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

Investigational Product: MAT9001 Omega-3 Pentaenoic Free Fatty Acid Capsules
Protocol MAT-002
IND Number: 122952

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CONFIDENTIAL

SPONSOR PROTOCOL SIGNATURE PAGE

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By my signature below, I approve of this protocol.

Sponsor Signature — Date: 11/21/19

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INVESTIGATOR PROTOCOL SIGNATURE PAGE

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By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) and I understand that any changes to the protocol must be approved in writing by the Sponsor and the IRB before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Approval Signature:

_____ _____

Investigator Signature Date

[Name]
[Clinic Name]
[Address]
[Telephone]
[Email]

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1. List of Abbreviations

AE	adverse event
Apo	apolipoprotein
BMI	body mass index
CFR	Code of Federal Regulations
DHA	docosahexaenoic acid
dL	deciliter
DPA	docosapentaenoic acid
ECG	electrocardiogram
eCRF	electronic case report form
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
G	gram
HbA_1C	glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
h	hour
HDL-C	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kg	kilogram
LDL-C	low-density lipoprotein cholesterol
m^2	meters squared
MB-CRC	MB Clinical Research and Consulting, LLC
MEDFICTS	Meats, Eggs, Dairy, Fried foods, In baked goods, Convenience foods, Table fats, Snacks
mg	milligram
min	minute(s)
mL	milliliters
mm Hg	millimeters of mercury
MRL	Medpace Reference Laboratory
non-HDL-C	non-high-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin kexin type 9
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial
SAE	serious adverse event
SAP	statistical analysis plan
SEM	standard error of the mean
SOP	standard operating procedure
TG	triglycerides
TLC	Therapeutic Lifestyle Changes
Total-C	total cholesterol
TSH	thyroid stimulating hormone
VLDL-C	very-low-density lipoprotein cholesterol
y	year

2. Protocol Synopsis

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

Objective
The objective of this study is to assess the pharmacodynamic 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.

Subjects
Subjects will be men and women ≥18 y of age with TG ≥150 and ≤499 mg/dL (at least 50% with TG values ≥200-499 mg/dL).

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

Study Design
This will be 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 three screening visits on days -14, -7 and -3 (visits 2, 3, and 3b), a randomization visit on 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 two 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 will be 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 which 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 RBC's will be analyzed from samples collected during treatment 1 only (visits 4, 5 and 6).

Primary Outcome Variable
The primary outcome variable will be the percent change from baseline to end of treatment in TG. Baseline will be the average of the values obtained during the final two (or possibly three, for subjects requiring visit 3b), 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.

Secondary Outcome Variables

- The secondary outcome variables will include changes or percent changes from baseline to end of treatment in the following parameters. For lipoprotein cholesterol and hs-CRP levels, baseline will be the average of the values obtained during the two (or three) pre-treatment visits and end of treatment will be the average of values collected at the treatment visits on days 22 and 29. For apolipoproteins and PCSK9, baseline will be the value obtained at day 1 and end of treatment will be the value obtained on day 29, except for plasma omega-3 fatty acids, for which day 29 will be considered the on-treatment value.
    - 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) A1
    - Apo B
    - Apo C3
    - PCSK9
    - hs-CRP
    - Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total) in plasma

Exploratory Outcome Variables

- Plasma phospholipid levels of omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total), expressed as a percentage of total fatty acids;
- Erythrocyte membrane levels of omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total), expressed as a percentage of total fatty acids, which will be assessed for the first treatment period only at days 22 and 29;
- Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total) in plasma for day 22 of each 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.

Safety and Tolerability Measurements

Safety and tolerability will be assessed by evaluation of treatment-emergent adverse events (AEs) and changes in clinical laboratory parameters (chemistry, hematology and urinalysis profiles). AEs will be collected at any point during the study through spontaneous subject reporting; Treatment emergent AE assessment will also be completed at each clinic visit using open-ended questions.

Statistical Analysis

Statistics described in the Statistical Analysis Plan (SAP) will be used to evaluate the performance of the test drug in relation to the reference product.

Sample Size

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 of 28% for the 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.

3. Background/Rationale

Long-chain omega-3 fatty acids, including EPA, DHA, and DPA have been shown in animal models and in humans to lower the circulating TG level when consumed in sufficient quantities. Both ethyl ester and carboxylic acid (also referred to as free fatty acid) formulations of long-chain omega-3 fatty acid concentrates have been cleared for marketing by the Food and Drug Administration (FDA) for the management of severe hypertriglyceridemia (fasting TG ≥500 mg/dL). However, ethyl ester formulations require consumption of a meal containing fat for optimal absorption, because dietary fat intake stimulates release of bile, which facilitates digestion, releasing the free fatty acids for absorption. Free fatty acid formulations of long-chain omega-3 fatty acids have been shown to have less dependence on co-administration of a fat-containing meal for bioavailability, which may be advantageous, particularly for patients with severe hypertriglyceridemia, who are generally advised to consume a low-fat diet to minimize chylomicronemia (Offman 2013).

In 2018, the results from the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) were released, which showed that 4 g/day of icosapent ethyl (Vascepa, EPA ethyl esters) lowered risk for major adverse cardiovascular events by 25% for the primary outcome variable in high and very-high risk patients on statin therapy with continued TG elevation (135-499 mg/dL) (Bhatt 2019). This has prompted several organizations, including the American Heart Association, the American Diabetes Association, the European Society for Cardiology and the European Atherosclerosis Society, to advocate the use of icosapent ethyl (EPA ethyl esters) for cardiovascular risk reduction (American Diabetes Association 2019, Mach 2019, Skulas-Ray 2019).

Matinas BioPharma is developing MAT9001, which is comprised of a mixture of long-chain omega-3 free fatty acids, including EPA and DPA. A prior pharmacokinetic and pharmacodynamic study showed that the EPA from MAT9001 was markedly more bioavailable, as reflected by the area under the plasma EPA concentration curve, than that from Vascepa, when administered with a very low-fat meal (Maki 2016, 2017). Moreover, the TG reduction with MAT9001 was larger (33% vs. 11%), which may reflect both greater bioavailability of the EPA from MAT9001 and the additional impact of TG-lowering from DPA. Studies in animal models have shown that DPA lowers the TG concentration to a greater extent than either EPA or DHA (Drouin 2019a, 2019b). However, at present, head-to-head comparison data are not available in humans regarding the relative bioavailability and pharmacodynamic effects of Vascepa and MAT9001 when both are consumed with a diet containing a more moderate level of fat, which is more typical of the prescribed diet for patients with borderline high and high levels of TG.

The current trial is designed to assess and compare the pharmacodynamic effects of MAT9001, relative to Vascepa, in male and female subjects with elevated TG levels who have been instructed to follow a low-saturated fat, low-to-moderate total fat (Therapeutic Lifestyle Changes; TLC) diet.

4. Objective

The objective of this study is to assess the pharmacodyanamic effects of MAT9001, compared with Vascepa (icosapent ethyl; EPA ethyl esters), on TG and other lipoprotein lipids, apolipoproteins, hs-CRP and PCSK9 concentrations in men and women with elevated TG.

5. Study Design and Procedures

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), a randomization visit on day 1 of treatment period 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 two visits after a 28-day washout period on days -7 and 1 (visits 7 and 8) to establish baseline for treatment period 2. The window to complete all screening procedures will not exceed 42 days with a minimum of 48 h between visits. A window of ±2 days will be allowed for visits on day 22 (visits 5 and 9); the window for visits on day 29 (visits 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.

At visit 1 (day -28), after subjects have provided informed consent, medical history information will be collected and the Meats, Eggs, Dairy, Fried foods, In baked goods, Convenience foods, Table fats, Snacks (MEDFICTS) dietary assessment questionnaire will be completed. Subjects who score <40 may proceed directly to visit 2 procedures. Subjects who score >40 will complete clinic visit procedures including measurements of height, body weight, resting heart rate and blood pressure, waist circumference, evaluation of inclusion/exclusion criteria and concomitant medication/supplement use (Appendix 1) and calculation of BMI. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. The average of the three measurements will determine eligibility for the study. Body mass index (BMI) will be calculated. Fasting (at least 9 hours, water only) blood samples will be collected for measurement of TG, total-C and HDL-C. Non-HDL-C will be calculated as total-C minus HDL-C; LDL-C and VLDL-C will be calculated using the Hopkins/Martin method. Subjects will receive instructions on the TLC diet (Appendix 3). Subjects must follow the TLC diet for the next 14 days prior to visit 2 (day -14) and the full 28 days prior to the first treatment period (visit 4, day 1). Subjects will be scheduled for visit 2 (day -14) and will receive written study instructions (Appendix 6).

At visit 2 (day -14), subjects will arrive to the clinic fasted (at least 9 h, water only). Clinic visit procedures will be performed including measurements of height and calculation of BMI (if not completed at visit 1), body weight, resting heart rate and blood pressure, waist circumference, evaluation of inclusion/exclusion criteria and concomitant medication/supplement use. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. The average of the three measurements will determine continued eligibility for the study. Subjects will be queried on compliance with the TLC diet and other study instructions and will complete the MEDFICTS Dietary Assessment Questionnaire (Appendix 4) to evaluate compliance. Fasting blood samples will be collected for a chemistry panel, hematology, and measurements of thyroid stimulating hormone (TSH) and lipids. For subjects with fasting glucose ≥126 mg/dL, or a history of type 2 diabetes mellitus, glycated hemoglobin (HbA1c) will be analyzed. A urine sample will be collected for urinalysis and all

female subjects <60 y of age will undergo an in-clinic urine pregnancy test. Instructions for the TLC diet will be reinforced and subjects will receive study instructions (Appendix 6). The next clinic visit will be scheduled.

At visit 3 (day -7), subjects will arrive to the clinic fasted (at least 9 h, water only). Clinic visit procedures will be performed including measurements of body weight, resting heart rate and blood pressure, waist circumference, evaluation of inclusion/exclusion criteria and concomitant medication/supplement use. Fasting blood samples will be collected for measurement of hs-CRP and lipids (total-C, HDL-C, LDL-C, non-HDL-C and VLDL-C. The hs-CRP Confounder Checklist will be completed (Appendix 5). A physical examination and 12-lead electrocardiogram (ECG) will be performed. The TLC diet instructions will be reinforced, and subjects will receive study instructions (Appendix 6).

Individuals whose average screening TG values fall outside the required range for entry (TG ≥150 mg/dL to ≤499 mg/dL) may return for a 3rd fasting (at least 9 h, water only) lipid measurement at visit 3b (day -3). Visit 3b must occur at least 3 days prior to visit 4. If a third sample is collected, entry into the study will be based on the average of the TG values from all 3 samples. The TLC diet instruction will be reinforced and study instructions provided (Appendix 6). Any newly eligible subjects will be scheduled for visit 4.

At visit 4 (day 1), subjects will arrive to the clinic fasted (at least 9 h, water only). Clinic visit procedures will be performed including measurements of body weight, resting heart rate and blood pressure, waist circumference, evaluation of inclusion/exclusion criteria and concomitant medication/supplement use. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. Subjects will be queried on compliance with study visit instructions. Fasting blood samples will be collected for a chemistry panel, hematology, and measurements of lipids, hs-CRP, omega-3 fatty acids, apolipoproteins and PCSK9. Plasma, serum and/or blood cells will be archived for possible later analysis. All female subjects <60 y of age will undergo an in-clinic urine pregnancy test. An hs-CRP Confounder Checklist will be completed (Appendix 5). Subjects will be queried on study instructions and will complete the MEDFICTS Dietary Assessment Questionnaire to evaluate compliance with the TLC diet. Subjects will be randomized and will take their first dose of study product with a TLC-compliant meal replacement bar at the clinic. Study product will be dispensed, and subjects will receive study instructions (Appendix 6). AEs will be assessed with open-ended questions. The TLC diet instructions will be reinforced and subjects will be scheduled for visit 5 (day 22). The window to schedule visit 5 will be ±2 days.

At visit 5 (day 22) subjects will arrive fasted (9-15 h, water only) to the clinic and clinic visit procedures will be performed including measurements of body weight, resting heart rate and blood pressure, waist circumference, review of continuation requirements and concomitant medication/supplement use. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. Subjects will be queried on compliance with study visit instructions. Fasting (at least 9 h, water only) blood samples will be collected for analysis of hs-CRP, lipids, and omega-3 fatty acids. The hs-CRP Confounder Checklist will be completed (Appendix 5). Study product will be collected to assess compliance, and remaining product will be re-dispensed to the subjects. AEs will be assessed with open-ended

questions. The TLC diet instructions will be reinforced and study instructions provided (Appendix 6). Visit 6 (day 29) will be scheduled with a window of minus 2 days (i.e., day 27, 28 or 29).

At visit 6 (day 29), subjects will arrive to the clinic fasted (9-15 h, water only) and clinic visit procedures will be conducted including measurements of body weight, resting heart rate and blood pressure, waist circumference, review of continuation requirements and concomitant medication/supplement use. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. Subjects will be queried on compliance with study visit instructions and unused study product will be collected to assess compliance. Subjects complete the MEDFICTS Dietary Assessment Questionnaire to evaluate compliance with the TLC diet. Fasting blood samples will be collected for a chemistry panel, hematology, hs-CRP, lipids, apolipoproteins, PCSK9, omega-3 fatty acids. Plasma, serum and/or blood cells will be archived for possible later analysis. An hs-CRP Confounder Checklist will be completed (Appendix 5). A urine sample will be collected for urinalysis and a 12-lead ECG will be conducted. AEs will be assessed using open-ended questions. Subjects will begin a washout period (minimum 28 days and maximum of 35 days) before crossing over to the other treatment. Subjects will be scheduled for visit 7 (7 days prior to the next treatment period) and study instructions will be provided and reviewed prior to subjects leaving the clinic (Appendix 6).

At visit 7 (day -7), subjects will arrive to the clinic fasted (9-15 h, water only) and clinic visit procedures will be conducted including measurements of body weight, resting heart rate and blood pressure, waist circumference, review of continuation requirements and concomitant medication/supplement use. Blood pressure measurements will be taken three times, each 1 min apart after the subject has been resting quietly for 5 min. Subjects will be queried on compliance with study visit instructions and will complete the MEDFICTS Dietary Assessment Questionnaire to evaluate diet compliance with the TLC diet. Fasting blood samples will be collected for measurement of hs-CRP and lipids. The hs-CRP Confounder Checklist will be completed (Appendix 5). AEs will be assessed using open-ended questions and study instructions will be provided and reviewed (Appendix 6). Subjects will be scheduled for visit 8.

Visits 8, 9 and 10 will follow the same procedures as visits 4, 5 and 6, respectively, with the following exceptions:

- Randomization will not occur on visit 8
- Subjects will not start a washout period on visit 10
- Subjects will not receive study instructions and TLC diet instructions on visit 10

6. Flow Chart

	Screening				Treatment 1			WO	Treatment 2		
Clinic Visit[1]	**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[2]	X										
Clinic Visit Procedures[3]	X	X	X		X	X	X	X	X	X	X
Medical History[4]	X										
Chemistry Panel		X			X		X		X		X
Hematology		X			X		X		X		X
HbA1c[5]		X									
TSH[6]		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[7]					X		X		X		X
Urinalysis		X					X				X
Urine Pregnancy Test[8]		X			X				X		
Physical Examination			X								
12-Lead ECG			X				X				X
TLC Diet Instruction/Reinforce[9]	X	X	X	X	X	X	X	X	X	X	
MEDFICTS Questionnaire[10]	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[11]							X				
Dose Study Product + TLC Bar[12]					X				X		
Dispense Study Product					X	X			X	X	
Collect SP/Assess Compliance						X	X			X	X
Fasting Omega-3 Fatty Acids[13]					X	X	X		X	X	X
Fasting Lipids[14]	X	X	X	X	X	X	X	X	X	X	X
Fasting Apolipoproteins[15]					X		X		X		X
Fasting PCSK9					X		X		X		X
Treatment Emergent AEs[16]					X	X	X	X	X	X	X

Footnotes:

[1]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 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) is 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.

[2]HIPAA = Health Insurance Portability and Accountability Act 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.
[3]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.
[4]Medical history will be completed with visit 1 procedures.
[5]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.
[6]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.
[7]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.
[8]A urine pregnancy test will be performed for all women <60 y of age.
[9]Subjects will receive instruction on the Therapeutic Lifestyle Changes (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.
[10]The Meats, Eggs, Dairy, Fried Foods, In baked goods, Convenience foods, Table fats, Snacks (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.
[11]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.
[12]The first dose of the study product for that treatment period will be administered at the clinic with a TLC-compliant meal replacement bar.
[13]Fasting plasma and plasma phospholipid levels of EPA, DHA, DPA and total omega-3 fatty acids will be assessed. Fatty acids from RBCs will be analyzed from samples collected at visit 4, 5 and 6 only (treatment 1).
[14]Fasting levels of TG, total-C and HDL-C will be measured, non-HDL-C, LDL-C, 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.
[15]Fasting levels of Apo A1, Apo B and Apo C3 will be measured.
[16]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.

7. Study Sample

7.1 Inclusion Criteria

1. Male or female, ≥18 y of age.
2. Judged by the Investigator to be in generally good health on the basis of medical history, physical examination, and screening measurements.
3. Fasting TG ≥150 mg/dL to ≤499 mg/dL during screening (average of values at visits 2 and 3). If the subject's average TG level from visits 2 and 3 falls outside the required range for entry, an additional fasting TG measurement may be obtained on visit 3b with a minimum window of 3 days prior to visit 4. If a third sample is collected, entry into the study will be based on the average of the TG values from all 3 samples.
4. For any individual taking a statin (with or without ezetimibe), oral diabetes medication, anti-hypertensive or hormone therapy, the dose must have been stable for at least 4 weeks prior to the first qualification visit (day -14).
5. Body mass index of ≥20.0 kg/m^2.
6. No clinically significant findings in a 12-lead ECG or physical examination.
7. Subject is willing and able to undergo the scheduled study procedures.

8. Subject is willing to maintain a Therapeutic Lifestyle Changes diet for the duration of the study.
9. Subject agrees to abstain from alcohol consumption for 24 hours prior to each clinic visit.
10. Subject agrees to maintain current physical activity level and to abstain from vigorous physical activity for 24 hours prior to each clinic visit.
11. Individual has no plans to donate blood during the study period.
12. Subject agrees not to consume more than one meal per week containing fish or seafood, and to avoid fish or seafood consumption for at least 48 hours prior to each clinic visit.
13. Subject has no plans to change smoking/vaping habits or other nicotine use during the study period.
14. Subject understands the study procedures and signs forms documenting informed consent to participate in the study and authorization for release of relevant protected health information to the study Investigator.

7.2 Exclusion Criteria

1. Individual has a laboratory test result of clinical significance based on the judgment of the Principal Investigator or qualified designee.
2. Individual has a clinically significant gastrointestinal, endocrine, cardiovascular, renal, hepatic, pulmonary, pancreatic, neurologic, or biliary disorder that, in the opinion of the Investigator, could interfere with the interpretation of the study results.
3. Individual has diabetes mellitus and uses an injectable therapy (e.g., insulin or glucagon-like peptide-1 receptor agonist) or has glycated hemoglobin >9.5% at screening.
4. Individual has uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg) at screening.
5. Individual has a history of cancer in the prior 2 years, except non-melanoma skin cancer or carcinoma *in situ* of the cervix.
6. Individual has a history of human immunodeficiency virus, hepatitis B or hepatitis C infection.
7. Individual has taken a PCSK9 inhibitor agent within 12 weeks prior to the first qualification visit (day -14).
8. Individual has used the following within 4 weeks of the first qualification visit (day -14): any medication intended to alter the lipid profile (with the exception of stable dose statin, with or without ezetimibe), including but not limited to bile acid sequestrants, fibrates, niacin (drug form), omega-3-ethyl ester drugs.
9. Individual has used the following foods or dietary supplements within 2 weeks of the qualification visit including, but not limited to, omega-3 fatty acid supplements (e.g., flaxseed, fish or algal oils) or foods fortified with omega-3 fatty acids; dietary supplements (red rice yeast supplements, garlic supplements, soy isoflavone supplements, niacin or its analogues at doses >400 mg/d, sterol/stanols or others at the discretion of the Investigator); irregular or inconsistent use of Metamucil® or other viscous fiber-containing supplements (consistent, daily use up to 1 tsp of a viscous-fiber supplement is acceptable). Omega-3 supplements containing ≤1 g

EPA/DHA are exclusionary within 2 weeks of qualification. Preparations containing >1 g of EPA/DHA are excluded within 4 weeks of the qualification visit.

10. Individual has an active systemic infection.
11. Individual has a history of paroxysmal atrial fibrillation, persistent atrial fibrillation, and/or history of ventricular tachycardic arrythmia (e.g., ventricular tachycardia/fibrillation).
12. Individual has a history of a bleeding disorder or is currently taking anticoagulant therapy.
13. Individual has a history of bariatric surgery, is currently taking a weight loss drug or actively attempting to lose or gain body weight. A 4-week washout for weight loss pharmaceutical agent use prior to the first qualification visit (day -14) is allowed.
14. Individual has had a weight gain or loss of ≥10 pounds within 2 months of the first qualification visit (day -14).
15. Individual has had an acute coronary syndrome or revascularization procedure in the 12 months prior to the first qualification visit (day -14).
16. Individual is a female who is pregnant, planning to be pregnant during the study period, lactating, or is of childbearing potential and is unwilling to commit to the use of a medically approved form of contraception throughout the study period.
17. Individual has a known allergy or sensitivity to any ingredients in the study products, including fish, seafood or omega-3 fatty acids.
18. Individual has been exposed to any non-registered drug product within 30 days of the first screening visit (day -28).
19. Individual has a current or recent history (past 12 months of screening) or strong potential for illicit drug or excessive alcohol intake defined as >14 drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1.5 oz hard liquor).
20. Individual has a condition the Investigator believes would interfere with his or her ability to provide informed consent, comply with the study protocol, which might confound the interpretation of the study results or put the person at undue risk.

7.3 Excluded Medications and Products/Subject Instructions

Excluded:

- Anti-coagulants
- Injectable therapies for diabetes mellitus

Excluded within 12 weeks of the first qualification visit (day -14) and throughout the study:

- Use of PCSK9 inhibitor

Excluded within 4 weeks of the first qualification visit (day -14) and throughout the study:

- Use of any medication intended to alter the lipid profile (with the exception of stable dose statin, with or without ezetimibe), including but not limited to: bile acid sequestrants, fibrates, niacin (drug form), omega-3-ethyl ester drugs
- Use of high-dose fish oil or omega-3 supplements containing >1 g of EPA/DHA

- Use of weight loss drugs (4-week washout prior to the first qualification visit [day -14] is permitted)

Excluded within 2 weeks of the first qualification visit (day -14) and throughout the study:

- Use of omega-3 fatty acid supplements (e.g., flaxseed, fish or algal oils) or fortified foods containing ≤1 g EPA/DHA
- Use of dietary supplements meant to regulate blood lipid levels, such as red rice yeast supplements, sterol/stanol foods & products, garlic supplements, soy isoflavone supplements, niacin or its analogues at doses >400 mg/day (or others at the discretion of the Investigator)
- Irregular or inconsistent use of Metamucil or other viscous fiber-containing supplements (consistent, daily use up to 1 tsp of a viscous-fiber supplement is acceptable)

Unstable use at least 4 weeks prior to visit 2 (day -14):

- Use of a statin (with or without ezetimibe), oral diabetes medication, anti-hypertensives or hormone therapy.

Should a subject require any of these medications or supplements during either treatment period, the study staff should consult with the Study Physician and Study Director to discuss the subject's continued participation in the trial.

Subjects will also receive the following instructions (Appendix 6):

- Avoid consuming fish or seafood more than once per week throughout the study.
- Avoid consuming fish or seafood for 48 h before any test visit.
- Maintain adequate hydration.
- Fast (water only) for at least 9 hours prior to each clinic visit.
- Avoid consuming EPA- and/or DHA supplements and fortified foods throughout the study.
- Notify the site if you are prescribed any new medication or begin taking a new supplement.
- If a smoker/vaper, abstain from smoking/vaping for at least 1 h prior to each clinic visit.
- Avoid vigorous physical activity for 24 h prior to each clinic visit.
- Avoid alcohol consumption for at least 24 h prior to each clinic visit.
- Take study product as directed with food. If a dose is missed, do not make up the dose on another day.

7.4 Randomization Procedures

Eligible subjects will be randomly assigned using a computer-generated randomization scheme. If a subject meets all inclusion and none of the exclusion criteria, the following steps should occur at visit 4 (day 1):

1. A staff member 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, which is a list of all study product received and dispensed at the site.

8. Study Products

8.1 Description

MAT9001, an omega-3 free fatty acid formulation manufactured by Matinas BioPharma Inc USA, is comprised of a mixture of EPA and DPA and is being developed as a lipid-lowering agent for adults as an adjunct to diet to reduce TG levels.

Vascepa, icosapent ethyl, is an ethyl ester of EPA made by Amarin Pharma Inc, USA. Icosapent ethyl is a lipid-lowering agent indicated for adults with severe hypertriglyceridemia as an adjunct to diet to reduce TG levels.

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.

8.2 Storage and Dispensing

Matinas BioPharma will provide sufficient quantities of MAT9001 (1 g capsules) and Vascepa (1 g capsules) for the study. Study products will be stored in a dry, secure location at room temperature (60-85 degrees Farenheit;15 to 30 degrees Celsius). Study product will be administered to subjects in the clinic during visits 4 and 8. On visits 4, 5, 8 and 9, sufficient study product will be provided to the subjects to last until their next clinic visit. Subjects will be instructed to take two capsules twice daily with meals and to not chew or break the study product prior to consumption. Subjects will be asked to bring any remaining study product and empty bottles back to the clinic at their next visit. If a dose is missed, the subject should not take the missed dose on a separate day.

Study product supplies are to be used only in accordance with this protocol and under the supervision of the Investigator. All records must be available for inspection by the Sponsor and are subject to regulatory agency inspection at any time. Copies of the records will be provided to the Sponsor at the conclusion of the study. A written explanation from the study staff will be required for any missing study product.

9. Laboratory Measurements and Study Procedures

Instructions for specimen collection and storage will be detailed in the Laboratory Manual. Laboratory parameters that are missing or have not been obtained must be entered in the data collection forms as "not done." The actual date and time of each laboratory measurement and blood collection will be recorded in the electronic case report form (eCRF).

9.1 Laboratory Measurements

9.1.1 Chemistry panel

A fasting (at least 9 h, water only) chemistry panel will be measured at screening visit 2 (day -14), treatment 1 visits 4 and 6 (days 1 and 29) and treatment 2 visits 8 and 10 (days 1 and day 29).

9.1.2 Hematology

Hematology will be measured at screening visit 2 (day -14), treatment 1 visits 4 and 6 (days 1 and day 29) and treatment 2 visits 8 and 10 (days 1 and day 29).

9.1.3 Glycated hemoglobin

HbA1c will be measured at visit 2 (day -14) in individuals with a history of type 2 diabetes mellitus or a fasting glucose concentration ≥126 mg/dL.

9.1.4 Urinalysis

Urinalysis will be performed on screening visit 2 (day -14), treatment 1 visit 6 (day 29) and treatment 2 visit 10 (day 29).

9.1.5 Urine pregnancy test

An in-clinic urine pregnancy test will be obtained from all female subjects <60 y of age at screening visit 2 (day -14), treatment 1 visit 4 (day 1) and treatment 2 visit 8 (day 1).

9.1.6 Thyroid stimulating hormone

TSH will be measured at screening visit 2 (day -14) to determine uncontrolled hyper- or hypothyroid conditions.

9.1.7 Pharmacodynamic sampling

Fasting lipids

Blood samples for fasting lipids will be collected at screening visits 1, 2, 3 and, possibly, 3b (days -28, -14, -7 and -3), treatment 1 visits 4, 5 and 6 (days 1, 22 and 29), treatment 2 visits 8, 9 and 10 (days 1, 22 and 29) and washout visit 7 (day -7). Fasting levels of TG, total-C and HDL-C will be measured. Non-HDL-C will be calculated as total-C minus HDL-C. LDL-C, VLDL-C will be calculated using the Hopkins/Martin method.

Fasting apolipoproteins

Blood samples for fasting apolipoproteins will be collected at treatment 1 visits 4 and 6 (days 1 and 29) and treatment 2 visits 8 and 10 (days 1 and 29). Fasting levels of Apo A1, Apo B and Apo C3 will be measured.

Fasting PCSK9
Blood samples for fasting PCSK9 will be collected at treatment 1 visits 4 and 6 (days 1 and 29) and treatment 2 visits 8 and 10 (days 1 and 29).

hs-CRP
Blood samples for hs-CRP will be collected at screening visit 3 (day -7), treatment 1 visits 4, 5, and 6 (days 1, 22 and 29), washout visit 7 (day -7) and treatment 2 visits 8, 9, and 10 (days 1, 22 and 29).

9.1.9 Fasting omega-3 fatty acids
Blood samples for fasting plasma and plasma phospholipid omega-3 fatty acids will be collected at treatment 1 visits 4, 5 and 6 (days 1, 22 and 29) and treatment 2 visits 8, 9 and 10 (days 1, 22 and 29). Fasting plasma levels of EPA, DHA, DPA and total omega-3 fatty acids will be assessed. Fatty acids from RBC's will be analyzed from samples collected during treatment 1 only (visits 4, 5, and 6).

9.1.10 Archiving samples
Plasma, 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 at visits 4, 6, 8, and 10.

9.2 Clinic visit procedures

9.2.1 Demographics, medical history, inclusion/exclusion criteria
Demographic information (date of birth, sex, race and ethnicity) will be recorded at screening visit 1 (day -28). Relevant medical history (previous 5 y), including history of current disease, body weight changes in the past 2 months, other pertinent health history, and information regarding underlying diseases will be recorded at screening visit 1 (day -28). The evaluation of prior and concomitant medication/supplement use will be conducted at each visit. A review of inclusion/exclusion criteria will be conducted at visits 1, 2, 3 and 4 (days -28, -14, -7 and 1) and review of the continuation requirements will occur at the remaining visits. Once randomized, subjects should continue throughout the end of the study, if possible, even if they no longer meet all inclusion/exclusion criteria requirements. Visit 3b is only for subjects needing an additional TG measurement for screening, so no additional review of inclusion/exclusion criteria will be conducted.

9.2.2 Anthropometrics
Height will be measured and BMI will be calculated at the first screening visit only. Body weight and waist circumference will be assessed at all visits. Subjects are to remove shoes and any heavy layers of clothing that could impact

body weight at each visit. Visit 3b is only for subjects needing an additional TG measurement for screening, so no anthropometrics will be recorded.

9.2.3 Vital signs

Vital signs (seated, resting blood pressure and heart rate) will be assessed after resting for 5 min at all visits. Blood pressure and heart rate will be measured three times, each separated by 1 min, and all three will be averaged. The same arm and cuff size should be used for consistency purposes. Visit 3b is only for subjects needing an additional TG measurement for screening, so no vital signs will be recorded.

9.2.4 hs-CRP Confounder Checklist

The hs-CRP Confounder Checklist (Appendix 5) will assess non-study-related factors that may confound the evaluation of the hs-CRP response and will be administered on the same visits when blood levels of hs-CRP are measured. This includes screening visit 3 (day -7), treatment 1 visits 4, 5 and 6 (days 1, 22 and 29), treatment 2 visits 8, 9 and 10 (days 1, 22 and 29) and washout visit 7 (day -7).

9.2.5 Physical examination

A physical examination will be performed by qualified study staff at screening visit 3 (day -7).

9.2.6 12-lead ECG

A 12-lead ECG will be performed at screening visit 3 (day -7) and at the end of each treatment (treatment 1 visit 6, day 29 and treatment 2 visit 10, day 29).

9.2.7 TLC Diet Instructions

Subjects will receive instruction on the TLC diet (Appendix 3) at the first screening visit (day -28) and instructions will be reinforced at each study visit (except visit 10). Subjects must meet a minimum TLC diet lead-in of 14 days prior to the qualification visit (visit 2, day -14) and remain on the diet for the duration of the study. If the subject is determined to already be following a TLC diet at screening visit 1 (day -28) (supported by the MEDFICTS score of <40), they will proceed directly to visit 2 procedures. Subjects will continue to follow the TLC diet during the washout between treatment periods.

9.2.8 Dispensing study product

Subjects will be provided with study product and written instructions for taking the product when leaving the clinic at visits 4, 5, 8 and 9. At visit 4 and 8 (day 1 of treatment 1 and treatment 2, respectively) subjects will be provided sufficient study product to last until their next treatment visit (day 22 for each treatment) plus 2 days to accommodate the study visit window. Subjects will be instructed to take two capsules twice daily with meals and to not chew or break the study product prior to consumption. Subjects will be asked to bring any remaining study product, including empty bottles, back to the clinic at their next visit. At

visits 5 and 9 (day 22 of treatment 1 and treatment 2, respectively) subjects will be re-dispensed the remaining study product to last until their final treatment visit (day 29 for each treatment). The final clinic visit in each treatment period can be scheduled for no later than day 29 but may be scheduled for up to 2 days prior (days 27 or 28).

9.2.9 Study Instructions

Written study instructions will be provided and reviewed with subjects at every visit (Appendix 6). These instructions will include foods/medications/beverages to avoid or limit, instructions on what to bring to clinic visits, instructions for study product consumption, phone numbers to call in case of illness, and date and time of their next clinic visit.

9.2.10 Adverse events

Treatment-emergent AEs will be assessed at visits 4-10 using open-ended questions. 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.

9.3 Evaluations by Visit

Screening (visit 1, day -28)

- Informed Consent/HIPAA
- Medical history
- MEDFICTS Questionnaire (if < 40, proceed to visit 2 procedures)
- Clinic visit procedures
  - Height
  - Weight
  - BMI calculation
  - Waist circumference
  - Vital signs (resting blood pressure and heart rate)
  - Prior and current medication/supplement use
  - Inclusion/exclusion criteria
- Fasting lipids
- TLC diet instruction
- Study instructions

Screening (visit 2, day -14)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
  - Height (if not completed at visit 1)
  - Weight
  - BMI Calculation (if not completed at visit 1)
  - Waist circumference
  - Vital signs (resting blood pressure and heart rate)

    - Prior and current medication/supplement use
    - Inclusion/exclusion criteria
- Chemistry panel
- Hematology
- HbA1c (for those with history of type 2 diabetes or fasting glucose ≥126 mg/dL)
- TSH
- Fasting lipids
- Urinalysis
- Urine pregnancy test (women <60 y of age)
- Study instructions
- TLC diet reinforcement

Screening (visit 3, day -7)

- Query study instructions and TLC diet compliance
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use
    - Inclusion/exclusion criteria
- Physical examination
- 12-lead ECG
- Fasting lipids
- hs-CRP
- hs-CRP Confounder Checklist
- TLC diet reinforcement
- Study instructions
- Record average TG from Visits 2 and 3 from Medpace Reference Laboratory (MRL) Report

Screening (visit 3b, day -3)

- Query study instructions and TLC diet compliance
- Fasting lipids
- TLC diet reinforcement
- Study instructions
- Record average TG from Visits 2, 3 and 3b from MRL Report

Treatment 1 (visit 4, day 1)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)

    - Prior and current medication/supplement use
    - Inclusion/exclusion criteria
- Chemistry panel
- Hematology
- hs-CRP
- Fasting lipids
- Fasting omega-3 fatty acids
- Fasting apolipoproteins
- Fasting PCSK9
- Archive samples
- Urine pregnancy test (women <60 y of age)
- hs-CRP Confounder Checklist
- Randomization
- Dose study product + TLC bar
- Dispense study product, provide instructions
- Assess AEs
- TLC diet reinforcement
- Study instructions

Treatment 1 (visit 5, day 22)

- Query study instructions and TLC diet compliance
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use
    - Continuation requirements
- hs-CRP
- Fasting lipids
- Fasting omega-3 fatty acids
- hs-CRP Confounder Checklist
- Collect study product
- Assess study product compliance
- Re-dispense study product
- Assess AEs
- TLC diet reinforcement
- Study instructions

Treatment 1 (visit 6, day 29)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
    - Weight
    - Waist circumference

    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use
    - Continuation requirements
- Chemistry Panel
- Hematology
- Urinalysis
- hs-CRP
- Fasting omega-3 fatty acids
- Fasting lipids
- Fasting apolipoproteins
- Fasting PCSK9
- hs-CRP Confounder Checklist
- 12-lead ECG
- Collect study product
- Assess study product compliance
- Assess AEs
- Start washout period
- TLC diet reinforcement
- Study instructions

Washout (visit 7, day -7)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use
    - Continuation requirements
- hs-CRP
- Fasting lipids
- hs-CRP Confounder Checklist
- Assess AEs
- TLC diet reinforcement
- Study instructions

Treatment 2 (visit 8, day 1)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use

    - Continuation requirements
- Chemistry panel
- Hematology
- hs-CRP
- Fasting lipids
- Fasting omega-3 fatty acids
- Fasting apolipoproteins
- Fasting PCSK9
- Archive samples
- Urine pregnancy test (women <60 y of age)
- hs-CRP Confounder Checklist
- Dose study product + TLC bar
- Dispense study product
- Assess AEs
- TLC diet reinforcement
- Study instructions

Treatment 2 (visit 9, day 22)

- Query study instructions and TLC diet compliance
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use
    - Continuation requirements
- hs-CRP
- Fasting omega-3 fatty acids
- Fasting lipids
- hs-CRP Confounder Checklist
- Collect study product
- Assess study product compliance
- Re-dispense study product
- Assess AEs
- TLC diet reinforcement
- Study instructions

Treatment 2 (visit 10, day 29)

- Query study instructions
- MEDFICTS Questionnaire
- Clinic visit procedures
    - Weight
    - Waist circumference
    - Vital signs (resting blood pressure and heart rate)
    - Prior and current medication/supplement use

- Continuation requirements
- Chemistry panel
- Hematology
- hs-CRP
- Fasting omega-3 fatty acids
- Fasting lipids
- Fasting apolipoproteins
- Fasting PCSK9
- Archive samples
- Urinalysis
- 12-lead ECG
- hs-CRP Confounder Checklist
- Collect study product
- Assess study product compliance
- Assess AEs

9.4 Early Termination Procedures

The term "Early Termination" refers to a subject's non-completion of the study. Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a subject is withdrawn from the study, the reason for the withdrawal and the party who initiated the withdrawal (subject or Investigator) will be documented. Should the subject decide to withdraw, documentation of early termination and any AEs and concomitant medication use should be recorded. Prior to a subject's withdrawal from the study, an attempt will be made to conduct an early termination visit (visit 10 procedures).

The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

Adverse Event – event which results in discontinuation of the study product by the subject or that in the judgment of the Investigator for the best interest of the subject requires discontinuation of study product (includes all categories of study product relatedness; Not Related, Unlikely, Possibly, Probably, and Definitely).

Death – death of the subject.

Withdrawal of Consent – subject desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the Investigator.

Lost to Follow-Up – subject did not return for one or more follow-up visit(s) following dispensing of study product and could not be contacted thereafter. The reason for withdrawal was unknown and could not be documented.

Other – causes of premature termination from the study other than the above, such as theft or loss of study products, termination of study by Sponsor, etc.

10. Assessment of Outcomes

10.1 Primary Outcome Variable

The primary outcome variable will be the percent change from baseline to end of treatment in TG. Baseline will be the average of the values obtained during the final two (or possibly three, for subjects requiring visit 3b) 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.

10.2 Secondary Outcome Variables

The secondary outcome variables will include changes or percent changes from baseline to end of treatment in the following parameters. For lipoprotein cholesterol and hs-CRP levels, baseline will be the average of the values obtained during the two (or three) pre-treatment visits and end of treatment will be the average of values collected at the treatment visits on days 22 and 29. For apolipoproteins and PCSK9, baseline will be the value obtained at day 1 and end of treatment will be the value obtained on day 29, except for plasma omega-3 fatty acids, for which day 29 will be considered the on-treatment value.

- Total-C
- LDL-C
- VLDL-C
- HDL-C
- Non-HDL-C
- Apo A1
- Apo B
- Apo C3
- PCSK9
- hs-CRP
- Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total)

10.3 Exploratory Outcome Variables

- Phospholipid levels of omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total), expressed as a percentage of total fatty acids;
- Erythrocyte membrane levels of omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total), expressed as a percentage of total fatty acids, which will be assessed for the first treatment period only at days 22 and 29;
- Omega-3 fatty acids (EPA, docosahexaenoic acid [DHA], docosapentaenoic acid [DPA], total) in plasma for day 22 of each 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.

10.3 Safety Outcomes

Safety and tolerability will be assessed by evaluation of treatment-emergent AEs and changes in clinical laboratory parameters (chemistry, hematology and urinalysis profiles). Treatment-emergent AEs will be collected at any point during the study through spontaneous subject reporting; AE assessment will also be completed at each clinic visit using an open-ended question.

11. Data Analysis and Statistical Methods

All requirements for data analyses are briefly described in this protocol. A Statistical Analysis Plan (SAP), documenting the details of the procedures for data analysis, will be finalized before the database is locked and prior to analysis of the study data. Instances where the details of the SAP and this protocol differ, the SAP will be used as the source of the procedures for data analyses. Any deviations from the analyses described below will be included in the SAP.

11.1 Sample Size

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 of 28% for the 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.

11.2 Study Populations

11.2.1 Intention-to-Treat/Safety Dataset

The intention-to-treat/safety dataset will include subjects who and randomized and receive at least one dose of any study treatment.

11.2.2 Pharmacodynamic Dataset

Subjects from whom the estimation of pharmacodynamic parameters will be possible for two periods will be included in the pharmacodynamic dataset.

11.2.3 Per Protocol Dataset

A per protocol (PP) dataset and analysis will include all subjects who are included in the pharmacodynamic dataset for whom compliance for both study periods was within the range of 80% to 120%, 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.

11.3 Baseline Comparability

Baseline characteristics (demographic, anthropometric, blood pressure, and laboratory variables) will be presented by treatment sequence group and for the overall sample. Descriptive statistics [number of subjects, mean, standard error of the mean (SEM),

median, minimum, maximum, and interquartile range] will be reported for continuous variables. Frequency and percent of total will be reported for categorical variables.

11.4 Pharmacodynamic analysis

The pharmacodynamic analyses will be performed on available data from subjects in the pharmacodynamic PP datasets.

11.5 Statistical Analyses

An SAP, documenting the details of the procedures for data analysis, will be developed and finalized for this study prior to database lock. Differences between the SAP and the protocol may be noted; in such situations, the SAP will take precedence over the protocol. Statistics described in the SAP will be used to evaluate the performance of the test formulation in relation to the reference product.

Statistical analyses will be conducted using SAS® software version 9.4 or later.

11.6 Criteria for Evaluation

The criteria described in the SAP will be used to evaluate the performance of the test formulation in relation to the reference product.

11.7 Safety Analysis

An assessment of safety will be based primarily on the frequency and severity of AEs. AEs will be tabulated by treatment and subject number for all subjects in the safety dataset. A complete description of the safety analysis will be included in the SAP.

12. Study Monitoring

12.1 Concomitant Medication/Supplements

Subjects in this study may be taking concomitant medications. Allowed medication should be prescription or over-the-counter medications that are approved by the investigator during the screening period. All concomitant medications/supplements will be documented at clinic visits and at early termination, if applicable. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured from visit 1 (day -28) for the duration of the study.

Use of the medications described in the "Exclusion Criteria" section is not allowed during this study. If an individual requires any of these medications, the individual may not enroll in the study. Should a subject enrolled in the study require any of these medications or supplements, the study staff should consult with the Study Physician or Study Director to discuss the subject's continued participation in the trial prior to the conclusion of the study visit.

Clinic staff may also administer non-drug treatment(s) that do not deviate from the procedures outlined in the protocol (e.g., ice pack, allowing the subject to lie down). All treatment(s) provided will be documented.

12.2 Compliance Monitoring

Compliance with the TLC diet will be assessed verbally and with administration of the MEDFICTS Questionnaire on visits 1, 2, 4, 6, 7, 8 and 10 (screening days -28 and -14, treatment 1 days 1 and 29, washout day -7, and treatment 2 days 1 and 29). When study product is consumed at the clinic, dosing compliance will be assessed by clinic staff by mouth check. Compliance with consumption of study product off site will be assessed verbally and by collection of excess study product returned on days 22 and 29 of each treatment period. Study product compliance percent is calculated as the number of capsules consumed divided by the number of capsules prescribed multiplied by 100. If calculated compliance is less than 80%, subjects will receive additional instructions about treatment regimens. In addition, a protocol deviation will be completed, the Study Director or designee will be notified. Compliance with all other study instructions will be assessed verbally at each visit. All measures of compliance will be recorded.

Non-compliance will be defined as:

- Not consuming study product administered at the clinic
- Not consuming the instructed daily dose of study product during the treatment periods defined as the calculated compliance of < 80%
- Not following written study instructions provided prior to clinic visits
- Not adhering to the TLC diet as assessed by the MEDFICTS questionnaire

If any of the above events occur, the study staff should consult with the Project Manager or Study Director to discuss the subject's continued participation in the trial.

12.3 Adverse Event Monitoring

An AE is defined as any untoward medical occurrence in a clinical investigation subject following written informed consent that does not necessarily have a causal relationship with the study product. An AE can be any unfavorable or unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product whether or not related to the investigational product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures (including laboratory test abnormalities).

Events should be considered AEs if they:

- Result in discontinuation from the study;
- Require treatment or any other therapeutic intervention;
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality);

- Are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

Events that occur with comparable frequency and severity to the subject's baseline condition should not be considered AEs. Elective hospitalizations planned prior to a subject providing informed consent (e.g., elective cosmetic procedures) are not AEs. If a woman becomes pregnant during the study, the subject must be immediately discontinued from study product, and the pregnancy followed through to delivery. Every effort will be documented to retrieve the information on both mother and child at the time of delivery.

12.3.1 Grading and Severity

The Investigator will evaluate all AEs with respect to their severity, and record the outcome and action taken on the AE eCRF. AEs will be graded as:

Mild: Awareness of symptoms but easily tolerated
Moderate: Discomfort enough to interfere with but not prevent daily activity
Severe: Unable to perform usual activity

12.3.2 Relationship

The Investigator will also judge the likelihood that the AE was related to the study product and document this on the appropriate eCRF as:

NOT RELATED	This category applies to those adverse experiences which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY	In general, this category can be considered applicable to those experiences that, after careful medical consideration at the time they are evaluated, are judged to be unlikely related to the study product administered.
POSSIBLY	This category applies to those adverse experiences for which, after careful medical consideration at the time they are evaluated, a connection with the study product administration appears possible but cannot be ruled out with certainty.
PROBABLY	This category applies to those adverse experiences that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study product.
DEFINITELY	This category applies to those adverse experiences which the Investigator feels are incontrovertibly related to the study product.

The Investigator may assess and provide follow up instruction to the subject in accordance with good medical practice.

12.3.3 Serious Adverse Event Definition/Qualification

A serious adverse event (SAE) is defined as an AE that results in any of the following outcomes:

- Death (note that death is the outcome of a SAE and the cause of death should be listed as the AE)
- Life-threatening event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Any other important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

In the event of a SAE, the subject may be dropped from the study if the Investigator deems it necessary.

12.3.4 Serious Adverse Event Reporting Instructions
If in the opinion of the Investigator the event meets the criteria of a SAE the following procedures will be followed:

- The Investigator will report the SAE by telephone to Covance Clinical & Periapproval Services immediately upon becoming aware of the event.
- In addition, the initial SAE report should be scanned with other applicable information (such as medical history, concomitant medications, AEs) to MB-CRC within 24 h of reporting the event to the attention of:

  Cathleen E. Maki, MSN, RN
  MB Clinical Research and Consulting, LLC
  211 East Lake Street, Suite 3
  Addison, IL 60101
  Tel: (630) 469-6600
  Fax: (773) 980-7151
  Mobile: 630-222-4593
  E-mail: cmaki@mbclinicalresearch.com

- The Study Director will be:

  Kevin C. Maki, PhD
  President and Chief Scientist
  MB Clinical Research and Consulting, LLC
  211 East Lake Street, Suite 3
  Addison, IL 60101
  Tel: (630) 469-6600

Fax: (773) 980-7151
Email: kmaki@mbclinicalresearch.com

- The SAE form also needs to be reported within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria) to:

  Covance Clinical & Periapproval Services Limited
  Bulgaria House, 49B Blvd Bulgaria, 1404 Sofia, Bulgaria
  SAE Reporting Email: SAEintake@covance.com
  SAE Reporting Fax No.:1-888-887-8097

- All SAEs occurring from the time of informed consent until 30 days following the last administration of study product must be reported to the Sponsor's Representatives within the stated timeline.

- All serious adverse events that an Investigator considers related to study product occurring after the 30-day follow-up period must be reported to the Sponsor.

- The Investigator will also notify the Institutional Review Board (IRB) of the event within the parameters and timeframe specified under the IRB Standard Operating Procedures (SOP) after becoming aware of the SAE. An initial report followed promptly by a complete report will be forwarded to the IRB.

- Follow-up information relating to a SAE must be submitted to MB-CRC and Covance by telephone, fax, or e-mail as soon as additional data related to the event are available.

- If a subject is hospitalized or hospitalization is prolonged due to the SAE, the hospital discharge summary will be obtained if possible when it becomes available.

- If a death occurs and an autopsy is performed, a copy of the autopsy report will be obtained if possible when it becomes available. All efforts must be undertaken to obtain follow-up information promptly.

12.3.5 eCRF Recording of Adverse Events

All AEs will be recorded on the AE eCRF page. For subjects who have an ongoing AE at the final study visit, a follow-up AE eCRF page will be collected after 30 days. Subjects will be instructed to notify the clinic immediately should new AEs emerge for an additional 7 days following their last clinic visit. All SAEs must be recorded on the SAE eCRF page.

12.3.6 Serious Adverse Event Follow-Up

For all SAEs occurring during the study or within 30 days of the last administration of study product, the Investigator must submit follow-up reports to MB-CRC and Covance regarding the subject's subsequent course. All SAEs that are ongoing at the end of the study or upon discontinuation of the subject's participation must be followed until either:

- The event resolves, or;
- The event/condition has stabilized (e.g. in the case of persistent impairment), or;
- The event returns to baseline, if a baseline value is available, or;
- The subject dies, or;
- The event can be attributed to other than the study product, or to other than the study conduct.

13. Conduct of the Study

13.1 Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and US 21 Code of Federal Regulations (CFR). Signed written informed consent for participation in the study will be obtained from all participants before protocol-specific procedures are carried out. Participants will be informed of their right to withdraw from the study at any time.

13.2 Institutional Review Board

The Investigator will ensure that an appropriately constituted IRB, in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study. Before the study is started, the Investigator will forward copies of the protocol and consent form for this study to the IRB for review and approval. IRB approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review. The IRB must be informed of all subsequent protocol amendments. No alterations, modifications to IRB-approved documents, including the protocol, protocol summary, consent form, recruitment materials and questionnaires will be allowed. The IRB must also be informed of all SAEs and of unexpected AEs as outlined in the IRB's SOPs or reporting guidelines. In addition, the Investigator will immediately forward copies of all correspondence with the IRB to MB-CRC.

13.3 Informed Consent and Protected Health Information

The study will be explained verbally as well as on the informed consent document. Each subject will be given ample opportunity to inquire about details of the study and to read and understand the consent form before signing it.

Consent must be documented by the dated signature of the subject. Each subject's signed informed consent document must be kept on file by the Investigator for possible inspection by regulatory authorities or by the Sponsor. The subject should receive a copy of the written informed consent document once he/she has signed it.

The Sponsor recognizes the importance of protecting the privacy of subject data. Therefore, for study sites within the United States, the informed consent form will incorporate, or be accompanied by, a separate document incorporating HIPAA-compliant wording, by which subjects authorize the use and disclosure of their Protected Health Information by the Investigator and by those persons who need that information for the purposes of this study.

A subject may not be admitted to the study unless informed consent of the subject (or his/her legally authorized representative) has been obtained.

13.4 Subject Confidentiality

The Investigator is responsible for ensuring that volunteers' anonymity will be maintained. eCRFs or other documents will identify volunteers by initials, number, or code, and not by name. The Investigator will keep a separate log showing codes, names, and addresses. All documents showing the volunteers' identity will be kept in strict confidence by the Investigator. However, the Investigator agrees that the Sponsor, its employees or agents, the IRB, as well as representatives of the FDA, will have the right to audit and review pertinent medical records relating to this clinical trial and that the volunteers will provide written informed consent to this effect.

All references to the Sponsor in this section include all designees e.g., Contract Research Organizations or Consultants acting on behalf of the Sponsor.

13.5 Withdrawal of Subjects from the Study

Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a subject is withdrawn from the study, the reason for the withdrawal and the party who initiated the withdrawal (subject or Investigator) will be documented. Should the subject decide to withdraw, documentation of early termination and any AEs and concomitant medication use should be recorded in the eCRF. Prior to a subject's withdrawal from the study, an attempt will be made to conduct an early termination visit.

The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

Adverse Event – event which results in discontinuation of the study product by the subject or that in the judgment of the Investigator for the best interest of the subject requires discontinuation of study product (includes all categories of study product relatedness; Not Related, Unlikely, Possibly, Probably, and Definitely).

Death – death of the subject.

Withdrawal of Consent – subject desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the Investigator.

Lost to Follow-Up – subject did not return for one or more follow-up visit(s) following dispensing of study product and could not be contacted thereafter. The reason for withdrawal was unknown and could not be documented.

Other – causes of premature termination from the study other than the above, such as theft or loss of study products, termination of study by Sponsor, etc.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable, therefore, unnecessary withdrawal of subjects should be avoided.

14. Administrative Matters

All references to the Sponsor in this section include all designees e.g., Contract Research Organizations or Consultants acting on behalf of the Sponsor.

14.1 Changes to the Protocol

All changes to the protocol must be documented by amendments to the protocol signed by the Sponsor and the Investigator. The amended protocol and a revised informed consent form will be submitted for approval to the IRB. A copy of the approval will be provided to MB-CRC. Where the local IRB regulations regarding protocol amendments differ from this policy, the local regulations will apply.

The above-mentioned requirements do not preclude any immediate action from being taken in the interests of subjects' safety.

14.2 Protocol Deviations and 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 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 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.

14.3 Case Report Forms

Data collected in the eCRF will be documented in an anonymous fashion (e.g., the subject will be identified only by a study number and their initials). Each evaluation recorded in the eCRF will be performed at the time specified in the protocol.

All information required by the protocol should be documented in the source records and provided in the eCRF. An explanation must be given for any omissions. All eCRFs must be completed and made available as soon as possible after the subject's visit, in order that the monitor may verify the validity and completeness of the data on the eCRFs and permit prompt transmission of the data. The Investigator should review and sign (as required) all eCRFs for completeness, accuracy, and legibility prior to and during monitoring visits, as changes to the eCRF may be made during the monitoring visits by the site staff.

The Investigator must agree to complete and maintain source documents for each subject participating in the study.

All information on the eCRFs must be traceable back to the source documents. The source documents should contain all demographic and medical information.

14.4 Clinical Monitoring

An initiation meeting will be conducted prior to study start. At this meeting the protocol, eCRFs, and pertinent aspects of the eCRF will be reviewed with the Investigator and all study staff.

External monitoring visits will be conducted as per the monitoring plan. The Investigator will make a reasonable amount of time available to the external /Sponsor monitor on reasonable notice to assist with monitoring of the eCRFs.

At each visit the external /Sponsor monitor will review eCRFs and source documents to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The subjects' clinical records will be reviewed to confirm that:

- The data are consistent with the Investigator's clinical source records;
- The background clinical and laboratory data and concomitant medications are documented in the eCRFs;
- There is an accurate account of the dosage and schedule of administration of concomitant medications;
- The dosage and schedule of administration of the study product conform to the protocol;
- Information has been recorded in the appropriate place in the eCRF;
- The study product is being stored correctly and an accurate record of its dispensing to the subjects is being maintained.

Incorrect or inappropriate entries onto the eCRFs will be returned to the Investigator for correction. No data disclosing the identity of subjects will leave the study center.

The Investigator must ensure that the eCRFs and other study documentation are stored in a secure location. During the course of the study, the responsible MB-CRC staff will be available to discuss any matters relating to the conduct of the study.

14.5 Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. The Sponsor representatives or a regulatory agency such as the FDA may conduct the audit. If a regulatory agency requests an audit of the study site, the Investigator is required to inform the Sponsor and MB-CRC immediately.

14.6 Records Retention

All study documentation generated in connection with this study will be retained for at least five years after the last approval of a marketing application in an International Conference on Harmonization (ICH)-region and until there are no pending or contemplated marketing applications in an ICH-region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need be retained. The study documents include IRB approvals for the study protocol and all amendments, all source documents and laboratory records, eCRF copies, signed subject informed consent forms, and any other pertinent study document. The Investigator agrees to supply MB-CRC with a written confirmation that these procedures are in place and will be adhered to.

14.7 Termination of Study

The Sponsor and the Investigator reserve the right to terminate the study at any time. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of each subject's interest.

14.8 Final Report/Publications

A final report will be provided by MB-CRC to the Sponsor. Sponsor solely owns the right to decide whether to publish or present this work in a public forum.

14.9 Study Product

All study product will be supplied to the Investigator. Product supplies must be kept in an appropriate, secure area (see Section 8.2) and maintained under the storage conditions specified in the protocol.

The Investigator will oversee that an accurate record regarding the shipment and dispensing of the study product is maintained, using a product accountability log. An accurate product accountability log will be kept specifying the date and amount dispensed to each subject and any supplies either destroyed or returned to the Sponsor. This inventory record must be available for inspection by and is subject to regulatory inspection at any time. Copies of this record will be provided to the Sponsor by the Investigator at the conclusion of the study.

Product supplies are to be used only in accordance with this protocol and under the supervision of the Investigator. The Investigator agrees not to destroy any labels or unused product supply.

15. Disclosure

By conducting this study, the Investigator agrees that all information provided will be maintained by the Investigator and his/her staff in strict confidence. Such information may be communicated to the Scientific Committee and/or IRB/Ethics Committee under a similar, appropriate understanding of the confidential nature of the information. Study documents provided (protocols, investigators' brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. It is understood that the confidential information provided to the Investigator will not be disclosed to others without written authorization, except to the extent necessary to obtain informed consent from those volunteers who are eligible and choose to participate in the study. Such information will not be provided to potential volunteers or volunteers by telephone or to any other individual.

16. References

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Appendix 1: Excluded Medications/Supplements

CLASS OF DRUG/PRODUCT	GENERIC/BRAND NAME	
Unstable use of the following within <u>four</u> weeks of visit 2, day -14		
Anti-hypertensives:		
Aldosterone antagonists	Inspra (Eplerenone) Spironolactone	Aldosterone antagonists
Alpha-2 agonists	Catapres, Catapres TTS (clonidine)	
Angiotensin-converting enzyme inhibitors	Accupril (Quinipril) Accuretic (Quinipril + hydrocholorothiazide) Aceon (Perinodopril erbumine) Altace(Ramapril) Capoten (Captopril) Capozide (Captopril + hydrocholorthiazide) Lotensin (Benazapril) Lotensin HCT (Benazapril + hydrochlorothiazide) Mavik (Trandolapril) Monopril (Fosinopril)	Prinivil (Lisinopril) Prinzide (Lisinopril + hydrocholorothiazide) Tarka (Trandolapril + verapamil) Uniretic (Moexipril + hydrocholorothiazide) Univasc (Moexipril) Vaseretic (Enalopril + hydorcholorithiazide) Vasotec (Enalopril) Zestoretic (Lisinopril + hydrocholorothiazide) Zestril (Lisinopril)
Angiotensin II receptor antagonists	Atacand, Atacand HCT (Candesartan) Avalide (Irbesartan + hydrocholorthiazide) Avapro (Irbesartan) Benicar (Olmesartan) Benicar HCT (Olmesartan + hydrocholorothiazide) Teveten (Eprosartan) Teveten HCT (Eprosartan + hydrocholorothiazide) Tribenzor (Olmesartan + amlodipine + thiazide diuretic)	Cozaar (Losartan) Diovan, Diovan HCT (Valsartan) Edarbi (Azilsartan medoxomil) Hyzaar (Losartan + hydrocholothiazide) Micardis, Micardis HCT (Telmisartan) Twynsta (Telmisartan + amlodipine) Valturna (Valsartan + aliskiren)

Alpha-adrenergic blockers	Cardura (Doxazosin) Flomaxtra/Flomax (Tamsulosin) Hytrin (Terazosin)	Minipress (Prazosin) Phenoxybenzamine Phentolamine (Rogitine) Uroxatral (Alfuzosin)
Beta-adrenergic blockers	Betapace (Sotalol) Brevibloc (Esmolol) Blocadren (Timolol) Bystolic (Nebivolol) Cartrol (Carteolol) Corgard (Nadolol) Coreg CR (Carvedilol) Inderal, Innopran XL (Propranolol) Inderide (Propranolol + hydrochlorothiazide) Kerlone (Betaxolol) Levatol (Penbutolol) Lopressor (Metoprolol)	Lopressor HCT (Metroprolol + hydrocholorothiazide) Normodyne (Labetalol) Sectral (Acebutolol) Tenoretic (Atenolol + chlorthialidone) Tenormin (Atenolol) Timolol maleate Toprol XL (Metoprolol) Trandate (Labetalol) Visken (Pindolol) Zebeta (Bisoprolol) Ziac (Bisoprolol + hydrochlorthiazide)
Calcium Channel Blockers	Adalat CC (Nifedipine) Afeditab CR (Nifedipine) Amturnide (Aliskiren, amlodipine and hydrochlorothiazide) Azor (Amlodipine + olmesartan) Calan, Calan SR (Verapamil) Cardene, Cardene CR (Nicardipine) Cardizem, Dilacor XR, Cardizem LA, Diltiazem (Benzothiazepine) Covera-HS (Verapamil) DynaCirc CR, DynaCirc IR (Isradipine) Tekamlo (Aliskiren +amlodipine) Tiazac (Diltiazem)	Exforge (Amlodipine + valsartan) Isoptin, Isoptin SR (Verapamil) Lotrel (Amlodipine + benazepril) Nicardipine Nifediac CC, Nifedical XL, Nifedical XR (Nifedipine) Nimotop (Nimodipine) Norvasc (Amlodipine) Plendil (Felodipine) Procardia, Procardia XL (Nifedipine) Sular (Nisoldipine) Twynsta (Telmisartan + amlodipine) Vascor (Bepridil) Verelan PM (Verapamil)

	Tribenzor (Olmesartan + amlodipine + thiazide diuretic)	
Direct Renin Inhibitor	Tekamlo (Aliskiren +amlodipine) Tekturna (Aliskiren) Tekturna HCT (Aliskerin + hydrocholorthiazide)	Symlin (Pramlintide acetate) Victoza (Liraglutide)
Oral Diabetes Medications		
Meglitinides	Prandimet (Repaglinide + metformin) Prandin (Repaglinide) Starlix (Nateglinide)	
Sulfonylureas and Combination Sulfonylureas	Amaryl (Glimepiride) Avandaryl (Posiglitazone + glimepiride) Diabinese (Chlorpropamide) DiaBeta (Glyburide) Duetact (Pioglitazone + glimepiride) Dymelor (Acetohexamide) Glucotrol, Glucotrol XL (Glipizide)	Glynase PresTab (Glipizide) Glucovance (Glyburide + metformin) Metaglip (Glipizide + metfomin) Micronase (Glyburide) Orinase (Tolbutamide) Tolinase (Tolazamide)
Statins with or without ezetimibe		
	Atorvastatin calcium (Lipitor) Dual amlodipine/atorvastatin (Caduet) Fluvastatin (Lescol) Lovastatin (Advicor,	Mevacor, Altoprev) Pravastatin sodium (Pravachol) Aspirin + pravastatin (Pravigard PAC) Rosuvastatin calcium (Crestor) Simvastatin (Vytorin, Zocor)
Hormone Therapy (https://www.drugs.com/drug-classes.html)		
Sex Hormones	Androgens and anabolic steroids Contraceptives Estrogens Gonadotropin releasing hormones Gonadotropins Progestins Sex hormone combinations	

Thyroid Hormones	Thyroid drugs	Anti-thyroid agents
Excluded from the study:		
Anti-coagulants	Warfarin (Coumadin) Rivaroxaban (Xarelto) Apixaban (Eliquis)	Edoxaban (Savaysa) Dabigatran (Pradexa)
Injectable Therapy for Type 2 Diabetes	Insulin Exanatide ER (Bydureon) Dulaglutide (Trulicity) Pramlintide (Symlin) Semaglutide (Ozembic)	Exenatide (Byetta) Liraglutide (Victoza) Albiglutide (Tanseum) Lixisenatide (Adlyxin)
Excluded within 12 weeks of visit 2, day -14		
PCSK9 Inhibitors	Alirocumab (Praluent) Evolocumab (Repatha)	
Excluded within 4 weeks of visit 2, day -14		
Lipid-lowering medications (with the exception of stable dose statins/ezetimibe)	Cholestyramine (Questran, Questran Lite, Prevalite) Clofibrate (Atromid-S) Colesevelam HCl (WelChol) Colestipol HCl (Colestid)	Fenofibrate (Tricor; Antara; Lofibra; Triglide; Trilipix Fenoglide) Gemfibrozil (Lopid) Niacin (Niaspan, Advicor)
High-dose fish oil/supplements containing >1 g EPA/DHA	Omega-3-acid ethyl esters (Lovaza, Vascepa) Supplements Containing >1 g EPA/DHA	
Weight Loss Medications (4-week wash-out is permitted)	Benzphetamine HCl (Didrex) Naltrexone and bupropion (Contrave) Diethylpropion HCl (Tenuate,Tenuate Dospan) Mazindol (Sanorex) Orlistat (Xenical, Alli) Phendimetrazine tartrate (Adipost, Anorex-SR,	Phentermine (Adipex-P, Ionamin, Obenix, Oby-Cap, Pro Fast-SA, Teramine, Zantryl) Sibutramine (Meridia) Phentermine and topiramate (Qsymia) Lorcaserin (Belviq)

	Appecon, Bontril, Bontril SR, Melfiat, Obesine, Phendiet, Plegine, Prelu-2, Statobex)	
Excluded within 2 weeks of visit 2, day -14		
Lipid-lowering supplements	Catechin supplements (green tea supplements or catechin extracts. Green tea is allowed.) Inconsistent use of viscous fiber supplements (Metamucil) Omega-3 fatty acid supplements/supplemented food products (e.g., flaxseed; fish; or algal oils) Pantesin (pantethine)	Red rice yeast supplements Supplements containing sterols/stanols (e.g. CholestOff with Reducol, Naturemade Cholestoff, Cardio Chews Cardio Sterol, Piper Gummies) Niacin or its analogues at doses >400 mg/d Soy isoflavone supplements Sytrinol

Appendix 2: TLC Diet Recommendations

Subjects will receive instructions on a weight-maintenance TLC diet as described below.

Nutrient	Recommended Intake
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrate†	50 to 60% of total calories
Fiber	20 to 30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

*Trans fatty acids are another LDL-raising fat that should be kept at a low intake.

†Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits and vegetables.

‡Daily energy expenditure should include at least moderate physical activity.

Appendix 3: TLC Diet Instructions

The Therapeutic Lifestyle Changes (TLC) diet is recommended by the National Cholesterol Education Program of the U.S. National Institutes of Health. The diet's main focus is to reduce the amount of saturated fat you eat, because saturated fat elevates your cholesterol. You can reduce the saturated fat in your diet by limiting the amount of meat and milk products you eat. Choose low-fat products from those food groups instead. Replace most of the animal fat in your diet with unsaturated fat, especially monounsaturated oils, such as olive, canola, or peanut oil.
The TLC diet calls for less than 7% of your daily calories to come from saturated fat and for eating no more than 200 mg of dietary cholesterol a day. But the diet allows 25% to 35% of daily calories from fat, mainly from unsaturated fat.1 Most of the fat should be monounsaturated, and only 10% should be polyunsaturated fat. Your diet should include only enough calories to maintain your desired weight and avoid gaining weight.

Therapeutic Lifestyle Changes (TLC) diet recommendations

Food group	Number of servings	Serving size
Lean meat, poultry, fish, dry beans, and dry peas	No more than 5 ounces total a day	5 ounces maximum a day of lean meat, poultry, or fish Substitute ¼ cup dry beans or peas for 1 ounce of meat.
Eggs	No more than 2 yolks a week	1 whole egg. Egg whites or substitutes are not limited.
Low-fat milk and milk products	2–3 a day	1 cup nonfat or 1% milk 1 cup nonfat or low-fat yogurt 1 ounce nonfat or low-fat cheese (3 grams of fat or less per ounce)
Fruits	2–4 a day	1 piece fruit, such as apple, orange, or ½ a banana ½ cup canned fruit 1 cup berries or melon ¾ cup fruit juice
Vegetables	3–5 a day	1 cup raw leafy greens ½ cup cooked or raw vegetables ¾ cup vegetable juice

Bread, cereals, pasta, rice, and other grains	6–11 a day	1 slice of bread ½ hot dog or hamburger bun, bagel, or English muffin 1 ounce cold cereal ½ cup cooked pasta, rice, noodles, or other grains
Fat and oils	6–8 a day	1 teaspoon monounsaturated oil, such as canola, olive, or peanut 1 teaspoon polyunsaturated oil, such as corn or safflower 1 teaspoon soft margarine (one that does not contain hydrogenated oils) 2 tablespoon salad dressing 1 teaspoon mayonnaise 3 tablespoons nuts or seeds
Sweets and snacks	Within calorie limit	Choose snacks that are low in fat or are made with unsaturated fat.

HELPFUL HINTS

- Eat no more than five ounces of meat, preferably skinless chicken or fish.
- Eat two to three servings of low-fat or fat-free dairy per day.
- Eat three to five servings of vegetables, dry beans, or peas per day.
- Eat two to four servings of fruit per day.
- Eat six or more servings of breads, cereals (THAT DO NOT CONTAIN STEROLS/STANOLS IN THE LABEL), or grains per day.
- Eat no more than two egg yolks per week, including the yolks in baked goods and cooked or processed foods.
- Consume no more than one alcoholic beverage a day for women and two for men

What to Do When Eating Out

If you're eating healthy food at home to keep cholesterol in check, don't blow it when you eat out. Restaurant food can be loaded with saturated fat, calories, and sodium. Even healthy choices may come in super-size portions. Try these tips to stay on track: • Choose broiled, baked, steamed, and grilled foods – not fried. • Get sauces on the side.

Look for Hidden Traps

A close look at nutrition labels is essential for a heart-healthy diet. Try these tips:

• Check serving sizes. The nutrition info may look good, but does the package contain two servings instead of one?

• If the label says "whole grain," read the ingredients. Whole wheat or whole grain should be the first one.

• A food with "0 grams cholesterol" could still raise your LDL cholesterol. Saturated fat is the other culprit to watch for.

Start Your Day With Whole Grains

A bowl of oatmeal or whole-grain cereal has benefits that last all day. The fiber and complex carbohydrates in whole grains help you feel fuller for longer, so you'll be less tempted to overeat at lunch.

Give Yourself a Hand

Most Americans eat super-sized meals, with portions that are twice the size recommended for good health. That can contribute to weight gain and high cholesterol. Here's an easy way to practice portion control for a meal: Use your hand. One serving of meat or fish is about what fits in the palm of your hand. One serving of fresh fruit is about the size of your fist. A serving of cooked vegetables, rice, or pasta should fit in your cupped hand.

Low Fat Substitutes

Full Fat Food	Lower Fat Substitution
Hard shortening, lard, or bacon grease	Olive, safflower, corn, sunflower, canola, or soybean oil.
Creamy salad dressings like blue cheese	Oil and vinegar, lemon juice, or reduced-calorie dressings.
Fats or oils for frying or sautéing	Nonstick cooking spray.
Added fat, like oil, butter, margarine, or gravy	Herbs and spices, onion, garlic, low- fat broth, or wine.
Mayonnaise	Sour cream Plain nonfat or low-fat yogurt or nonfat sour cream.
Whole milk, nondairy creamers, half-and-half	Skim (nonfat) or low-fat (1 percent) milk.
Hard full-fat cheeses	Lower-fat cheeses like part-skim ricotta, low-fat and cream cheese, Jarlsberg, cottage cheese, and Neufchatel.
Full-fat Ice cream	Nonfat or low-fat frozen yogurt, ice milk, fruit ices, or sherbet.
A whole egg	Two egg whites or 1/4 cup egg substitute.
Fat in baking recipes	Equal amounts fruit puree like prune, or applesauce.
Whipping or heavy cream	Evaporated skim milk or one part skim milk and one part cream.
Frying	Bake or roast on a rack, broil, grill, steam, or microwave.

Appendix 4: MEDFICTS Dietary Assessment Questionnaire

Subject Initials: _____ **Screen #:** _____ **Date:** _____

Sample Dietary Assessment Questionaire
MEDFICTS*

In each food category for both Group 1 and Group 2 foods check one box from the "Weekly Consumption" column (number of servings eaten per week) and then check one box from the "Serving Size" column. If you check Rarely/Never, do not check a serving size box. See next page for score.

Food Category	Weekly Consumption: Rarely/ never	3 or less	4 or more		Serving Size: Small <5 oz/d 1 pt	Average 5 oz/d 2 pts	Large >5 oz/d 3 pts	Score
Meats								
• Recommended amount per day: ≤5 oz (equal in size to 2 decks of playing cards). • Base your estimate on the food you consume most often. • Beef and lamb selections are trimmed to 1/8" fat.								
Group 1. 10g or more total fat in 3 oz cooked portion **Beef –** Ground beef, Ribs, Steak (T-bone, Flank, Porterhouse, Tenderloin), Chuck blade roast, Brisket, Meatloaf (w/ground beef), Corned beef **Processed meats –** 1/4 lb burger or lg. sandwich, Bacon, Lunch meat, Sausage/knockwurst, Hot dogs, Ham (bone-end), Ground turkey **Other meats, Poultry, Seafood –** Pork chops (center loin), Pork roast (Blade, Boston, Sirloin), Pork spareribs, Ground pork, Lamb chops, Lamb (ribs), Organ meats[1], Chicken w/skin, Eel, Mackerel, Pompano	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	_____
Group 2. Less than 10g total fat in 3 oz cooked portion **Lean beef –** Round steak (Eye of round, Top round), Sirloin[1], Tip & bottom round[1], Chuck arm pot roast[1], Top Loin[1] **Low-fat processed meats –** Low-fat lunch meat, Canadian bacon, "Lean" fast food sandwich, Boneless ham **Other meats, Poultry, Seafood –** Chicken, Turkey (w/o skin)[1], most Seafood[1], Lamb leg shank, Pork tenderloin, Sirloin top loin, Veal cutlets, Sirloin, Shoulder, Ground veal, Venison, Veal chops and ribs[1], Lamb (whole leg, loin, fore-shank, sirloin)[1]	☐	☐	☐	x	☐	☐	☐ 6 pts	_____
Eggs – Weekly consumption is the number of times you eat eggs each week					Check the number of eggs eaten each time			
Group 1. Whole eggs, Yolks	☐	☐ 3 pts	☐ 7pts	x	☐ ≤1 ☐ 1 pt	☐ 2 ☐ 2 pts	☐ ≥3 ☐ 3 pts	_____
Group 2. Egg whites, Egg substitutes (1/2 cup)	☐	☐	☐		☐	☐	☐	_____
Dairy								
Milk – Average serving 1 cup **Group 1.** Whole milk, 2% milk, 2% buttermilk, Yogurt (whole milk)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	_____
Group 2. Fat-free milk, 1% milk, Fat-free buttermilk, Yogurt (Fat-free, 1% low fat)	☐	☐	☐		☐	☐	☐	_____
Cheese – Average serving 1 oz **Group 1.** Cream cheese, Cheddar, Monterey Jack, Colby, Swiss, American processed, Blue cheese, Regular cottage cheese (1/2 cup), and Ricotta (1/4 cup)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	_____
Group 2. Low-fat & fat-free cheeses, Fat-free milk mozzarella, String cheese, Low-fat, Fat-free milk & Fat-free cottage cheese (1/2 cup) and Ricotta (1/4 cup)	☐	☐	☐		☐	☐	☐	_____
Frozen Desserts – Average serving 1/2 cup **Group 1.** Ice cream, Milk shakes	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	_____
Group 2. Low-fat ice cream, Frozen yogurt	☐	☐	☐		☐	☐	☐	_____

FIG MEDFICTS assessment tool.
* MEDFICTS was orginally developed for and printed in ATP II[2]

Sample Dietary Assessment Questionaire (Continued)

MEDFICTS*

Food Category	Weekly Consumption: Rarely/never	3 or less	4 or more		Serving Size: Small <5 oz/d 1 pt	Average 5 oz/d 2 pts	Large >5 oz/d 3 pts	Score
Frying Foods – Average servings: see below. This section refers to method of preparation for vegetables and meat								
Group 1. French fries, Fried vegetables (1/2 cup), Fried chicken, fish, meat (3 oz)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Vegetables, not deep fried (1/2 cup), Meat, poultry, or fish- prepared by baking, broiling, grilling, poaching, roasting, stewing: (3 oz)	☐	☐	☐		☐	☐	☐	
In Baked Goods – † Average serving								
Group 1. Doughnuts, Biscuits, Butter rolls, Muffins, Croissants, Sweet rolls, Danish, Cakes, Pies, Coffee cakes, Cookies	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Fruit bars, Low-fat cookies/cakes/pastries, Angel food cake, Homemade baked goods with vegetable oils, breads, bagels	☐	☐	☐		☐	☐	☐	
Convenience Foods								
Group 1. Canned, Packaged, or Frozen dinners: e.g., Pizza (1 slice), Macaroni & cheese (1 cup), Pot pie (1), Cream soups (1 cup), Potato, rice & pasta dishes with cream/cheese sauces (1/2 cup)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Diet/Reduced calorie or reduced fat dinners (1), Potato, rice & pasta dishes without cream/cheese sauces (1/2 cup)	☐	☐	☐		☐	☐	☐	
Table Fats – Average serving: 1 Tbsp								
Group 1. Butter, Stick margarine, Regular salad dressing, Mayonnaise, Sour cream (2 Tbsp)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Diet and tub margarine, Low-fat & fat-free salad dressing, Low-fat & fat-free mayonnaise	☐	☐	☐		☐	☐	☐	
Snacks								
Group 1. Chips (potato, corn, taco), Cheese puffs, Snack mix, Nuts (1 oz), Regular crackers (1/2 oz), Candy (milk chocolate, caramel, coconut) (about 1 1/2 oz), Regular popcorn (3 cups)	☐	☐ 3 pts	☐ 7pts	x	☐ 1 pt	☐ 2 pts	☐ 3 pts	
Group 2. Pretzels, Fat-free chips (1 oz), Low-fat crackers (1/2 oz), Fruit, Fruit rolls, Licorice, Hard candy (1 med piece), Bread sticks (1- 2 pcs), Air-popped or low-fat popcorn (3 cups)	☐	☐	☐		☐	☐	☐	

† Organ meats, shrimp, abalone, and squid are low in fat but high in cholesterol.
‡ Only lean cuts with all visible fat trimmed. If not trimmed of all visible fat, score as if in Group 1.
¶ Score 6 pts if this box is checked
§ All parts not listed in group 1 have <10g total fat

Total from page 1 _____

Total from page 2 _____

Final Score _____

To Score: For each food category, multiply points in weekly consumption box by points in serving size box and record total in score column. If Group 2 foods checked, no points are scored (except for Group 2 meats, large serving = 6 pts).

Example:

☐	☐ 3 pts	☑ 7 pts	x	☐ 1 pt	☐ 2 pts	☑ 3 pts	21 pts

Add score on page 1 and page 2 to get final score.

Key:
≥70 Need to make some dietary changes
40- 70 Heart-Healthy Diet
<40 TLC Diet

FIG. MEDFICTS assessment tool.
* MEDFICTS was orginally developed for and printed in ATP II.[2]

Source: National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. NIH Pub. No. 93-3095. Bethesda, MD: National Heart, Lung, and Blood Institute, 1993.

Appendix 5: hs-CRP Confounder Checklist

1. Has the subject experienced any **infections** within the last 7 days (with or without the use of analgesics or anti-inflammatory drugs)? If yes, please explain: _____	Yes	No
2. Has the subject experienced **joint pain** within the last 7 days (with or without the use of analgesics or anti-inflammatory drugs)? If yes, please explain: _____	Yes	No
3. Has the subject experienced any **soft tissue injury** within the last 7 days (with or without the use of analgesics or anti-inflammatory drugs)? If yes, please explain: _____	Yes	No
4. Has the subject consumed any **alcoholic beverages** within the last 7 days? If yes, please indicate how many: _____	Yes	No
5. Has the subject participated in **vigorous exercise** within the last 7 days? If yes, please explain: _____	Yes	No

Appendix 6: Study Instructions

MAT-002 SUBJECT INSTRUCTIONS

REMINDERS for Visits 2, 3, 3b, 7

- Your visit is scheduled on ____/____/____ @ ____:____ am
- No food or drinks, except water for **at least 9 hours** before your next clinic visit.
- Drink plenty of fluids, water only the evening before all clinic visits.
- Maintain your regular physical activity patterns and avoid any vigorous physical activity **for at least 24 h before** your next clinic visit.
- Avoid alcohol consumption for **at least 24 h** before your next clinic visit.
- If you are a smoker, avoid smoking/vaping for **at least 1 hour** before your study visit.
- Notify the site if you are prescribed any new medication or begin taking a new supplement.
- Avoid all fish and seafood, other than 1 time per week.
- Avoid any fish or seafood for 48 hours before your next visit.
- Avoid all vitamins/supplements/foods containing EPA/DHA (omega-3's).
- Continue to follow the TLC diet instructions.
- Please call the clinic at **[clinic phone number]** if you get sick and/or are prescribed an antibiotic.
- Record any questions or changes to your health/medications in the spaces provided below.

Comments:

_____

_____

_____

_____

MAT-002 SUBJECT INSTRUCTIONS

REMINDERS for Visits 4, and 8

- Your visit is scheduled on ____/____/____ @ ____:____ am
- No food or drinks, except water, for **at least 9 hours** before your next clinic visit
- Drink plenty of fluids, water only the evening before all clinic visits.
- Maintain your regular physical activity patterns and avoid any vigorous physical activity **for at least 24 hours before** your next clinic visit
- Avoid alcohol consumption for **at least 24 h** before your next clinic visit.
- If a smoker/vaper, abstain from smoking/vaping for **at least 1 h prior to** your next clinic visit.
- You are being provided with enough study product to last until your next scheduled visit. Take 2 capsules twice daily with food. **If you forget a dose, do not make up for the missing dose on a separate day**. Do not chew or break apart the capsules before consuming. Do not throw away any of the capsules, instead **bring back any unused capsules in the original container provided at your next visit as well as any empty bottles.**
- Notify the clinic if you are prescribed any new medication or begin taking a new supplement.
- Avoid all fish and seafood, other than 1 time per week.
- Avoid any fish or seafood for 48 hours before your next visit
- Avoid all vitamins/supplements/foods containing EPA/DHA (omega-3's).
- Continue to follow the TLC diet instructions.
- Please call the clinic at **[clinic phone number]** if you get sick and/or are prescribed an antibiotic.
- Record any questions or changes to your health/medications in the spaces provided below.

Comments:

_____

_____

_____

_____

MAT-002 SUBJECT INSTRUCTIONS

REMINDERS for Visits 5, 6, 9 and 10

- Your visit is scheduled on ____/____/____ @ ____:____ am
- No food or drinks, except water for **at least 9 hours** before your next clinic visit.
- Drink plenty of fluids, water only, the evening before all clinic visits. Do not take study product before coming to the clinic.
- Maintain your regular physical activity patterns and avoid any vigorous physical activity **for at least 24 hours before** your next clinic visit.
- Avoid alcohol consumption for **at least 24 hours** before your next clinic visit.
- If a smoker/vaper, abstain from smoking/vaping for at least 1 hour prior to your next clinic visit.
- You are being provided with enough study product to last until your next scheduled visit. Take 2 capsules twice daily with food. **If you forget a dose, do not make up for the missing dose on a separate day**. Do not chew or break apart the capsules before consuming. Do not throw away any of the capsules, instead **bring back any unused capsules in the original container they were provided in at your next visit as well as any empty bottles.**
- Notify the site if you are prescribed any new medication or begin taking a new supplement.
- Avoid all fish and seafood, other than 1 time per week.
- Avoid any fish or seafood for 48 hours before your next visit
- Avoid all vitamins/supplements/foods containing EPA/DHA (omega-3's).
- Continue to follow the TLC diet instructions.
- Please call the clinic at **[clinic phone number]** if you get sick and/or are prescribed an antibiotic.
- Record any questions or changes to your health/medications in the spaces provided below.

Comments:

_____

_____

_____

_____

MAT-002 SUBJECT INSTRUCTIONS

REMINDERS for Visits 6 and 10

- Your visit is scheduled on ____/____/____ @ ____:____ am
- No food or drinks, except water for **at least 9 hours** before your next clinic visit.
- Drink plenty of fluids, water only, the evening before all clinic visits. Do not take study product before coming to the clinic.
- Maintain your regular physical activity patterns and avoid any vigorous physical activity **for at least 24 hours before** your next clinic visit.
- Avoid alcohol consumption for **at least 24 hours** before your next clinic visit.
- If a smoker/vaper, abstain from smoking/vaping for at least 1 hour prior to your next clinic visit.
- Notify the site if you are prescribed any new medication or begin taking a new supplement.
- Avoid all fish and seafood, other than 1 time per week.
- Avoid any fish or seafood for 48 hours before your next visit
- Avoid all vitamins/supplements/foods containing EPA/DHA (omega-3's).
- Continue to follow the TLC diet instructions.
- Please call the clinic at **[clinic phone number]** if you get sick and/or are prescribed an antibiotic.
- Record any questions or changes to your health/medications in the spaces provided below.

Comments:

_____

_____

_____

_____