was completed and if the investigator does recommend that the patient continues to complete eDiary for self-monitoring of blood glucose will be listed.

7.5.4 Vital signs

Vital signs measurements will be performed at each visit, before any blood samples are taken. The following vital sign parameters are obtained:

- Systolic blood pressure [mmHg] - seated and resting for five minutes
- Diastolic blood pressure [mmHg - seated and resting for five minutes]
- Heart rate [beats per min] – taken at rest
- Temperature [°C]: - taken as per clinic practice

The analysis for systolic/diastolic blood pressure is described in section 7.3. The analysis for heart rate and temperature will be performed as described in section 6.2 by visit using the Safety Analysis Set considering values as well as changes from baseline.

7.5.5 ECG

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.

The number/percentage of patients with normal results, abnormal results with clinical significance and abnormal results without clinical significance will be summarised overall and by visit for the Safety Analysis Set (as described in section 6.2.

7.5.6 Physical Examination

A physical examination, including height (Visit 1/Screening 1 only), weight, BMI and waist circumference measurement, will be performed 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.

The analysis for weight is described in section 7.3, the analysis for waist circumference is described in section 7.4. The analysis for BMI values and height values will be performed as described in section 6.2 by visit using the Safety Analysis Set.

7.5.7 Safety Laboratory data

Safety laboratory include haematology, serum biochemistry and coagulation:

- 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)

Those parameters are not evaluated as efficacy/exploratory endpoints. The value and change from baseline will be summarised descriptively by visit as described in section 6.2.

For all parameters a summary will display the number/percentage of patients with normal results, abnormal results with clinical significance and abnormal results without clinical significance overall and by visit.

Per parameter, a shift table will display the category (normal / abnormal, not clinically significant / abnormal, clinically significant) of the patient's baseline value vs. the worst category observed post-baseline.

All analyses for the safety laboratory will be based on the Safety Analysis Set.

Laboratory values outside the normal range will be listed separately in detail.

7.5.8 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.

Urinalysis assessment results will be summarised descriptively by visit as described in section 6.2 as applicable. Reflex microbiology data will be listed only.

7.5.9 Further safety endpoints

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 and at 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.

Pregnancy test data and counselling on contraception will be listed only.

7.6 Further Analyses

7.6.1 Previous and concomitant medication

All administered concomitant medications should be recorded throughout the study.

The incidence of previous and concomitant medication will be displayed by ATC classification (level 2 and preferred term). The analysis will be performed separately for previous medications and concomitant medications for the Safety Analysis Set (cf. section 5.3.6).

7.6.2 Study medication

Drug accountability

If documented in the eCRF, the Drug Accountability data (i.e. amount of dispensed / returned medication and other related information) will be listed.

Exposure data

Treatment duration [days] will be summarised descriptively by visit as described in section 6.2 for the Safety Analysis Set.

7.6.3 Patients' study termination status

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

- Unacceptable AEs
- Patient's decision (withdrawal of consent to participate)
- Investigator's discretion
- Intercurrent illness
- Pregnancy
- Patient lost to follow-up
- Reason not specified

The number/percentage of patients completing the study will be given, the number/percentage of patients with premature study termination will be given overall and per main reason. The analysis will be performed separately for screening failures, i.e. non-randomised patients, and for all randomised patients.

7.6.4 Study duration and analysis sets

The date of the first patient in the study (i.e. the date of first informed consent) and the date of the last patient out of the study (i.e. the last date of a patient visit/patient assessment in the study) will be given for the Enrolled Set as well as for the Safety Set.

The number of patients in each analysis set will be given overall and by centre nested in countries. All patients will be listed with their assignment to the analysis populations and if applicable the reason for exclusion from specific analysis sets.

The patient's visit dates will be listed including an indication of the corresponding study days.

7.6.5 Protocol deviations

Protocol deviations identified in the BDRM will be listed including the decision if these constitute a minor or major protocol violation.

Based on the number of protocol deviations observed a summary may be considered during the BDRM.

7.6.6 Pharmacokinetic sampling

Pharmacokinetic sampling and associated biostatistical evaluation is described in section 7.4.

8 Tables, Figures and Listings

FAS MI: Full Analysis Set with multiple imputation data, FAS LOCF: Full Analysis Set with LOCF data, FAS: Full Analysis Set complete-case analysis

Item No.	Title	Population	Content Description
14.1	**Demographic data, Baseline Characteristics, Patient disposition , concomitant medication**		
	Patient disposition		
14.1.1	Study termination status	Randomised patients	Descriptive statistics
14.1.2	Study termination reasons for screening failures	Non-randomised patients	Descriptive statistics
14.1.3	Duration of study	ES, SAS	Date of first patient in and last patient out
14.1.4	Number of patients in analysis sets by country, centre and overall	ES	Descriptive statistics
14.1.5	Treatment duration of study medication	SAS	Descriptive statistics of treatment duration
	Demographic data, Baseline characteristics, concomitant medication		
14.1.6	Demographics / Smoking status	SAS	Descriptive statistics (incl. age, age group, gender, ethnic origin, smoking status)
14.1.7	Diabetes history and complications	SAS	Descriptive statistics for time since diagnosis and possibly other parameters
14.1.8	Medical History	SAS	Descriptive statistics by MedDRA SOC and preferred term
14.1.9.1	Previous medication	SAS	Descriptive statistics by ATC classification (level 2) and preferred term
14.1.9.2	Concomitant medication	SAS	Descriptive statistics by ATC classification (level 2) and preferred term

Item No.	Title	Population	Content Description
14.2	**Efficacy**		
14.2.1	**Primary Endpoint**		
14.2.1.1.1 to 14.2.1.1.3	Percent change in triglycerides from baseline to week 16: Wilcoxon Test with Hodges Lehmann median	FAS MI, FAS LOCF, PPS	Wilcoxon rank sum tests (per Epeleuton dose level and pooled Epeleuton dose) with the Hodges Lehmann median and 95% confidence intervals estimates
14.2.1.1.4 to 14.2.1.1.6	Triglycerides values and changes by visit	FAS MI, FAS LOCF, PPS	Descriptive summaries incl. a pooled Epeleuton dose, absolute and percentage change
14.2.1.2.1 to 14.2.1.2.3	Change in HbA1c from baseline to week 26: ANCOVA	FAS MI, FAS LOCF, PPS	Mixed model analysis of covariance (per Epeleuton dose level and pooled Epeleuton dose) with baseline value as a covariate
14.2.1.2.4 to 14.2.1.2.6	HbA1c values and changes by visit	FAS MI, FAS LOCF, PPS	Descriptive summaries incl. a pooled Epeleuton dose, absolute and percentage change
14.2.2	**Secondary Endpoints**		
14.2.2.1.1 to 14.2.2.1.3	Percent change in triglycerides from baseline per visit: Wilcoxon Test with Hodges Lehmann median	FAS MI, FAS LOCF, PPS	Wilcoxon rank sum tests (per Epeleuton dose level and pooled Epeleuton dose) with the Hodges Lehmann median and 95% confidence intervals estimates, per visit
14.2.2.2.1 to 14.2.2.2.3	Change in HbA1c from baseline per visit: ANCOVA	FAS MI, FAS LOCF, PPS	Mixed model analysis of covariance (per Epeleuton dose level and pooled Epeleuton dose) with baseline value as a covariate, per visit
14.2.2.3.1	Proportion of patients with HbA1c below 7.0% per visit: Logistic regression	FAS MI	Logistic regression with baseline HbA1c as a covariate, per visit

Item No.	Title	Population	Content Description
14.2.2.4.1	Proportion of patients with HbA1c below 6.5% per visit: Logistic regression	FAS MI	Logistic regression with baseline HbA1c as a covariate, per visit
14.2.2.5.1	Percent change in VLDL-C per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.6.1	Percent change in non-HDL-C per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.7.1	Percent change in total cholesterol per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.8.1	Change in fasting plasma glucose per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.9.1	Percent change in ApoB per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.10.1	Percent change in RLP-C per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.11.1	Percent change in HDL-C per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.12.1	Percent change in LDL-C per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.13.1 to 14.2.2.13.2	Change in body weight per visit: Significance Test	FAS MI, FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.14.1	Change in hsCRP per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.15.1	Change in systolic blood pressure per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.16.1	Change in diastolic blood pressure per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.2.17.1	Change in UACR per visit: Significance Test	FAS MI	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test

Item No.	Title	Population	Content Description
14.2.3	**Exploratory Analyses**		
14.2.3.1.1	Change in waist circumference per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.2.1	Percent change in ApoCIII per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.3.1	Percent change in ApoA1 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.4.1	Percent change in Lp(a) per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.5.1	Percent change in HDL-P per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.6.1	Percent change in LDL-P per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.7.1	Percent change in Large LDL-P per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.8.1	Percent change in LDL size per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.9.1	Percent change in VLDL size per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.10.1	Percent change in HDL size per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.11.1	Change in fasting plasma insulin per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.12.1	Change in HOMA-IR per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.13.1	Change in HOMA-β per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test

Item No.	Title	Population	Content Description
14.2.3.14.1	Change in IL-6 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.15.1	Change in IL-1β per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.16.1	Change in PAI-1 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.17.1	Change in VCAM-1 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.18.1	Change in ICAM-1 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.19.1	Change in MCP-1 per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.20.1	Change in RDW per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.21.1	Change in haemoglobin per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.22.1	Change in reticulocyte count per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.23.1	Change in erythrocyte (red blood cell) count per visit: Significance Test	FAS LOCF	ANCOVA mixed model, if feasible, otherwise Wilcoxon-rank-sum test
14.2.3.24	Trough plasma concentrations of total and unesterified 15(S)-HEPE: Descriptive summary by visit	FAS LOCF	Descriptive summary incl. a pooled Epeleuton dose
14.2.3.25	Trough plasma concentrations of EPA: Descriptive summary by visit	FAS LOCF	Descriptive summary incl. a pooled Epeleuton dose

Item No.	Title	Population	Content Description
14.3	**Safety**		
14.3.1	**Adverse events**		
14.3.1.1	Summary of adverse events	SAS	Overall incidences of specific adverse event types (AE, SAE, …)
14.3.1.2	Adverse events by MedDRA SOC, preferred term and worst severity	SAS	Descriptive statistics by MedDRA SOC, preferred term and worst severity
14.3.1.3	Serious adverse events by MedDRA SOC, preferred term and worst severity	SAS	Descriptive statistics by MedDRA SOC, preferred term and worst severity
14.3.1.4	Adverse events related to study medication by MedDRA SOC, preferred term and worst severity	SAS	Descriptive statistics by MedDRA SOC, preferred term and worst severity
14.3.1.5	Adverse events leading to permanent discontinuation of study drug by MedDRA SOC, preferred term and worst severity	SAS	Descriptive statistics by MedDRA SOC, preferred term and worst severity
14.3.1.6	Adverse events with at least 5% incidence, by MedDRA SOC, preferred term	SAS	Descriptive statistics by MedDRA SOC and preferred term
14.3.1.7	Hypoglycaemia: Incidence on patient level	SAS	Descriptive summary
14.3.1.8	Hypoglycaemia: Incidence on event level	SAS	Descriptive summary
14.3.5	**Vital signs**		
14.3.5.1	Vital signs	SAS	Descriptive statistics of values and changes to baseline for heart rate+temperature
14.3.6	**Laboratory values**		
14.3.6.1	Serum biochemistry: absolute values and change from baseline	SAS	Descriptive statistics of absolute values and changes to baseline for each parameter

Item No.	Title	Population	Content Description
14.3.6.2	Serum biochemistry: number and percentage of normal and abnormal values	SAS	Descriptive statistics for each parameter (normal and abnormal values with and without clinical significance)
14.3.6.3	Serum biochemistry: Shift tables of normality	SAS	Shift table for change from baseline to the worst value post-baseline
14.3.6.4	Haematology: absolute values and change from baseline	SAS	Descriptive statistics of absolute values and changes to baseline for each parameter
14.3.6.5	Haematology: number and percentage of normal and abnormal values	SAS	Descriptive statistics for each parameter (normal and abnormal values with and without clinical significance)
14.3.6.6	Haematology: Shift tables of normality	SAS	Shift table for change from baseline to the worst value post-baseline
14.3.6.7	Coagulation: absolute values and change from baseline	SAS	Descriptive statistics of absolute values and changes to baseline for each parameter
14.3.6.8	Coagulation: number and percentage of normal and abnormal values	SAS	Descriptive statistics for each parameter (normal and abnormal values with and without clinical significance)
14.3.6.9	Coagulation: Shift tables of normality	SAS	Shift table for change from baseline to the worst value post-baseline
14.3.6.10	Urinalysis	SAS	Descriptive statistics for each parameter
14.3.7	**ECG**		
14.3.7.1	ECG: number and percentage of normal and abnormal values	SAS	Descriptive statistics for each parameter (normal and abnormal values with and without clinical significance) by visit and overall
14.3.8	**Physical Examination**		

Item No.	Title	Population	Content Description
14.3.8.1	Physical examination: Descriptive summary	SAS	Descriptive statistics for height and (by visit) BMI
16	**Appendices**		
16.2	**Patient data listings**		
16.2.1.1	Study termination	Randomised patients	Individual patient data listing of premature termination yes/no incl. reason for termination if applicable
16.2.1.2	Screening failures	Non-randomised patients	Individual patient data listing incl. reason for screening failures, only non-randomised patients
16.2.2	Protocol deviations	ES	Individual patient data listing of protocol deviations incl. decision if minor or major
16.2.3	Listing of patient assignment to analysis sets	ES	Individual patient data listing incl. randomisation number, randomisation date, randomised treatment, reason for exclusions from analysis sets
16.2.4.1	Demographic data / Informed consent	ES	Individual patient data listing
16.2.4.2	Medical history	ES	Individual patient data listing incl. history of CVD, history of liver disease and Hypercholesterolaemia
16.2.4.3	Diabetes history and complications	ES	Individual patient data listing
16.2.4.4	Previous/ Concomitant medications	ES	Individual patient data listing
16.2.5	Study medication administration	SAS	Individual patient data listing of study medication data
16.2.7	**Adverse Events Listings**		
16.2.7.1	Adverse events	ES	Individual patient data listing

Item No.	Title	Population	Content Description
16.2.7.2	AEs related to study medication	ES	Individual patient data listing
16.2.7.3	Serious adverse events	ES	Individual patient data listing
16.2.7.4	Symptomatic hypoglycaemic episodes	ES	Individual patient data listing
16.2.8	**Listing of individual laboratory measurements**		
16.2.8.1	Listing of laboratory values	All	Individual patient data listing of laboratory results, lab tests grouped by test panel (PK, Panel 1 to 5, UACR, Urinalysis, TSH)
16.2.8.2	Listing of abnormal laboratory values	All	Individual patient data listing of laboratory results, lab tests grouped by test panel (PK, Panel 1 to 5, UACR, Urinalysis, TSH)
16.2.8.3	Pregnancy test and Contraception	All	Individual patient data listing
16.2.8.4	Exploratory biomarker samples: Sampling dates	All	Individual patient data listing
16.2.9	**Other Listings**		
16.2.9.1	Vital signs / Physical examination	All	Individual patient data listing
16.2.9.2	ECG	All	Individual patient data listing
16.2.9.3	Self-Monitoring of Blood Glucose	All	Individual patient data listing
16.2.9.4	Visit dates	All	Individual patient data listing incl. study days

9 References

FDA: Center for Drug Evaluation and Research (CDER): Draft Guidance for Industry: Multiple Endpoints in Clinical Trials (2017)

Guideline on multiplicity issues in clinical trials, EMA/CHMP/44762/2017