

STATISTICAL ANALYSIS PLAN

Protocol MAT-002

Pharmacodynamic Effects of a Free-fatty Acid Formulation of Omega-3 Pentaenoic Acid to ENHANCE Efficacy in Adults with Hypertriglyceridemia: The ENHANCE-IT Trial

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Omega-3 Pentaenoic Acid to ENHANCE Efficacy in Adults with
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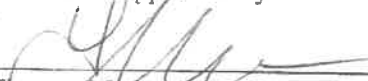
By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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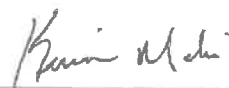

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LIST OF ABBREVIATIONS

AE	adverse event
Apo	apolipoprotein
BMI	body mass index
CRU	clinical research unit
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
ECG	electrocardiogram
eCRF	electronic case report form
EPA	eicosapentaenoic acid
HDL-C	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
IRB	Institutional Review Board
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LS	least squares
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MEDFICTS	Meats, Eggs, Dairy, Fried Foods, In baked goods, Convenience foods, Table fats, Snacks
MI	multiple imputation
Non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin kexin type 9
PD	pharmacodynamic
PP	per protocol
Q1	first quartile (25 th percentile)
Q3	third quartile (75 th percentile)
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TLC	therapeutic lifestyle changes
TG	triglycerides
total-C	total cholesterol
VLDL-C	very low-density lipoprotein cholesterol

DEFINITIONS

Baseline	Baseline will be the average of the values obtained during the final two pre-treatment visits for each treatment period for lipoprotein cholesterol and hsCRP, and the last value before each treatment period for apolipoproteins, PCSK9, and all omega-3 fatty acid outcomes. For the safety analysis, baseline will be the last value before each treatment period for clinical laboratory assessments and the average of the values (or average if duplicate or triplicate data are collected) obtained during the final two pre-treatment visits for each treatment period for vital signs and anthropometrics. If predose data are not collected after the washout period for Period 2 for baseline, then the last value before the first dose in Period 1 may be used as the Baseline for both periods.
Intention-to-treat population	The ITT population will include all randomized subjects.
Period	There are 2 periods defined for this study. Period 1 consists of Visits 4, 5, and 6 and Period 2 consists of Visits 8, 9, and 10.
Pharmacodynamic population	The PD population will include subjects for whom the estimation of PD parameters will be possible for 2 periods. This will be the primary population for PD analyses.
Per protocol population	The PP population will include all subjects who are included in the PD population for whom compliance for both study periods was at least 80%, and for whom no clinically important protocol violations or deviations occurred during the trial.
Safety population	The safety population will include subjects who are randomized and receive at least one dose of any study treatment. This will be the primary population for safety analyses.
Sequence	The order in which subjects receive the treatments: Sequence A: MAT9001 / Vascepa Sequence B: Vascepa / MAT9001
Study day	Study day is a calculation included in all datasets and is defined as the number of days from the first dose date in Period 1 and will be presented in all data listings where a complete date is presented. The first dose day is day 1. The previous day is day -1. There is no day 0.
Treatment	There are 2 treatments defined for this study: 4 g/day MAT9001 (2 g with each of two meals) 4 g/day Vascepa (2 g with each of two meals)

1 OBJECTIVES AND ENDPOINTS

1.1 Objective

The objective of this study is to assess the pharmacodynamic (PD) effects of MAT9001, compared with Vascepa® (icosapent ethyl; eicosapentaenoic acid [EPA] ethyl esters), on triglycerides (TG) and other lipoprotein lipids, apolipoproteins, high-sensitivity C-reactive protein (hs-CRP) and proprotein convertase subtilisin kexin type 9 (PCSK9) concentrations in men and women with elevated TG.

1.2 Endpoints

The primary outcome variable is the percent change from baseline to end of treatment in TG. Baseline will be the average of the values obtained during the final two, pre-treatment visits for each treatment period, and end of treatment will be the average of values collected at the treatment visits on Days 22 and 29.

The secondary outcome variables include percent changes from baseline to end of treatment in the following parameters:

- Total cholesterol (Total-C);
- Low-density lipoprotein cholesterol (LDL-C);
- Very low-density lipoprotein cholesterol (VLDL-C);
- High-density lipoprotein cholesterol (HDL-C);
- Non-HDL-C;
- Apolipoprotein (Apo) AI;
- Apo B;
- Apo C3;
- PCSK9;
- hs-CRP;
- Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total EPA+DHA+DPA) in plasma.

The exploratory outcome variables include percent changes from baseline to end of treatment, unless otherwise specified, in the following parameters:

- Plasma phospholipid levels of omega-3 fatty acids (EPA, DHA, DPA, total EPA+DHA+DPA) for Days 22 and 29 of each treatment period, expressed as a concentration and a percentage of total fatty acids;
- Omega-3 fatty acids (EPA, DHA, DPA, total EPA+DHA+DPA) in plasma for Day 22 of each treatment period.
- TG, for the first treatment period only;
- Total-C, for the first treatment period only;
- LDL-C, for the first treatment period only;
- VLDL-C, for the first treatment period only;
- HDL-C, for the first treatment period only;

- Non-HDL-C, for the first treatment period only;
- Apo A1, for the first treatment period only;
- Apo B, for the first treatment period only;
- Apo C3, for the first treatment period only;
- PCSK9, for the first treatment period only;
- hs-CRP, for the first treatment period only;
- Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total EPA+DHA+DPA) in plasma for Days 22 and 29 of the first treatment period only;
- Plasma phospholipid levels of omega-3 fatty acids (EPA, DHA, DPA, total EPA+DHA+DPA) for Days 22 and 29 of the first treatment period only, expressed as a concentration and a percentage of total fatty acids;
- Erythrocyte membrane levels of omega-3 fatty acids (EPA, DHA, DPA, total EPA+DHA+DPA), expressed as a percentage of total fatty acids, which will be assessed for the first treatment period only at Days 22 and 29;

For lipoprotein cholesterol (Total-C, LDL-C, VLDL-C, HDL-C, non-HDL-C) and hs-CRP levels, baseline will be the average of the values obtained during the final two pre-treatment visits and end of treatment will be the average of the values collected at treatment visits on Days 22 and 29. For apolipoproteins (Apo A1, Apo B, Apo C3) and PCSK9, baseline will be the value obtained at Day 1 and end of treatment will be the value obtained on Day 29 in each treatment period. Plasma omega-3 fatty acids baseline will be the value obtained at Day 1 and end of treatment will be the value obtained on Day 29 in each treatment period. For plasma phospholipid levels of omega-3 fatty acids, baseline will be the value obtained at Day 1 in each treatment period. For erythrocyte membrane levels of omega-3 fatty acids, baseline will be the value obtained at Day 1 for the first treatment period.

Plasma, serum and/or blood cells will be archived for possible future non-genetic testing of analytes related to cardiometabolic health and/or lipid metabolism.

The safety and tolerability endpoints include:

- Treatment-emergent adverse events (TEAEs);
- Changes in vital signs and anthropometrics;
- Changes in clinical laboratory parameters (chemistry, hematology, and urinalysis).

2 DESIGN OVERVIEW

2.1 Number of Subjects

This study will enroll 100 male and female subjects in general good health who satisfy all of the inclusion and none of the exclusion criteria and who have satisfied all screening evaluations before enrollment in the study including having a TG average ≥ 150 mg/dL to ≤ 499 mg/dL.

2.2 Sample Size Considerations

Based on results from prior research, a sample size of 85 evaluable subjects is needed to detect a difference of 10% in TG response between treatment conditions, based on an alpha of 0.05, beta of 0.10 (90% power) and a standard deviation (SD) of 28% for the difference between treatments in change from baseline in TG concentration (Maki 2017). A sample of 100 subjects will be randomized to allow for subject attrition. A minimum of 50% of the study sample (as controlled through randomization stratification) will have a qualifying TG value in the range of 200-499 mg/dL.

2.3 Study Design

This is an open-label, randomized, crossover study with a visit to initiate a 4-week diet lead-in period at Day -28 (visit 1), up to 3 screening visits on Days -14, -7 and -3 (visits 2, 3, and 3b [only for subjects needing an additional TG measurement to qualify for inclusion]), a randomization visit on Period 1 Day 1 (visit 4), two visits at the end of each treatment period (Days 22 and 29; visits 5 and 6 in treatment period 1 and visits 9 and 10 in treatment period 2), and 2 visits after a 28-day washout period to establish baseline for treatment period 2 on Days -7 and 1 (visits 7 and 8). At visit 4, subjects are randomly assigned to a treatment sequence, and they will receive the first dose of study product during each treatment period at the clinic along with a therapeutic lifestyle changes (TLC)-compliant meal replacement bar. Subjects will continue to take their study product daily for 28 days and return to the clinic on Days 22 and 29 in each treatment period for evaluation. Pharmacodynamic assessments including fasting concentrations of TG and lipoprotein cholesterol, apolipoproteins, hs-CRP, PCSK9, as well as plasma phospholipid omega-3 fatty acids will be completed at the beginning and end of each treatment period (depending on the parameter, beginning and end may refer to multiple visits). Fatty acids from red blood cells (RBC) will be analyzed from samples collected during treatment 1 only (visits 4, 5 and 6).

Each subject will receive a 4-g/day dose of each treatment, according to randomized crossover design. Study product is provided in 1 g capsules.

- 4 g/day MAT9001 (2 g with each of two meals)
- 4 g/day Vascepa (2 g with each of two meals)

The first doses during each treatment period will be administered at the clinic as two capsules taken along with a TLC-compliant meal replacement bar. The remaining capsules will be sent home with the subjects with instructions to take two capsules twice daily with meals each day of the treatment period.

A schedule of procedures is presented in Table 1.

Table 1: Schedule of Events

Clinic Visit ^a	Screening				Treatment 1			WO	Treatment 2		
	1	2	3	3b	4	5	6	7	8	9	10
Day	-28	-14	-7	-3	1	22	29	-7	1	22	29
Informed consent/HIPAA ^b	X										
Clinic visit procedures ^c	X	X	X		X	X	X	X	X	X	X
Medical history ^d	X										
Chemistry panel		X			X		X		X		X
Hematology		X			X		X		X		X
HbA1c ^e		X									
TSH ^f		X									
hs-CRP			X		X	X	X	X	X	X	X
hs-CRP confounder checklist			X		X	X	X	X	X	X	X
Archive samples ^g					X		X		X		X
Urinalysis		X					X				X
Urine pregnancy test ^h		X			X				X		
Physical examination			X								
12-lead ECG			X				X				X
TLC diet instruction/reinforce ⁱ	X	X	X	X	X	X	X	X	X	X	
MEDFICTS questionnaire ^j	X	X			X		X	X	X		X
Provide/review study instructions	X	X	X	X	X	X	X	X	X	X	X
Randomization					X						
Start washout period ^k							X				
Dose study product + TLC bar ^l					X				X		
Dispense study product					X	X			X	X	
Collect SP/assess compliance						X	X			X	X
Fasting Omega-3 fatty acids ^m					X	X	X		X	X	X
Fasting lipids ⁿ	X	X	X	X	X	X	X	X	X	X	X
Fasting apolipoproteins ^o					X		X		X		X
Fasting PCSK9					X		X		X		X
Treatment-emergent AEs ^p					X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECG, electrocardiogram; HbA1C, hemoglobin A1c; HIPAA, Health Insurance Portability and Accountability Act; hs-CRP, high-sensitivity C-reactive protein; MEDFICTS, Meats, Eggs, Dairy, Fried Foods, In baked goods, Convenience foods, Table fats, Snacks; PCSK9, proprotein convertase subtilisin kexin type 9; SP, study product; TLC, Therapeutic Lifestyle Changes; TSH, thyroid stimulating hormone; WO, washout.

- ^a To adjust for subject scheduling, the allowable window to complete all screening procedures will not exceed 42 days with a minimum of 48 hours between all visits. If the subject is already following a Therapeutic Lifestyle Changes (TLC) diet at visit 1 supported by the Meats, Eggs, Dairy, Fried Foods, In baked goods, Convenience foods, Table fats, Snacks (MEDFICTS) score, they can proceed directly to visit 2 procedures. A TLC diet lead-in of 14 days prior to the qualification visit (visit 2, Day -14) will be required. A window of ±2 days will be allowed for visits on Day 22 (visits 5 and 9); the window for visits on Day 29 (visit 6 and 10) will be minus 2 days only, i.e., Days 27, 28 or 29. The washout period between treatments (between visits 6 and 7) should be a total of at least 28 days, but not more than 35 days.
- ^b Health Insurance Portability and Accountability Act (HIPAA) authorization for disclosure of protected health information. Signed document authorizes the use and disclosure of the subject's Protected Health Information by the Investigator and by those persons who need that information for the purposes of the study. If a subject does not require a dietary lead-in based on MEDFICTS score, the first two visits should be combined.
- ^c Study procedures include assessments of height (visit 1 only), weight, vital signs (heart rate and blood pressure), waist circumference, evaluation of inclusion and exclusion criteria (visits 1 - 4), review of continuation requirements (visits 5 - 10) and concomitant medication use.
- ^d Medical history will be completed with visit 1 procedures.
- ^e Glycated hemoglobin (HbA1c) will be analyzed only for subjects with a history of type 2 diabetes mellitus OR a fasting glucose concentration ≥126 mg/dL.
- ^f Thyroid stimulating hormone (TSH) will be assessed at screening visit 2 (Day -14). Uncontrolled hyper- or hypothyroid conditions are exclusionary based on the opinion of the Investigator.
- ^g Plasma and/or serum and/or blood cells will be collected, processed and stored for possible later analysis of non-genetic

-
- analytes for assessment of cardiometabolic health and/or lipid metabolism.
- ^h A urine pregnancy test will be performed for all women <60 years of age.
 - ⁱ Subjects will receive instruction on the TLC diet at the first screening visit and instructions will be reinforced for the duration of the study. Subjects will continue to follow the TLC diet during the washout between treatment periods.
 - ^j The MEDFICTS Dietary Assessment Questionnaire will be completed at screening to determine whether the subject is already following a TLC diet, and it will be completed periodically during the study to evaluate compliance with the TLC diet instructions. If the subject is not following a TLC diet at screening, a TLC diet lead-in of 28 days prior to the first treatment phase (visit 4, Day 1) will be required.
 - ^k At the conclusion of visit 6, subjects will begin a washout period of at least 28 days, but not more than 35 days, prior to visit 7.
 - ^l The first dose of the study product for that treatment period will be administered at the clinic with a TLC-compliant meal replacement bar.
 - ^m Fasting plasma and plasma phospholipid levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and total omega-3 fatty acids will be assessed. Fatty acids from red blood cells (RBCs) will be analyzed from samples collected at visit 4, 5 and 6 only (treatment 1).
 - ⁿ Fasting levels of triglyceride (TG), total-cholesterol (total-C) and high-density lipoprotein cholesterol (HDL-C) will be measured, non-HDL-C, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) will be calculated. A minimum of 50% of enrolled subjects will have a TG value ≥ 200 -499 mg/dL as assessed at screening.
 - ^o Fasting levels of apolipoprotein (Apo) A1, Apo B and Apo C3 will be measured.
 - ^p Treatment-emergent AE's will be assessed at visits 4 through 10. AEs that occur prior to visit 4 will be considered medical history. AEs will also be collected from spontaneous subject reporting at any time during the study.

3 RANDOMIZATION PROCEDURES

This is an open-label study. Eligible subjects will be randomly assigned using a computer-generated randomization scheme stratified by TG group (TG values <200 mg/dL or TG values \geq 200-499 mg/dL). If a subject meets all inclusion and none of the exclusion criteria, the following steps should occur at visit 4 (Day 1):

1. Site will utilize an Interactive Web Response System to randomize the subject. The randomization number/sequence will be recorded with the subject's source documentation.
2. Site will complete a Master Study Product Log upon dispensement of study product, which is a list of all study product received and dispensed at the site.

4 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered *a priori* analyses in that they have been defined before locking the database. All unplanned statistical analyses, if any, designed after the SAP is finalized, will be considered *post hoc* analyses and will be applied as exploratory methodology. All *post hoc* analyses will be identified as such in the clinical study report in the changes to the planned analyses section, as appropriate. Instances where the details of the SAP differ from the protocol, the SAP will be used as the source of the procedures for data analyses.

All statistical tests will be tested at $\alpha = 0.05$, 2-sided significance level, unless otherwise stated. Descriptive statistics for continuous variables will include number of subjects/observations (N, n), mean, median, standard deviation (SD), minimum, maximum, and first [25th percentile] and third [75th percentile] quartiles (Q1, Q3), unless otherwise noted. Confidence intervals will be presented where appropriate. Descriptive statistics for categorical variables will consist of frequency and percentage.

Summary statistics will be presented as follows: N and n will be presented without any decimals, minimum and maximum to the same precision as the reported values, means and median to 1 more level of precision than the reported values, and SD to 2 more levels of precision than the reported values, or as otherwise decided upon by the study team. Data listings will be sorted by subject number.

All statistical analyses will be conducted using SAS[®] Version 9.4 (SAS Institute Inc., Cary, NC) or later using procedures appropriate for the particular analysis.

5 ANALYSIS POPULATIONS AND DATASETS

5.1 Definition of Analysis Populations

Statistical analysis and data tabulation will be performed using the following subject populations unless specified otherwise:

- Intention-to-treat (ITT) population;
- Safety population;
- Pharmacodynamic (PD) population;
- Per protocol (PP) population.

The ITT population will include all subjects who are randomized to a treatment sequence.

The safety population will include subjects who are randomized and receive at least one dose of any study treatment. This will be the primary population for safety analyses.

The PD population will include subjects for whom the estimation of PD parameters will be possible for 2 periods. This will be the primary population for PD analyses. PD parameters cannot be estimated accurately for subjects who have been off of study drug for an extended period prior to measurements. The half-life of EPA from Vascepa is approximately 89 hours (Vascepa Prescribing Information, accessed 01Dec20) and that for EPA from MAT9001 administered in the fed state is approximately 27 hours (MAT-001 clinical study report, 07Jul20). Measurements will not be used for PD estimation from samples obtained from subjects who have been off of study drug for 3 days (72 hours) or more.

The PP population will include all subjects who are included in the PD population for whom compliance for both study periods was at least 80%, and for whom no clinically important protocol violations or deviations occurred during the trial. All decisions regarding inclusion in the PP dataset will be made and documented prior to database lock.

5.2 Handling of Missing Data

Multiple imputation (MI) will be used in the ITT analyses to impute missing data for the lipoprotein cholesterol, apolipoproteins, PCSK9, hsCRP, and omega-3 fatty acid outcome variables. The MI procedure in SAS will use the Markov chain Monte Carlo (MCMC) method with a single chain to create at least 5 imputations or more in order to obtain a stable result. Each iteration is analyzed and the final result reported will be the summarized values using the MIANALYZE procedure in SAS.

No imputation will be done for missing data in the safety, PD, or PP analyses. Data that are excluded from the descriptive or inferential analyses will be included in the data listings. This will include those measurements from excluded subjects or measurements from unscheduled visits/collections. If values are reported as below or above the limit of quantitation, they will be set to the quantitation limit and included in the summaries and analyses. For calculations of average values, all values provided will be included, even if only 1 value of the average is reported.

6 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

6.1 Subject Enrollment and Disposition

The number of subjects who screened, screen failed, randomly assigned, and completed in the study will be presented for each sequence, TG group (TG values <200 mg/dL or TG values ≥200-499 mg/dL), and overall. The frequency and percentage of subjects who withdraw or discontinue from the study will be summarized for each sequence and overall for all subjects who are randomly assigned to a sequence. The number of subjects included in each analysis population will be presented for each sequence and overall.

A data listing for subject disposition, including study completion status, will be provided. In addition, analysis populations and reasons for exclusion from the analysis populations will be presented in a data listing.

6.2 Protocol Deviations/Violations

A protocol deviation is a minor departure from the protocol that is approved by the Study Director or authorized designee prior to implementation and does not compromise subject safety or the integrity of the data. The site should accurately document the deviation and approval in the source document and complete the protocol deviation/violation electronic case report form (eCRF).

No deviations from the inclusion/exclusion criteria will be allowed prior to randomization in order to enroll a subject into the study.

A protocol violation is a divergence from the Institutional Review Board (IRB)-approved protocol that is not approved by the Study Director or authorized designee prior to implementation. A violation can be classified as major or minor. A major violation compromises the safety of the subject or the integrity of the data collected. A minor violation is a less-significant departure from the protocol that, though not pre-approved, does not compromise the safety of the subject or the integrity of the data collected. The site should accurately document the violation in the source document and complete the protocol deviation/violation eCRF. Violations that could significantly influence subject safety will be reported to the IRB.

Subjects to be excluded from the PP population will be determined prior to locking the study database for the final analysis and the list of exclusions approved by the study statistician and medical monitor. A listing of these subjects, with the reason for exclusion, will also be generated (Listing 16.2.3.1).

Protocol deviations and violations will be presented in a data listing.

6.3 Demographic and Baseline Characteristics

Subject demographics and baseline data (race, ethnicity, sex, age, weight, height, waist circumference, HbA1c, TSH, mean systolic and diastolic blood pressure and heart rate at baseline, PD parameters at baseline, and body mass index [BMI]) will be summarized by sequence, TG group, and overall for the ITT, safety, PD, and PP populations. Disease characteristics of Type 2 diabetes from medical history and lipid drug use, statin drug use, and ezetimibe use from the medication data will be included.

Categorical data will be summarized using the number and percentage of subjects with a particular attribute. The denominators for calculating the percentages will be the number of subjects in each sequence and/or TG group and population with data.

Numerical data will be summarized using descriptive statistics including the mean, median, SD, minimum, maximum, Q1, Q3, and number of subjects.

Demographics will be provided in a data listing by subject. The baseline characteristics of systolic and diastolic blood pressure, heart rate, weight, height, waist circumference, and BMI will be included in the vital signs data listing. The baseline characteristics of HbA1c, TSH, and laboratory parameters will be included in the safety laboratory data listings. The PD parameter baseline values will be provided in the PD parameter listing.

6.4 Medical History

Medical history will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA Version 22.0 or higher) system organ classifications and preferred terms and will be listed by subject identifier, medical condition reported term, onset date, and ongoing status/resolution date.

6.5 Nicotine Use

Current nicotine use will be collected for each subject. This information will be used for qualifying subjects for enrollment and not listed.

6.6 Other Screening Assessments

The following screening information and variables will be provided in data listings:

- Inclusion criteria met and exclusion criteria not met;
- Physical examination;
- Randomization schedule.

7 PHARMACODYNAMIC ANALYSES

7.1 Pharmacodynamic Data

The pharmacodynamic analyses will be performed on available data from subjects in the PD population and repeated for the ITT and PP populations.

The PD outcome variables will be summarized using descriptive statistics by treatment at baseline, each postdose visit, and end of treatment (if the average) for the results, change from baseline, and percent change from baseline values. The PD outcomes will be presented in a data listing by parameter for each subject with data. Individual and mean values will be presented, as applicable.

7.2 Pharmacodynamic Statistical Analyses

TG response to each treatment will be summarized using geometric means for baseline values and least squares (LS) geometric means for end of treatment and percent change from baseline. Variability in the geometric means and LS geometric means will be reported as 95% confidence intervals (CIs). LS geometric means and 95% CIs for end of treatment will be computed as the back-transformed LS means and 95% CIs obtained from a mixed effects model using the natural log (ln)-transformed end of treatment values as the dependent variable in the model with terms for the ln-transformed baseline as a covariate, and period, sequence, treatment, and TG group as fixed effects and subject nested within sequence as a random effect. The treatments will be compared using a mixed effects model for the PD population for the primary outcome variable using the ln-transformed values of percent change from baseline in TG + scaling factor of 100 (scaling factor used to account for possible negative values) as the dependent variable in the model with terms for the ln-transformed baseline as a covariate, and period, sequence, treatment, and TG group as fixed effects and subject nested within sequence as a random effect. LS geometric means and 95% CIs for percent change from baseline will be computed as the back-transformed, scaled down LS means and 95% CIs for each treatment. Treatment difference as measured by LS mean differences and 95% CIs will be constructed for the ln-scale values, back-transformed, and expressed as the ratio of geometric means. All subjects with available data will be included in the analyses.

The SAS PROC MIXED code is as follows:

```
PROC MIXED DATA=dataset;  
  BY paramn paramcd param;  
  CLASS subjid trtseqp trta aperiodc TG_group;  
  MODEL ln_pchg=ln_base trtseqp trta aperiodc TG_group / ddfm=kenwardroger;  
  RANDOM subjid(trtseqp);  
  ESTIMATE 'MAT9001 vs Vascepa' trta 1 -1 / cl;  
RUN;
```

In the above statements:

- PARAMN, PARAMCD, and PARAM represent each PD outcome in numeric, short, and long parameter variables;

- SUBJID represents the subject identifier for the study;
- TRTSEQP represents the treatment sequence;
- TRTA represents the treatment (MAT9001 or Vascepa);
- APERIODC represents the treatment period (Period 1 or Period 2);
- TG_GROUP represents the stratified group where subjects were stratified into 1 of 2 TG groups (TG values <200 mg/dL or TG values ≥200-499 mg/dL);
- LN_PCHG represents the ln scale of 100+percent change from baseline in TG;
- LN_BASE represents the ln scale baseline values.

Additional covariates may be added to the model, such as gender, age, BMI, and so on, as necessary, to explain the variability in the data.

Similar analyses will be provided for all secondary outcomes, plasma phospholipid levels of omega-3 fatty acids for Days 22 and 29 of each treatment period, and plasma omega-3 fatty acids for Day 22 of each treatment period and also repeated for the ITT and PP populations.

Exploratory analyses of lipids, apolipoproteins, PCSK9, hs-CRP, and plasma, plasma phospholipid, and erythrocyte membrane levels of omega-3 fatty acids will be performed using data from the first treatment period only. As such, the mixed effect models for the ln-transformed values of percent change from baseline + scaling factor of 100 and the ln-transformed end of treatment values will include terms for the ln-transformed baseline as a covariate, and treatment and TG group as fixed effects. Response within each treatment and treatment differences will be summarized as described for the primary outcome.

An exploratory analysis may be included using the same model as previously described with an added interaction term of Treatment-by-TG group and comparisons of treatment tested for each TG group presented.

Assumptions of normality of residuals will be examined for substantial departures from normality. If there are substantial departures from normality after the ln transformation, another transformation may be applied to the data where the rank transformation of the original values will be used for the analysis in place of the ln transformation.

There will be no adjustment for multiplicity, i.e., multiple testing of secondary outcomes.

8 SAFETY ANALYSES

Safety analyses will be presented using the safety population.

8.1 Adverse Events

Adverse events will be coded using MedDRA, Version 23.0 or higher. Each event will be mapped to a system organ class and preferred term. A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during the treatment period after first dosing through 30 days post-last dose. An on-treatment TEAE is defined as a TEAE that occurs during a treatment period after first dosing through the last dose. An off-treatment TEAE is defined as a TEAE that occurs during the first 30 days after the last treatment dose. Each TEAE will be assigned to a single treatment period according to the date of onset. TEAEs that continue over multiple treatment periods will be counted only once in the period during which the event started.

Related TEAEs include all those classified by the investigator as possibly, probably, or definitely related to the study drug. Unrelated TEAEs are those events classified as unlikely or not related..

Multiple events will be counted only once per subject in each of the previously mentioned summaries by treatment and onset (on-treatment, off-treatment, and overall). In the presentation, system organ class and preferred term (within each system organ class) will be sorted in order of descending frequency (by overall percentage of unique TEAEs) and then in alphabetical order, if necessary to break ties.

An overall summary of TEAEs will be provided summarizing subjects with at least 1 of the following: TEAE, related TEAE, severe TEAE, serious TEAE, related serious TEAE, TEAE leading to study discontinuation, or related TEAE leading to study discontinuation as well as the number of events within each of the previously mentioned categories by associated treatment and by onset (on-treatment, off-treatment, and overall). Subjects with at least 1 TEAE and the number of events will also be summarized by severity (mild, moderate, severe) and relationship to the treatment (unrelated, unlikely, possible, probable, definitely), by onset (on-treatment, off-treatment, and overall) within the associated treatment.

In addition, summaries of unique TEAEs will be presented by system organ class, preferred term, and by onset (on-treatment, off-treatment, and overall) within the associated treatment and will include the number and percentage of subjects who experienced the unique event for all TEAEs and all related TEAEs and number of events.

All AEs captured in the database will be presented in by-subject data listings and identified as a non-TEAE, on-treatment TEAE, or off-treatment TEAE. However, only TEAEs will be summarized.

8.2 Clinical Laboratory Assessments (Hematology, Serum Chemistry, and Urinalysis)

Clinical laboratory evaluations of hematology, serum chemistry, and urinalysis will be performed. Results and change from baseline will be summarized by treatment using descriptive statistics for numeric parameters and using counts and percentages for categorical parameters, where baseline is defined as the last value collected before the Day 1 dose in each treatment

period. Values reported with a “<” or “>” sign will be converted to numeric values and summarized.

All clinical laboratory data will be presented in data listings in chronological order by date for unscheduled or repeated values.

8.3 Vital Signs and Anthropometrics

Average blood pressure and heart rate and anthropometrics of body weight will be summarized using descriptive statistics for measurements obtained at baseline and each postdose visit and changes from baseline at each visit, by treatment, where baseline is defined as the average of the values obtained during the two pre-treatment visits in each period. Differences in the change from baseline between the treatments will be compared using a paired t-test or Wilcoxon-signed rank test depending on the distribution of the data.

All vital sign and anthropometrics data will be presented in a data listing, and data collected in duplicate will be averaged and both the individual and mean values will be presented in the data listing.

9 OTHER ANALYSES

The data presented in this section will be presented using the safety population.

9.1 Prior and Concomitant Medications

Medications will be classified according to the World Health Organization Drug dictionary (March 2019 Version) and presented in a data listing by Anatomical Therapeutic Chemical Class Level 3 and preferred drug name. Medications with an end date occurring before the first dose date/time, will be classified as prior medications. A concomitant medication will be defined as any medication taken during the study, from the time after the first dose of study drug through the last completed visit. Medications with missing dates will be assigned as prior medications unless they are indicated as occurring during the study.

Medications will be provided in a data listing by subject.

9.2 Treatment Compliance

Subjects will be instructed to take two capsules of study drug twice per day with meals during each treatment period. The number of planned capsules during each treatment period will be calculated as the number of days during the treatment period multiplied by 4 capsules/d. If a subject's treatment period spans 28 days, for example, the number of planned capsules will be 112. Study compliance (%) for each treatment period will be calculated as the number of capsules consumed divided by the number of planned capsules multiplied by 100. Overall compliance for the treatment period and number of days during the treatment period (unadjusted and adjusted for compliance) will be summarized by treatment using descriptive statistics. Compliance-adjusted days during the treatment period will be computed as the number of days during the treatment period multiplied by percent compliance for the treatment period divided by 100. The number and percentage of subjects with an overall compliance $\leq 80\%$ and $>80\%$ will also be presented by treatment. Compliance at the Day 22 visit and for the overall treatment period and the number of days during the treatment period (unadjusted and adjusted for compliance) will be provided for each treatment in a data listing by subject.

9.3 Other Ancillary Data

The 12-Lead ECG assessments, MEDFICTS total score, and urine pregnancy test results will be provided in data listings. Data collected in duplicate or triplicate will be averaged and both the individual and mean values will be presented in the data listings, if applicable.

9.4 Changes From the Protocol

Changes made to the planned analyses in the protocol while all study staff were still blinded to the treatment sequences are summarized below.

- The baseline for Period 1 PD parameters is changed to use the last 2 values, rather than all 3 values if there is an additional screening visit. This change is to avoid bias between the calculation of baseline for both periods.
- The PP dataset and analysis will include all subjects who are included in the PD population for whom compliance for both study periods was at least 80%, and for whom

no clinically important protocol violations or deviations occurred during the trial.

- The PD dataset will include subjects for whom the estimation of PD parameters will be possible for 2 periods. PD parameters will not be estimated from measurements obtained more than three days (72 hours) after the most recent dose of study drug.
- The ITT dataset will include all subjects who are randomized to a treatment sequence.
- All secondary and exploratory outcomes are changed to percent change from baseline, rather than change from baseline as previously designated for hsCRP and all omega-3 fatty acid endpoints.
- Changes in plasma phospholipid levels of omega-3 fatty acids from baseline to Days 22 and 29 of each treatment period will be analyzed both as a concentration and a percentage of total fatty acids. These analyses will be exploratory.
- Exploratory analyses of lipids, apolipoproteins, PCSK9, hs-CRP, and plasma, plasma phospholipid, and erythrocyte membrane levels of omega-3 fatty acids will be performed using data from the first treatment period only.
- Changes in vital signs and anthropometrics will be assessed as safety outcomes.

10 REFERENCES

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