Statistical Analysis Plan

Title:	A RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID 180 MG + EZETIMIBE 10 MG FIXED-DOSE COMBINATION COMPARED TO EZETIMIBE AND PLACEBO IN SUBJECTS WITH TYPE 2 DIABETES AND ELEVATED LDL-CHOLESTEROL
Protocol:	1002FDC-058
Clinical Phase:	2
Product:	Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination (FDC)
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Table of Contents

1 List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FSH	Follicle-stimulating hormone
HbA_{1C}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies

Abbreviation or Specialist Term	Explanation
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
IMP	Investigational Medicinal product
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LMT	Lipid Modifying Therapy
LSM	Least square mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
Na	Sodium
non-HDL-C	Non-high-density lipoprotein cholesterol
PE	Physical exam
PT	Preferred Term
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
T2D	Type 2 diabetes
TB	Total bilirubin
TC	Total cholesterol

Abbreviation or Specialist Term	Explanation
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in 1002FDC-058. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to both Protocol 1002FDC-058 (Protocol Amendment 1, 14 Mar 2018) and Administrative Change Letter #1 (16 Oct 2018).

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

3 Study Objectives and Endpoints

3.1 Objectives

The co-primary objectives of this study are:

- To assess the efficacy of FDC versus PBO on LDL-C lowering in subjects with T2D treated for 12 weeks; and
- To assess the efficacy of FDC versus EZE on LDL-C lowering in subjects with T2D treated for 12 weeks

The secondary objectives are:

- To assess the efficacy of EZE versus PBO on LDL-C lowering in subjects with T2D treated for 12 weeks;
- To assess the efficacy of FDC versus PBO, FDC versus EZE, and EZE versus PBO on high-sensitivity C-reactive protein (hs-CRP), non-HDL-C, total cholesterol (TC), apolipoprotein B (apoB), TG, and HDL-C in subjects with T2D treated for 12 weeks;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C level <70 mg/dL;
- To assess the effect of FDC, EZE, and PBO on percent of subjects achieving LDL-C reduction ≥50%; and
- To characterize the safety and tolerability of FDC, EZE, and PBO in subjects with T2D treated for 12 weeks.

Exploratory objective of this study is:

- To assess the effect of FDC versus PBO and EZE on hemoglobin A1C (HbA1C), fasting glucose, [redacted] homeostatic model assessment of insulin sensitivity (HOMA-IR) and [redacted] and 2-hour postprandial glucose (PPG) in subjects with T2D treated for 12 weeks.

3.2 Primary Endpoint

- Percent change from baseline to Week 12/End of Study (EOS) in LDL-C

3.3 Secondary Endpoints

- Percent change from baseline to Week 12 in hs-CRP, non-HDL-C, TC, apoB, TG, and HDL-C
- Status of LDL-C <70 mg/dL at Week 12 (Yes or No)
- Status of LDL-C reduction ≥50% from baseline to Week 12
- Change and percent change from baseline to Week 12 in HbA1C (Changed from an exploratory endpoint as specified in the protocol due to clinical needs.)

3.4 Safety Endpoints

- TEAEs, SAEs, Death;
- Clinical safety laboratories (hematology, clinical chemistry and urinalysis);
- Vital signs;
- PE findings
- ECG

3.5 Exploratory Endpoints

[redacted]

Change and percent change from baseline at [redacted] Week 12 in the following:

- Plasma glucose (fasting and 2-hour PPG);

[redacted]

[redacted]

– HOMA-IR index;

[redacted]

4 Study Design

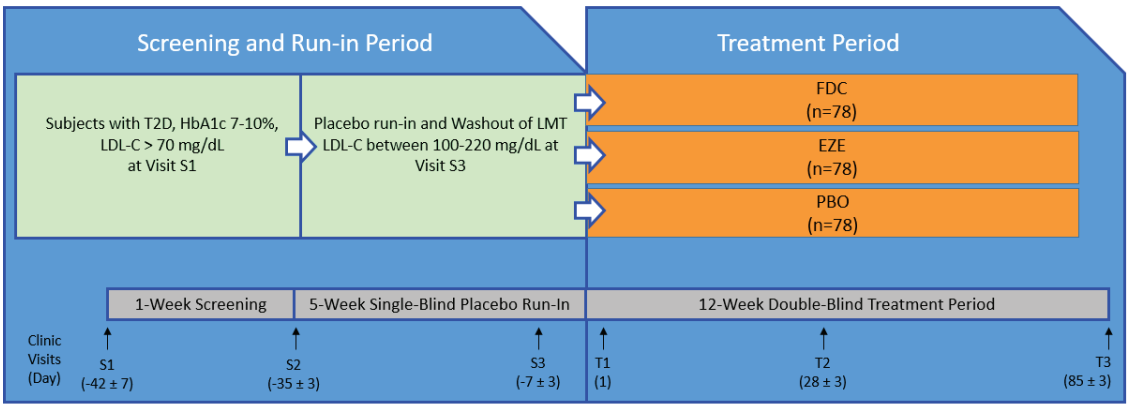
4.1 Study Design

This is a Phase 2, randomized, double-blind, parallel-group, multicenter study of Bempedoic Acid (BA) 180 mg and Ezetimibe (EZE) 10 mg FDC versus Placebo (PBO) and EZE 10 mg administered for 12 weeks in subjects with type 2 diabetes (T2D) and elevated LDL-C.

Approximately 234 male and female subjects with a history of T2D for at least 6 months and who meet the inclusion and exclusion criteria will be enrolled and randomized in a 1:1:1 ratio to receive FDC (n = 78) or EZE (n = 78) or PBO (n = 78).

The expected study duration is approximately 126 days, including an approximate 42-day screening period (Visit S1/Day -42, followed by a 5-week single-blind PBO run-in/lipid-modifying therapy (LMT) washout period from Day -35 to Day -1), an 84-day treatment period beginning at Visit T1/Day 1, and an EOS visit (Visit T3/Day 85).

Figure 1. Study 1002FDC-058 Study Design



T2D = type 2 diabetes; HbA1c = hemoglobin A1c; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; BA = bempedoic acid; EZE = ezetimibe; FDC = fixed dose combination.

4.2 Study Treatments and Assessments

Subjects will receive one FDC-matched PBO tablet and one EZE-matching PBO capsule once daily for 35 ± 3 days during the run-in period prior to randomization.

Subjects will be randomized to receive treatment with:

- One (1) BA 180 mg + EZE 10 mg FDC tablet and 1 EZE-matching PBO capsule once daily for 84 ± 3 days, or
- One (1) EZE 10 mg over-encapsulated tablet and 1 FDC-matched PBO tablet once daily for 84 ± 3 days; or
- One (1) FDC-matched PBO tablet and 1 EZE-matching PBO capsule once daily for 84 ± 3 days.

All IMP will be taken orally, at a similar time (approximate 24-hour intervals), in the morning with or without food.

The investigational products are listed in Table 1 below:

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product			
Product Name:	**Bempedoic Acid + Ezetimibe FDC Tablet**	**Ezetimibe Over-encapsulated Tablet**	**FDC-matched Placebo Tablet**	**Ezetimibe-matched Placebo Capsule**
Dosage Form:	Film-coated tablets	Over-encapsulated tablets	Film-coated tablets	Capsules
Unit Dose:	180 mg bempedoic acid + 10 mg ezetimibe	10 mg	Not applicable	Not applicable
Container	Blister cards with child resistant closures	Blister cards with child resistant closures	Blister cards with child resistant closures	Blister cards with child resistant closures
Route of Administration:	Oral with water with our without food	Oral with water with or without food	Oral with water with our without food	Oral with water with or without food
Physical Description:	[redacted]			

FDC = Fixed Dose Combination

Subjects with a history of T2D for at least 6 months will be screened for eligibility at an initial screening visit (Visit S1), which will be conducted approximately 42 days before planned randomization into the study. Subjects who have an LDL-C level >70 mg/dL and who meet all other inclusion/exclusion criteria will be return for Visit S2 approximately 5 weeks prior to planned randomization into the study to washout of all LDL-C-lowering therapies and begin taking single-blind (subject) PBO. Subjects will return to the study site approximately 7 days before planned randomization into the study for Visit S3. Subjects who have an LDL-C level ≥100 mg/dL and who continue to meet the study inclusion/exclusion criteria will be scheduled for their first treatment visit.

Subjects will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Subjects who continue to meet the study inclusion/exclusion criteria will be randomized in a 1:1:1 ratio to receive either FDC (n = 78), EZE (n = 78), or PBO (n = 78) once daily for 12 weeks. Randomized subjects will return for clinic visits at Week 4 (Visit T2) and Week 12 (Visit T3/EOS). Subjects who withdraw from IMP treatment will be asked to continue to be followed for safety and efficacy using the protocol-specified visit schedule and procedures. Subjects will be dispensed IMP at Visit T1/Day 1 and will be instructed to take the IMP in the morning at 24-hour intervals, with approximately 8 ounces of water, after a minimum 10-hour fast (only water allowed) and to continue fasting for 1 hour after ingesting the IMP with or without food. For details of study assessments, see Appendix 1: Schedule of Events (Patient Visit Schedule).

4.3 Randomization and Blinding

Subjects will receive single-blind PBO beginning at visit S2 and concluding with last dose on Day -1 (the day prior to Visit T1) during the Run-in period.

During the Treatment period, subjects will receive double-blind IMP. On Day 1 (Visit T1), subjects will be randomized to receive either FDC or EZE or PBO, randomized 1:1:1. Interactive web response system (IWRS) will be used to dispense randomized assigned blinded study drug to the subjects

Sponsor, site personnel, contract research organization (CRO), and subject will all be unaware of subject's treatment assignment during the Treatment period.

Blinding of treatment must be maintained for all subjects unless, in the opinion of the investigator, the safety of the subject may be at risk. Only under the rarest of circumstances should the investigator consider breaking the blind and only when medical/supportive care cannot be provided without determining if the subject is receiving active drug treatment. In the event that the blind needs to be broken prior to completion of the study, the investigator should contact the appropriate Medical Monitor by telephone. If the blind must be broken prior to consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind.

At the initiation of the study, the clinical site will be instructed on procedures for breaking the blind via the IWRS. In all cases of breaking the blind, the investigator must document in the subject's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

Post-randomization values for individual laboratory measures for LDL-C, hs-CRP, non-HDL-C, TC, TG, and HDL-C that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the subject, the Sponsor, or the CRO.

4.4 Sample Size Justification

The sample size of approximately 78 subjects per treatment arm (1:1:1) in this study (234 subjects total) is selected to provide adequate power for each of the co-primary endpoint as well as the co-primary endpoint family as a whole.

4.5 Interim Analyses, Final Analyses and Unblinding

No interim analysis is planned for this study.

The final analysis will be performed after the database is locked, the treatment assignments are unblinded using the actual randomization, and the database released.

4.6 Changes from Protocol Planned Analyses

Not applicable.

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

The BA + EZE FDC treatment group will be displayed in the tables, listings and figures (TLFs) as "BA (180 mg) + EZE (10 mg) FDC", the EZE 10 mg will be displayed as "Ezetimibe 10 mg" and Placebo group will be displayed as "PBO"

In general, all safety and PD data will be reported as observed. No imputation will be performed for missing data, except for the missing lipid efficacy data (Please refer to

Section 5.3.2 for more details). Descriptive statistics (n, mean, standard deviation [SD], Q1, Q3, median, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for SD.

Categorical data will be summarized using n and percentage based on number of non-missing values. Percentage will be presented with one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients have missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage.

Listings will be sorted in the order of patient, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in format DDMMMYYYY.

Relative day calculations will be [date of interest – relative date + (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.

Baseline for fasting lipid parameters including LDL-C, TC, HDL-C, non-HDL-C, and Triglycerides are defined as the average of S3 and T1 values (last two non-missing values on or prior to Day 1). If only one value is available, the single value will be used as baseline. For other parameters including apoB and hs-CRP, the baseline is defined as the last value/result where assessment date is less than or equal to the date of first study treatment, unless otherwise specified. If last dose of study treatment is missing, then the date of last visit at which study assessments were obtained on CRF will be used in its place.

The visit schedule and windows for assessments that occur at Baseline, Week 4, and Week 12 are shown below:

Visit	S1	S2	S3	T1	T2	T3/EOS
Slotted Study Week	-6	-5	-1	1	4	12
Target Study Day	-42	-35	-7	1	28	85
Study Day Range	[-∞, -39]	[-38, -21]	[-20, -1]	1	[2, 56]	[57, ∞]

The visit schedule and windows for assessments that occur at Baseline and Week 12 only, are shown below:

Visit	S1	S2	S3	T1	T3/EOS
Slotted Study Week	-6	-5	-1	1	12
Target Study Day	-42	-35	-7	1	85
Study Day Range	[-∞, -39]	[-38, -21]	[-20, -1]	1	[2, ∞]

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is defined as all randomized subjects who receive at least 1 dose of study drug. FAS will be used for pharmacodynamics analyses. Subjects in FAS will be analyzed as per their randomized treatment group regardless of actual treatment they received.

5.2.1.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) is defined as FAS excluding 3 study sites (Sites [redacted]). These sites were suspected of good clinical practice (GCP) violation in an earlier phase 3 study [redacted] and are under investigation. Therefore, to ensure the integrity and quality of the data and related analyses, we will use the Efficacy Analysis Set for the primary efficacy analyses. We will also conduct sensitivity analysis for efficacy analyses using FAS.

5.2.1.3 Treatment Completer Analysis Set

The Treatment Completer analysis set is a subset of the FAS excluding 3 sites ([redacted], [redacted]) and will include subjects who complete 12 weeks of treatment as indicated on the end of treatment CRF.

5.2.1.4 Safety Analysis Set

The Safety Analysis Set will include all subjects who randomized and received at least 1 dose of IMP. Subjects will be included in the treatment group that they actually received regardless of their randomized treatment.

5.2.2 Protocol Deviations

A full list of protocol deviations will be compiled and reviewed by the Esperion team to define each deviation as “major” or “minor” before final database lock. Major deviations will be those that are judged to have an impact on the integrity of data or endanger subject rights, safety and/or welfare. All other deviations will be judged as minor.

Protocol deviation information will be displayed for the safety analysis set in a subject listing.

Major protocol deviation will be summarized by treatment and categories in a table.

5.2.3 Patient Disposition

The number of patients screened, randomized and included in each analysis population, along with study completion status, will be summarized by treatment group as well as overall. In addition, the number of patients who withdraw from the study and withdraw from IMP will be summarized by discontinuation reason.

5.2.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group, as well as overall, for the safety analysis set and for the FAS: age (years), age will be summarized as a continuous variable and by age group (<65, >=65), gender, race, ethnicity, height (cm), weight (kg), body mass index (kg/m^2), BMI group (< 25, 25 - < 30, ≥ 30 kg/ m^2), systolic and diastolic blood pressure (mmHg), fasting lipid parameters (TC [mg/dL], calculated LDL-C [mg/dL], HDL-C [mg/dL], non-HDL-C [mg/dL] and TGs [mg/dL]), apoB (mg/dL), hs-CRP (mg/dL), history of hypertension, eGFR category, tobacco history, alcohol history, and weekly average number of alcoholic drinks, hemoglobin A1C (HbA1C), fasting glucose, [redacted] Diabetes mellitus duration, Diabetes mellitus duration categories (0 - <5, 5 - <10, >=10 years), No. of prior diabetes mellitus therapies (0, 1, 2, >=3), Type of prior diabetes mellitus therapies, Type of prior diabetes mellitus therapies ("Metformin", "Sulfonylurea" "No prior therapies indicated"). Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall.
The baseline estimated glomerular filtration rate (eGFR) categories are: normal: ≥90 $mL/min/1.73m^2$; mild Renal Impairment: 60-89 $mL/min/1.73m^2$; moderate Renal Impairment: 30-59 $mL/min/1.73m^2$, and severe Renal Impairment (15-29 $mL/min/1.73m^2$).

5.2.5 Subgroup Variables

Subgroups defined by below variables will be evaluated for safety and the primary and secondary efficacy endpoints. The reference level for each subgroup/covariate variable is indicated with (ref).

1) Gender (male (ref) vs. female)
2) Age (< 65 yrs.(ref) vs. ≥65 yrs.)
3) Race (White vs. other)
4) Baseline LDL category (< 160mg/dL (ref) vs. ≥160 mg/dL)
5) Baseline HbA1C (the categories will be divided by median)
6) Years of T2D (0 - <5, >=5 year)

In case the number of patients within a subgroup is too small, e.g. less than 5% of the overall population, the analyses may not be performed or the subgroup levels may be combined. Subgroup analysis will be conducted on primary endpoint and exploratory PD endpoint analyses.

5.2.6 Medical History

General medical history and cardiovascular history/risk factors will be summarized by treatment group, as well as overall, for FAS population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or later.

5.2.7 Baseline Serology, Serum and Urine Pregnancy Test and TSH

Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and serum pregnancy test (only for females of childbearing potential), follicle stimulating hormone ([FSH], only for females who are < 55 years old and > 1 year without menses), urine pregnancy test Day 1 prior to randomization and thyroid-stimulating hormone (TSH) will be presented in a by-patient listing.

5.2.8 Prior and Concomitant Medications

Prior medications are defined as medications that ended prior to the first dose of IMP. Concomitant medications are defined as medications that were ongoing at the time of first dose of IMP or new medications that started after first dose of IMP and within 30 days following the date of the last dose of IMP.

Medications will be coded using WHO Drug (March, 2018 or later). The use of prior or concomitant medications will be summarized by treatment group, as well as overall, for the safety analysis set according to Anatomical Therapeutic Chemical (ATC) class and coded medication name. Prior and concomitant medications will be listed for each patient.

5.2.9 IMP Exposure and Compliance

The length of exposure to IMP (FDC, and EZE) will be calculated as the number of days from the first dose of double-blind IMP to the last dose of double-blind IMP, regardless if the patient missed one or more doses of IMP. Length of exposure will be summarized by treatment group using descriptive statistics for the safety analysis set. The length of exposure will be calculated as first dose of PBO to the last dose of PBO in respective periods.

The number and percentage of patients who were compliant with taking IMP will be summarized by treatment group for the safety analysis set for the following categories 0-<80%; >= 80%.

Overall compliance will be calculated as: 100* (Total Number of Tablets Dispensed – Total Number of Tablets Returned) / (2*Treatment Duration in Days). The IMP administration and compliance data, including reasons for poor compliance, if noted in CRF will be listed for each patient.

Same approach will be applied in calculating exposure and compliance for single-blinded PBO run-in period. Listing and table will be provided separately to IMP during treatment period.

5.3 Primary Efficacy Endpoints and Analyses

For all efficacy analyses, the EAS will be used, with patients included in their randomized group, regardless of the treatment they actually received.

5.3.1 Analysis for the Efficacy Parameters

For the primary efficacy analysis, percent change in LDL-C at week 12 and the secondary endpoints of percent change in hs-CRP, non-HDL-C, HDL-C, TC, TG, and apoB at week 12 will be analyzed using the analysis of covariance (ANCOVA) method. The ANCOVA model will include treatment as factor, and baseline value as covariate. The model assumptions for ANCOVA will be assessed and if these assumptions are severely violated, alternative non-parametric approach will be performed.

An example SAS code for ANCOVA analysis is shown as below:

```
PROC MIXED DATA=adeff;
    class armcd;
    model pchg = blres armcd / solution ddfm=kenwardroger;
    ;
    lsmeans armcd / diff=control ('ref') cl;
```

The least square mean (LSM) and standard error (SE) for percent change estimate will be provided for all the treatment groups, along with PBO-corrected LSM, its 95% confidence interval (CI) and associated p-value.
For hs-CRP and TG, a non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval will also be performed because based on historical knowledge, publication precedence (Brendan et al., 2006) and recent data available, hs-CRP and TG are known to be skewed by extreme values and have non-normal distribution.

For other secondary endpoints, number and percent of subjects with LDL-C < 70mg/dL at week 12 will be tabulated by treatment. Number and percent of subjects LDL-C reduction ≥ 50% from baseline to Week 12 will be tabulated by treatment. Chi-sq test or fisher exact test will be performed between the FDC-treated arm and EZE-treated arm and PBO-treated arm for those two endpoints. Only observed data will be used, i.e. the denominator will be number of subjects who have LDL-C value at perspective time point. Efficacy data (actual value, change and percent change from baseline) from all visits will be presented using descriptive statistics using both conventional and standard units. A figure of mean (+/- SE) value or median (IQR) as appropriate, over time will be provided for these efficacy parameters.

Efficacy data will also be listed.

5.3.2 Missing Data Imputation

Missing LDL-C data at week 12 will be imputed using the last post baseline observation carried forward (LOCF).

Observed data and LOCF data will be analyzed separately for primary and secondary efficacy endpoints.

5.3.3 Sensitivity Analysis for Efficacy Endpoints

- A sensitivity analysis for primary and secondary efficacy endpoints will be performed using the ANCOVA model on Treatment Completer Analysis Set.
- The observed case data only (no imputations for missing data) analyses will also be used for sensitivity analyses for primary and secondary endpoints. Observed data analysis will be conducted using FAS.
- By-visit summary for all efficacy endpoints (LDL-C, non-HDL-C, HDL-C, TC, TG, ApoB, hs-CRP) will be provided for both conventional and standard units.

5.4 Exploratory Analyses

For exploratory endpoints (change and percent change from baseline to Week 12 in HbA1C, fasting glucose, HOMA-IR index, and 2-hour PPG), the data will be analyzed in the similar fashion as for the primary endpoints. For fasting plasma glucose, HbA1C, 2-hour PPG and the baseline is the predose Day 1/Week 0 (Visit T1) value. If no value is available at Visit T1, then the last value prior to first dose of IMP will be used as baseline.

Sensitivity analyses will be used to examine if the potential data issues previously identified at 3 sites in Study (Sites) impact the

efficacy results of this study. The sensitivity analysis will repeat selected key analyses including all FAS subjects, as listed below:

1. Patient Disposition
2. Demographic and Baseline Characteristics - Full Analysis Set
3. Summary Statistical Analysis of Percent Change from Baseline in Primary Efficacy Endpoints at Week 12 Full Analysis Set
4. Summary Statistical Analysis of Percent Change from Baseline in Secondary Efficacy Endpoints at Week 12 Full Analysis Set
5. Statistical Analysis of Median Percent Change from Baseline in hs-CRP and TG at Week 12 via Non-parametric Approach (Observed Data) Full Analysis Set
6. Statistical Analysis of Percent Change from Baseline in HbA1C Full Analysis Set
7. Statistical Analysis of Percent Change from Baseline in Fasting Glucose Full Analysis Set
8. [redacted]
9. [redacted]

Additional exploratory and sensitivity analyses may be performed as needed.

5.5 Safety Endpoints and Analyses

The safety and tolerability of FDC, EZE and PBO will be assessed by examination of TEAEs (including muscle related events and other AESI), physical exams, vital signs, electrocardiograms (ECGs), clinical laboratory values (serum chemistry, hematology, coagulation and urinalysis), and weight. All patients included in the Safety Analysis Set will be evaluated in the safety analyses.

Unless otherwise stated, descriptive summaries will be displayed by treatment group actually received and based on the Safety Analysis Set.

5.5.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or later and will be categorized by system organ class (SOC) and preferred term (PT). Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last study visit, whichever comes first. Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged).

In summary tables, TEAEs will be counted as "Not Related" if relationship to IMP was recorded as 'Not Related' or "Unlikely". Events will be counted as "Related" if relationship to IMP was recorded as 'Possible', 'Probable', 'Definite' or if relationship to IMP is missing.

The severity of the AE will be characterized as mild, moderate, or severe, to the following definitions:

- Mild: Events are usually transient and do not interfere with the subject's daily activities
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe: Events interrupt the subject's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

Overviews of TEAEs will include total number of TEAEs and patient incidence of TEAE, TE SAE, related TEAE, related TE SAE, AESI, withdrew due to TEAE, Fatal TEAE. An individual TEAE summary will be presented by treatment group containing the following counts and percentages for:

- patients with TEAEs
- patients with TEAEs by PT
- patients with TEAEs by SOC, PT and maximum severity
- patients with treatment-related TEAEs
- patients with treatment related TEAEs by PT
- patients with treatment related TEAEs by SOC, PT and maximum severity
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs by PT
- patients with TE SAEs by SOC, PT and maximum severity
- patients with treatment-related TE SAEs
- Fatal AEs by SOC and PT
- withdrawal from IMP due to TEAEs

Patient incidence (percent of patients experiencing the AE) will be provided for overall TEAE, treatment related TEAE, TE SAE, treatment related TE SAE, and AESI.

The AE overview summaries will count a patient at most once in each AE category (at the "highest/most extreme" designation of each category regardless of preferred term) and percentages will be based on the total number of patients in the safety analysis set.

In addition to a comprehensive listing of all AEs (with non-TEAEs flagged), separate listings will be generated for SAEs, AEs resulting in withdrawal of IMP, and AEs with a fatal outcome.

5.5.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be identified based a pre-defined list of preferred terms provided by the sponsor (Appendix 2).

AESI will be presented in a listing and summarized by SOC, PT and treatment group.

In addition to adverse events, AESI is also being evaluated based on safety lab parameters.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of subjects with abnormal values for ALT, AST and TB will be summarized. All liver-associated laboratory abnormalities will be assessed by Hy's Law criteria (>3 x ULN for either ALT or AST, with accompanying TB > 2 x ULN in the absence of other known causes) will also be applied to the data. Any potential Hy's Law cases will be listed separately.

Musculoskeletal Adverse Events

Muscle related adverse events as reported on the general AE CRF will be summarized by SOC and PT. In addition, the number and percent of subjects with abnormal CK values will be summarized. All muscle related events and details associated with it including cause and location will be provided in a listing.

Hyperglycemia/Hypoglycemia

Cases of new onset and worsened events will be recorded as AEs and will be summarized using appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group.

Renal Safety

Baseline eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group.

Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Neurocognitive events will be summarized using pre-specified MedDRA terms by treatment group.

Metabolic Acidosis

Metabolic acidosis events will be monitored by clinical safety laboratory chemistries. These events will be summarized by treatment group.

5.5.3 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology, coagulation, urinalysis, urinalysis [microscopic]) listed in Table 2; fasting serum glucose, and HbA1c will be summarized using descriptive statistics for the observed value and the change, percent change from baseline. Missing values for any of the safety laboratory evaluations will not be imputed; that is, only observed case data will be used. Baseline is defined as the last value prior to the first dose of study medication. Categorical urinalysis data will be listed, but will not be summarized.

As part of the AESI evaluation, below safety lab abnormality will be summarized by treatment group. All post-baseline lab values are being considered. Further details are provided in Section 5.5.3.1 through 5.5.3.4.

- ALT or AST (> 3x ULN and >5xULN)
- TB (> 2x ULN)
- Potential Hy's Law case: (ALT and/or AST > 3xULN with concurrent TB > 2xULN)
- CK (> 5x ULN) and (>10x ULN)
- Fasting Serum Glucose (mg/dL) (≤50, and ≥126)
- HbA1C (≥x%) (the median of HbA1C at baseline)
- Creatinine (change from baseline for >1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –< 30 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥2 g/dL)
- Hgb (<8 g/dL)

- **Table 2: Clinical Laboratory Parameters (Safety)**

Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %) Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Blood Chemistry (serum, fasting) • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid Coagulation (Visit S1 for all patients, Visit T1 and 3-7 days after Visit T1 in subjects receiving anticoagulation therapy only) • Prothrombin time (PT) • International normalized ration (INR)

The number and percentage of patients with laboratory abnormalities (i.e., laboratory values outside the stated laboratory normal range) will be summarized at each time point (i.e., including baseline and post-baseline time points) for each laboratory parameter. The determination of laboratory abnormalities will take into account any unscheduled

laboratory assessments. Additional lab-related summaries will be provided as follows for hepatic safety, musculoskeletal safety, diabetes and glycemia, and renal safety.

5.5.3.1 Hepatic Safety

For liver-associated enzymes and total bilirubin (TB), the number and percent of patients with abnormal values for ALT (> 3 × ULN, > 5 × ULN), AST (> 3 × ULN, > 5 × ULN), and TB (> 2×ULN) will be summarized by overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB for overall safety analysis set.

Hy's law criteria (> 3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB > 2 × ULN,) will also be applied to the data; any potential Hy's law cases will be listed.

A separate listing for direct TB will be provided for those who have Gilbert's syndrome.

5.5.3.2 Musculoskeletal Safety

CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit as well as baseline eGFR category. In addition, the number and percent of patients with abnormal CK values (>5 x ULN, > 10 x ULN) will be summarized for overall safety analysis set. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.5.3.3 Diabetes and Glycemia

For fasting serum glucose and HbA1C (%), a shift table from baseline with the number and percent of patients will be categorized as below:

Fasting glucose: >=126 mg/dL 100-<126 mg/dL, 50-<100 mg/dL, and <50 mg/dL; HbA1C (%) <8% and >= 8% at baseline, and <7% and >= 7% at post baseline visits. These categories may be adjusted depending on observed data. These tables will be summarized by treatment groups.

Descriptive summary for fasting serum glucose and HbA1C will be provided by treatment group at each scheduled visit.

5.5.3.4 Renal Safety

By-visit summary and shift tables of eGFR by baseline category will be provided by treatment group.

In addition, renal function abnormality will be identified as: (1) A creatinine change from baseline of > 1 mg/dL (2) eGFR value <30 mL/min/1.73m^2. A shift table from baseline with the number and percent of patients using the two categories will be presented.

5.5.4 Physical Examinations (PEs)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.' Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AE outcomes.

5.5.5 Vital Signs

Actual values, changes and percent change from baseline in vital signs (pulse rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and BMI) will be summarized using descriptive statistics by treatment group and post-baseline time point. Baseline is defined as the last value prior to the first dose of double-blind study medication.

Vital signs data will be listed for each patient.

5.5.6 Electrocardiogram (ECG)

Shift tables for ECG data from baseline to end-of-study will be provided by treatment group. The data will be categorized as 'Normal'; 'Abnormal, not clinically significant'; and 'Abnormal, clinically significant.' Listings of ECG data will include only those records where the baseline ECG was either 'Normal' or 'Abnormal, not clinically significant', but the end-of-study ECG was marked as 'Abnormal, clinically significant'.

6 Changes from Previous Statistical Analysis Plan

Section	Item	Update
All	Bookmarks	• Incremented the version in order to fix the bookmarks throughout the document
7 References	21	• Added reference number 21 as it was inadvertently excluded from other versions despite being referenced in the SAP text.

7 Reference

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8 Appendices

Appendix 1: Schedule of Events (Patient Visit Schedule)

	Study Period:	**Screening and Run-in**			**Treatment**		
	Study Visit:	**S1**	**S2**	**S3**	**T1**	**T2**	**T3/EOS[a]**
	Study Week:	**-6**	**-5**	**-1**	**1**	**4**	**12**
Procedure	**Study Day:**	**-42 ± 7**	**-35 ± 3**	**-7 ± 3**	**1**	**28 ± 3**	**85 ± 3**
Informed consent		X					
Inclusion/Exclusion criteria[b]		X	X	X	X		
Demographics		X					
Medical history		X					
Prior and/or Concomitant medications		X	X	X	X	X	X
Adverse event recording			X	X	X	X	X
Physical examination		X					X
Weight/BMI [c]		X		X	X		X
Height		X					
12-Lead ECG[d]			X				
Vital signs[e]		X	X	X	X	X	X
Serum pregnancy test/FSH[f]		X					
Urine pregnancy test[h]					X		X
Basic fasting lipid panel[g]		X		X	X	X	X

	Study Period:	Screening and Run-in			Treatment		
	Study Visit:	**S1**	**S2**	**S3**	**T1**	**T2**	**T3/EOS[a]**
	Study Week:	**-6**	**-5**	**-1**	**1**	**4**	**12**
Procedure	**Study Day:**	**-42 ± 7**	**-35 ± 3**	**-7 ± 3**	**1**	**28 ± 3**	**85 ± 3**
Special lipids and other biomarkers[h]		X			X	X	X
Coagulation panel[i]		X					
TSH		X					
Serology[j]			X				
Clinical safety laboratories[k]		X		X	X	X	X
Urine drug screen		X			X		
Reserve Sample for Potential Exploratory Biomarkers[l]					X		X
Calculate eGFR		X					
Washout LMT			X	X	X	X	X
Randomization					X		
Ensure breakfast drink[m]					X	X	X
PPG glucose sample[n]					X	X	X
Diet and exercise counseling		X	X	X	X	X	
Dispense single-blind IMP			X				
Return single-blind IMP and assess dosing adherence				X	X		

	Study Period:	Screening and Run-in			Treatment		
	Study Visit:	**S1**	**S2**	**S3**	**T1**	**T2**	**T3/EOS[a]**
	Study Week:	**-6**	**-5**	**-1**	**1**	**4**	**12**
Procedure	**Study Day:**	**-42 ± 7**	**-35 ± 3**	**-7 ± 3**	**1**	**28 ± 3**	**85 ± 3**
Dispense double-blind IMP					X	X	
Return double-blind IMP and assess dosing adherence						X	X

ApoB = apoprotein B; BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; HCV-AB = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IMP = investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

[a] All procedures will be completed at EOS or at time of early termination from the study. The last dose of IMP will be taken on the morning of Day 84 or the day prior to Visit T3/EOS. Visit T3/Day 85 represents 24 hours after the last dose of IMP.

[b] Subject must have a fasting calculated LDL-C level between 100 and 220 mg/dL after 5-week washout of all LDL-C-lowering drugs and nutritional supplements. If TG level is >400 mg/dL, a repeat assessment may be obtained; the repeat assessment will be used to determine study eligibility and screening will be extended by 1 week.

[c] Weight will be measured on a calibrated scale in the morning while fasting, in street clothing, and after voiding. BMI will be calculated using height from Visit S1 and measured weight at respective visits.

[d] A single 12-lead ECG will be obtained after the subject has rested quietly in the supine position for at least 10 minutes

[e] Systolic blood pressure, diastolic blood pressure, and pulse rate will be obtained after the subject has been seated quietly for at least 5 minutes in a chair with the back supported, the feet flat on the ground, and the arms bared and supported at heart level.

[f] Pregnancy tests will be obtained for women of childbearing potential and for surgically sterile women; FSH level will be obtained for women <55 years old and ≥1 year without menses.

[g] Basic fasting lipid panel includes calculated TC, calculated LDL-C, HDL-C, calculated non-HDL-C, and TGs.

[h] Special lipids and other biomarkers include apoB, hs-CRP, glucose, [redacted] and HbA_{1C}.

[i] Coagulation panel (see Table 3 of the study protocol) will be performed only at Visit S1/Day -42 unless the subject is receiving an anticoagulant agent in which case the coagulation panel will be repeated at Visit T1/Day 1 and 3 to 7 days after starting the IMP.

[j] The serology assessment includes HbsAg and HCV-AB.

[k] Clinical safety laboratories include hematology, clinical chemistry, and urinalysis; the required assays are listed in Table 3 of the study protocol.

[l] Reserve blood sample for potential future exploratory biomarkers will be collected at Visits T1 and T3; separated into K2-edta plasma and serum separator tubes; and processed plasma and serum samples will be stored frozen for potential future analysis.

[m] Subjects will consume 1 serving of Ensure Original Vanilla® breakfast drink (Abbott Laboratories: 220 calories, 32 g of total carbohydrate) at approximately 9:00 AM and site staff will record the time of the start and completion of the meal. The entire serving should be consumed within 5 minutes.

[n] PPG blood glucose sample will be collected 2 hours ± 5 minutes after the subject begins to consumes the Ensure breakfast drink

Appendix 2: Adverse Event of Special Interest (AESI)

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
Creatine kinase elevations	Blood creatine phosphokinase abnormal
Creatine kinase elevations	Blood creatine phosphokinase increased
Creatine kinase elevations	Blood creatine phosphokinase MM abnormal
Creatine kinase elevations	Blood creatine phosphokinase MM increased
New onset or worsening diabetes mellitus	Blood glucose abnormal
New onset or worsening diabetes mellitus	Blood glucose increased
New onset or worsening diabetes mellitus	Diabetes mellitus
New onset or worsening diabetes mellitus	Diabetes mellitus inadequate control
New onset or worsening diabetes mellitus	Diabetic ketoacidosis
New onset or worsening diabetes mellitus	Glucose tolerance impaired
New onset or worsening diabetes mellitus	Glucose urine present
New onset or worsening diabetes mellitus	Glycosuria
New onset or worsening diabetes mellitus	Glycosylated haemoglobin increased
New onset or worsening diabetes mellitus	Hyperglycaemia
New onset or worsening diabetes mellitus	Impaired fasting glucose
New onset or worsening diabetes mellitus	Ketoacidosis
New onset or worsening diabetes mellitus	Ketosuria
New onset or worsening diabetes mellitus	Ketosis

New onset or worsening diabetes mellitus	Type 2 diabetes mellitus
New onset or worsening diabetes mellitus	Urine ketone body present
Hepatic disorders	Alanine aminotransferase abnormal
Hepatic disorders	Alanine aminotransferase increased
Hepatic disorders	Aspartate aminotransferase abnormal
Hepatic disorders	Aspartate aminotransferase increased
Hepatic disorders	Blood bilirubin abnormal
Hepatic disorders	Blood bilirubin increased
Hepatic disorders	Hepatic enzyme abnormal
Hepatic disorders	Hepatic enzyme increased
Hepatic disorders	Hypertransaminaseaemia
Hepatic disorders	Liver function test abnormal
Hepatic disorders	Liver function test increased
Hepatic disorders	Transaminases abnormal
Hepatic disorders	Transaminases increased
Hypoglycemia	Blood glucose abnormal
Hypoglycemia	Blood glucose decreased
Hypoglycemia	Hypoglycaemia
Hypoglycemia	Hypoglycaemic coma
Hypoglycemia	Hypoglycaemic encephalopathy
Hypoglycemia	Hypoglycaemic seizure

Hypoglycemia	Shock hypoglycaemic
Metabolic acidosis	Metabolic acidosis
Muscular disorders	Muscular weakness
Muscular disorders	Muscle necrosis
Muscular disorders	Muscle spasms
Muscular disorders	Myalgia
Muscular disorders	Myoglobin blood increased
Muscular disorders	Myoglobin blood present
Muscular disorders	Myoglobin urine present
Muscular disorders	Myoglobinaemia
Muscular disorders	Myoglininuria
Muscular disorders	Myopathy
Muscular disorders	Myopathy toxic
Muscular disorders	Necrotizing myositis
Muscular disorders	Pain in extremity
Muscular disorders	Rhabdomyolysis
Neurocognitive/Neurologic disorders	Amnesia
Neurocognitive/Neurologic disorders	Cognitive disorder
Neurocognitive/Neurologic disorders	Confusional state
Neurocognitive/Neurologic disorders	Disorientation
Neurocognitive/Neurologic disorders	Memory impairment

Neurocognitive/Neurologic disorders	Mental status changes
Renal disorders	Acute kidney injury
Renal disorders	Acute prerenal failure
Renal disorders	Blood creatinine abnormal
Renal disorders	Blood creatinine increased
Renal disorders	Blood urea abnormal
Renal disorders	Blood urea increased
Renal disorders	Blood urea nitrogen/Creatinine ratio increased
Renal disorders	Creatinine renal clearance abnormal
Renal disorders	Creatinine renal clearance decreased
Renal disorders	Glomerular filtration rate abnormal
Renal disorders	Glomerular filtration rate decreased
Renal disorders	Gout
Renal disorders	Oliguria
Renal disorders	Prerenal failure
Renal disorders	Renal failure
Renal disorders	Renal function test abnormal
Renal disorders	Renal impairment