STATISTICAL ANALYSIS PLAN

EFFICACY DATA INTEGRATION (PHASE 3 STUDIES)

INDICATION OF HYPERTRIGLYCERIDEMIA (SEVERE)

ACA-CAP-001

ACA-CAP-002

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 20 October, 2020).

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Version	Date of Version	Author	Significant Changes from Previous Authorized Version
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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide the framework for the integration (data pooling) of efficacy data for CaPre® and to describe the statistical methods to be used in analyzing the efficacy data and in generating the statistical outputs that will result from the analyses.

This SAP will consider data from the two (2) pivotal Phase 3 studies (ACA-CAP-001 and ACA-CAP-002) in subjects with severe hypertriglyceridemia (fasting TG levels ≥500 mg/dL and ≤1500 mg/dL).

The studies within the CaPre program that will be included in this SAP are described below:

- **ACA-CAP-001**: A Phase 3, multi-center, placebo-controlled, randomized, double-blind, 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia.

  This is a multi-center, randomized, double-blind, placebo-controlled, 2-arm parallel-group (CaPre 4 g/day or placebo), Phase 3 efficacy and safety study in subjects ≥ 18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥ 500 mg/dL and ≤ 1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study includes a 26-week double-blind treatment period, and a 4-week safety follow-up period. A total of 1017 subjects were consented at 71 study centers, from which 256 were randomized and treated, and 242 subjects analyzed for efficacy.

- **ACA-CAP-002**: A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia.

  This is a multi-center, multi-national, randomized, double-blind, placebo-controlled, 2-arm parallel-group (CaPre 4 g/day or placebo), Phase 3 efficacy and safety study in subjects ≥18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study includes a 26-week double-blind treatment period and a 4-week safety follow-up period. A total of 1082 subjects were consented at 93 study centers in the United States, Mexico, and Canada, from which 278 were randomized and treated, and 278 subjects analyzed for efficacy.

Table 1 provides a summary of these two studies included in this SAP.

Table 1: Efficacy Studies of CaPre included in this SAP

Study	Duration (weeks)	CaPre 4g Number of Subjects[1]	Placebo Number of Subjects[1]
ACA-CAP-001	26	173	69

[1] For study ACA-CAP-001, 14 subjects randomized and treated at Site 163 are not included in the main analyses, therefore a total of 242 subjects are analyzed for efficacy in the intent to treat (ITT) analysis set.

ACA-CAP-002	26	199	79

1.1. IMPORTANT DIFFERENCES BETWEEN STUDIES

Both studies were identical in design, patient population, dosage, etc. The only difference is that ACA-CAP-001 was a national study that enrolled sites in the US only, while ACA-CAP-002 was a multi-national study, with sites in Canada, Mexico and the US.

1.2. APPROACH FOR INTEGRATION OF DATA

Datasets of the two individual studies followed CDISC standards. No up-versioning of coding will be undertaken as both studies were coded using same dictionaries (MedDRA, WHO). Integrated analysis datasets (AdAMs) will be built using individual ADaM datasets from individual studies, respectively. No Data Integration Plan (DIP) will be provided.

A single pool will be summarized for the ISE.

- Phase 3 Pooled Analysis Cohort (Analysis at Week 12 and Week 26 for duration of effect): This pool will include the data from the two(2) Phase 3 studies (ACA-CAP-001 and ACA-CAP-002).

This pool analyses will be conducted by the following summary groups.

Placebo (N=148)	CaPre 4g (N=372)

2. STUDY OBJECTIVES

2.1. EFFICACY OBJECTIVE

The primary objective of this pooled analysis is:

- To determine the clinical efficacy of CaPre for the treatment of severe hypertriglyceridemia (fasting TG ≥ 500 mg/dL) in subjects from two different phase 3 trials (protocols ACA-CAP-001 and ACA-CAP-002) after 12 and 26 weeks of treatment.

The secondary objectives of this pooled analysis are:

- To evaluate the clinical efficacy of CaPre across various subgroups of subjects from the two combined phase 3 trials (protocols ACA-CAP-001 and ACA-CAP-002).
- To explore the change in plasma phospholipid eicosapentaenoic acid (EPA), total docosahexaenoic acid (DHA), and EPA+DHA in subjects from the two combined phase 3 trials (protocols ACA-CAP-001 and ACA-CAP-002) after 12 and 26 weeks of treatment, and the relationship with the clinical efficacy of CaPre.

3. ANALYSIS SETS

3.1. INTENT-TO-TREAT ANALYSIS SET [ITT]

The intent-to-treat (ITT) analysis set will include all subjects who were randomized to study treatment.
For analyses and displays based on the ITT analysis set, following the ITT principle, subjects will be analyzed according to the treatment to which they were randomized regardless of any departures from the original assigned group.

3.2. MODIFED INTENT-TO-TREAT ANALYSIS SET [MITT]

The modified Intent-to-Treat (mITT) analysis set will contain all subjects in the ITT set whose TG value at baseline is within the study inclusion range (500 mg/dL ≤ TG ≤ 1500 mg/dL). Subjects with a missing baseline value will be added by default to the mITT analysis set.

3.3. PER PROTOCOL ANALYSIS SET [PP]

The per-protocol (PP) analysis set will contain all subjects in the ITT analysis set who did not have protocol deviations that could influence the primary endpoint assessment defined as (but not limited to):

- Subject randomized despite not satisfying inclusion/exclusion criteria and that may have confounded the primary endpoint assessment
- Subject with non-evaluable primary endpoint or who completed assessments significantly outside of the specified visit windows.
- Subjects who did not receive the treatment to which they were randomized
- Subjects who did not reach compliance to study medication between 80-120%
- Subjects who significantly deviated from the protocol requirements regarding prohibited and/or allowed medications that may have confounded the primary endpoint assessment
- Any other major protocol deviation that is thought to interfere with the primary endpoint assessment.

3.4. PHARMACOKINETIC ANALYSIS SET [PK]

The pharmacokinetic (PK) analysis set will contain all subjects whose serum samples were analyzed at the end of the study for the quantitative determination of eicosapentaenoic acid (EPA) and total docosahexaenoic acid (DHA) in serum total lipids using a validated liquid chromatographic method with tandem mass spectrometry detection.

4. GENERAL CONSIDERATIONS

All data analyses will be performed using SAS®9.2 or higher version.

All computations will be performed prior to rounding.

Summaries for continuous variables will present actual values and, where applicable, change and percent change from baseline values by visit. Summaries will be presented for each study and for the pooled analysis cohort by treatment (CaPre and placebo), and will include number of patients (n), mean, standard deviation (SD), least squares means (LSMs) (when applicable), median, minimum, and maximum.

Summaries of categorical variables will be presented for each study and for the pooled analysis cohort by treatment (CaPre and placebo) and will include the number and percentage of patients within a category for the population by visit.

Patients who may have participated in both studies are expected to be low (less than 1%) and will be treated as separate patients for the analyses.

4.1. BASELINE

Baseline values for all efficacy endpoints will be taken as derived in each study according to the below definitions:

For lipid endpoints of TG, non-HDL-C, HDL-C, and Total Cholesterol (TC), the baseline is defined as the average of the last 3 measurements obtained prior to or on the date of randomization (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification). If one or the other measurement is missing, the baseline is to be based on the remaining available value(s).

For VLDL-C (ultracentrifugation) and LDL-C (ultracentrifugation), the baseline is defined as the average of 2 measurements obtained prior to or on the date of randomization (average of Week -1 and 0 corresponding to measurements taken at Visits 3, and 4). No VLDL-C and LDL-C measurements were taken at Visit 3.1. If one or the other measurement is missing, the baseline is to be based on the remaining available value.

For the other efficacy endpoints, unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the reference start date (including unscheduled assessments). In the case where the last non-missing measurement date and the reference start date coincide, this last measurement will be considered baseline. The reference start date is defined as:

- the day of the first dose of study medication (Day 1 is the day of the first dose of study medication) for treated subjects.
- the randomization (Visit 4, week 0) visit date for subjects who were randomized but not treated.

4.2. DERIVED TIMEPOINTS

The Week 12 and Week 26 endpoint values will be taken as derived in each study according to the windowing conventions described in section 4.4.

For lipid endpoints of TG, non-HDL-C, VLDL-C, HDL-C, LDL-C and Total Cholesterol (TC), the Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is, Week 11 and Week 12. Should there be only one measurement available at either Week 11 or Week 12, that measurement will be used as the Week 12 endpoint value.

4.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For post baseline visits of all efficacy endpoints: unscheduled/retest visits will be used if they are the nearest to the target day per the time windows defined in Section 4.4.

For baseline visits of all efficacy endpoints: scheduled visits will be used. Should a scheduled visit be missing, it will be replaced by its unscheduled/retest value as long as the unscheduled/retest value is taken prior to the next visit.

In case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries. If no measurement is available at the nominal visit, or no retest is available, then the assessment will be considered missing for the visit.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

4.4. WINDOWING CONVENTIONS

No time windows prior to the first dose will be considered. For all efficacy endpoints, the following post dose time windows will be used:

Visit Name	Window	Target
Week 4	Day 24 to Day 35	Day 28
Week 11-12*	Day 71 to Day 94	Day 84
Week 12**	Day 78 to Day 94	Day 84
Week 18	Day 121 to Day 136	Day 126
Week 26	Day 176 to Day 192	Day 182

*Week 12 endpoint based on the average of 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12).
**Week 12 endpoint based on 1 measurement obtained at the end of the 12-week double-blind treatment period, at Visit 7 (Week 12).

4.5. STATISTICAL TESTS

The default significance level will be set at alpha=0.05 (5%); confidence intervals (CIs) will be set at 95%; and all tests will be two-sided, unless otherwise specified in the description of the analyses. The primary comparisons will be between the CaPre 4.0 g and the placebo groups.

5. STATISTICAL CONSIDERATIONS

5.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN THE ANALYSES

For all efficacy parameters, analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as covariates will be used to perform the hypotheses tests.

For the analysis of subjects who have a fasting TG level below 500 mg/dL at the end of 12 weeks and at 26 weeks of double-blind treatment, a Cochran-Mantel-Haenszel (CMH) test will be used, controlling for qualifying TG category (≤750 mg/dL vs. >750 mg/dL) and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization.

5.2. EXAMINATION OF SUBGROUPS

The following subgroups will be assessed:

- Age: ≤ 65 years vs. > 65 years
- Race: White/Caucasian vs. non-White/Caucasian
- Ethnicity: Hispanic or Latino vs. Non-Hispanic or Latino
- Gender: male vs. female
- Study: ACA-CAP-001 vs. ACA-CAP-002
- Countries: US vs. Canada vs. Mexico
- Qualifying TG level: ≤ 750 mg/dL vs. > 750 mg/dL
- Use of statin, CAI, or PCSK9I, alone or in combination, vs. non-use at randomization
- Use of fibrate vs. non-use at randomization
- Subjects with diabetes (type 2 diabetes mellitus, defined as subjects with history of diabetes, use of anti-diabetic medication, or with HbA1c level >= 6.5%) vs. no diabetes at randomization
- Baseline level of EPA+DHA: ≤ median vs. > median

A list of all subgroup analyses is provided in Appendix 2.

6. DISPOSITION AND WITHDRAWALS

Subject disposition and withdrawals will be presented for the ITT and mITT analysis sets, and will include the number of patients in the analysis dataset, the number of patients who completed the study, the subject status at the final visit, the reasons for study withdrawal, the number of patients who completed the treatment and the reasons for study medication withdrawal.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT and mITT analysis sets. Demographic and baseline characteristics will be compared between the two treatment groups by using a Student t-test for continuous variables and a Chi-Square test for categorical variables.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent and per category (≤ 65 vs. > 65 years old)
- Countries: (US vs non-US) (%)
- Gender (Male vs. Female) (%)
- Race/ethnicity (White/Caucasian, Asian, Black/African-American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Unknown, Other) (%). In each racial category, the proportion of subjects of Hispanic or Latino ethnicity will be reported (%)
- Weight (kg)
- BMI (kg/m2)
- Tobacco use (Never, Former, Current) (%)
- Alcohol use (Never, Former, Current) (%)
- Baseline, qualifying and pre-randomization parameters:
    - Baseline TG
    - Baseline TG category (<500 mg/dL vs. ≥500 mg/dL)
    - TG at Week 0
    - TG at Week 0 category (<500 mg/dL vs. ≥500 mg/dL)
    - Qualifying TG
    - Qualifying TG category (≤750 mg/dL vs. >750 mg/dL)
    - Baseline Non-HDL-C
    - Baseline VLDL-C
    - Baseline HDL-C
    - Baseline LDL-C
- Concomitant Medications
    - Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization
    - Use of statin
    - Use of CAI
    - Use of PCSK9
    - Use of Fibrate vs. non-use at randomization
- Baseline HbA1c
- Baseline level of plasma phospholipid EPA, DHA, and EPA+DHA (percent of fatty acids)
- Subjects with Diabetes Mellitus, which are subjects who have a history of diabetes or use anti-diabetic medication or have HbA1c >= 6.5% at baseline (randomization visit)
    - HbA1c

- Subjects with diabetes mellitus with HbA1c < vs. ≥ 7.0%

8. STUDY MEDICATION EXPOSURE AND COMPLIANCE

Exposure to study medication in days will be presented for subjects in the ITT and mITT analysis sets. The exposure will be computed as the last treatment dose date minus the first dose date. Interruptions and compliance are not considered for duration of the exposure.

Compliance to study medication will be presented for subjects in the ITT, mITT and PK analysis sets and will be summarized for the following visits: between Visit 4 (Week 0) and Visit 7 (Week 12), between Visit 7 (Week 12) and Visit 9 (Week 26), and overall. Descriptive statistics will be presented and the number and percentage of subjects in each of the following categories will also be presented: '< 80%', '80-120%' '>120%'.

Exposure and compliance data will be taken directly from each study.

9. OUTPUT PRESENTATIONS

A separate output templates document will be provided with this SAP and will describe the presentations for this study. The format and content of the summary tables, figures, and listings will be more amply defined in this Output templates document.

10. EFFICACY OUTCOMES

10.1. PRIMARY EFFICACY VARIABLES

The primary efficacy endpoint is:

- Percent change from baseline to Week 12 in TG.

10.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy estimand is the difference between the randomized treatment groups, CaPre 4g and placebo, in percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. To estimate this estimand, all subjects will be included regardless of adherence to study medication and use of subsequent rescue therapies.

A second efficacy estimand is defined as the difference between the randomized treatment groups, CaPre 4g and placebo, in percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in mITT subjects (i.e. subjects who qualified and maintained baseline TG levels ≥500 mg/dL and ≤1500 mg/dL). To estimate this estimand, all subjects will be included regardless of adherence to study medication and use of subsequent rescue therapies.

The baseline is taken as derived in each study separately (as described in section 4.1), the Week 12 endpoint is also taken as derived directly from each study (as described in section 4.2) according to the windowing conventions described in section 4.4.

10.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLES

In case of a non-evaluable endpoint, prior to any imputation, the following replacement strategy will be followed:

- Should the baseline and/or a given endpoint for TG be non-calculable (i.e. values at baseline and/or at the given endpoint from the primary TG analysis method are all missing), making the change from baseline non-evaluable, then TG measurements from the lipoprotein fractionation (ultracentrifugation) panel[2], if available, should be used to derive both the baseline and the given endpoint.

All collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at the Week 12 endpoint will be included in the primary analysis. Subjects who withdraw consent for study participation overall and are not assessed at the Week 12, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 4.3), will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at the Week 12 endpoint.

A subject with complete data will have measurements at baseline, Week 4, Week 11 and/or 12, Week 18 and Week 26. A subject with missing data at any visit prior to Week 12 (or Week 26) and a non-missing value at any subsequent visit(s) up to Week 12 (or Week 26) is said to have intermittent (non-monotone) missing data. A subject with missing data at a post baseline visit and at all subsequent visits is said to have monotone missing data.

Imputed data will consist of 100 imputed datasets. The random seed number for the multiple imputation (MI) of intermittent missing data will be 20191016 and the random seed number for the imputation of monotone missing data using the sequential regression MI will be 191016. The same random seeds will be used for these two steps when imputing data for the primary analysis as well as for sensitivity analyses, although the imputation models will be different.

10.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLES

The primary objective is to test the null hypothesis that the percent change from baseline to the Week 12 endpoint of fasting TG level in the active group (CaPre 4.0g) is the same as that in the placebo group. The alternative hypothesis is that the percent change from baseline of fasting TG level in the active group (CaPre 4.0g) is NOT the same as that in the placebo group.

[2] TG was measured by a satellite central laboratory as part of the ultracentrifugation analyses (for the determination of LDL-C and VLDL-C), for quality control purpose.

The primary efficacy analysis will be performed for subjects in the ITT analysis set and will also be carried out for subjects in the mITT analysis set in a secondary fashion. Finally, the primary analysis will be repeated for the PP analysis set as a supportive analysis.

An analysis of covariance (ANCOVA) model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL), use of statin and/or CAI at randomization, and baseline TG value as a covariate will be used to estimate the least squares (LS) means (LSM) for the primary endpoints (percent change in TG levels at Week 12 and Week 26). LSMs for each treatment group, with 2-sided 95% CI will be provided by visit. Treatment difference (i.e. difference in LSMs) at Week 12 and Week 26 between the active and placebo groups will be calculated, with the corresponding two-sided 95% confidence interval (CI) and p-values. Descriptive statistics for each treatment group will also be provided by visit.

MI will be implemented in two steps to impute missing values of the Week 12 and Week 26 primary endpoints. First, partial imputation assuming a missing-at-random (MAR) mechanism will be carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. A separate model will be used for each treatment group. The imputation model will include qualifying TG category (≤ 750 mg/dL vs. > 750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization as fixed covariates and observed TG values at baseline, Week 4, Week 11, Week 12, Week 18 and Week 26. The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior. In case of non-convergence or non-estimability issues, a ridge prior and single model will be considered with treatment group added as explanatory variable to model.

Then, the remaining monotone missing data will be imputed using sequential regression multiple imputation. The response to be imputed will be change at each visit from the last pre-discontinuation value. A separate regression model is estimated for imputation of the change from the last pre-discontinuation value to each visit. Each regression model will include explanatory variables for the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, treatment group, treatment duration, baseline triglycerides and last value before discontinuation. The MONOTONE REGRESSION statement in the MI procedure in SAS will be used. For the primary analysis, the imputation model at this step will be estimated only from the reference group of subjects who discontinued their randomized treatment early but remained in the study and were assessed at Week 11 and/or 12. This will be implemented using the MNAR statement in the MI procedure in SAS with the MODELOBS option. A flag identifying subjects belonging to the reference group as described above will be derived and used in the MODELOBS option to identify the subset of subjects from whom the imputation models are to be derived. If the model does not converge, then the strata will be removed from the model. After the imputation is done on the change from the last value before discontinuation, the imputed value for the triglyceride measure will be derived by adding to the last value pre-discontinuation the imputed change for each visit.

Should there be not enough non-adherers to model the method described above, a BOCF (Baseline Observation-Carried Forward) like imputation model will be used. After a monotone dataset has been created, a set of baseline values are imputed for each subject. The model for the baseline measure of the triglycerides will include other

values measured at baseline (O'Kelly et al., 2014). The other explanatory variables in the model will include the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and treatment group. The multiply imputed baseline triglyceride values for each subject are then "stored" and used to multiply impute the missing post-baseline values. This approach to BOCF is preferred because a) the model for the imputed baseline values captures observed associations of baseline triglyceride with other values measured at baseline; 2) the imputed baseline values reflect the two sources of variance noted by Rubin, i.e. the imputed baseline values reflect both the variability inherent in the baseline random variable, and the uncertainty as to the likely mean of the underlying distribution of that baseline, for each subject

No rounding or range restrictions will be applied.

For those 100 imputed datasets with a variable "_IMPUTATION_" from 1 to 100, the ANCOVA analysis will be repeated in each of the dataset (by using BY _IMPUTATION_ as a statement). Each analysis will use some output statements to create an output dataset that matches the input specifications in the combining procedure. Then, the SAS PROC MIANALYZE will be used to combine data from multiple imputed datasets, in which the point estimates can be simply averaged over imputations, whereas statistics are combined according to Rubin's (1987) rules, which involve adjusting the standard error and degrees of freedom for between imputation variance.

10.1.4. SENSITIVITY ANALYSES OF PRIMARY EFFICACY VARIABLE(S)

Due to relatively large sample size of the Phase 3 Pooled Analysis Cohort (>500 subjects), the use of a parametric model based on means is expected to be robust against departure from normality. In any case, the normality assumptions will be investigated with the Shapiro-Wilk test on the residuals and a non-parametric rank-based analysis of covariance (ANCOVA) will be performed as sensitivity analysis. The model will include main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization and baseline TG value as a covariate.

For each of the 100 imputed datasets, the non-parametric ANCOVA based on ranks will be performed as follows: the percent change from baseline in TG value and the TG baseline value will be transformed to modified ridit scores within stratum (qualifying TG category [⩽750 mg/dL vs. >750 mg/dL] and use of statin [CAI or PCSK9I, alone or in combination] vs. non-use at randomization). Modified ridit scores are ranks standardized for the different sample sizes per stratum. In the second step, ordinary Least Square (LS) regression applied to the modified ridit scores of the percent change from baseline and baseline will be performed within each stratum using the model:
Percent change from baseline = baseline.

In the third step, residuals from these regression models will be used. In that final step, the residuals from all strata will be included in a stratified extended Cochran-Mantel-Haenszel (CMH) test of the residuals (i.e., stratum by treatment by residual) to analyze the treatment effect. CMH test statistics (the Row Mean Score Differ statistic will be used, this will be obtained with the CMH2 option in the TABLES statement of PROC FREQ) obtained from each of the multiple imputed datasets will be combined using the Rubin's combination rule after applying a normalizing Wilson-Hilferty transformation for a chi-square distributed statistic. The transformation will be applied as follows:

$$wh\_cmh^{(m)} = \sqrt[3]{cmh^{(m)}/df}$$

where $cmh^{(m)}$ is the CMH statistic computed from the mth imputed dataset $m = 1, \ldots, 100$, df is the number of degrees of freedom associated with the CMH statistic, and $wh\_cmh^{(m)}$ is the transformed value. The transformed statistic is approximately normally distributed with mean $1 - 2/(9 \times df)$ and variance $2/(9 \times df)$ under the null hypothesis. This transformed statistic will be standardized to obtain a variable that is normally distributed with mean 0 and variance 1:

$$st_{wh\_cmh}{}^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt[2]{\frac{2}{9 \times df}}}$$

This transformed statistic and the corresponding standard error of 1 will be combined using Rubin's rule.

Quantile regression, adjusting for the same baseline covariates (as specified in the ANCOVA model above) will be used to obtain an adjusted estimate of the median treatment difference with associated two-sided 95% CI. Rubin's combination rule will be used to combine the estimates from multiple imputed datasets.

Another sensitivity analysis using observed cases (no imputation of otherwise missing data) will be conducted using the primary analysis defined in section 10.1.3

Finally, a sensitivity analysis will be carried on by excluding subjects with an outlying percent change from baseline in TG at Week 12 and Week 26. Outliers will be identified by using some of the following methods:
a) Box plots and histograms
b) Univariate distribution tables
c) Extreme values
d) Distribution plots for subgroups
e) Multivariate scatter plots.

This analysis will be conducted using the primary analysis defined in section 10.1.3. A separate table will summarize outliers identified in each treatment group with the following parameters: age, gender, subject status or disposition, baseline TG, rescue therapy post-randomization, change and percent change from baseline TG at Week 12 and Week 26, and type of response [observed vs. MI]).

All above sensitivity analyses will be conducted on the same analysis set (ITT and mITT) as for the primary analysis.

10.2. KEY SECONDARY EFFICACY

The key secondary efficacy endpoint is:

- Percent change from baseline to Week 26 in TG

The key secondary efficacy analyses will be performed for the ITT and mITT analysis sets only.

10.2.1. KEY SECONDARY EFFICACY VARIABLES & DERIVATIONS

The baseline is taken as derived in each study separately (as described in section 4.1), the Week 26 endpoints is also taken as derived directly from each study (as described in section 4.2) according to the windowing conventions described in section 4.4.

10.2.2. MISSING DATA METHODS FOR KEY SECONDARY EFFICACY VARIABLES

Similar methods as described in section 10.1.2 will be applied.

10.2.3. ANALYSIS OF KEY SECONDARY EFFICACY VARIABLES

Similar analyses as specified above for the primary efficacy analysis will be conducted on the key secondary efficacy endpoint. Similar sensitivity analyses as for the primary efficacy variables will be conducted (refer to section 10.1.4).

10.3. OTHER SECONDARY EFFICACY

The secondary efficacy endpoints are:

- Percent change from baseline to Week 12 and Week 26 in non-HDL-C
- Percent change from baseline to Week 12 and Week 26 in VLDL-C (ultracentrifugation)
- Percent change from baseline to Week 12 and Week 26 in HDL-C
- Percent change from baseline to Week 12 and Week 26 in LDL-C (ultracentrifugation)

The secondary efficacy analyses will be performed for the ITT and mITT analysis sets only.

10.3.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The baseline is taken as derived in each study separately (as described in section 4.1), the Week 12 and 26 endpoints are also taken directly from each study (as described in section 4.2) according to the windowing conventions described in section 4.4.

10.3.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

Similarly, to the primary analysis, all collected data, including those from subjects who discontinue the study

medication early but remain on study and are assessed at the Week 12 and/or Week 26 endpoints, will be included in the analysis of the secondary endpoints. In case of a non-evaluable endpoint, the following replacement strategy will be followed:

- Should the baseline and/or Week 12 endpoint for LDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing), making the change from baseline non-evaluable, then LDL-C (direct) measurements, if available, should be used to derive both the baseline and the Week 12 endpoint.
- Similarly, should the baseline and/or Week 12 endpoint for VLDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing), making the change form baseline non-evaluable, then VLDL-C will be derived using the following formula: VLDL-C = TC – HDL-C – LDL-C(direct)

Subjects who withdraw consent for study participation overall and are not assessed at Week 12 and/or Week 26 endpoint, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 4.3) will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

10.3.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Similar analyses as specified above for the primary efficacy analysis will be conducted on all the secondary efficacy endpoints. Only the non-parametric rank-based analysis of covariance (ANCOVA) will be performed as sensitivity analysis for the secondary efficacy variables (refer to section 10.1.4).

10.4. EXPLORATORY EFFICACY AND PHARMACOKINETICS VARIABLES

The exploratory efficacy endpoints are:

- Percent of subjects with TG < 500 mg/dL at baseline, and after 12 and 26 weeks of treatment.
- Percent change from baseline to Week 12 and Week 26 in Total Cholesterol
- Percent change from baseline to Week 12 and Week 26 in apo B, apo C3 and apo A5
- Percent change from baseline to Week 12 and to Week 26 in LDL particle concentrations.
- Percent change from baseline to Week 12 and to Week 26 in hs-CRP and log hs-CRP
- Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in fasting serum glucose, and HbA1c in all subjects and in those with Diabetes Mellitus.

Additional exploratory efficacy endpoints may be analyzed if deemed relevant and include:

- Percent change from baseline to Week 12 and Week 26 in apo A1, and ratio of apo B to apo A1
- Percent change from baseline to Week 12 and to Week 26 in various other lipoprotein particle concentrations (HDL, non-HDL, IDL and VLDL)
- Percent change from baseline to Week 12 and Week 26 in oxidized LDL-C and Lp-PLA2.
- Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in fasting insulin, HOMA-IR

and HOMA-β in all subjects and in those with Diabetes Mellitus.

Additional exploratory endpoints may be analyzed using the pre-randomization value of the parameter at Week 0 as baseline in the subset of subjects whose TG levels at Week 0 are within the protocol inclusion range (i.e. 500 mg/dL $\leqslant$ TG $\leq$ 1500 mg/dL) :

- Percent change from baseline (Week 0) to Week 12 and Week 26 in TG.
- Percent change from baseline (Week 0) to Week 12 and Week 26 in non-HDL-C, VLDL-C, HDL-C and LDL-C.

The pharmacokinetic endpoints are:

- Change and Percent change from baseline to all visits in plasma phospholipid EPA, DHA, and EPA+ DHA relative concentrations (percent of fatty acids).
- Change and Percent change from baseline to Week 12 and Week 26 in EPA, DHA and EPA+ DHA in serum total lipids.

10.4.1. EXPLORATORY EFFICACY AND PHARMACOKINETICS VARIABLES & DERIVATIONS

The baseline is taken as derived in each study separately (as described in section 4.1). The Week 12 endpoint is derived as described in section 4.2. Both the Week 12 and Week 26 endpoints are taken directly from each study according to the windowing conventions described in section 4.4.

Certain analyses may be conducted using the pre-randomization value of the parameter at Visit 4 (Week 0) as baseline.

For pharmacokinetic endpoints, blood samples for fatty acid measurements in plasma phospholipid (EPA, DHA, EPA+DHA) were obtained at Week 0 (Baseline), prior to first study medication dose, and additional samples were obtained at Week 4, Week 12, Week 18, Week 26, and as applicable at Early Termination. Additionally, following completion of the study, serum samples for storage at -80°C (until analysis) obtained at Week 0, Week 12, and Week 26 were selected for quantitative determination of Total EPA and DHA using a validated liquid chromatographic method with tandem mass spectrometry detection by a bioanalytical facility.

10.4.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY AND PHARMACOINETICS VARIABLES

For exploratory efficacy endpoints , except as applicable for replacement of missing TG (section 10.1.2) and missing LDL-C and VLDL-C (section 10.2.2), subjects with otherwise missing data at the analysis time points of interest will be handled using the same MI approaches as specified for the primary and secondary analyses.

Missing data for pharmacokinetic endpoints will not be replaced or imputed.

10.4.3. ANALYSIS OF EXPLORATORY EFFICICACY AND PHARMACOKINETIC VARIABLES

For exploratory efficacy endpoints defined as change or percent change from baseline, similar analyses as specified

above for the primary and secondary efficacy endpoints will be conducted. Similar sensivity analyses as for the primary efficacy variables may conducted if deemed relevant (refer to section 10.1.4).

The exploratory efficacy analyses will be performed for the ITT and mITT analysis set only, unless analyses are to be carried in specific subset of subjects.

Regarding the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 10.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

A p-trend analysis for the Percent Change from baseline in TG at Week 12 and 26 will be conducted for the treatment effect across quintiles (n=5 groups) of baseline TG, which will involve assigning subjects the median value of their respective quintile group and evaluating this as a continuous variable.

For pharmacokinetic endpoints, treatment group comparison will be done using a MMRM model including treatment, visit (Week 4, Week 12, Week 18, Week 26), treatment-by-visit interaction, and baseline values as covariate, and subjects as random effect. LSMs for each treatment group, with two-sided 95% CI will be provided by visit. Treatment difference (i.e. difference in LSMs) at each visit between the active and placebo groups will be calculated, with corresponding two-sided 95% CI and p-values. Descriptive statistics by visit for each treatment group will also be provided.

The correlation between the change from baseline in plasma phospholipid EPA, DHA, and EPA+DHA (independent variable) and the percent change from baseline in fasting TG levels (dependent variable) at Week 12 and Week 26 will be presented in a scatter plot graph for each treatment group, and for both treatment groups combined. Statistics will include sample size, correlation coefficient (r) with corresponding two-sided 95% CI and significance level for correlation (p-value) by treatment and visit. A similar correlation will be established by excluding subjects in the active group with change from baseline in plasma phospholipid EPA, DHA, and EPA+DHA (independent variable) lower or equal to 0.

The above PK analyses will be performed on the ITT and mITT analysis sets, except for the endpoint of Total EPA, DHA and EPA+DHA in serum that will be presented for the PK analysis set only.

10.5. SUBGROUP ANALYSES

Subgroups are listed in section 5.2 and Appendix 2. Descriptive statistics will be summarized for each subgroup.

Each subgroup will be tested by including a main effect of subgroup and a treatment-by-subgroup interaction effect within the same model as described in the primary efficacy analysis in Section 10.1.3. Subgroups will be considered

significant if the p-value for the treatment-by-subgroup interaction is ≤ 0.10. In case a subgroup reaches significance, demographic and baseline characteristics for the subgroup will be provided. Other efficacy variables may be explored in the subgroups of interest.

Treatment effect within each subgroup will be estimated using the same model as described in the primary efficacy analysis in Section 10.1.3 for each subgroup. Multiple imputation models (for non-monotone and monotone missing data imputation) will include a main effect for subgroup and a treatment-by-subgroup interaction effect. If there are estimability issues, then the interaction term will be removed from the model.

A Forest plot will be produced to show the treatment effects and the corresponding CIs (overall and within each subgroup), along with the p-value for the treatment-by-interaction subgroup.

10.6. MULTIPLE COMPARISONS/MULTIPLICITY

All efficacy analyses are considered exploratory in nature. Accordingly, no adjustment for multiplicity will be performed, and as such, nominal p-values will be reported.

11. REFERENCES

O'Kelly, M., Ratitch, B. (editors). Clinical Trials with Missing Data: A Guide for Practitioners. Wiley, 2014.

Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. *Proceedings of the National Academy of Sciences*, Washington, 17, 684–688.

APPENDIX 1. LIPID MODIFYING DRUGS

Part A: Statins, CAI, PCSK9 and Fibrates

Class of Product	Drug	Brand Name
Fibrates	Fenofibrate	Triglide, Tricor, Lipofen, Lipidil, Fenoglide, Antara, Trilipix, Gemfibrozil, Gemfibrozilo
	Fenofibric Acid	
	Choline Fenofibrate	
	Gemfibrozil	
Statins	Rosuvastatin Calcium	Crestor
	Rosuvastatin	
	Atorvastatin Calcium Trihydrate	Lipitor, Liptruzet (with ezetimibe), Caduet (with amlodipine)
	Atorvastatin	
	Lovastatin	Mevacor, Altocor, Altoprev
	Fluvastatin Sodium	Lescol, Canef, Vastin,
	Fluvastatin	
	Pravastatin Sodium	Pravachol
	Pravastatin	
	pitavastatin calcium	Livalo, Zypitamag
	pitavastatin magnesium	
	pitavastatin	
	Simvastatin	Zocor, Vytorin and generics (with ezetimibe)
Cholesterol Absorption Inhibitor	Ezetimibe	Zetia, Ezetrol, Vytorin and generics (with simvastatin), Liptruzet (with atorvastatin)
PCSK9 Category	Evolocumab	Repatha
	Alirocumab	Praluent

Fixed dose combination products are counted in each class of product of their respective drug (e.g. Vytorin is counted in both Statin and Cholesterol Absorption Inhibitor)

Part B: Niacin products, bile acid sequestrants, Omega-3

Niacin	Niacin	Niacor, Niaspan
Other	Lomitapide	Juxtapid
	Lomitapide Mesylate	
	Mipomersen	Kynamro
	Mipomersen Sodium	
Bile Acid Sequestrant	Cholestyramine	Prevalite, Questran, Cholestryamine Light
	Colestipol	Colestid and generics

	Colesevelam	Welchol and generics
Omega-3	Omega-3 ethyl esters	Lovaza and generics
	Icosapent ethyl	Vascepa
	Omega-3 carboxyylic acids	Epanova
Herbal product or dietary supplements taken for their lipid-altering effects	Omega-3	
	EPA	
	DHA	
	EPA/DHA	
	Fish oil	
	Krill oil	
	Red yeast extract	
	Apple cider vinegar	
	Alpha lipoic acid	
	Niacinamide	

APPENDIX 2. LIST OF SUBGROUP ANALYSES

Lipid Parameters at Weeks 12 and 26					
	Percent change from BL				
SUBGROUP	TG	Non-HDL-C	VLDL-C	HDL-C	LDL-C
Age: ≤65 years vs. >65 years	X	X	X	X	X
Race: White/Caucasian vs. Non-White/Caucasian.	X	X	X	X	X
Ethnicity: Hispanic or Latino vs. Non-Hispanic or Latino	X	X	X	X	X
Gender: Male vs. non-Male.	X	X	X	X	X
Study: ACA-CAP-001 vs. ACA-CAP-002	X				
Countries: US vs. Canada vs. Mexico	X	X	X	X	X
Qualifying TG levels: ≤750 mg/dL vs. >750 mg/dL	X	X	X	X	X X
Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization.	X	X	X	X	X
Use of fibrate vs non-use at randomization.	X	X	X	X	X
Subjects with diabetes* vs. no diabetes at randomization.	X	X	X	X	X
Baseline level of EPA+DHA: ≤ median vs. > median	X	X	X	X	X
Glycemic Parameters at Weeks 12 and 26					
	Change and Percent change from BL				
SUBGROUP	FSG		HbA1c		
Age: ≤65 years vs. >65 years					
Race: White/Caucasian vs. Non-White/Caucasian.					
Ethnicity: Hispanic or Latino vs. Non-Hispanic or Latino					
Gender: Male vs. non-Male.					
Study: ACA-CAP-001 vs. ACA-CAP-002					
Countries: US vs Canada vs. Mexico					
Qualifying TG levels: ≤750 mg/dL vs. >750 mg/dL					
Baseline TG Levels: ≤750 mg/dL vs. >750 mg/dL					
Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization.					
Use of fibrate vs non-use at randomization.					
Subjects with diabetes* vs. no diabetes at randomization.	X		X		
Baseline level of EPA+DHA: ≤ median vs. > median					

FSG: Fasting serum glucose.
*Type 2 diabetes mellitus defined as subjects with history of diabetes, use of anti-diabetic medication , or with HbA1C level >=6.5%

APPENDIX 3. PROGRAMMING CONVENTIONS FOR OUTPUTS

A3.1 OUTPUT CONVENTIONS

Outputs will be presented according to the following conventions:

A3.1.1 ABBREVIATIONS

CGM Computer graphics metafile
ODS Output Delivery System
RTF Rich text file format

A3.1.2 INTRODUCTION

This section applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures.

A3.1.3 OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
As far as possible, output files should be in RTF format, although .DOC (.DOCX) files are also permitted.
The output files and corresponding SAS programs will have the same name. The filename will start with 'T', 'L' or 'F', respectively for table, listing or figure. The letter will be followed by the table number using leading zeroes ('0') when the number is smaller than 10. The last part will be a brief description of the table content. Elements in the file name will be separated by underscores '_'. For example:

Output type and number	**Title**	**File name**
Table 14.1-1.1	Subject Disposition – All Subjects Enrolled Population	T141_01_01_dispo.rtf T141_01_01_dispo.sas
Figure 14.2-2.2.1	Mean Plasma Concentration over Time – Pharmacokinetic Analysis Population	F142_02_02_01_Mean_Conc_PK.rtf F142_02_02_01_Mean_Conc_PK.sas

A3.1.4 PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.

The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

A3.1.5 FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New" .
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof97l
gaccess = gsasfile;
filename gsasfile "….cgm";
```

A3.1.6 HEADER INFORMATION

Headers should be defined as follows:
• The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
• The customer name and protocol number should appear in row 1, left-aligned, along with the delivery designation (e.g., Interim analysis, Dry-run, Final Analysis, etc.) as appropriate. The page identification in the format Page X of Y (where Y is the total number of pages for the output) should also appear in row 1 of the header, right aligned.
• The output identification number should appear in row 2, centered
• The output title should start in row 3, centered
• The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Full Analysis Set in preference to FAS.
• Mixed case should be used for titles
• The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g., Vital Signs) followed by metric (e.g., Change from Baseline): Vital Signs – Change from Baseline.
• Titles should not contain quotation marks or footnote references
• Column headings spanning more than one column should be underlined and should be centered
• Column headings containing numbers should be centered
• Column headings should be in sentence case
• In general, the population count should appear in the column header in the form "(N=XXX)"
• "Statistic" should be the column header over n, Mean, SE, n (%) etc.
• As a rule, all columns should have column headings.

A3.1.7 TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left-hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Text and number alignment will follow standard alignment conventions.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- If the original data has N decimal places, then the summary statistics should have the following decimal places:

Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)
50 (64.9%)
0 (0.0%)

- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

E.g. (<0.1%)
(6.8%)
(>99.9%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and

standard errors to two places more than the raw data

- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

(-0.12, -0.10)
(9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or subject listing.
- When information is not available, then "No observations available" will be used to reflect that observations are not available for a specific table/figure/listing.
- The 'Missing' category, when appropriate, will only be presented if subjects qualify for this category. Otherwise, the row for 'Missing' will not be presented.

A3.1.8 FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
- The image should be clear and of high quality when viewed in the Word document, and when printed.

• In general, boxes around the figures should be used.

Note: Figures in this document should be regarded as shells and final deliverables might look different to the examples presented here:

• A legend for treatment should always be presented, preferably below the actual graph, “N=xxxx” should be concatenated to the treatment group description

• If color is used, color should be linked to the same treatment; and similarly, the line type should be used for the same treatment and treatments should be differentiable for black and white printing.

A3.1.9 FOOTNOTE INFORMATION

Footers should be defined as follows:

• Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table

• The program path and name and version number (if applicable) should appear as last footnote, at the bottom of the page, left aligned, along with the date/time stamp, right aligned.

• Footnotes should be left-aligned.

• Footnotes should be in sentence case.

• The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.

• If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary

2.) Abbreviations and definitions

3.) Formulae

4.) P-value significance footnote

5.) Symbols

6.) Specific notes

• Common notes from table to table should appear in the same order.

• The symbols should appear in the same order as they are defined in the table or listing, from left to right.

A3.1.10 PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table, listing or figure shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words “Programming Note” followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

Please disregard current examples of precision in shells.

A3.2 DATES & TIMES

Dates and time will follow ISO 8601 format (as prescribed by CDISC standards). Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Imputed dates, as defined in Appendix 3 of this statistical analysis plan, will NOT be presented in the listings.

A3.3 SPELLING FORMAT

English US.

A3.4 PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Pool 1:

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
Placebo	Placebo	Placebo
CaPre 4g	CaPre4g	CaPre 4g

A3.5 PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening (Visit 1)	Scr (V1)
TG Qual Visit 2	Qual V2
TG Qual Visit 3 need also Visit 3.1	Qual V3 need also Qual 3.1
Baseline (Visit 4)	BL (V4)
Week 4 (Visit 5)	W4 (V5)
…	…
Week 26 (Visit 9)	W26 (V9)
End of Treatment	EOT
Contact Follow-up	Fup
Unscheduled Visit (Visit x)	UNS (Vx)

A3.7 EDITORIAL CHANGES

Any editorial changes such as corrections of typographical errors, modification of spelling, or change of wording in

titles or footnotes that leave the meaning unchanged can be done without requiring an amendment of this document. Footnote changes might also be necessary during the programming of displays depending upon the particular needs for special data handling. These changes will not require an amendment to this document.

APPENDIX 4. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

STATISTICAL ANALYSIS PLAN

ACA-CAP-001

A PHASE 3, MULTI-CENTER, PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND 26-WEEK STUDY TO ASSESS THE SAFETY AND EFFICACY OF CAPRE® IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA

AUTHOR: IRENE DEHEM/GINO COLAVITA

VERSION NUMBER AND DATE: FINAL V2.0 03DEC2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 03DEC2019) for Protocol ACA-CAP-001.

	Name	Signature	Date
Author:	Irene Dehem		5 DEC 2019
Position:	Statistical Scientist		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Gino Colavita		05DEC 2019
Position:	Statistical Scientist		
Company:	IQVIA		
Approved By:	Pierre Lemieux		05 Dec. 2019
Position:	Chief Operation and Scientific Officer (COO and CSO)		
Company:	Acasti Pharma Inc.		
Approved By:	Jean-François Lapointe		05 Dec, 2019
Position:	Director of Clinical Development		
Company:	Acasti Pharma Inc.		
Approved By:	Dariush Mozaffarian, MD DrPH		December 4, 2019
Position:	Lead Principal Investigator		
Company:	Tufts Friedman School of Nutrition Science and Policy		

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V1.0 (Dated 03DEC2019 for Protocol ACA-CAP-001.

	Name	Signature	Date
Author:	Irene Dehem		
Position:	Statistical Scientist		5DEC2019
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Gino Colavita		05 DEC2019
Position:	Statistical Scientist		
Company:	IQVIA		
Approved By:	Pierre Lemieux		05 Dec. 2019
Position:	Chief Operation and Scientific Officer (COO and CSO)		
Company:	Acasti Pharma Inc.		
Approved By:	Jean-François Lapointe		05 Dec. 2019
Position:	Director of Clinical Development		
Company:	Acasti Pharma Inc.		
Approved By:	Dariush Mozaffarian, MD DrPH		December 4, 2019
Position:	Lead Principal Investigator		
Company:	Tufts Friedman School of Nutrition Science and Policy		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Draft 1.0	16MAY2019	Irene Dehem/Gino Colavita	Not Applicable – First Version
V2.0	02DEC2019	Irene Dehem/Gino Colavita	Including FDAs recommendation RefID: 4521719

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Arachidonic acid
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BLQ	Below lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
CAI	Cholesterol-absorption inhibitor
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
DHA	Docosahexaenoic acid
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ENR	All Subjects Enrolled
EPA	Eicosapentaenoic acid
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone

Abbreviation	Definition
GGT	Gamma-glutamyltransferase
HbA1c	Glycosated hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostatis model assessment
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
ITT	Intent-to-treat analysis set
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA2	Lipoprotein-associated phospholipase A2
LS	Least squares
MAR	Missing-at-random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Effect Model Repeat Measurement
NCEP	National Cholesterol Education Program
OM3	Omega-3
OM6	Omega-6
PCSK9I	Proprotein convertase subtilisin/kexin type 9 serine protease inhibitors

Abbreviation	Definition
	Pharmacokinetics
PK	
PP	Per-protocol analysis set
PT	Preferred term
RDW	Red blood cell distribution width
Ridit	Relative to an identified distribution integral transformation
RLP-C	Remnant-like particle cholesterol
RR	Respiratory Rate for Vital Signs, or in context Relative Risk or RR interval (time between QRS complexes) for ECG
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SOCBP	Subject of child-bearing potential
T_4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent AE
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantification
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK) data for Protocol ACA-CAP-001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment no. 1, dated 22 MAY 2018. Approximately 50% of all patients will be randomized under the amended protocol.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting triglycerides (TG) levels in subjects with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are as follows:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by Adverse Events (AEs), vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C after 12 weeks of treatment.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of the study are as follows:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.
- To compare the proportion of patients achieving TG values below 500 mg/dL between CaPre and placebo.
- To determine the effect of CaPre, compared to placebo, on plasma phospholipid eicosapentaenoic
- acid (EPA), docosahexaenoic acid (DHA), the sum of EPA and DHA, arachidonic acid (AA) concentrations (expressed as percent of fatty acids), and on the omega-6/omega-3 and EPA/AA ratios.
- To explore the interaction of qualifying fasting TG levels (≤750 mg/dL or >750 mg/dL) on the change in primary, secondary and selected PK endpoints, for CaPre compared to placebo.

- To explore the interaction of selected demographic and baseline characteristics on the change in primary and secondary efficacy endpoints, for CaPre compared to placebo.
- To explore the interaction of selected demographic and baseline characteristics on the changes in plasma phospholipid EPA, DHA and EPA+DHA for CaPre compared to placebo.
- To explore the relationship between changes in plasma phospholipid EPA, DHA, and EPA+DHA and the change in fasting serum TG levels.
- To determine the effect of CaPre on apo B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on fasting serum glucose, insulin and on HbA1c.
- To explore the effect of CaPre on insulin resistance and beta-cell function (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on hsCRP and Lp-PLA2.
- To compare the proportion of subjects between CaPre and Placebo with increasing doses of current lipid-lowering medication or initiating new lipid-lowering medication following randomization.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multi-center, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre 4 g/day or placebo), Phase 3 efficacy and safety study in subjects ≥18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study duration will be up to 39 weeks, consisting of an initial diet, lifestyle and medication stabilization period of 4 or 6 weeks, a 2 or 3-week TG qualifying period, a 26-week double-blind treatment period, and a 4-week contact follow-up. Approximately 653 subjects were initially planned to be screened to obtain 245 randomized subjects at approximately 84 centers.

Screening Period

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study. Appendix 2 of the protocol provides information outlining the principles of NCEP-TLC dietary patterns focused on lowering cholesterol.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not taking any lipid-altering agents or who are already receiving prior to screening (Visit 1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment should not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements specifically taken for their lipid-altering effects.
Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to screening.

Qualifying Period

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, then an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

This is considered the qualifying TG to be used for stratification at randomization.

Subjects who fail to meet the average TG inclusion level will be considered screening failure. Rescreening of these subjects will not be allowed.

Double-Blind Treatment Period

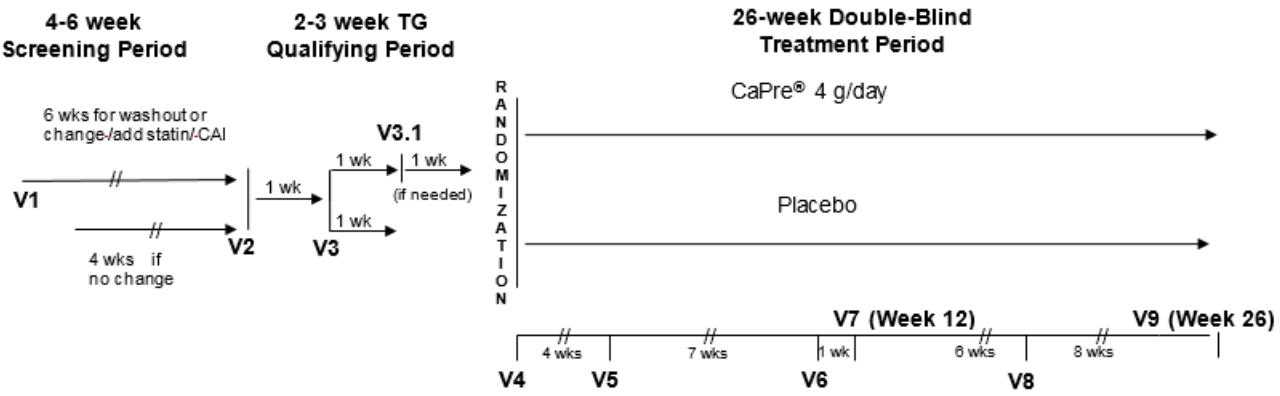
After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily or placebo daily. Subjects will receive instructions to take the study medication at a meal. Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated with statin, CAI or PCSK9I alone or in combination).

Following randomization at Visit 4 (Week 0), subjects are to return to the study center at Visit 5 (Week 4), Visit 6

(Week 11), Visit 7 (Week 12), Visit 8 (Week 18) and for the last visit at Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety assessment is required 4 weeks after Final Visit (Visit 9 or early termination). Centralized laboratory testing was configured such that all study personnel was to remain blinded to all lipids, biomarkers, and EPA, DHA results from the randomization visit. The results will only be received once the treatment unblinding request form has been signed.

The study design is presented in Table A.

Table A: Schematic of Study Design



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 1, after Section 4.1.8 in the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The following exploratory objectives were changed, clarified or expanded compared to the protocol:

From:
To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol.

To:
To determine the effect of CaPre compared to placebo on total cholesterol (TC).

From:
To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.

To:
To explore the interaction of qualifying fasting TG levels (≤750 mg/dL or >750 mg/dL) on the change in primary, secondary and selected PK endpoints, for CaPre compared to placebo.

From:
To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.

To:
To explore the interaction of selected demographic and baseline characteristics on the changes in plasma phospholipid EPA, DHA and EPA+DHA, for CaPre compared to placebo.

From:
To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.

To:
To explore the interaction of selected demographic and baseline characteristics on the change in primary and secondary efficacy endpoints, for CaPre compared to placebo.

The following exploratory objectives were added compared to the protocol:

To compare the proportion of subjects between CaPre and Placebo with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization.

The following changes on the exploratory endpoints occurred compared to the protocol:

From:
Percent change from baseline (Week 0) to Week 12 and Week 26 in FSG, insulin and HbA1c

To:
Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c in all randomized subjects, and in those with Diabetes Mellitus.

From:
Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-B.

To:
Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β in all randomized subjects, and in those with Diabetes Mellitus.

From:

Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma phospholipid EPA and DHA concentrations.

To:
Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma phospholipid EPA, DHA and EPA+DHA relative concentrations (expressed as percent of fatty acids).

The following exploratory endpoints were added compared to the protocol:

Proportion of Subjects with Diabetes Mellitus with HbA1c below 7% at Week 12 and at Week 26.
Proportion of subjects with increasing doses of current lipid-lowering medication or initiating new lipid-lowering medication following randomization.

The following exploratory endpoint was removed compared to the protocol:
Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index in red blood cells;

4. PLANNED ANALYSES

There will be no interim analysis or periodic data review by an independent data monitoring committee (DMC).

Only a Final Analysis will be performed for this study.

Due to GCP non-compliance uncovered during regular monitoring and site audit activities that remained unresolved[1] at the time of database closure, site 163 will be removed from all analyses. A sensitivity analysis will be performed on the primary and secondary efficacy endpoint with the site included. A separate listing of adverse events of the site 163 will be provided.

4.1. DATA MONITORING COMMITTEE

There will be no DMC for this study.

[1] Sponsor has been unable to complete planned audit activities as site had moved locations without providing notice to the CRO or the Sponsor. Since then, several attempts have been made, via phone, email and certified letter to contact the principal investigator (PI) and site staff with no success and without any response from these individuals. Site and PI are considered in breach of their regulatory and contractual obligations to maintain Study records and to allow IQVIA and Sponsor representative's access to the site and the study records for auditing and monitoring purposes.

4.2. INTERIM ANALYSIS

There will be no interim analysis for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Acasti Pharma Inc. authorization of this SAP, database lock, analysis sets and unblinding of treatment.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled set (ENR) will contain all subjects who provide informed consent for this study.

5.2. INTENT-TO-TREAT ANALYSIS SET [ITT]

The intent-to-treat (ITT) analysis set will contain all subjects in the ENR set who were randomized to study medication.
For analyses and displays based on ITT analysis set, following the ITT principle, subjects will be analyzed according to the treatment to which they were randomized regardless of any departures from the original assigned group.

5.3. PER PROTOCOL ANALYSIS SET [PP]

The per-protocol (PP) analysis set will contain all subjects in the ITT analysis set who did not have protocol deviations that could influence the primary endpoint assessment defined as (but not limited to):

- Subject randomized despite not satisfying inclusion/exclusion criteria and that may have confounded the primary endpoint assessment
- Subject with non-evaluable primary endpoint or who completed assessments significantly outside of the specified visit windows.
- Subjects who did not receive the treatment to which they were randomized
- Subjects who did not reach compliance to study medication between 80-120%
- Subjects who significantly deviated from the protocol requirements regarding prohibited and/or allowed

medications that may have confounded the primary endpoint assessment
- Any other major protocol deviation that is thought to interfere with the primary endpoint assessment

Protocol deviations that have the potential to affect interpretation of the study results will be reviewed and approved by the blinded study team prior to final analysis set and prior to unblinding.

5.4. SAFETY ANALYSIS SET [SAF]

The safety (SAF) analysis set will contain all subjects in the ENR who receive at least one dose of study medication. Subjects will be classified according to treatment received.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.
Reference start date is defined as:
- The day of the first dose of study medication (Day 1 is the day of the first dose of study medication) for treated subjects.
- The randomization (Visit 4, week 0) visit date for subjects who were randomized but not treated.

Thus,
- If the date of the event is on or after the reference date, then:
  - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  - Study Day = (date of event – reference date).

The reference start date and Study Day will appear in every listing where an assessment date or event date appears In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

For related assessments (e.g. systolic and diastolic BP), it will be desirable that both baseline values come from the same measurement and not from different dates/visits in case one value is missing.

For subjects in the ITT analysis set, if subjects were randomized but not treated, then baseline is defined as the last non-missing measurement taken on or before the randomization (Visit 4) visit date.

For the fasting TG levels (primary endpoint), non-HDL-C and HDL-C, the baseline value is defined as the average of the last 3 measurements obtained prior to or on the date of randomization (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification).

For the VLDL-C (ultracentrifugation) and LDL-C (ultracentrifugation), the baseline value is defined as the average of 2 measurements obtained prior to or on the date of randomization (average of Week -1 and 0 corresponding to measurements taken at Visits 3, and 4. No VLDL-C and LDL-C measurements are taken at Visit 3.1.

6.3. DERIVED TIMEPOINTS

For primary endpoint (percent change from baseline in fasting TG levels), key secondary efficacy endpoints [percent change from baseline in non-HDL-C, VLDL-C (ultracentrifugation), HDL-C, LDL-C (ultracentrifugation)] and exploratory endpoint total Cholesterol, the Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12).

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For post baseline visits of all efficacy endpoints: unscheduled/retest visits will be used if they are the nearest of the target day per the time windows defined in Section 6.5.

For baseline visits of all efficacy endpoints: scheduled visits will be used. Should a scheduled visit be missing it will be replaced by its unscheduled/retest value as long as the unscheduled/retest value is taken prior to the next visit.

For safety parameters: data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/ worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries. If no measurement is available at the nominal visit or no retest is available, the assessment will be considered missing for the visit.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

No time windows will be performed prior to the first dose.

For all efficacy endpoints, the following post dose time windows will be used:

Visit Name	Window	Target
Week 4	Day 24 to Day 35	Day 28
Week 11-12*	Day 71 to Day 94	Day 84
Week 12**	Day 78 to Day 94	Day 84
Week 18	Day 121 to Day 136	Day 126
Week 26	Day 176 to Day 192	Day 182

*Week 12 endpoint based on the average of 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12).
** Week 12 endpoint based on 1 measurement obtained at the end of the 12-week double-blind treatment period, at Visit 7 (Week 12).

6.6. STATISTICAL TESTS

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

And percent change from baseline will be calculated as:

- 100 x (Test Value at Visit X – Baseline Value) / Baseline Value

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage of available data for each class of the parameter will be presented. Unless otherwise specified, percentages will be based on the available data. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), the mean, the standard deviation (SD), the median, the minimum and maximum values. The summary statistical Tables will be generated for the raw (actual) assessments and as applicable for the Change from Baseline and the Percent Change from Baseline.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

For the primary efficacy analysis and key secondary efficacy analysis, a non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as a covariate will be used to perform the hypothesis test.

For the exploratory endpoint of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a Cochran-Mantel-Haenszel (CMH) test will be used, controlling for qualifying TG category (≤750 mg/dL vs. >750 mg/dL) and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization.

7.2. MULTICENTER STUDY

Approximately 84 clinical centers is expected to participate in this study and approximately 245 subjects to be randomized, thus it is anticipated that most centers will evaluate less than 5 patients. Therefore, due to the relatively low number of patients per site, no inferential analyses of site-specific effects or differences between sites will be performed, and no adjustment for site will be made in the analyses.

7.3. MISSING DATA

Missing safety data will not be imputed except for the missing dates to identify treatment-emergent adverse events (TEAEs) (see Appendix 3 of this SAP).

Missing efficacy data will be handled as described in section 15 (and subsections) of this SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The experiment-wise type I error will be controlled to a maximum of two-sided 5% by using a hierarchical closed testing procedure: secondary efficacy endpoints will only be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment. Similarly, the later secondary endpoint in the hierarchy will be considered for statistical significance only if all former preceding secondary endpoints are found to be statistically significant.

Specifically, the following testing order will be followed for the overall type I error control:

1. Percent change from baseline to Week 12 in TG (primary endpoint)
2. Percent change from baseline to Week 12 in non-HDL-C
3. Percent change from baseline to Week 12 in VLDL-C
4. Percent change from baseline to Week 12 in HDL-C
5. Percent change from baseline to Week 12 in LDL-C

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided).

For all exploratory variables, nominal p-values will be reported in an exploratory fashion.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis section (15.3.4).

The following subgroups will be assessed and described below for either the primary, secondary or PK endpoints at Week 12 (EPA, DHA and EPA+DHA).

- Baseline age group: ≤65 years vs. >65 years. ***Primary and PK endpoints***.
- Race: White/Caucasian vs. Non-White/Caucasian. ***Primary and PK endpoints***.
- Gender: Male vs. non-Male. ***Primary and PK endpoint***.
- Qualifying TG levels: ≤750 mg/dL vs. >750 mg/dL (or ≤8.5 mmol/L vs. >8.5 mmol/L). ***Primary, secondary and PK endpoints***.
- Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization. ***Primary, secondary and PK endpoints***.
- Use of fibrate vs non-use at randomization. ***Primary and PK endpoints***.
- Baseline plasma phospholipid EPA+DHA ≤ median value versus > the median value in the ITT population. ***Primary and PK endpoints***.
- Presence of co-morbidities:
  - Subjects with diabetes (Type 2 diabetes mellitus, defined as subjects with history of diabetes, use of anti-diabetic medication, or with HbA1c level >= 6.5%) vs. no diabetes at randomization. ***Primary, secondary and PK endpoints***.

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study. The format and content of the summary tables, figures, and listings will be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.
Subject disposition and withdrawals, reasons for exclusion from each analysis set, and protocol deviations (including inclusion and exclusion criteria) will be presented for the ITT analysis set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT, SAF and PP analysis sets. Demographic and baseline characteristics will be compared between the two treatment groups by using a t-test for continuous variables and Chi-Square test for categorical variables.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent and per category (≤ 65 > 65 years old)
- Gender (%)
- Race/ethnicity (White/Caucasian, White/Caucasian, Asian, Black/African-American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Unknown, Other). In each racial category, the proportion of subjects of Hispanic or Latino ethnicity will be reported. (%)
- Weight (kg)
- BMI (kg/m^2)
- Tobacco use (Never, Former, Current) (%)
- Alcohol use (Never, Former, Current) (%)
- Baseline efficacy parameters:
  - TG Levels
  - Qualifying TG category (≤750 mg/dL vs. >750 mg/dL)
  - Non-HDL-C
  - VLDL-C
  - HDL-C
  - LDL-C
- Concomitant Medications
  - Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization
  - Use of statin
  - Use of CAI
  - Use of PCSK9

  - Use of of Fibrate vs non-use at randomization
- HbA1c
- Subjects with Diabetes Mellitus, which are subjects who have a history of diabetes or use anti-diabetic medication or have HbA1c >= 6.5% at baseline (randomization visit).
  - HbA1c
  - Subjects with diabetes mellitus with HbA1c < vs. ≥ 7.0%

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ $height^2$ $(m)^2$
- eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
- Where:
- Scr is serum creatinine in mg/dL;
- κ is 0.7 for females and 0.9 for males;
- α is -0.329 for females and -0.411 for males;
- min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr /κ or 1;
- Age in years

11. MEDICAL HISTORY AND CONCOMITANT ILLNESSES

Medical history and concomitant illnesses will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 20.1 (or higher), and the information will be presented for the subjects in the SAF analysis set by system organ class (SOC) and preferred term (PT).

Medical history conditions are defined as those conditions which stop prior to or at Screening while concomitant illnesses are conditions (other than the indication being studied) which started prior to or at Screening and are ongoing at the date of Screening.

12. MEDICATIONS

Medications will be coded using the most current version of the WHODrug Global (Conventional medicines and herbal remedies) version 01 Sep 2017 (or higher) and will be presented for subjects in the SAF analysis set.

See Appendix 3 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication in the double-blind period.
- 'Concomitant' medications are medications which:

  - started prior to, on, or after the first dose of double-blind study medication and started no later than the day of the last dose of study medication,
  - AND ended on or after the date of first dose of double-blind study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started one (1) day following the last dose of study medication.

Prior and concomitant medications will be summarized by PT and presented in a subject data listing, while post-treatment medications will only be presented in a subject data listing.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for subjects in the SAF analysis set.

The date of first study medication administration will be taken from the eCRF "Randomization" form. The date of last study medication will be taken from the eCRF "End of Treatment" form. In the case of missing data on the eCRF, the date of randomization will be used to determine the first date of study medication and the earliest record of the last contact date and the last date of medication returned will be used as a date of last dose.

Interruptions and compliance are not considered for duration of exposure.

13.1. DERIVATIONS

Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

14. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for subjects in the SAF analysis set, for each study visit where it is assessed (Week 4, Week 12, Week 18 and Week 26/ET), between Week 4 and Week 12, between Week 12 and Week 26, and overall. Descriptive statistics will be presented and the number and percentage of subjects in each of the following categories will also be presented: '< 80%', '80-120%' '>120%'.

14.1. DERIVATIONS

Compliance with double-blind study medication—based on the drug accountability data—will be calculated as the number of capsules consumed divided by the prescribed number of capsules expressed as a percentage (see calculations below).

It is assumed that all subjects will take 4 capsules once daily, expected starting from the visit day at which their medication is initially dispensed to the day prior to the morning of their last medication return date. For example, if

the initial dispense date is Day1 and the last return date is Day10, then the subject should have taken 4 capsules on Days 1 to 9 (subjects don't take medication prior to attending the visit); hence, the total number of prescribed capsules would be 9×4 = 36. Compliance will be based on the nominal visit dates and not the actual date entered in the CRF, as medication may be returned late.

For non-completers, compliance will be calculated up until the last visit completed, or until the early termination visit if it is available. For subjects with no early termination visit, no compliance will be derived between the last visit completed and the time of discontinuation.

For non-adherers, which are subjects who discontinue receiving the study medication but agree to allow some or all data collection through the planned duration of the trial, compliance will be calculated up until the last visit under treatment completed. Compliance will be 0% for subsequent visits completed and for which no study medication dispensation occurred.

Θ = Number of capsules required to be taken per day.

- "Per Visit" Compliance to study medication will be calculated as follows:

$$\frac{\{(\text{N of capsules consumed at Visit Xn})\} \div \Theta}{[\text{Date of Visit Xn}] - [\text{Date of Visit Xn}-1]} \times 100$$

- Overall Compliance to study medication will be calculated as follows:

$$\frac{\{([\text{N of Capsules consumed at Visit 5}]) + \cdots + [\text{N of Capsules consumed at Visit X(n)}])\} \div \Theta}{[\text{Date of Visit X(n)}] - [\text{Date of Visit 4}]} \times 100$$

For subjects non-completers, the "Date of Visit X(n)" will be the date of the early termination visit, or the date of the last visit completed if no early termination visit was performed.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies.

The baseline TG level is calculated as described in section 6.2, the Week 12 endpoint value is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12), and the percent change from baseline to the Week 12 endpoint will be calculated as defined in section 6.7, unscheduled visits and retests will be treated as defined in section 6.4. Should there be only one measurement available at either Visit 6 (Week 11) or Visit 7 (Week 12), then that measurement will be used as the Week 12 endpoint value.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

All collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the primary analysis. Subjects who withdraw consent for study participation overall and are not assessed at both Week 11 and 12, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 6.4), will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or 12. No imputation is required if one of the week has a non-missing value.

A subject with complete data will have measurements at baseline (the average of the last 3 measurements obtained prior to dosing, i.e., average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification), Week 4, and Week 11 and/or 12. A subject with missing data at any visit prior to Week 12 and a non-missing value at any subsequent visit(s) up to Week 12 is said to have intermittent (non-monotone) missing data. A subject with missing data at a post baseline visit and at all subsequent visits is said to have monotone missing data.

Imputed data will consist of 100 imputed datasets. The random seed number for the multiple imputation (MI) of intermittent missing data will be 20180712 and the random seed number for the imputation of monotone missing data using the sequential regression MI will be 180712. The same random seeds will be used for these two steps when imputing data for the primary analysis as well as for sensitivity analyses, although the imputation models will be different.

Results of the analysis model (ANCOVA as described in section 15.1.3) from multiple imputed datasets will be combined using the Rubin's combination rule as implemented in the MIANALYZE procedure in SAS.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to test the null hypothesis that the percent change from baseline to Week 12 of fasting TG level in the active group is the same as that in the placebo group for all randomized subjects. The alternative hypothesis is that the percent change from baseline of fasting TG level in the active group is NOT the same as that in the placebo group.

The primary efficacy analysis will be performed for subjects in the ITT analysis set and will also be carried out for the PP analysis set as supportive analysis.

Descriptive statistics will be provided and statistical testing will be performed to compare the median values in percent change from baseline to Week 12 in TG levels.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used to test the null hypothesis on the primary efficacy variable.

MI will be implemented in two steps to impute missing values of the primary endpoint. First, partial imputation assuming a missing-at-random (MAR) mechanism will be carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. The model will be estimated using only subjects who discontinued treatment at some stage in the study, treatment group will be included as covariate. The imputation model will include the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization as fixed covariates and observed TG values at Baseline, Week 4, Week 11, Week 12, Week 18 and Week 26. The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior. In case of non-convergence the model will be reduced to the baseline and the visit values.

Then, the remaining monotone missing data will be imputed using sequential regression multiple imputation. The response to be imputed will be the change at each visit from the last pre-discontinuation value. A separate regression model is estimated for imputation of the change from the last pre-discontinuation value to each visit. Each regression model will include explanatory variables for the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, treatment group, treatment duration, baseline triglycerides and last value before. The MONOTONE REGRESSION statement in the MI procedure in SAS will be used. For the primary analysis, the imputation model at this step will be estimated only from the reference group of subjects who discontinued their randomized treatment early but remained in the study and were assessed at Week 11 and/or 12. This will be implemented using the MNAR statement in the MI procedure in SAS with the MODELOBS option. A flag identifying subjects belonging to the reference group as described above will be derived and used in the MODELOBS option to identify the subset of subjects from whom the imputation models are to be derived, if the model does not converge the strata will be removed from the model.

After the imputation is done on the change from the last value before discontinuation, the imputed value for the triglyceride measure will be derived by adding to the last value pre-discontinuation the imputed change for each visit.

Should there be not enough non-adherers to model the method described above, a BOCF like imputation model will be used. After a monotone dataset has been created, a set of baseline values are imputed for each subject. The model for the baseline measure of the triglycerides will include other values measured at baseline (O'Kelly et al., 2014). The other baseline measurements in the model will include the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, treatment group. The multiply imputed baseline triclyceride values for each subject are then "stored" and used to multiply impute the missing post-baseline values. This approach to BOCF is preferred because a) the model for the imputed baseline values captures observed associations of baseline triglyceride with other values measured at baseline; 2) the imputed baseline values reflect the two sources of variance noted by Rubin, i.e. the imputed baseline values reflect both the variability inherent in the baseline random variable, and the uncertainty as to the likely mean of the underlying distribution of that baseline, for each subject.

No rounding or range restrictions will be applied.

For each of the 100 imputed datasets, the non-parametric ANCOVA based on ranks will be performed as follows: the percent change from baseline in TG value and the TG baseline value will be transformed to modified ridit scores within stratum (qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin [CAI or PCSK9I, alone or in combination] vs. non-use at randomization). Modified ridit scores are ranks standardized for the different sample sizes per stratum. In the second step, ordinary Least Square (LS) regression applied to the modified ridit scores of the percent change from baseline and baseline will be performed within each stratum using the model:
Percent change from baseline = baseline.

In the third step, residuals from these regression models will be used. In that final step, the residuals from all strata will be included in a stratified extended Cochran-Mantel-Haenszel (CMH) test of the residuals (i.e., stratum by treatment by residual) to analyze the treatment effect. CMH test statistics (the Row Mean Score Differ statistic will be used, this will be obtained with the CMH2 option in the TABLES statement of PROC FREQ) obtained from each of the multiple imputed datasets will be combined using the Rubin's combination rule after applying a normalizing Wilson-Hilferty transformation for a chi-square distributed statistic. The transformation will be applied as follows:

$$wh\_cmh^{(m)} = \sqrt[3]{cmh^{(m)}/df}$$

where $cmh^{(m)}$ is the CMH statistic computed from the m[th] imputed dataset $m = 1, \ldots, 100$, df is the number of degrees of freedom associated with the CMH statistic, and $wh\_cmh^{(m)}$ is the transformed value. The transformed statistic is approximately normally distributed with mean $1 - 2/(9 \times df)$ and variance $2/(9 \times df)$ under the null hypothesis.

This transformed statistic will be standardized to obtain a variable that is normally distributed with mean 0 and variance 1:

$$st_{wh\_cmh}{}^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt[2]{\frac{2}{9 \times df}}}$$

This transformed statistic and the corresponding standard error of 1 will be combined using the Rubin's rule.

Quantile regression, adjusting for the same baseline covariates (as specified in the ANCOVA model above) will be used to obtain an adjusted estimate of the median treatment difference with associated two-sided 95% CI. Rubin's combination rule will be used to combine the estimates from multiple imputed datasets.

As supportive analysis, Hodges-Lehmann estimate for the median of the treatment differences and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied. Bootstrap in combination with MI will be performed as follows:

- Format the analysis dataset using a horizontal structure, i.e., with one record per subject, with the longitudinal values in columns (as variables).
- Obtain bootstrap datasets $b = 1, \ldots, B$ of the same size as the original dataset (the same number of subjects) by sampling with replacement the entire subject records from the original data (by treatment, adherers and strata). The number of bootstrap datasets will be $B = 2000$. The random seed for generation of bootstrap datasets will be set to 30180712.
- Perform multiple imputation as described above for each bootstrap dataset with the number of imputations M=10. This will result in M imputed datasets generated for each bootstrap dataset, i.e., $B \times M$ in total.
- Obtain a Hodges-Lehmann estimate for the median of the treatment differences in each bootstrap / imputed dataset: $\hat{\delta}_{m,b}, m = 1, \ldots, M, b = 1, \ldots, B$.
- Estimate an average treatment difference for each bootstrap dataset: $\bar{\delta}_b = \frac{1}{M}\sum_{m=1}^{M} \hat{\delta}_{m,b}$,
- Estimate the overall Hodges-Lehmann estimate as: $\hat{\delta} = \frac{1}{B}\sum_{b=1}^{B} \bar{\delta}_b$
- Estimate 95% CI using percentiles of the bootstrap distribution, i.e., use the 2.5% and 97.5% percentiles of the $\bar{\delta}_b$values sorted in ascending order as the lower and upper limit of the 95% CI respectively.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the primary analyses by using other strategies for dealing with missing data.

Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed at Week 11 and/or 12. This approach assumes that some subjects discontinuing the study will do so for non-treatment related reasons and would have similar outcomes to subjects who are able to complete the treatment.

This analysis will be implemented in a similar manner to the primary analysis, except that when the monotone data are imputed, the MNAR statement in the MI procedure will not be used, and therefore, all subjects with available data will be used for the estimation of the imputation model.

If the number of subjects who discontinue the study medication early and are assessed at Week 11 and/or 12 after having started an alternative therapy is large (e.g., > 5% of all ITT subjects), then an additional sensitivity analysis will be performed where data from these subjects will be excluded from analysis and these subjects will be treated as having missing data, i.e., will be imputed under the MAR assumption. This analysis will serve to assess the contribution of the alternative therapies to the estimate of the total treatment effect.

A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study by a pre-specified adjustment in the primary efficacy (O'Kelly and Ratitch, 2014, Chapter 7).

The steps to implement the sensitivity analyses are detailed in Appendix 4.

All sensitivity analyses will be conducted for the ITT analysis set only.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the ITT analysis set only.

The secondary efficacy endpoints for this study are (in order of importance for the control of the type 1 error):

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (ultracentrifugation).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (ultracentrifugation).

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The baseline value is defined in the same way as for the primary analysis, namely, as the average of the 3 last measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification) except for VLDL-C and LDL-C determined ultracentrifugation (average of Week -1 and 0 corresponding to measurements taken at Visits 3 and 4).

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE

Similarly to the primary analysis, all collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the analysis of key secondary endpoints. In case of a non-evaluable endpoint, the following replacement strategy will be followed:

- Should the baseline and/or Week 12 endpoint for LDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing) making the change from baseline non-evaluable, then LDL-C (direct) measurements, if available, should be used to derive both the baseline and the Week 12 endpoint.
- Similarly, should the baseline and/or Week 12 endpoint for VLDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing) making the change form baseline non-evaluable, then VLDL-C will be derived using the following formula:

  VLDL-C = TC – HDL-C – LDL-C(direct)

Subjects who withdraw consent for study participation overall and are not assessed at both Week 11 and 12, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 6.4) will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Similar analyses as specified above for the primary efficacy analysis will be conducted on all the secondary efficacy endpoints.

A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo based on the multiply-imputed data as described for the primary analysis.

15.3. EXPLORATORY EFFICACY

The exploratory efficacy endpoints of the study are the following:

- Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (i.e. Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and Week 12) and Week 26 in TC.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 26 in non-HDL-C and HDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII and apo A5.

- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (HDL Particle Number, LDL Particle Number, Non-HDL Particle Number, HDL Small, HDL Large, LDL Very Small-d, LDL Very Small-c, LDL Very Small-b, LDL VERY Small-a LDL Small, LDL Medium, LDL Large-b, LDL Large-a, IDL Small, IDL Large, VLDL Small, VLDL Medium, VLDL Large, LDL Pattern, LDL Peak Size).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL-C.
- Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c in all randomized subjects, and in those with Diabetes Mellitus.
- Proportion of Subjects with Diabetes Mellitus with HbA1c below 7% at Week 12 and at Week 26.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β in all randomized subjects, and in those with Diabetes Mellitus.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP, log hs-CRP and Lp-PLA2.
- Proportion of subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization.

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

Except when otherwise defined above (15.3), the baseline value for other exploratory efficacy endpoints is defined as the value obtained prior to dosing (measurement taken at Visit 4 (Week 0); Week 12 endpoint is defined as the value obtained at Visit 7 (Week 12) and Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26), whenever applicable.

Log hs-CRP will be derived.

HOMA-IR will be derived as:

HOMA-IR = (Insulin (U/L) X Glucose (mmol/L)) / 22.5

HOMA-β will be derived as:
HOMA-β = (20 X Insulin (U/L)) / (Glucose (mmol/L) – 3.5) and result is expressed as %β

Subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization will be flagged as:

- Subjects having a prior medication of the list of lipid modifying drug listed in part A of Appendix 1:
  - Start date of the first entry is prior to randomization and the stop date is after randomization or is ongoing.
  - The dose increased compared to baseline, or
  - The frequency increased compared to baseline

- Subjects not having any prior medication but have concomitant medication from any product in the list of lipid modifying drug listed in Appendix 1
  - No entry prior to randomization, and at least one entry with start date on or after randomization. May be ongoing or stopped.

The final list of subjects with these criteria will be reviewed by the medical monitor.

15.3.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLE(S)

Subjects with missing data at the analysis time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

15.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

All exploratory efficacy endpoints defined as percent change from baseline will be analyzed as specified above for the primary and secondary efficacy endpoints and will be conducted on the ITT analysis set only. A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo based on the multiply-imputed data as described for the primary analysis.

The persistence of the effect of CaPre on the TG profile will be explored by comparing the percent change in fasting TG levels from Baseline to different time points. Descriptive statistics will be presented by treatment group at each visit and will also be summarized using graphical representation over time (from Baseline to end of study Week 26).

Regarding the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

For analysis of the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a sensitivity analysis will also be performed where subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

Regarding the proportion of subjects with Diabetes Mellitus who achieve HbA1c below 7% at Week 12 and at Week 26, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

Regarding the proportion of subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization (derived as in section 15.3.1), at Week 12 and at Week 26, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or

PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

No multiplicity adjustment will be applied to the exploratory efficacy analyses. As such, nominal p-values will be reported in an exploratory fashion.

15.3.4. SUBGROUP ANALYSES

Subgroups are listed in section 7.5. Descriptive statistics will be summarized for each subgroup.

The treatment effect within each subgroup will be estimated using the same quantile regression model as described in the primary efficacy analysis in Section 15.1.3 for each subgroup. Multiple imputation models (for non-monotone and monotone missing data imputation) will include a main effect for subgroup and a treatment-by-subgroup interaction effect. If there are estimability issues, then the interaction term will be removed from the model. A Forest plot will be produced to show the treatment effects and the corresponding CIs (overall and within each subgroup).

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF analysis set.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the most current version of MedDRA dictionary, version 20.1 (or higher). Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study medication.

See Appendix 3 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and will be broken

down further by maximum severity and relationship to study medication.

16.1.1.1. Severity

Severity[2] will be classified as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject report a TEAE more than once within that SOC/ PT, then the AE with the worst severity will be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, will be classified as "not related[3]", "unlikely related", "possibly related", "probably related" and "related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related", "probably related" or "related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "probably related" to study medication. If a subject report the same AE more than once within that SOC/ PT, then the AE with the worst relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the 'Action taken with study medication" field on the Adverse Events page of the eCRF. TEAEs with action of "study medication withdrawal" or "withdrawal from study" will be considered as leading to discontinuation of study medication.

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

16.1.4. Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

[2] Severity is equivalent to Intensity as defined in study protocol for adverse event characterization and reporting.
[3] Not related is equivalent to Unrelated as defined in study protocol for adverse event characterization and reporting

16.1.5. ADVERSE EVENTS OF SPECIAL INTEREST

The following list of SMQs are considered of special interest:

- Hyperglycaemia/new onset diabetes mellitus (SMQ)
- Anaphylactic reaction (SMQ)
- Angioedema (SMQ)
- Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)
- Haemorrhages (SMQ)
- Hepatic disorders (SMQ)
- Hypersensitivity (SMQ)
- Rhabdomyolysis/myopathy (SMQ)
- Anaphylactic/anaphylactoid shock conditions (SMQ)

A summary of TEAEs of Special Interest by SOC and PT will be prepared. Due to the fact that the study is blinded we do not expect any LDL-C increase in the adverse events, they will be seen through shift tables in the laboratory analysis.

16.2. LABORATORY EVALUATIONS

Results from the central laboratory for hematology, chemistry, coagulation, urinalysis, fasting lipids and other analytes will be included in the reporting of this study for parameters listed in Table B below. Biomarkers and pharmacokinetic (PK) parameters will be covered in sections 17 of this SAP respectively.

Table B Laboratory Assessments

Hematology (Visit 1, 4, 5, 7 and 9[1])	**Clinical Chemistry** (Visit 1, 4, 5, 7 and 9[1])	**Lipids (fasting)** (All study Visits)	**Biomarkers** (Visit 4,7 and 9[1])
Hemoglobin Hematocrit Erythrocyte count Leukocyte count Leukocyte differential count (including neutrophils, lymphocytes , monocytes , eosinophils and basophils) Platelet count MCV MCH MCHC RDW Coagulation (Visit 1, 4, 5, 7 and 9[1]) PT INR aPTT Other analytes Hepatitis B and C (Visit 1) HbA1c (Visit 1,4, 7 and 9) Insulin (fasting) (Visit 4,7 and 9)	Albumin ALP ALT Amylase AST GGT Bilirubin, Total Lipase Urea Nitrogen/Urea Uric acid Creatinine Creatine Kinase (CK) Calcium Chloride Magnesium Glucose Potassium Sodium Bicarbonate Pregnancy test (SOCBP, serum testing at Visit 1) FSH (as required for post-menopausal subjects only) Creatinine Clearance and estimated Glomerular Filtration Rate (eGFR) (calculated at Visit 1, 4, 5, 7 and 9)	Triglycerides (TG) Total cholesterol (TC) non-HDL-C (calculated) HDL-C LDL-C (direct) * VLDL-C (calculated)* _____ Urinalysis ** (Visit 1, 4, 5, 7 and 9[1]) Color Clarity/Appearance Specific gravity pH Glucose Blood (includes erythrocytes) Protein Leukocyte Esterase Ketones Nitrites Bilirubin Urobilinogen Creatinine Proteinuria (estimated by urine protein/creatinine ratio - UPCR) (calculated at Visit 1)	AA Apo AI Apo B Apo CIII Apo A5 Lp-PLA2 hsCRP Lipoprotein (particles concentration & size)*** oxidized LDL-C omega 6 FA omega 3 FA Pharmacokinetics DHA, EPA, EPA+DHA, Arachidonic acid, omega-6/omega-3 ratio and EPA/AA ratio. (Visits 4, 5, 7, 8 and 9[1]) Thyroid Function (Visit 1) TSH T_4

[1] All laboratory assessments required at visit 9 will also be made at the Early Termination Visit.

* LDL-C and VLDL-C to be also obtained via preparative ultracentrifugation at Visit 3,4,6,7 and 9.

**Urine Microscopy will be performed if blood, protein, leukocyte esterase, and/or urobilinogen is abnormal.

*** Includes HDL Particle Number, LDL Particle Number, Non-HDL Particle Number, HDL Small, HDL Large, LDL Very Small-d, LDL Very Small-c, LDL Very Small-b, LDL VERY Small-a LDL Small, LDL Medium, LDL Large-b, LDL Large-a, IDL Small, IDL Large, VLDL Small, VLDL Medium, VLDL Large, LDL Pattern, LDL Peak Size.

Presentations will use Conventional Units.

The following summaries will be provided for laboratory data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group (for quantitative measurements). Incidence of abnormal values (categorized as Low or High) according to reference range criteria
- Shift from baseline according to reference range criteria (for quantitative measurements and categorical measurements), by visit and for each treatment group.
- Laboratory measurements which are collected only on one visit will be presented in listings only.

All laboratory data will also be provided in subject data listings.

Laboratory out of standard reference ranges will be presented in a separate listing.

16.2.1. LABORATORY SPECIFIC DERIVATIONS

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

16.2.2. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in conventional units and categorized as:

- Low (L): Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High(H): Above the upper limit of the laboratory reference range.

16.3. ECG EVALUATIONS

Electrocardiogram (ECG) results as collected on the 12-Lead ECG eCRF page at Visits 2 (Week -2), 7 (Week 12) and 9 (Week 26) will be included in the reporting of this study. Baseline is defined as the Week -2 value. The following ECG parameters will be reported for this study:

- PR Interval (msec)
- HR (bpm)
- RR Interval (sec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)

- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived]

The following summaries will be provided for ECG data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group (for quantitative measurements).
- Frequency and percentage of overall assessment of ECG (investigator's judgment) will be presented i.e. the percentage of patients in categories such as normal, abnormal/not clinically significant and abnormal/clinically significant.
- All ECG data will also be provided in subject data listings

16.3.1. ECG SPECIFIC DERIVATIONS

QTcB and QTcF values are already provided on the 12-Lead ECG (e)CRF page. These values are obtained as follows:

- Bazett's Correction (msec)
  - $QTcB\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$

- Fridericia's Correction (msec)
  - $QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

For purposes of data analysis, QTcF will be considered as primary.

16.4. VITAL SIGNS AND BODY MEASUREMENTS

Vital signs will be recorded at Visit 1 (screening), Visit 2 (Week -2), Visit 3 (Week -1), Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week 18), Visit 9 (Week 26) and Early Termination. The following vital signs and body measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)
- Weight (kg)
- BMI (kg/m^2)
- Waist Circumference (cm)

The following summaries will be provided for vital signs and body measurements data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group.

- All vital signs and body measurements data will also be provided in subject data listings.

16.4.1. BODY MEASUREMENTS SPECIFIC DERIVATIONS

- BMI (kg/ m^2) = weight (kg) / height $(m)^2$

16.5. PHYSICAL EXAMINATION

Results for the physical examination, complete evaluation (at Visit 1) and brief physical examination (at all visits with the exception of Visit 1, Visit 3/3.1, and Visit 6) will be presented in a subject data listing only.

17. PHARMACOKINETICS AND BIOMARKERS

Blood samples for fatty acid measurements in plasma phospholipid (EPA, DHA, EPA+DHA, AA, omega-6/omega-3 ratio and EPA/AA ratio) are obtained at Visit 4 (Baseline), prior to first study medication dose, and additional samples are obtained at Visit 5 (Week 4), Visit 7 (Week 12), Visit 8 (Week 18) and Visit 9 (Week 26), and as applicable at Early Termination.

The PK endpoints include exploration of:
- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma phospholipid EPA, DHA and EPA+DHA relative concentrations (percent of fatty acids);
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in AA, in plasma phospholipid omega-6/omega-3 and in EPA/AA ratios;

The following summaries will be provided for each PK endpoint:
- Actual (observed), change from baseline and percent change from baseline. Descriptive statistics by visit for each treatment group.
- Summaries will also be presented by subgroups for EPA, DHA and EPA+DHA at Week 12, using the same subgroups as described in section 7.5.
- Treatment group comparison will be done using a MMRM model including treatment, visit, treatment-by-visit interaction, baseline TG levels as fixed effects, baseline values as covariate and subjects as random effect. LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMEANs will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided.

Additionally, the relationship between changes in plasma phospholipid EPA, DHA, and EPA+DHA and the change in fasting TG levels will be presented in a scatter plot graph presenting the change in EPA/DHA/EPA+DHA vs. the change in TG levels.

18. REFERENCES

O'Kelly, M., Ratitch, B. (editors). Clinical Trials with Missing Data: A Guide for Practitioners. Wiley, 2014.

Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. *Proceedings of the National Academy of Sciences*, Washington, 17, 684–688.

APPENDIX 1. LIPID MODIFYING DRUGS

Part A: Statins, CAI, PCSK9 and Fibrates

Class of Product	Drug	Brand Name
Fibrates	Fenofibrate	Triglide, Tricor, Lipofen, Lipidil, Fenoglide, Antara, Trilipix, Gemfibrozil, Gemfibrozilo
	Fenofibric Acid	
	Choline Fenofibrate	
	Gemfibrozil	
Statins	Rosuvastatin Calcium	Crestor
	Rosuvastatin	
	Atorvastatin Calcium Trihydrate	Lipitor
	Atorvastatin	
	Lovastatin	Mevacor, Altocor, Altoprev
	Fluvastatin Sodium	Lescol, Canef, Vastin, Advicor (with niacin)
	Fluvastatin	
	Pravastatin Sodium	Pravachol
	Pravastatin	
	pitavastatin calcium	Livalo, Zypitamag
	pitavastatin magnesium	
	pitavastatin	
	Simvastatin	Zocor
Cholesterol Absorption Inhibitor	Ezetimibe	Zetia (with simvastatin), Ezetrol (with simvastatin), Liptruzet (with atorvastatin)
PCSK9 Category	Evolocumab	Repatha
	Alirocumab	Praluent

Part B: Niacin products, bile acid sequestrants, Omega-3

Other	Lomitapide	Juxtapid
	Lomitapide Mesylate	
	Mipomersen	Kynamro
	Mipomersen Sodium	
	Niacin	Niaspan
Combinations	Ezetimibe + atorvastatin	
	Ezetimibe + rosuvastatin	
	Ezetimibe + simvastatin	Vytorin and generics
	Atorvastatin + acetylsalicylic	
Bile Acid Sequestrant	Cholestyramine	Prevalite, Questran, Cholestryamine Light
	Colestipol	Colestid and generics
	Colesevelam	Welchol and generics
Omega-3	Omega-3 ethyl esters	Lovaza and generics
	Icosapent ethyl	Vascepa
	Omega-3 carboxyylic acids	Epanova

Herbal product or dietary supplements taken for their lipid-altering effects	Omega-3	
	EPA	
	DHA	
	EPA/DHA	
	Fish oil	
	Krill oil	
	Red yeast extract	
	Apple cider vinegard	
	Alpha lipoic acid	
	Niacinamide	

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

A2.1IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA Biostatistics output conventions:

A2.1.1 ABBREVIATIONS

CGM Computer graphics metafile
ODS Output Delivery System
RTF Rich text file format

A2.1.2 INTRODUCTION

This section applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. Most formatting instructions and conventions are built-in existing standard IQVIA proprietary SAS macros.

A2.1.3 OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
As far as possible, output files should be in RTF format, although .DOC (.DOCX) files are also permitted.
The output files and corresponding SAS programs will have the same name. The filename will start with 'T', 'L' or 'F', respectively for table, listing or figure. The letter will be followed by the table number using leading zeroes ('0') when the number is smaller than 10. The last part will be a brief description of the table content. Elements in the file name will be separated by underscores '_'. For example:

Output type and number	**Title**	**File name**
Table 14.1-1.1	Subject Disposition – All Subjects Enrolled Population	T141_01_01_dispo.rtf T141_01_01_dispo.sas
Figure 14.2-2.2.1	Mean Plasma Concentration over Time – Pharmacokinetic Analysis Population	F142_02_02_01_Mean_Conc_PK.rtf

		F142_02_02_01_Mean_Conc_PK.sas

A2.1.4 PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.
The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

A2.1.5 FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New" .
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof97l
gaccess = gsasfile;
filename gsasfile "….cgm";
```

A2.1.6 HEADER INFORMATION

Headers should be defined as follows:
• The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
• The customer name and protocol number should appear in row 1, left-aligned, along with the delivery designation (e.g., Interim analysis, Dry-run, Final Analysis, etc.) as appropriate. The page identification in the format Page X of Y (where Y is the total number of pages for the output) should also appear in row 1 of the header, right aligned.
• The output identification number should appear in row 2, centered
• The output title should start in row 3, centered
• The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Full Analysis Set in preference to FAS.
• Mixed case should be used for titles
• The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g., Vital Signs) followed by metric (e.g., Change from Baseline): Vital Signs – Change from Baseline.

• Titles should not contain quotation marks or footnote references
• Column headings spanning more than one column should be underlined and should be centered
• Column headings containing numbers should be centered
• Column headings should be in sentence case
• In general, the population count should appear in the column header in the form "(N=XXX)"
• "Statistic" should be the column header over n, Mean, SE, n (%) etc.
• As a rule, all columns should have column headings.

A2.1.7 TABLE AND LISTING OUTPUT CONVENTIONS

General:
• The first row in the body of the table or listing should be blank
• The left-hand column should start in column 1. No indenting or centering of the output should occur.
• Rounding should be done with the SAS function ROUND.
• Numbers in tables should be rounded, not truncated.
• Text and number alignment will follow standard alignment conventions and be implemented by use of existing IQVIA standard proprietary macros.
• The first letter of a text entry should be capitalized
• Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
• The study drug should appear first in tables with treatments as columns
• If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
• All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).

Univariate Statistics:
• Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
• If the original data has N decimal places, then the summary statistics should have the following decimal places:
Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):
• Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
77 (100.0%)
50 (64.9%)
0 (0.0%)
• Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
E.g. (<0.1%)
(6.8%)

(>99.9%)
Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
• Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:
• As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
• Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
• Boundary values of confidence intervals should be separated by a comma.
• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
• An example is given below:
(-0.12, -0.10)
(9.54, 12.91)

P-values:
• P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:
• Ratios should be reported to one more decimal place than the original data.

Spacing:
• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:
• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:
• A "0" should be used to indicate a zero frequency.
• A blank will be used to indicate missing data in an end-of-text table or subject listing.
• When information is not available, then "No observations available" will be used to reflect that observations are not available for a specific table/figure/listing.
• The 'Missing' category, when appropriate, will only be presented if subjects qualify for this category. Otherwise, the row for 'Missing' will not be presented.

A2.1.8 FIGURE OUTPUT CONVENTIONS

• Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.
Note: Figures in this document should be regarded as shells and final deliverables might look different to the examples presented here:
• A legend for treatment should always be presented, preferably below the actual graph, "N=xxxx" should be concatenated to the treatment group description
• If color is used, color should be linked to the same treatment; and similarly, the line type should be used for the same treatment and treatments should be differentiable for black and white printing.

A2.1.9 FOOTNOTE INFORMATION

Footers should be defined as follows:
• Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
• The program path and name and version number (if applicable) should appear as last footnote, at the bottom of the page, left aligned, along with the date/time stamp, right aligned.
• Footnotes should be left-aligned.
• Footnotes should be in sentence case.
• The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
• If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
Ordering of footnotes should be as follows:
1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes
• Common notes from table to table should appear in the same order.
• The symbols should appear in the same order as they are defined in the table or listing, from left to right.

A2.1.10 PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table, listing or figure shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.
Please disregard current examples of precision in shells.

A2.2 DATES & TIMES

Dates and time will follow ISO 8601 format (as prescribed by CDISC standards). Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Imputed dates, as defined in Appendix 3 of this statistical analysis plan, will NOT be presented in the listings.

A2.3 SPELLING FORMAT

English US.

A2.4 PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	**For Tables and Graphs**	**For Listings (include if different to tables)**
CaPre 4g/day	CaPre 4g/day	CaPre 4g/day
Placebo	Placebo	Placebo

A2.5 PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening (Visit 1)	Scr (V1)
TG Qual Visit 2	Qual V2
TG Qual Visit 3 need also Visit 3.1	Qual V3 need also Qual 3.1
Baseline (Visit 4)	BL (V4)
Week 4 (Visit 5)	W4 (V5)
…	…
Week 26 (Visit 9)	W26 (V9)
End of Treatment	EOT
Contact Follow-up	Fup
Unscheduled Visit (Visit x)	UNS (Vx)

A2.6 LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):
- cohort,
- center-subject ID,
- visit date/event date (where applicable), and in the case of multiple observations per visit date/event date, the observations should be sorted alphabetically within visit date/event date

The subjects' age, gender and race will be included in the listing header and the subjects' inclusion status in the applicable analysis populations will also be displayed, when appropriate.

A2.7 EDITORIAL CHANGES

Any editorial changes such as corrections of typographical errors, modification of spelling, or change of wording in titles or footnotes that leave the meaning unchanged can be done without requiring an amendment of this document. Footnote changes might also be necessary during the programming of displays depending upon the particular needs for special data handling. These changes will not require an amendment to this document.

APPENDIX 3. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing, prior medication can not be assigned If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 4. IMPLEMENTATION OF SENSITIVITY ANALYSES

Delta (δ) -adjusted Tipping Point analysis

Sensitivity to departures from the assumption made for the primary analysis will be investigated using a tipping point analysis. Departures from the primary assumption will be assessed assuming that subjects who discontinue the study early from the CaPre 4g daily arm have, on average, efficacy outcomes after discontinuation that are worse by some amount δ compared to other similar subjects who discontinued their CaPre 4g daily treatment early but remained in the study and have observed data (i.e., compared to a value which would have been assumed under the primary imputation model in the experimental treatment arm).

A series of analyses will be performed with increasing values of δ until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that overturns the primary results will represent a tipping point. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided.

Percent changes from baseline in TG levels score will be analyzed based on data observed while the subject remains on study as well as data imputed using MI methodology for time points at which no value is observed. Imputed values in CaPre 4g daily arm will first be sampled from the multiple imputation model as described for the primary analysis and then a value of $\delta = \{\Delta\}$ will be added to all imputed values in the CaPre 4g daily arm prior to analyzing multiply imputed data. This approach assumes that the marginal mean of imputed subject measurements is worse by δ at each time point after discontinuation compared to the marginal mean of subjects with observed data at the same time point for the CaPre 4g daily arm.

Analyses will be conducted with values of δ starting from 0 (corresponding to the primary analysis, i.e., no adjustment) with increments of 0.5 until the null hypothesis can no longer be rejected.

As for the primary analysis, this approach uses MCMC for partial imputation of non-monotone data under MAR followed by sequential MI regression for monotone data.

STATISTICAL ANALYSIS PLAN

ACA-CAP-002

A PHASE 3, MULTI-CENTER, MULTI-NATIONAL, PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND 26-WEEK STUDY TO ASSESS THE SAFETY AND EFFICACY OF CAPRE® IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA

AUTHOR: IRENE DEHEM/GINO COLAVITA

VERSION NUMBER AND DATE: FINAL V1.0 23JUN2020

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 23JUN2020) for Protocol ACA-CAP-002.

	Name	Signature	Date
Author:	Irene Dehem		
Position:	Statistical Scientist		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Gino Colavita		
Position:	Statistical Scientist		
Company:	IQVIA		
Approved By:	Pierre Lemieux		29 July, 2020
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Approved By:	Dariush Mozaffarian, MD DrPH		July 13, 2020
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Company:	Tufts Friedman School of Nutrition Science and Policy		

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V1.0 (Dated 27JUN2020) for Protocol ACA-CAP-002.

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Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

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Company:	Tufts Friedman School of Nutrition Science and Policy		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Version1.0	23JUN2020	Irene Dehem/Gino Colavita	Not Applicable – First Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Arachidonic acid
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BLQ	Below lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
CAI	Cholesterol-absorption inhibitor
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
DHA	Docosahexaenoic acid
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ENR	All Subjects Enrolled
EPA	Eicosapentaenoic acid
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone

Abbreviation	Definition
GGT	Gamma-glutamyltransferase
HbA1c	Glycosated hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostatis model assessment
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
ITT	Intent-to-treat analysis set
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA2	Lipoprotein-associated phospholipase A2
LS	Least squares
MAR	Missing-at-random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Effect Model Repeat Measurement
NCEP	National Cholesterol Education Program
OM3	Omega-3
OM6	Omega-6
PCSK9I	Proprotein convertase subtilisin/kexin type 9 serine protease inhibitors

Abbreviation	Definition
PK	Pharmacokinetics
PP	Per-protocol analysis set
PT	Preferred term
RDW	Red blood cell distribution width
Ridit	Relative to an identified distribution integral transformation
RLP-C	Remnant-like particle cholesterol
RR	Respiratory Rate for Vital Signs, or in context Relative Risk or RR interval (time between QRS complexes) for ECG
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SOCBP	Subject of child-bearing potential
T_4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent AE
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantification
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK) data for Protocol ACA-CAP-002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol dated 22 MAY 2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting triglycerides (TG) levels in subjects with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are as follows:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by Adverse Events (AEs), vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C after 12 weeks of treatment.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of the study are as follows:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.
- To compare the proportion of patients achieving TG values below 500 mg/dL between CaPre and placebo.
- To determine the effect of CaPre, compared to placebo, on plasma phospholipid eicosapentaenoic
- acid (EPA), docosahexaenoic acid (DHA), the sum of EPA and DHA, arachidonic acid (AA) concentrations (expressed as percent of fatty acids), and on the omega-6/omega-3 and EPA/AA ratios.
- To explore the interaction of qualifying fasting TG levels (≤750 mg/dL or >750 mg/dL) on the change in primary, secondary and selected PK endpoints, for CaPre compared to placebo.
- To explore the interaction of selected demographic and baseline characteristics on the change in primary and

secondary efficacy endpoints, for CaPre compared to placebo.

- To explore the interaction of selected demographic and baseline characteristics on the changes in plasma phospholipid EPA, DHA and EPA+DHA for CaPre compared to placebo.
- To explore the relationship between changes in plasma phospholipid EPA, DHA, and EPA+DHA and the change in fasting serum TG levels.
- To determine the effect of CaPre on apo B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on fasting serum glucose, insulin and on HbA1c.
- To explore the effect of CaPre on insulin resistance and beta-cell function (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on hsCRP and Lp-PLA2.
- To compare the proportion of subjects between CaPre and Placebo with increasing doses of current lipid-lowering medication or initiating new lipid-lowering medication following randomization.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multi-center, multi-national, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre 4 g/day or placebo), Phase 3 efficacy and safety study in subjects ≥18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study duration will be up to 39 weeks, consisting of an initial diet, lifestyle and medication stabilization period of 4 or 6 weeks, a 2 or 3-week TG qualifying period, a 26-week double-blind treatment period, and a 4-week contact follow-up. Approximately 653 subjects were initially planned to be screened to obtain 245 randomized subjects at approximately 70 centers.

Screening Period

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study. Appendix 2 of the protocol provides information outlining the principles of NCEP-TLC dietary patterns focused on lowering cholesterol.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not taking any lipid-altering agents or who are already receiving prior to screening (Visit 1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment should not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I

should be on a stable dose at least 12 weeks prior to screening.

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements specifically taken for their lipid-altering effects.
Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to screening.

Qualifying Period

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, then an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

This is considered the qualifying TG to be used for stratification at randomization.

Subjects who fail to meet the average TG inclusion level will be considered screening failure. Rescreening of these subjects will not be allowed.

Double-Blind Treatment Period

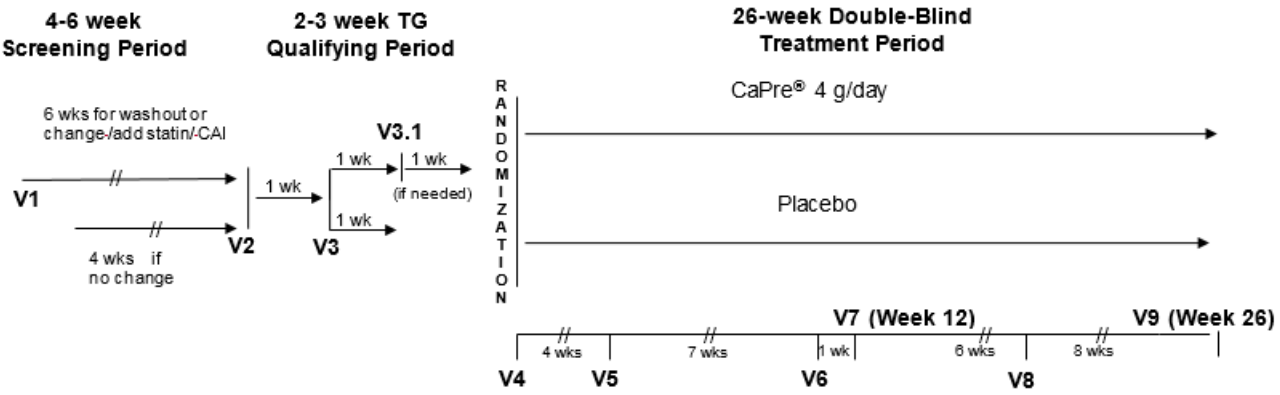
After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily or placebo daily. Subjects will receive instructions to take the study medication at a meal. Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated with statin, CAI or PCSK9I alone or in combination).

Following randomization at Visit 4 (Week 0), subjects are to return to the study center at Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week 18) and for the last visit at Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety assessment is required 4 weeks after Final Visit (Visit 9 or early

termination). Centralized laboratory testing was configured such that all study personnel was to remain blinded to all lipids, biomarkers, and EPA, DHA results from the randomization visit. The results will only be received once the treatment unblinding request form has been signed.

The study design is presented in Table A.

Table A: Schematic of Study Design



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 1, after Section 4.1.8 in the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

i. The following changes were implemented:

A pharmacokinetic analysis (PK) set was added;
Sensitivity analyses for evaluating the impact of the type of baseline for primary efficacy variable were added;

ii. The following exploratory objectives were changed, clarified or expanded compared to the protocol:

From:
To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol.
To:

To determine the effect of CaPre compared to placebo on total cholesterol (TC).

From:
To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.
To:
To explore the interaction of qualifying fasting TG levels (≤750 mg/dL or >750 mg/dL) on the change in primary, secondary and selected PK endpoints, for CaPre compared to placebo.

From:
To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.
To:
To explore the interaction of selected demographic and baseline characteristics on the changes in plasma phospholipid EPA, DHA and EPA+DHA, for CaPre compared to placebo.

From:
To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.
To:
To explore the interaction of selected demographic and baseline characteristics on the change in primary and secondary efficacy endpoints, for CaPre compared to placebo.

iii. The following exploratory objectives were added compared to the protocol:

To compare the proportion of subjects between CaPre and Placebo with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization.

iv. The following changes on the exploratory endpoints occurred compared to the protocol:

From:
Percent change from baseline (Week 0) to Week 12 and Week 26 in FSG, insulin and HbA1c
To:
Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c in all randomized subjects, and in those with Diabetes Mellitus.

From:
Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-B.
To:
Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β in all randomized subjects, and in those with Diabetes Mellitus.

From:
Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma phospholipid EPA and DHA concentrations.
To:
Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma

phospholipid EPA, DHA and EPA+DHA relative concentrations (expressed as percent of fatty acids).

v. The following exploratory endpoints were added compared to the protocol:

- Proportion of Subjects with Diabetes Mellitus with HbA1c below 7% at Week 12 and at Week 26.
- Proportion of subjects with increasing doses of current lipid-lowering medication or initiating new lipid-lowering medication following randomization.
- Percent change from baseline to Week 12 and to 26 in direct LDL-C.

Additional exploratory analyses of the below endpoints can be conducted using the pre-randomization value of the parameter at Visit 4 (Week 0) as baseline in the ITT analysis set and in the subset of subjects whose TG levels at Visit 4 are within the protocol inclusion range (i.e. 500 mg/dL ≤ TG ≥ 1500 mg/dL)

- Percent change from baseline to all visits in TG.
- Percent change from baseline to Week 12 and Week 26 in non-HDL-C, VLDL-C, HDL-C, LDL-C and TC.

vi. The following exploratory endpoint was removed compared to the protocol:

Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index in red blood cells;

vii. The following PK endpoints were added compared to the protocol:

Change and percent change from baseline (Week 0) to Week 12 and Week 26 in Total EPA, DHA and EPA+DHA in serum (µg/mL for EPA and DHA, and µmol/L for sum of EPA+DHA);

4. PLANNED ANALYSES

There will be no interim analysis or periodic data review by an independent data monitoring committee (DMC).

Only a Final Analysis will be performed for this study.

4.1. DATA MONITORING COMMITTEE

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Acasti Pharma Inc. authorization of this SAP, database lock, analysis sets and unblinding of treatment.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled set (ENR) will contain all subjects who provide informed consent for this study.

5.2. INTENT-TO-TREAT ANALYSIS SET [ITT]

The intent-to-treat (ITT) analysis set will contain all subjects in the ENR set who were randomized to study medication.
For analyses and displays based on ITT analysis set, following the ITT principle, subjects will be analyzed according to the treatment to which they were randomized regardless of any departures from the original assigned group.

5.3. PER PROTOCOL ANALYSIS SET [PP]

The per-protocol (PP) analysis set will contain all subjects in the ITT or mITT analysis set who did not have protocol deviations that could influence the primary endpoint assessment defined as (but not limited to):

- Subject randomized despite not satisfying inclusion/exclusion criteria and that may have confounded the primary endpoint assessment
- Subject with non-evaluable primary endpoint or who completed assessments significantly outside of the specified visit windows.
- Subjects who did not receive the treatment to which they were randomized
- Subjects who did not reach compliance to study medication between 80-120%
- Subjects who significantly deviated from the protocol requirements regarding prohibited and/or allowed medications that may have confounded the primary endpoint assessment
- Any other major protocol deviation that is thought to interfere with the primary endpoint assessment ~~of efficacy~~

Protocol deviations that have the potential to affect interpretation of the study results will be reviewed and approved by the blinded study team prior to final analysis set and prior to unblinding.

5.4. PHARMACOKINETIC ANALYSIS SET [PK]

The pharmacokinetic (PK) analysis set will contain all subjects whose serum samples were analysed at the end of the study for the quantitative determination of total eicosapentaenoic acid (EPA) and total docosahexaenoic acid (DHA) using a validated liquid chromatographic method with tandem mass spectrometry detection.

5.5. SAFETY ANALYSIS SET [SAF]

The safety (SAF) analysis set will contain all subjects in the ENR who receive at least one dose of study medication. Subjects will be classified according to treatment received.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as:

- The day of the first dose of study medication (Day 1 is the day of the first dose of study medication) for treated subjects.
- The randomization (Visit 4, week 0) visit date for subjects who were randomized but not treated.

Thus,

- If the date of the event is on or after the reference date, then:
  - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  - Study Day = (date of event – reference date).

The reference start date and Study Day will appear in every listing where an assessment date or event date appears In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline, but AEs and medications

commencing on the reference start date will be considered post-baseline.

For related assessments (e.g. systolic and diastolic BP), it will be desirable that both baseline values come from the same measurement and not from different dates/visits in case one value is missing.

For subjects in the ITT analysis set, if subjects were randomized but not treated, then baseline is defined as the last non-missing measurement taken on or before the randomization (Visit 4) visit date.

For lipid endpoints the baseline value will be defined as the average of the last 3 measurements obtained prior to or on the date of randomization (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification) for TG, non-HDL-C, HDL-C, TC and direct LDL-C. If one or the other measurement is missing, the average is to be based on remaining available value(s).

For the VLDL-C(ultracentrifugation) and LCL-C(ultracentrifugation) the average of 2 measurements obtained prior to or on the date of randomization (average of Week -1 and 0 corresponding to measurements taken at Visits 3, and 4. No VLDL-C and LDL-C measurements are taken at Visit 3.1. If one or the other measurement is missing, the baseline is to be based on the remaining available value.

For certain sensitivity and exploratory analyses, the baseline value will be the single value of the parameter obtained at Visit 4 (Week 0). If the value at Week 0 is missing, the baseline will be considered non-calculable.

6.3. DERIVED TIMEPOINTS

For primary endpoint (percent change from baseline in fasting TG levels), key secondary efficacy endpoints [percent change from baseline in non-HDL-C, VLDL-C (ultracentrifugation), HDL-C and LDL-C (ultracentrifugation)] and exploratory endpoints of TC and direct LDL-C, the Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12).

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For post baseline visits of all efficacy endpoints: unscheduled/retest visits will be used if they are the nearest of the target day per the time windows defined in Section 6.5.

For baseline visits of all efficacy endpoints: scheduled visits will be used. Should a scheduled visit be missing it will be replaced by its unscheduled/retest value as long as the unscheduled/retest value is taken prior to the next visit.

For safety parameters: data recorded at the nominal visit will be presented. Unscheduled measurements will not be

included in by-visit summaries but will contribute to the best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries. If no measurement is available at the nominal visit or no retest is available, the assessment will be considered missing for the visit.

Early termination data will be mapped to the next available visit number for by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

No time windows will be performed prior to the first dose.

For all efficacy endpoints, the following post dose time windows will be used:

Visit Name	Window	Target
Week 4	Day 24 to Day 35	Day 28
Week 11-12*	Day 71 to Day 94	Day 84
Week 12**	Day 78 to Day 94	Day 84
Week 18	Day 121 to Day 136	Day 126
Week 26	Day 176 to Day 192	Day 182

*Week 12 endpoint based on the average of 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12).
**Week 12 endpoint based on 1 measurement obtained at the end of the 12-week double-blind treatment period, at Visit 7 (Week 12).

6.6. STATISTICAL TESTS

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:
- Test Value at Visit X – Baseline Value

And percent change from baseline will be calculated as:
- 100 x (Test Value at Visit X – Baseline Value) / Baseline Value

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage of available data for each class of the parameter will be presented. Unless otherwise specified, percentages will be based

on the available data. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), the mean, the standard deviation (SD), the median, the minimum and maximum values. The summary statistical Tables will be generated for the raw (actual) assessments and as applicable for the Change from Baseline and the Percent Change from Baseline.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

For the primary efficacy analysis and key secondary efficacy analysis, a non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as a covariate will be used to perform the hypothesis test.

For the exploratory endpoint of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a Cochran-Mantel-Haenszel (CMH) test will be used, controlling for qualifying TG category (≤750 mg/dL vs. >750 mg/dL) and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization.

7.2. MULTICENTER STUDY

Approximately 70 clinical centers in three Countries (US, Mexican and Canadian) are expected to participate in this study and approximately 245 subjects to be randomized, thus it is anticipated that most centers will evaluate less than 5 patients. Therefore, due to the relatively low number of patients per site, no inferential analyses of site-specific effects or differences between sites will be performed, and no adjustment for site nor country will be made in the analyses.

7.3. MISSING DATA

Missing safety data will not be imputed except for the missing dates to identify treatment-emergent adverse events (TEAEs) (see Appendix 3 of this SAP).

Missing efficacy data will be handled as described in section 15 (and subsections) of this SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The experiment-wise type I error will be controlled to a maximum of two-sided 5% by using a hierarchical closed testing procedure: secondary efficacy endpoints will only be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment. Similarly, the later secondary endpoint in the hierarchy will be considered for statistical significance only if all former preceding secondary endpoints are found to be statistically significant.

Specifically, the following testing order will be followed for the overall type I error control:

1. Percent change from baseline to Week 12 in TG (primary endpoint)
2. Percent change from baseline to Week 12 in non-HDL-C
3. Percent change from baseline to Week 12 in VLDL-C
4. Percent change from baseline to Week 12 in HDL-C
5. Percent change from baseline to Week 12 in LDL-C

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided).

For all exploratory variables, nominal p-values will be reported in an exploratory fashion.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis section (15.3.4).

The following subgroups will be assessed and described below for either the primary, secondary or PK endpoints at Week 12 (EPA, DHA and EPA+DHA).

- Baseline age group: ≤65 years vs. >65 years. ***Primary and PK endpoints***.
- Race: White/Caucasian vs. Non-White/Caucasian. ***Primary and PK endpoints***.
- Gender: Male vs. non-Male. ***Primary and PK endpoint***.
- Country: Canada, Mexico, US. Primary, secondary, and PK endpoints
- Qualifying TG levels: ≤750 mg/dL vs. >750 mg/dL (or ≤8.5 mmol/L vs. >8.5 mmol/L). ***Primary, secondary and PK endpoints***.
- Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization. ***Primary, secondary and PK endpoints***.
- Use of fibrate vs non-use at randomization. ***Primary and PK endpoints***.
- Baseline plasma phospholipid EPA+DHA ≤ median value versus > the median value in the ITT population. ***Primary and PK endpoints***.
- Presence of co-morbidities:
  - Subjects with diabetes (Type 2 diabetes mellitus, defined as subjects with history of diabetes, use of anti-diabetic medication, or with HbA1c level >= 6.5%) vs. no diabetes at randomization. ***Primary, secondary***

and PK endpoints.

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study. The format and content of the summary tables, figures, and listings will be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.
Subject disposition and withdrawals, reasons for exclusion from each analysis set, and protocol deviations (including inclusion and exclusion criteria) will be presented for the ITT, mITT and PK analysis set, as applicable.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT, SAF, PP and PK analysis sets. Demographic and baseline characteristics will be compared between the two treatment groups by using a t-test for continuous variables and Chi-Square test for categorical variables.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
  - Age (≤ 65, > 65 years old)
- Gender (%)
- Race/ethnicity (White/Caucasian, White/Caucasian, Asian, Black/African-American, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Unknown, Other, More than one race). In each racial category, the proportion of subjects of Hispanic or Latino ethnicity will be reported. (%)
- Country (US, Canada, Mexico) (%)
- Weight (kg)
- BMI (kg/m^2)
- Tobacco use (Never, Former, Current) (%)
- Alcohol use (Never, Former, Current) (%)
- Qualifying TG category (≤750 mg/dL vs. >750 mg/dL)
- Baseline efficacy parameters:
  - TG levels
  - TG category at baseline (<500 mg/dLvs. >=500 mg/dl)
  - Non-HDL-C
  - VLDL-C
  - HDL-C
  - LDL-C
- Concomitant Medications

- Use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization
- Use of statin
- Use of CAI
- Use of PCSK9
- Use of of Fibrate vs non-use at randomization

- HbA1c
- Subjects with Diabetes Mellitus, which are subjects who have a history of diabetes or use anti-diabetic medication or have HbA1c >= 6.5% at baseline (randomization visit).
  - HbA1c
  - Subjects with diabetes mellitus with HbA1c < vs. ≥ 7.0%

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ $height^2$ $(m)^2$
- eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
- Where:
- Scr is serum creatinine in mg/dL;
- κ is 0.7 for females and 0.9 for males;
- α is -0.329 for females and -0.411 for males;
- min indicates the minimum of Scr /κ or 1, and max indicates the maximum of Scr /κ or 1;
- Age in years;

11. MEDICAL HISTORY AND CONCOMITANT ILLNESSES

Medical history and concomitant illnesses will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 20.1 (or higher), and the information will be presented for the subjects in the SAF analysis set by system organ class (SOC) and preferred term (PT).

Medical history conditions are defined as those conditions which stop prior to or at Screening while concomitant illnesses are conditions (other than the indication being studied) which started prior to or at Screening and are ongoing at the date of Screening.

Medical History and concomitant illnesses will be presented for the Safety analysis set, as applicable.

12. MEDICATIONS

Medications will be coded using the most current version of the WHODrug Global (Conventional medicines and herbal remedies) version 01 Sep 2017 (or higher) and will be presented for subjects in the SAF analysis set.

See Appendix 3 for handling of partial dates for medications. In the case where it is not possible to define a

medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication in the double-blind period.
- 'Concomitant' medications are medications which:
  - started prior to, on, or after the first dose of double-blind study medication and started no later than the day of the last dose of study medication,
  - AND ended on or after the date of first dose of double-blind study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started one (1) day following the last dose of study medication.

Prior and concomitant medications will be summarized by PT and presented in a subject data listing, while post-treatment medications will only be presented in a subject data listing. Prior and concomitant medications will be presented for the Safety analysis set, as applicable.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for subjects in the SAF analysis set.

The date of first study medication administration will be taken from the eCRF "Randomization" form. The date of last study medication will be taken from the eCRF "End of Treatment" form. In the case of missing data on the eCRF, the date of randomization will be used to determine the first date of study medication and the earliest record of the last contact date and the last date of medication returned will be used as a date of last dose.

Interruptions and compliance are not considered for duration of exposure.

13.1. DERIVATIONS

Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

14. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for subjects in the SAF analysis set, for each study visit where it is assessed (Week 4, Week 12, Week 18 and Week 26/ET), between Week 4 and Week 12, between Week 12 and Week 26, and overall. Descriptive statistics will be presented and the number and percentage of subjects in each of the following categories will also be presented: '< 80%', '80-120%' '>120%'.

14.1. DERIVATIONS

Compliance with double-blind study medication—based on the drug accountability data—will be calculated as the number of capsules consumed divided by the prescribed number of capsules expressed as a percentage (see calculations below).

It is assumed that all subjects will take 4 capsules once daily, expected starting from the visit day at which their medication is initially dispensed to the day prior to the morning of their last medication return date. For example, if the initial dispense date is Day1 and the last return date is Day10, then the subject should have taken 4 capsules on Days 1 to 9 (subjects don't take medication prior to attending the visit); hence, the total number of prescribed capsules would be 9×4 = 36. Compliance will be based on the nominal visit dates and not the actual date entered in the CRF, as medication may be returned late.

For non-completers, compliance will be calculated up until the last visit completed, or until the early termination visit if it is available. For subjects with no early termination visit, no compliance will be derived between the last visit completed and the time of discontinuation.

For non-adherers, which are subjects who discontinue receiving the study medication but agree to allow some or all data collection through the planned duration of the trial, compliance will be calculated up until the last visit under treatment completed. Compliance will be 0% for subsequent visits completed and for which no study medication dispensation occurred.

Θ = Number of capsules required to be taken per day.

- "Per Visit" Compliance to study medication will be calculated as follows:

$$\frac{\{(\text{N of capsules consumed at Visit Xn})\} \div \Theta}{[\text{Date of Visit Xn}] - [\text{Date of Visit Xn}-1]} \times 100$$

- Overall Compliance to study medication will be calculated as follows:

$$\frac{\{([\text{N of Capsules consumed at Visit 5}]) + \cdots + [\text{N of Capsules consumed at Visit X(n)}])\} \div \Theta}{[\text{Date of Visit X(n)}] - [\text{Date of Visit 4}]} \times 100$$

For subjects non-completers, the "Date of Visit X(n)" will be the date of the early termination visit, or the date of the last visit completed if no early termination visit was performed.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

The primary efficacy endpoints for this study is:

- Percent change from baseline to Week 12 (average of Week 11 and 12) in TG.

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies.

The baseline TG level is calculated as described in section 6.2.1, the Week 12 endpoint value is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12), and the percent change from baseline to the Week 12 endpoint will be calculated as defined in section 6.7, unscheduled visits and retests will be treated as defined in section 6.4. Should there be only one measurement available at either Visit 6 (Week 11) or Visit 7 (Week 12), then that measurement will be used as the Week 12 endpoint value.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

In case of a non-evaluable endpoint, prior to any imputation, the following replacement strategy will be followed:

- Should the baseline and/or a given endpoint for TG be non-calculable (i.e. values at baseline and/or at the given endpoint from the primary TG analysis method are all missing) making the change from baseline non-evaluable, then TG measurements from the lipoprotein fractionation (ultracentrifugation) panel[1], if available, should be used to derive both the baseline and the given endpoint.

All collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the primary analysis. Subjects who withdraw consent for study participation overall and are not assessed at both Week 11 and 12, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 6.4), will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or 12. No imputation is required if one of

[1] TG was measured by a satellite central laboratory as part of the ultracentrifugation analyses (for the determination of LDL-C and VLDL-C), for quality control purpose.

the week has a non-missing value.

A subject with complete data will have measurements at baseline (see section 6.2), Week 4, and Week 11 and/or 12. A subject with missing data at any visit prior to Week 12 and a non-missing value at any subsequent visit(s) up to Week 12 is said to have intermittent (non-monotone) missing data. A subject with missing data at a post baseline visit and at all subsequent visits is said to have monotone missing data.

Imputed data will consist of 100 imputed datasets. The random seed number for the multiple imputation (MI) of intermittent missing data will be 20191009 and the random seed number for the imputation of monotone missing data using the sequential regression MI will be 191009. The same random seeds will be used for these two steps when imputing data for the primary analysis as well as for sensitivity analyses, although the imputation models will be different.

Results of the analysis model (ANCOVA as described in section 15.1.3) from multiple imputed datasets will be combined using the Rubin's combination rule as implemented in the MIANALYZE procedure in SAS.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to test the null hypothesis that the percent change from baseline to Week 12 of fasting TG level in the active group is the same as that in the placebo group for all randomized subjects. The alternative hypothesis is that the percent change from baseline of fasting TG level in the active group is NOT the same as that in the placebo group.

The **primary efficacy analysis will be performed for subjects in the ITT analysis set** and will also be carried out for the corresponding PP analysis set as supportive analysis.

Descriptive statistics will be provided and statistical testing will be performed to compare the median values in percent change from baseline to Week 12 in TG levels.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization and baseline TG value as a covariate will be used to test the null hypothesis on the primary efficacy variable.

MI will be implemented in two steps to impute missing values of the primary endpoint. First, partial imputation assuming a missing-at-random (MAR) mechanism will be carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. The model will be estimated using only subjects who discontinued treatment at some stage in the study, treatment group will be included as covariate. The imputation model will include the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization as fixed covariates and observed TG values at Baseline, Week 4, Week 11, Week 12, Week 18 and Week 26. The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior. In case of non-convergence the model will be reduced to the baseline and the visit values.

Then, the remaining monotone missing data will be imputed using sequential regression multiple imputation. The

response to be imputed will be change at each visit from the last pre-discontinuation value. A separate regression model is estimated for imputation of the change from the last pre-discontinuation value to each visit. Each regression model will include explanatory variables for the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, treatment group, treatment duration, baseline triglycerides and last value before discontinuation. The MONOTONE REGRESSION statement in the MI procedure in SAS will be used. For the primary analysis, the imputation model at this step will be estimated only from the reference group of subjects who discontinued their randomized treatment early but remained in the study and were assessed at Week 11 and/or 12. This will be implemented using the MNAR statement in the MI procedure in SAS with the MODELOBS option. A flag identifying subjects belonging to the reference group as described above will be derived and used in the MODELOBS option to identify the subset of subjects from whom the imputation models are to be derived, if the model does not converge the strata will be removed from the model. After the imputation is done on the change from the last value before discontinuation, the imputed value for the triglyceride measure will be derived by adding to the last value pre-discontinuation the imputed change for each visit.

Should there be not enough non-adherers to model the method described above, a BOCF like imputation model will be used. After a monotone dataset has been created, a set of baseline values are imputed for each subject. The model for the baseline measure of the triglycerides will include other values measured at baseline (O'Kelly et al., 2014). The other baseline measurements in the model will include the qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, treatment group. The multiply imputed baseline triglyceride values for each subject are then "stored" and used to multiply impute the missing post-baseline values. This approach to BOCF is preferred because a) the model for the imputed baseline values captures observed associations of baseline triglyceride with other values measured at baseline; 2) the imputed baseline values reflect the two sources of variance noted by Rubin, i.e. the imputed baseline values reflect both the variability inherent in the baseline random variable, and the uncertainty as to the likely mean of the underlying distribution of that baseline, for each subject

No rounding or range restrictions will be applied.

For each of the 100 imputed datasets, the non-parametric ANCOVA based on ranks will be performed as follows: the percent change from baseline in TG value and the TG baseline value will be transformed to modified ridit scores within stratum (qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin [CAI or PCSK9I, alone or in combination] vs. non-use at randomization). Modified ridit scores are ranks standardized for the different sample sizes per stratum. In the second step, ordinary Least Square (LS) regression applied to the modified ridit scores of the percent change from baseline and baseline will be performed within each stratum using the model:
Percent change from baseline = baseline.

In the third step, residuals from these regression models will be used. In that final step, the residuals from all strata will be included in a stratified extended Cochran-Mantel-Haenszel (CMH) test of the residuals (i.e., stratum by treatment by residual) to analyze the treatment effect. CMH test statistics (the Row Mean Score Differ statistic will be used, this will be obtained with the CMH2 option in the TABLES statement of PROC FREQ) obtained from each of the multiple imputed datasets will be combined using the Rubin's combination rule after applying a normalizing Wilson-Hilferty transformation for a chi-square distributed statistic. The transformation will be applied as follows:

$$wh\_cmh^{(m)} = \sqrt[3]{cmh^{(m)}/df}$$

where $cmh^{(m)}$ is the CMH statistic computed from the m[th] imputed dataset $m = 1, \ldots, 100$, df is the number of degrees of freedom associated with the CMH statistic, and $wh\_cmh^{(m)}$ is the transformed value. The transformed statistic is approximately normally distributed with mean $1 - 2/(9 \times df)$ and variance $2/(9 \times df)$ under the null hypothesis.

This transformed statistic will be standardized to obtain a variable that is normally distributed with mean 0 and variance 1:

$$st_{wh\_cmh}{}^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt[2]{\frac{2}{9 \times df}}}$$

This transformed statistic and the corresponding standard error of 1 will be combined using the Rubin's rule.

Quantile regression, adjusting for the same baseline covariates (as specified in the ANCOVA model above) will be used to obtain an adjusted estimate of the median treatment difference with associated two-sided 95% CI. Rubin's combination rule will be used to combine the estimates from multiple imputed datasets.

As supportive analysis, Hodges-Lehmann estimate for the median of the treatment differences and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied. Bootstrap in combination with MI will be performed as follows:

- Format the analysis dataset using a horizontal structure, i.e., with one record per subject, with the longitudinal values in columns (as variables).
- Obtain bootstrap datasets $b = 1, \ldots, B$ of the same size as the original dataset (the same number of subjects) by sampling with replacement the entire subject records from the original data (by treatment, adheres and strata). The number of bootstrap datasets will be $B = 2000$. The random seed for generation of bootstrap datasets will be set to 30191008.
- Perform multiple imputation as described above for each bootstrap dataset with the number of imputations M=10. This will result in M imputed datasets generated for each bootstrap dataset, i.e., $B \times M$ in total.
- Obtain a Hodges-Lehmann estimate for the median of the treatment differences in each bootstrap / imputed dataset: $\hat{\delta}_{m,b}, m = 1, \ldots, M, b = 1, \ldots, B$.
- Estimate an average treatment difference for each bootstrap dataset: $\bar{\delta}_b = \frac{1}{M}\sum_{m=1}^{M} \hat{\delta}_{m,b}$,
- Estimate the overall Hodges-Lehmann estimate as: $\hat{\delta} = \frac{1}{B}\sum_{b=1}^{B} \bar{\delta}_b$
- Estimate 95% CI using percentiles of the bootstrap distribution, i.e., use the 2.5% and 97.5% percentiles of the $\bar{\delta}_b$values sorted in ascending order as the lower and upper limit of the 95% CI respectively.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

Sensitivity analyses will be performed to assess the impact of several factors on the results of the primary analyses such as the type of baseline and strategies for dealing with missing data. All sensitivity analyses pertaining to the handling of missing data will be conducted on the same analysis set as for the primary analysis.

A sensitivity analysis will be performed in the ITT analysis set using the pre-randomization value Visit 4 (Week 0) as the baseline TG value. The purpose of this analysis is to explore whether inclusion of the two TG qualification visit values obtained prior to randomization (corresponding to Week -2 and Week -1) for the calculation of the baseline may result in an artefactual overestimation of the pre-treatment TG levels in the presence of significant pre-randomization TG reduction.

Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed at Week 11 and/or 12. This approach assumes that some subjects discontinuing the study will do so for non-treatment related reasons and would have similar outcomes to subjects who are able to complete the treatment. This analysis will be implemented in a similar manner to the primary analysis, except that when the monotone data are imputed, the MNAR statement in the MI procedure will not be used, and therefore, all subjects with available data will be used for the estimation of the imputation model.

If the number of subjects who discontinue the study medication early and are assessed at Week 11 and/or 12 after having started an alternative therapy is large (e.g., > 5% of all ITT subjects), then an additional sensitivity analysis will be performed where data from these subjects will be excluded from analysis and these subjects will be treated as having missing data, i.e., will be imputed under the MAR assumption. This analysis will serve to assess the contribution of the alternative therapies to the estimate of the total treatment effect.

A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study by a pre-specified adjustment in the primary efficacy (O'Kelly and Ratitch, 2014, Chapter 7).

The steps to implement the sensitivity analyses are detailed in Appendix 4.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed in the ITT analysis set only.

The secondary efficacy endpoints for this study are (in order of importance for the control of the type 1 error):

- Percent change from baseline to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline to Week 12 (average of Week 11 and 12) in VLDL-C (ultracentrifugation).
- Percent change from baseline to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline to Week 12 (average of Week 11 and 12) in LDL-C (ultracentrifugation).

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The baseline value of the parameter is calculated as described in section 6.2.1. The Week 12 endpoint value is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12), and the percent change from baseline to the Week 12 endpoint will be calculated as defined in section 6.7, unscheduled visits and retests will be treated as defined in section 6.4. Should there be only one measurement available at either Visit 6 (Week 11) or Visit 7 (Week 12), then that measurement will be used as the Week 12 endpoint value.

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE

Similarly, to the primary analysis, all collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the analysis of key secondary endpoints. In case of a non-evaluable endpoint, prior to any imputation, the following replacement strategy will be followed:

- Should the baseline and/or Week 12 endpoint for LDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing) making the change from baseline non-evaluable, then LDL-C (direct) measurements, if available, should be used to derive both the baseline and the Week 12 endpoint.
- Similarly, should the baseline and/or Week 12 endpoint for VLDL-C (ultracentrifugation) be non-calculable (i.e. all values at baseline or both values at Week 11 and 12 are missing) making the change form baseline non-evaluable, then VLDL-C will be derived using the following formula:

  VLDL-C = TC – HDL-C – LDL-C(direct)

Subjects who withdraw consent for study participation overall and are not assessed at both Week 11 and 12, even after having mapped data captured at early termination visits (if any) to the next scheduled visit (refer to section 6.4) will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Similar analyses as specified above for the primary efficacy analysis will be conducted on all the secondary efficacy endpoints.

A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo based on the multiply-imputed data as described for the primary analysis.

15.3. EXPLORATORY EFFICACY

The choice of the analysis set for the exploratory efficacy analyses will follow that of the primary analysis (ITT).

The exploratory efficacy endpoints of the study are the following:

- Percent change from baseline to all measured visits other than Week 12 (i.e. Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26.
- Percent change from baseline to Week 12 and Week 26 in TC.
- Percent change from baseline to Week 26 in non-HDL-C, VLDL-C, HDL-C and LDL-C
- Percent change from baseline to Week 12 and to 26 in direct LDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII and apo A5.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (HDL Particle Number, LDL Particle Number, Non-HDL Particle Number, HDL Small, HDL Large, LDL Very Small-d, LDL Very Small-c, LDL Very Small-b, LDL VERY Small-a LDL Small, LDL Medium, LDL Large-b, LDL Large-a, IDL Small, IDL Large, VLDL Small, VLDL Medium, VLDL Large, LDL Pattern, LDL Peak Size).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL-C.
- Change and Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c in all randomized subjects, and in those with Diabetes Mellitus.
- Proportion of Subjects with Diabetes Mellitus with HbA1c below 7% at Week 12 and at Week 26.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β in all randomized subjects, and in those with Diabetes Mellitus.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP, log hs-CRP and Lp-PLA2.
- Proportion of subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization.

Additional exploratory analyses of the below endpoints can be conducted using the pre-randomization value of the parameter at Visit 4 (Week 0) as baseline in the ITT analysis set and in the subset of subjects whose TG levels at Visit 4 are within the protocol inclusion range (i.e. 500 mg/dL ≤ TG ≥ 1500 mg/dL):

- Percent change from baseline to all measured visits in TG.
- Percent change from baseline to Week 12 and Week 26 in non-HDL-C, VLDL-C, HDL-C, LDL-C and TC.

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

Except as described in section 6.2.1, the baseline value for other exploratory efficacy endpoints is defined as the value obtained prior to dosing (measurement taken at Visit 4 (Week 0); Week 12 endpoint is defined as the value obtained at Visit 7 (Week 12) and Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26), whenever applicable.

Log hs-CRP will be derived.

HOMA-IR will be derived as:

HOMA-IR = (Insulin (U/L) X Glucose (mmol/L)) / 22.5

HOMA-β will be derived as:
HOMA-β = (20 X Insulin (U/L)) / (Glucose (mmol/L) – 3.5) and result is expressed as %β

Subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization will be flagged as:

- Subjects having a prior medication of the list of lipid modifying drug listed in part A of Appendix 1:
  - Start date of the first entry is prior to randomization and the stop date is after randomization or is ongoing.
  - The dose increased compared to baseline, or
  - The frequency increased compared to baseline

- Subjects not having any prior medication but have concomitant medication from any product in the list of lipid modifying drugs listed in Appendix 1
  - No entry prior to randomization, and at least one entry with start date on or after randomization. May be ongoing or stopped.

The final list of subjects with these criteria will be reviewed by the medical monitor.

15.3.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLE(S)

In case of a non-evaluable endpoint, prior to any imputation, the same replacement strategy for TG and for LDL-C and VLDL-C as described under section 15.1.2 and 15.2.2, respectively, will be followed. Subjects with otherwise missing data at the analysis time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

15.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

All exploratory efficacy endpoints defined as percent change from baseline will be analyzed as specified above for the primary and secondary efficacy endpoints and will be conducted on the ITT analysis set only. A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline value (of parameter being analyzed) as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo based on the multiply-imputed data as described for the primary analysis.

The persistence of the effect of CaPre on the TG profile will be explored by comparing the percent change in fasting TG levels from Baseline to different time points. Descriptive statistics will be presented by treatment group at each visit and will also be summarized using graphical representation over time (from Baseline to end of study Week 26).

Regarding the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the

two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

For analysis of the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26-week double-blind treatment periods, a sensitivity analysis will also be performed where subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

Regarding the proportion of subjects with Diabetes Mellitus who achieve HbA1c below 7% at Week 12 and at Week 26, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

Regarding the proportion of subjects with increasing doses of current lipid-lowering medication at randomization or initiating new lipid-lowering medication following randomization (derived as in section 15.3.1), at Week 12 and at Week 26, a CMH (Row Mean Score Differ Statistic) test will be used, controlling for the two stratification factors that are used for randomization (i.e., qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization. Analysis will be performed on multiply-imputed data as described for the primary analysis. The Wilson-Hilferty transformation, as described in Section 15.1.3, will be applied to the CMH test statistics obtained from each imputed dataset before combining them using Rubin's rule.

No multiplicity adjustment will be applied to the exploratory efficacy analyses. As such, nominal p-values will be reported in an exploratory fashion.

15.3.4. SUBGROUP ANALYSES

Subgroups are listed in section 7.5. Descriptive statistics will be summarized for each subgroup.

The treatment effect within each subgroup will be estimated using the same quantile regression model as described in the primary efficacy analysis in Section 15.1.3 for each subgroup. A Forest plot will be produced to show the treatment effects and the corresponding CIs (overall and within each subgroup).

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF analysis set.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the most current version of MedDRA dictionary, version 20.1 (or higher). Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study medication.

See Appendix 3 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and will be broken down further by maximum severity and relationship to study medication.

16.1.1.1. Severity

Severity[2] will be classified as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject report a TEAE more than once within that SOC/ PT, then the AE with the worst severity will be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, will be classified as "not related[3]", "unlikely related", "possibly related", "probably related" and "related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related", "probably related" or "related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "probably related" to study medication. If a subject report the same AE more than once within that SOC/ PT, then the AE with the worst relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAES LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the 'Action taken with study medication" field on the Adverse Events page of the eCRF. TEAEs with action of "study medication withdrawal" or "withdrawal from study" will be considered as leading to discontinuation of study medication.

[2] Severity is equivalent to Intensity as defined in study protocol for adverse event characterization and reporting.
[3] Not related is equivalent to Unrelated as defined in study protocol for adverse event characterization and reporting

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

16.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

16.1.5. ADVERSE EVENTS OF SPECIAL INTEREST

The following list of SMQs are considered of special interest:

- Hyperglycaemia/new onset diabetes mellitus (SMQ)
- Anaphylactic reaction (SMQ)
- Angioedema (SMQ)
- Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)
- Haemorrhages (SMQ)
- Hepatic disorders (SMQ)
- Hypersensitivity (SMQ)
- Rhabdomyolysis/myopathy (SMQ)
- Anaphylactic/anaphylactoid shock conditions (SMQ)

A summary of TEAEs of Special Interest by SOC and PT will be prepared. Due to the fact that the study is blinded we do not expect any LDL-C increase in the adverse events, they will be seen through shift tables in the laboratory analysis.

16.2. LABORATORY EVALUATIONS

Results from the central laboratory for hematology, chemistry, coagulation, urinalysis, fasting lipids and other analytes will be included in the reporting of this study for parameters listed in Table B below. Biomarkers and pharmacokinetic (PK) parameters will be covered in sections 17 of this SAP respectively.

Table B Laboratory Assessments

Hematology (Visit 1, 4, 5, 7 and 9[1])	**Clinical Chemistry** (Visit 1, 4, 5, 7 and 9[1])	**Lipids (fasting)** (All study Visits)	**Biomarkers** (Visit 4,7 and 9[1])
Hemoglobin Hematocrit Erythrocyte count Leukocyte count Leukocyte differential count (including neutrophils, lymphocytes , monocytes , eosinophils and basophils) Platelet count MCV MCH MCHC RDW Coagulation (Visit 1, 4, 5, 7 and 9[1]) PT INR aPTT Other analytes Hepatitis B and C (Visit 1) HbA1c (Visit 1,4, 7 and 9) Insulin (fasting) (Visit 4,7 and 9)	Albumin ALP ALT Amylase AST GGT Bilirubin, Total Lipase Urea Nitrogen/Urea Uric acid Creatinine Creatine Kinase (CK) Calcium Chloride Magnesium Glucose Potassium Sodium Bicarbonate Pregnancy test (SOCBP, serum testing at Visit 1) FSH (as required for post-menopausal subjects only) Creatinine Clearance and estimated Glomerular Filtration Rate (eGFR) (calculated at Visit 1, 4, 5, 7 and 9)	Triglycerides (TG) Total cholesterol (TC) non-HDL-C (calculated) HDL-C LDL-C (direct) * VLDL-C (calculated)* _____ Urinalysis ** (Visit 1, 4, 5, 7 and 9[1]) Color Clarity/Appearance Specific gravity pH Glucose Blood (includes erythrocytes) Protein Leukocyte Esterase Ketones Nitrites Bilirubin Urobilinogen Creatinine Proteinuria (estimated by urine protein/creatinine ratio - UPCR) (calculated at Visit 1)	AA Apo AI Apo B Apo CIII Apo A5 Lp-PLA2 hsCRP Lipoprotein (particles concentration & size)*** oxidized LDL-C omega 6 FA omega 3 FA Pharmacokinetics DHA, EPA, EPA+DHA, Arachidonic acid, omega-6/omega-3 ratio and EPA/AA ratio. (Visits 4, 5, 7, 8 and 9[1]) Thyroid Function (Visit 1) TSH T_4

[1] All laboratory assessments required at visit 9 will also be made at the Early Termination Visit.
* LDL-C and VLDL-C to be also obtained via preparative ultracentrifugation at Visit 3,4,6,7 and 9.
**Urine Microscopy will be performed if blood, protein, leukocyte esterase, and/or urobilinogen is abnormal.
*** Includes HDL Particle Number, LDL Particle Number, Non-HDL Particle Number, HDL Small, HDL Large, LDL Very Small-d, LDL Very Small-c, LDL Very Small-b, LDL VERY Small-a LDL Small, LDL Medium, LDL Large-b, LDL Large-a, IDL Small, IDL Large, VLDL Small, VLDL Medium, VLDL Large, LDL Pattern, LDL Peak Size.

Presentations will use Conventional Units.

The following summaries will be provided for laboratory data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group (for quantitative measurements). Incidence of abnormal values (categorized as Low or High) according to reference range criteria
- Shift from baseline according to reference range criteria (for quantitative measurements and categorical measurements), by visit and for each treatment group.
- Laboratory measurements which are collected only on one visit will be presented in listings only.

All laboratory data will also be provided in subject data listings.

Laboratory out of standard reference ranges will be presented in a separate listing.

16.2.1. LABORATORY SPECIFIC DERIVATIONS

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

16.2.2. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in conventional units and categorized as:

- Low (L): Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High(H): Above the upper limit of the laboratory reference range.

16.3. ECG EVALUATIONS

Electrocardiogram (ECG) results as collected on the 12-Lead ECG eCRF page at Visits 2 (Week -2), 7 (Week 12) and 9 (Week 26) will be included in the reporting of this study. Baseline is defined as the Week -2 value. The following ECG parameters will be reported for this study:

- PR Interval (msec)
- HR (bpm)
- RR Interval (sec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- QTcF Interval (msec) [derived]

- QTcB Interval (msec) [derived]

The following summaries will be provided for ECG data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group (for quantitative measurements).
- Frequency and percentage of overall assessment of ECG (investigator's judgment) will be presented i.e. the percentage of patients in categories such as normal, abnormal/not clinically significant and abnormal/clinically significant.
- All ECG data will also be provided in subject data listings

16.3.1. ECG SPECIFIC DERIVATIONS

QTcB and QTcF values are already provided on the 12-Lead ECG (e)CRF page. These values are obtained as follows:

- Bazett's Correction (msec)
  - $QTcB\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt{RR\ (ms)/1000}}$

- Fridericia's Correction (msec)
  - $QTcF\ (\text{msec}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

For purposes of data analysis, QTcF will be considered as primary.

16.4. VITAL SIGNS AND BODY MEASUREMENTS

Vital signs will be recorded at Visit 1 (screening), Visit 2 (Week -2), Visit 3 (Week -1), Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week 18), Visit 9 (Week 26) and Early Termination. The following vital signs and body measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)
- Weight (kg)
- BMI (kg/m^2)
- Waist Circumference (cm)
-

The following summaries will be provided for vital signs and body measurements data:

- Actual (observed) and change from baseline. Descriptive statistics by visit for each treatment group.
-
- All vital signs and body measurements data will also be provided in subject data listings.

16.4.1. BODY MEASUREMENTS SPECIFIC DERIVATIONS

- BMI (kg/ m^2) = weight (kg) / height $(m)^2$

16.5. PHYSICAL EXAMINATION

Results for the physical examination, complete evaluation (at Visit 1) and brief physical examination (at all visits with the exception of Visit 1, Visit 3/3.1, and Visit 6) will be presented in a subject data listing only.

17. PHARMACOKINETICS AND BIOMARKERS

Blood samples for fatty acid measurements in plasma phospholipid (EPA, DHA, EPA+DHA, AA, omega-6/omega-3 ratio and EPA/AA ratio) are obtained at Visit 4 (Baseline), prior to first study medication dose, and additional samples are obtained at Visit 5 (Week 4), Visit 7 (Week 12), Visit 8 (Week 18) and Visit 9 (Week 26), and as applicable at Early Termination. Additionally, following completion of the study, serum samples for storage at -80°C (until analysis) obtained at Visit 4 (Week 0), Visit 7 (Week 12) and Visit 9 (Week 26) were selected for quantitative determination of Total EPA and DHA using a validated liquid chromatographic method with tandem mass spectrometry detection by a bioanalytical facility.

The PK endpoints include exploration of:

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in plasma phospholipid EPA, DHA and EPA+DHA relative concentrations (percent of fatty acids);
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in AA, in plasma phospholipid omega-6/omega-3 and in EPA/AA ratios;
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in Total EPA, DHA and EPA+DHA in serum (µg/mL for EPA and DHA, and µmol/L for sum of EPA+DHA);

The following summaries will be provided for each PK endpoint:

- Actual (observed), change from baseline and percent change from baseline. Descriptive statistics by visit for each treatment group.
- Summaries will also be presented by subgroups for EPA, DHA and EPA+DHA at Week 12, using the same subgroups as described in section 7.5.

Treatment group comparison will be done using a MMRM model including treatment, visit, treatment-by-visit interaction, baseline TG levels as fixed effects, baseline values as covariate and subjects as random effect. LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMEANs will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided.

Additionally, the relationship between changes in plasma phospholipid EPA, DHA, and EPA+DHA and the change in fasting TG levels will be presented in a scatter plot graph presenting the change in EPA/DHA/EPA+DHA vs. the change in TG levels.

The above PK analyses will be performed on the ITT analysis set, except for the PK endpoint of Total EPA, DHA and EPA+DHA in serum that will be presented for the PK analysis set only.

18. REFERENCES

O'Kelly, M., Ratitch, B. (editors). Clinical Trials with Missing Data: A Guide for Practitioners. Wiley, 2014.

Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. *Proceedings of the National Academy of Sciences*, Washington, 17, 684–688.

APPENDIX 1. LIPID MODIFYING DRUGS

Part A: Statins, CAI, PCSK9 and Fibrates

Class of Product	Drug	Brand Name
Fibrates	Fenofibrate	Triglide, Tricor, Lipofen, Lipidil, Fenoglide, Antara, Trilipix, Gemfibrozil, Gemfibrozilo
	Fenofibric Acid	
	Choline Fenofibrate	
	Gemfibrozil	
Statins	Rosuvastatin Calcium	Crestor
	Rosuvastatin	
	Atorvastatin Calcium Trihydrate	Lipitor, Liptruzet (with ezetimibe), Caduet (with amlodipine)
	Atorvastatin	
	Lovastatin	Mevacor, Altocor, Altoprev
	Fluvastatin Sodium	Lescol, Canef, Vastin,
	Fluvastatin	
	Pravastatin Sodium	Pravachol
	Pravastatin	
	pitavastatin calcium	Livalo, Zypitamag
	pitavastatin magnesium	
	pitavastatin	
	Simvastatin	Zocor, Vytorin and generics (with ezetimibe)
Cholesterol Absorption Inhibitor	Ezetimibe	Zetia, Ezetrol, Vytorin and generics (with simvastatin), Liptruzet (with atorvastatin)
PCSK9 Category	Evolocumab	Repatha
	Alirocumab	Praluent

Fixed dose combination products are counted in each class of product of their respective drug (e.g. Vytorin is counted in both Statin and Cholesterol Absorption Inhibitor)

Part B: Niacin products, bile acid sequestrants, Omega-3

Niacin	Niacin	Niacor, Niaspan
Other	Lomitapide	Juxtapid
	Lomitapide Mesylate	
	Mipomersen	Kynamro
	Mipomersen Sodium	
Bile Acid Sequestrant	Cholestyramine	Prevalite, Questran, Cholestryamine Light
	Colestipol	Colestid and generics
	Colesevelam	Welchol and generics
Omega-3	Omega-3 ethyl esters	Lovaza and generics
	Icosapent ethyl	Vascepa
	Omega-3 carboxyylic acids	Epanova
Herbal product or dietary supplements taken for	Omega-3	
	EPA	

their lipid-altering effects	DHA	
	EPA/DHA	
	Fish oil	
	Krill oil	
	Red yeast extract	
	Apple cider vinegar	
	Alpha lipoic acid	
	Niacinamide	

Fixed dose combination

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

A2.1IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA Biostatistics output conventions:

A2.1.1 ABBREVIATIONS

CGM Computer graphics metafile
ODS Output Delivery System
RTF Rich text file format

A2.1.2 INTRODUCTION

This section applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. Most formatting instructions and conventions are built-in existing standard IQVIA proprietary SAS macros.

A2.1.3 OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
As far as possible, output files should be in RTF format, although .DOC (.DOCX) files are also permitted.
The output files and corresponding SAS programs will have the same name. The filename will start with 'T', 'L' or 'F', respectively for table, listing or figure. The letter will be followed by the table number using leading zeroes ('0') when the number is smaller than 10. The last part will be a brief description of the table content. Elements in the file name will be separated by underscores '_'. For example:

Output type and number	Title	File name
Table 14.1-1.1	Subject Disposition – All Subjects Enrolled Population	T141_01_01_dispo.rtf T141_01_01_dispo.sas
Figure 14.2-2.2.1	Mean Plasma Concentration over Time – Pharmacokinetic Analysis Population	F142_02_02_01_Mean_Conc_PK.rtf F142_02_02_01_Mean_Conc_PK.sas

A2.1.4 PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.
The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

A2.1.5 FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New" .
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof97l
gaccess = gsasfile;
filename gsasfile "….cgm";
```

A2.1.6 HEADER INFORMATION

Headers should be defined as follows:
• The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
• The customer name and protocol number should appear in row 1, left-aligned, along with the delivery designation

(e.g., Interim analysis, Dry-run, Final Analysis, etc.) as appropriate. The page identification in the format Page X of Y (where Y is the total number of pages for the output) should also appear in row 1 of the header, right aligned.
• The output identification number should appear in row 2, centered
• The output title should start in row 3, centered
• The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Full Analysis Set in preference to FAS.
• Mixed case should be used for titles
• The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g., Vital Signs) followed by metric (e.g., Change from Baseline): Vital Signs – Change from Baseline.
• Titles should not contain quotation marks or footnote references
• Column headings spanning more than one column should be underlined and should be centered
• Column headings containing numbers should be centered
• Column headings should be in sentence case
• In general, the population count should appear in the column header in the form "(N=XXX)"
• "Statistic" should be the column header over n, Mean, SE, n (%) etc.
• As a rule, all columns should have column headings.

A2.1.7 TABLE AND LISTING OUTPUT CONVENTIONS

General:
· The first row in the body of the table or listing should be blank
· The left-hand column should start in column 1. No indenting or centering of the output should occur.
· Rounding should be done with the SAS function ROUND.
· Numbers in tables should be rounded, not truncated.
• Text and number alignment will follow standard alignment conventions and be implemented by use of existing IQVIA standard proprietary macros.
· The first letter of a text entry should be capitalized
· Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
· The study drug should appear first in tables with treatments as columns
· If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
· All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).

Univariate Statistics:
· Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
· If the original data has N decimal places, then the summary statistics should have the following decimal places:
Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):
· Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of

the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
77 (100.0%)
50 (64.9%)
0 (0.0%)
· Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
E.g. (<0.1%)
(6.8%)
(>99.9%)
Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
· Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:
· As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
· Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
· Boundary values of confidence intervals should be separated by a comma.
· Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
· An example is given below:
(-0.12, -0.10)
(9.54, 12.91)

P-values:
· P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:
· Ratios should be reported to one more decimal place than the original data.

Spacing:
· There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:
· If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
· Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:
· A “0” should be used to indicate a zero frequency.
· A blank will be used to indicate missing data in an end-of-text table or subject listing.
· When information is not available, then “No observations available” will be used to reflect that observations are not available for a specific table/figure/listing.
· The ‘Missing’ category, when appropriate, will only be presented if subjects qualify for this category. Otherwise, the row for ‘Missing’ will not be presented.

A2.1.8 FIGURE OUTPUT CONVENTIONS

· Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
· The image should be clear and of high quality when viewed in the Word document, and when printed.
· In general, boxes around the figures should be used.
Note: Figures in this document should be regarded as shells and final deliverables might look different to the examples presented here:
· A legend for treatment should always be presented, preferably below the actual graph, “N=xxxx” should be concatenated to the treatment group description
· If color is used, color should be linked to the same treatment; and similarly, the line type should be used for the same treatment and treatments should be differentiable for black and white printing.

A2.1.9 FOOTNOTE INFORMATION

Footers should be defined as follows:
· Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
· The program path and name and version number (if applicable) should appear as last footnote, at the bottom of the page, left aligned, along with the date/time stamp, right aligned.
· Footnotes should be left-aligned.
· Footnotes should be in sentence case.
· The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.
· If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
Ordering of footnotes should be as follows:
1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes

- Common notes from table to table should appear in the same order.
- The symbols should appear in the same order as they are defined in the table or listing, from left to right.

A2.1.10 PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table, listing or figure shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.
Please disregard current examples of precision in shells.

A2.2 DATES & TIMES

Dates and time will follow ISO 8601 format (as prescribed by CDISC standards). Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Imputed dates, as defined in Appendix 3 of this statistical analysis plan, will NOT be presented in the listings.

A2.3 SPELLING FORMAT

English US.

A2.4 PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
CaPre 4g/day	CaPre 4g/day	CaPre 4g/day
Placebo	Placebo	Placebo

A2.5 PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (Visit 1)	Scr (V1)

Long Name (default)	Short Name
TG Qual Visit 2	Qual V2
TG Qual Visit 3 need also Visit 3.1	Qual V3 need also Qual 3.1
Baseline (Visit 4)	BL (V4)
Week 4 (Visit 5)	W4 (V5)
…	…
Week 26 (Visit 9)	W26 (V9)
End of Treatment	EOT
Contact Follow-up	Fup
Unscheduled Visit (Visit x)	UNS (Vx)

A2.6 LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- cohort,
- center-subject ID,
- visit date/event date (where applicable), and in the case of multiple observations per visit date/event date, the observations should be sorted alphabetically within visit date/event date

The subjects' age, gender and race will be included in the listing header and the subjects' inclusion status in the applicable analysis populations will also be displayed, when appropriate.

A2.7 EDITORIAL CHANGES

Any editorial changes such as corrections of typographical errors, modification of spelling, or change of wording in titles or footnotes that leave the meaning unchanged can be done without requiring an amendment of this document. Footnote changes might also be necessary during the programming of displays depending upon the particular needs for special data handling. These changes will not require an amendment to this document.

APPENDIX 3. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing, prior medication can not be assigned If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 4. IMPLEMENTATION OF SENSITIVITY ANALYSES

Delta (δ) -adjusted Tipping Point analysis

Sensitivity to departures from the assumption made for the primary analysis will be investigated using a tipping point analysis. Departures from the primary assumption will be assessed assuming that subjects who discontinue the study early from the CaPre 4g daily arm have, on average, efficacy outcomes after discontinuation that are worse by some amount δ compared to other similar subjects who discontinued their CaPre 4g daily treatment early but remained in the study and have observed data (i.e., compared to a value which would have been assumed under the primary imputation model in the experimental treatment arm).

A series of analyses will be performed with increasing values of δ until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that overturns the primary results will represent a tipping point. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided.

Percent changes from baseline in TG levels score will be analyzed based on data observed while the subject remains on study as well as data imputed using MI methodology for time points at which no value is observed. Imputed values in CaPre 4g daily arm will first be sampled from the multiple imputation model as described for the primary analysis and then a value of $\delta = \{\Delta\}$ will be added to all imputed values in the CaPre 4g daily arm prior to analyzing multiply imputed data. This approach assumes that the marginal mean of imputed subject measurements is worse by δ at each time point after discontinuation compared to the marginal mean of subjects with observed data at the same time point for the CaPre 4g daily arm.

Analyses will be conducted with values of δ starting from 0 (corresponding to the primary analysis, i.e., no adjustment) with increments of 0.5 until the null hypothesis can no longer be rejected.

As for the primary analysis, this approach uses MCMC for partial imputation of non-monotone data under MAR followed by sequential MI regression for monotone data.

Clinical Study Protocol

Protocol Title:	**A Phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia**
Protocol Number:	**ACA-CAP-001**
Date of Protocol:	**Amended Protocol 22 May 2018** **Initial Protocol 02 November 2017**
Product:	**CaPre® (NKPL66)**
IND No.:	**104703**
EudraCT No.:	**NA**
Study Phase:	**3**
Sponsor:	**Acasti Pharma Inc.** **545, Promenade du Centropolis, Suite 100** **Laval, Québec, Canada, H7T 0A3**
Lead Principal Investigator	**Dr. Dariush Mozaffarian, MD, DrPH** **Tufts Friedman School of Nutrition Science and Policy** **150 Harrison Ave,** **Boston, MA, USA 02111**

Key Personnel and Facilities

Lead Principal Investigator	**Dariush Mozaffarian, MD DrPH** **Tufts Friedman School of Nutrition Science and Policy** **150 Harrison Ave,** **Boston, MA, USA 02111** **Office: 617-636-0876**
Sponsor's representative	**Laurent Harvey, B.Pharm., M.Sc.** **Vice President, Clinical and Non-Clinical** **545 Promenade Centropolis, Suite 100** **Laval, Québec H7T 0A3 Canada** **Office: 450-686-4555, x407** **Mobile: 514-210-0409** **Jean-François Lapointe, PhD** **Director of Clinical Development** **545 Promenade Centropolis, Suite 100** **Laval, Québec H7T 0A3 Canada** **Office: 450-686-4555 x434** **Mobile: 514-867-3990**
Contract Research Organization (CRO)	**IQVIA RDS, Inc.** **(formerly Quintiles IMS)** **4820 Emperor Blvd, Durham** **NC USA 27703** **Quebec, Canada**
Medical Monitor	**Dr. Jose Ferrari, MD** **IQVIA** **Ing. Butty 275 Flr 9 (C1001FA)** **Ciudad de Buenos Aires - Argentina** **Tel: 54 11 4132 6500**
Clinical Laboratory	**Q2 Solutions – Central Laboratories** **27027 Tourney Road** **Valencia, CA, USA 91355**

Protocol Approval Signatures

PROTOCOL TITLE: A Phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-001

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

Sponsor's representative

Signature: **Date:**

Laurent Harvey
Vice President, Clinical and Non-Clinical

DD/MMM/YYYY

Signature: **Date:**

Jean-François Lapointe
Director of Clinical Development

DD/MMM/YYYY

Lead Principal Investigator

Signature: **Date:**

Dariush Mozaffarian, MD DrPH

DD/MMM/YYYY

Revision History

Key change(s) to the Initial Protocol dated 02 November, 2017 are summarized below:

Amendment No.	Date	Change(s)
01	22 May, 2018	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2, to allow subjects taking stable dose of fibrate, and to clarify study requirements for stability of concomitant PCSK9I and fibrate prior to the screening visit (V1). Edits and footnotes added to clarify that individual TG values outside of the study inclusion range at the screening visit (V1), or during the TG qualification period (V2 and V3) , are not automatically exclusionary as randomization of subjects is based on an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) during the TG qualification period Add optional urine pregnancy test (test strip) prior to randomization (V4). New section added to clarify conditions under which the protocol may allow re-screening of subjects. New section added to clarify conditions under which re-testing of certain laboratory test may be allowed. Edits to the statistical section of the protocol to clarify that the sample size justification and primary analysis are based on non-parametric methods.

A detailed revision history is provided in Appendix 3.

SYNOPSIS

Name of Sponsor/Company:	Acasti Pharma Inc.	
Name of Finished Product:	CaPre®	
Name of Active Ingredient:	NKPL66	
Title of Study:	A Phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia.	
Protocol No:	ACA-CAP-001	
Investigators:	Approximately 84 U.S. Principal Investigators	
Study center(s):	Approximately 84 U.S. Study Centers.	
Study duration: The study duration will be up to 39 weeks, consisting of an initial screening period of 4 to 6 weeks, a 2- or 3-week triglyceride (TG) qualifying period , a 26-week double-blind treatment period and a follow-up contact after 4 weeks.		**Phase:** 3

Objectives:

Primary:

- To determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting triglyceride (TG) levels in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

Secondary:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by adverse events (AEs), vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-high-density lipoprotein cholesterol (non-HDL-C), very-low-density cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) after 12 weeks of treatment.

Exploratory:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol (RLP-C).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.

- To compare between CaPre and placebo the proportion of patients achieving TG values below 500 mg/dL.
- To determine the effect of CaPre, compared to placebo, on total plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations, on omega-3 (OM3) index, and on Arachidonic Acid (AA), omega-6/omega-3 and EPA/AA ratios.
- To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.
- To explore the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting TG levels.
- To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.
- To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.
- To determine the effect of CaPre on apolipoprotein (apo) B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL, and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on fasting serum glucose (FSG), insulin, and on glycosated hemoglobin A1c (HbA1c).
- To explore the effect of CaPre on insulin resistance and beta-cell function using the homeostatic model assessment (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2).

Methodology: Please refer to Table 1 for the Schedule of Events

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to aim to maintain this diet, as well as to reduce the intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate, or a combination of these agents.

Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening. PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1).

Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1). Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment.

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects .

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values. If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made one week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1. Subjects who fail to meet the average TG inclusion level will be considered screening failure. Re-screening of these subjects will not be allowed.

After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication with meals.

Following a 2.5:1 treatment allocation ratio (CaPre:placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying fasting TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5

mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated or not currently treated with statin, CAI or PCSK9I, alone or in combination). During the double-blind treatment period, subjects are to return to the study center at Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week18) and Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety will be made 4 weeks after final visit [Week 26 or early termination].	
Planned number of subjects:	Approximately 653 subjects will be screened to obtain 245 randomized subjects, with a treatment allocation ratio of 2.5:1 (CaPre:placebo).
Diagnosis and main criteria for inclusion:	**Main Inclusion Criteria:** Subjects may be entered in the study only if they meet all of the following criteria: 1. Subjects ≥18 years of age. 2. Isolated hypertriglyceridemia or mixed hyperlipidemia, with triglycerides ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated or not with a stable dose of statin, CAI, PCSK9I, fibrate, or a combination of these agents. If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening. If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of statin and/or CAI at time of screening. 3. Willingness to aim to maintain current physical activity level and diet consistent with NCEP-TLC and to reduce added sugars intake throughout the study. 4. Be informed of the nature of the study and give written consent prior to any study procedure. **Main Exclusion Criteria:** Subjects will not be entered in the study for any of the following reasons: 1. Allergy or intolerance to OM3 fatty acids, OM3-acid ethyl esters, OM3 phospholipids, fish, shell fish, or any component of the study medication.

	2. Subjects diagnosed with Familial Chylomicronemia Syndrome (FCS). 3. Subjects with lysosomal acid lipase deficiency. 4. Body mass index greater than 45 kg/m^2. 5. Subjects who are pregnant, lactating, and subjects of childbearing potential who are either planning to become pregnant or who are not using acceptable birth control methods during study participation. Subjects of childbearing potential are subjects who have experienced menarche and do not otherwise meet the criteria for subjects not of childbearing potential, defined as: • Subjects who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation); or • Subjects who are postmenopausal, i.e., who have had a cessation of menses for at least 12 months without an alternative medical cause. A follicle stimulating hormone (FSH) test ≥40 mIU/mL may be used to confirm the post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study and for 8 weeks following the last dose of study medication. 6. Subjects taking tamoxifen, estrogens, or progestins, or other medications or nutritional supplements with mechanisms modifying estrogen or progestogen pathways, who have had dosage changes within 4 weeks prior to Visit 1. 7. Use of oral or injected corticosteroids or anabolic steroids within 6 weeks prior to randomization. 8. History of pancreatitis within the last 6 months prior to Visit 1.

	9. History of symptomatic gallstone disease within the last 5 years, unless treated with cholecystectomy. 10. Diabetics requiring changes in glucose-lowering medication (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1. 11. Subjects with clinical evidence of hyperthyroidism or TSH level less than lower limit of normal (LLN) at Visit 1. Subjects diagnosed with hyperthyroidism must be treated with medication for at least 6 weeks prior to Visit 1. 12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN) within 6 weeks prior to Visit 1. 13. Thyroid hormone replacement therapy that has not been stable for more than 6 weeks prior to Visit 1. 14. History of cancer (other than basal cell carcinoma) within 2 years prior to Visit 1. 15. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, exacerbation of congestive heart failure requiring hospitalization or a change in treatment), life-threatening arrhythmia, or revascularization procedure within 6 months prior to Visit 1. 16. Use of other prohibited drugs: prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted); or anabolic steroids. Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed. 17. Use of any lipid-altering agents other than statins, CAI, PCSK9I, or fibrate, including niacin at a dose greater than 200

	mg/day, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), or any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued 8 weeks prior to randomization. 18. Resection of an aortic aneurysm or endovascular aortic repair within 6 months prior to Visit 1. 19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily. 20. Poorly controlled hypertension (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥100 mmHg). Subjects with hypertension adequately controlled with medication are eligible provided that their antihypertensive therapy has been stable for at least 4 weeks prior to Visit 1. 21. Recent history (past 12 months) of drug abuse or alcohol abuse, or alcohol use greater than 2 units per day (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks). 22. Hepatobiliary disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN; if ALT/AST is >3× ULN, the levels must have been stable for 3 months prior to Visit 1. 23. Severe renal disease as defined by less than 30 mL/min serum creatinine clearance calculated using the Cockcroft-Gault formula. 24. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) international normalized ratio (INR) of ≥1.5. Subjects using warfarin [Coumadin®] or heparin are allowed. Subjects receiving other anticoagulants dabigatran, rivaroxaban, or apixaban are allowed. Subjects receiving acetylsalicylic acid (ASA) alone or in combination with other anti-platelet agents (e.g., clopidogrel, prasugrel, ticagrelor) are also allowed.

	25. Unexplained creatine kinase concentration 3 × ULN. 26. Creatine kinase elevation owing to known hereditary or acquired muscle disease. 27. Exposure to any investigational product, within 4 weeks prior to Visit 1. 28. Presence of any other condition (such as severe pulmonary, gastrointestinal, or immunologic disease) the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk. 29. Any life-threatening disease expected to result in death within 2 years, require frequent hospitalizations, extensive surgery or changes in medications or diet.
Test product, dose and mode of administration:	CaPre 4 g, administered orally as 1 g capsules once a day with meals.
Reference therapy, dose and mode of administration:	Matching placebo (corn starch) capsules administered orally as 1 g capsules once a day with meals.

Criteria for evaluation:

Primary Efficacy Endpoint:

- Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L).

Secondary Efficacy Endpoints:

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

The secondary efficacy endpoints are listed in order of importance for the control of the type 1 error.

Exploratory efficacy endpoints:

- Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and Week 12) and Week 26 in TC.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and to Week 26 in RLP-C.
- Percent change from baseline (average of Week -1 and 0) to Week 26 in LDL-C (β-quantification) and VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 26 in non-HDL-C and HDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII and apo A5.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (LDL, non-HDL, HDL, IDL and VLDL).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP and Lp-PLA2.

Exploratory pharmacokinetic endpoints:

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations.
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in AA, in omega-6/omega-3 and in EPA/AA ratios.

Safety:

Adverse Events (AEs), vital signs and clinical laboratory measures.

Statistical methods:

Efficacy analyses will be based on the intent-to-treat (ITT) Population, defined as all randomized subjects. Analysis of the primary efficacy endpoint will be repeated on the per-protocol (PP) Population to test for robustness of results. The PP Population will include only those ITT subjects who have no major protocol deviations (which will be detailed in the Statistical Analysis Plan (SAP) before database lock).

The Safety Population will be used to assess safety and tolerability variables, defined as all randomized subjects who received at least 1 dose of study medication.

For the primary efficacy endpoint, i.e., the percent change in fasting TG levels from baseline to Week 12, descriptive statistics will be summarized and statistical testing will be performed. The baseline value is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification). The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of 12-weeks of double-blind treatment, approximately 1 week apart that is Visit 6 (Week 11) and Visit 7 (Week 12).

The primary estimand is the difference between the randomized treatment groups, CaPre 4 g daily and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. All collected data will be used in primary analysis.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline TG value as a covariate will be used to perform a hypothesis test for the primary endpoint (percent change in TG levels). Quantile regression, adjusting for same baseline covariates as specified for the ANCOVA model, will be used to obtain an adjusted estimate of the median treatment difference vs. placebo with associated two-sided 95% confidence intervals (CI). There is an expectation that the proportion of subjects who truly have missing data (who withdraw from study participation/data collection) will be small. Subjects who withdraw consent for study participation overall and are not assessed at Week 11 and 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or Week12. Results of the ANCOVA analysis from multiple imputed datasets will be combined using the Rubin's combination rule.

As supportive analysis, Hodges-Lehmann Estimates for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied.

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the analyses by using other strategies for dealing with missing data. Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed Week 11 and/or 12. This approach assumes that some subjects discontinuing the study will do so for non-treatment-related reasons and would have similar outcomes to subjects who are able to complete the treatment. A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study. Other sensitivity analysis methods may be performed and will be detailed in the SAP.

For lipid parameters defined as secondary and exploratory endpoints, the percent change from baseline to Week 12 and/or to Week 26 will be evaluated. The baseline value is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2, 3 and 4 or Visits 3, 3.1, and 4 in case an additional TG measurement is necessary during qualification), except for LDL-C (beta-quantification) which baseline is defined as the average of 2 measurements (Week -1 and 0 corresponding to Visits 3 and 4 or Visits 3.1 and 4 if applicable). For all lipid endpoints, the Week 12 endpoint is defined as the average of the values obtained at Visit 6 (Week 11) and Visit 7 (Week 12), and the Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26).

Similar analyses as specified above for the primary efficacy analysis will be conducted for the secondary efficacy endpoints on the ITT population. A non-parametric rank-based ANCOVA model and quantile regression with main effects of treatment, nominal qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate, will be used to estimate the treatment effect of the CaPre dose group vs. placebo.

The experiment-wise type I error will be controlled to a maximum of two-sided 5% by using a hierarchical closed testing procedure: secondary endpoints will only be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; similarly, the later secondary endpoint in the hierarchy will be considered for statistical significance only if all former preceding secondary endpoints are found to be statistically significant.

For other exploratory efficacy endpoints, the baseline value is defined as the value obtained prior to dosing (measurement taken at Visit 4 (Week 0); Week 12 endpoint is defined as the value obtained at Visit 7 (Week 12) and Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26), whenever applicable. These will be analyzed similarly as specified in the primary efficacy analysis to be conducted on the ITT population. For exploratory endpoints, nominal p-values will be reported in an exploratory fashion.

Regarding the proportion of subjects who have a fasting TG level <500 mg/dL at the end of 12-week and 26-week double-blind treatment period, a Cochran-Mantel-Haenszel (CMH) test will be used, controlling for the stratification factors that are used for randomization. Subjects with missing data at the analysis time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis. In a sensitivity analysis, subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

All treatment-emergent AEs (TEAEs) will be summarized by treatment group. Treatment-emergent AEs will also be summarized by relationship to the study medication and by intensity. Deaths, serious adverse events (SAEs) and AEs leading to study subject early termination will be tabulated and presented in data listings. Clinical laboratory results (chemistry, hematology, coagulation, urinalysis, etc.) will be summarized using descriptive statistics for each visit by treatment group. Observed values at each visit and changes from baseline to each post-baseline visit will be presented. Vital signs and ECGs will be summarized by treatment group for each applicable visit.

Approximately 245 subjects will be randomized to this study. Subjects will be randomized to 1 of 2 treatment groups (CaPre 4 g or placebo), following a 2.5:1 (CaPre: placebo) treatment allocation ratio. Accordingly, approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. A sample size of 245 subjects will provide at least 90% power to detect a median difference of at least 20 percentage points in percent decrease from baseline to Week 12 in TG between CaPre 4 g group and placebo (assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05, based on a non-parametric Wilcoxon-Mann-Whitney test). The overall median treatment difference of 20 percentage points is believed to be clinically relevant.

These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia).

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AA	Arachidonic acid
ADR	Adverse Drug Reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CAI	Cholesterol-absorption inhibitor
CI	Confidence Interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
DHA	Docosahexaenoic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
FFA	Free fatty acid
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase

Abbreviation	Definition
HbA1c	Glycosated Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HED	Human equivalent dosing
HIV	Human immunodeficiency virus
HOMA	Homeostatis model assessment
HPMC	Hydroxypropyl methyl cellulose
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IRT	Interactive Response Technology
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA2	Lipoprotein-associated phospholipase A2
LS	Least squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NCEP	National Cholesterol Education Program
NHPD	Natural Health Products Directorate
NNHPD	Natural and Non-prescription Health Products Directorate (previously NHPD)
NOAEL	No-Observed-Adverse-Effect-Level
NS	Not significant

Abbreviation	Definition
OM3	Omega-3
PCSK9I	Proprotein convertase subtilisin/kexin type 9 serine protease inhibitors
PK	Pharmacokinetics
PL	Phospholipid
PP	Per-protocol
PT	Prothrombin time
PUFA	Polyunsaturated fatty acids
RBC	Red blood cell
RDW	Red blood cell distribution width
RIDIT	Relative to an Identified Distribution Integral Transformation
RLP-C	Remnant-like particle cholesterol
RR	Respiratory Rate for Vital signs or in context Relative Risk or RR interval (time between QRS complexes) for ECG
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SoC	Standard of care
SOCBP	Subject of child-bearing potential
SOP	Standard Operating Procedures
T_4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent AE
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

2.0 INTRODUCTION

It is estimated that about one-third (31%) of the population aged 20 years and older in the United States (U.S.) has elevated levels of triglycerides (TG), including approximately 36 million people diagnosed with hypertriglyceridemia (TG ≥200 mg/dL) and between 1% to 2% with severe hypertriglyceridemia (TG ≥500 mg/dL) representing about 4 million people.[1] Hypertriglyceridemia is due to both genetic and environmental factors, including obesity, sedentary lifestyle and high-calorie diets and is also associated with comorbid conditions such as diabetes, chronic renal failure, pancreatitis and nephrotic syndrome.

Severe hypertriglyceridemia is associated with acute pancreatitis. While reduction in risk of recurrent pancreatitis by pharmacologic means has not been systematically studied, aggressive treatment of hypertriglyceridemia is generally believed to reduce the recurrence of pancreatitis in patients whose sole risk factor appears to be the hypertriglyceridemia.[2,3,4]

Based on data from the National Health and Nutrition Examination Surveys (NHANES) between 2001 and 2006, fewer than 4% of U.S. adults with severe hypertriglyceridemia receive prescription medication to lower their TG levels, representing a significant unmet medical need.[5] The first-line drug therapy in patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL) is often a prescription OM3, niacin or fibrates as adjunct to TLC diet. However, niacin is not well tolerated and safety, notably risk of myopathy, may be an issue with fibrates especially when used in combination with a statin [6,7]. Also, fibrates may substantially increase LDL-C in patients with more severe form of hypertriglyceridemia[8].

Lovaza (including 4 generic versions), Vascepa, Omtryg, and Epanova are prescription OM3 drugs currently approved for the treatment of severe hypertriglyceridemia in the U.S. CaPre, Acasti Pharma's prescription drug candidate, is an OM3 phospholipid concentrate derived from krill oil developed for the treatment of severe hypertriglyceridemia. Contrarily to previously approved OM3 prescription drugs in this indication, the form of OM3 found in CaPre (predominantly EPA and DHA) is a mixture of OM3 phospholipid conjugates and free fatty acids (FFA), which may offer better bioavailability over products containing OM3 in the form of ethyl esters.

The proposed indication for CaPre is as an adjunctive therapy to diet and exercise for patients with severe hypertriglyceridemia; therefore, the target population selected for the current study is adult subjects with isolated severe hypertriglyceridemia or mixed hyperlipidemia (TG ≥500 mg/dL to ≤1500 mg/dL). The main objective of the study is to show that CaPre 4 g daily, compared to placebo, is effective in lowering fasting TG levels in this patient population.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

The following paragraphs summarize background information from nonclinical and clinical studies of CaPre carried out by the Sponsor. Further details are presented in the CaPre Investigator's Brochure.

Nonclinical Data

The nonclinical program set forth to demonstrate that CaPre and more specifically its drug substance, NKPL66, can be deemed safe and tolerable for use in human clinical trials. Nonclinical studies completed so far on NKPL66 include pharmacodynamic, safety pharmacology (cardiovascular, neurological and respiratory systems), pharmacokinetic (PK), toxicology (acute, sub-chronic and chronic, as well as genotoxicity), and development and reproductive teratology (DART) in rodent and non-rodent species dosed up to 65 g/day human equivalent dose (HED) and up to 39 weeks.

Taken together, no NKPL66-related significant toxicological observations were evidenced from these nonclinical studies; results demonstrate that CaPre (NKPL66) can be considered safe and well-tolerated up to 65 g/day HED. Black (or very dark red) feces were noted in some animals treated with NKPL66. The red/black color of the feces was not due to blood but rather due to the presence of naturally-occurring carotenoid pigments contained in the NKPL66 tested. Coloration returned to normal during the recovery period.

Clinical Data

The current human exposure with CaPre consists of two Phase 1 PK clinical studies in healthy volunteers and two Phase 2 clinical studies in subjects with mild to severe hypertriglyceridemia (200 mg/dL ≤ TG <877 mg/dL).

All together, these four clinical studies included 773 subjects among which 611 subjects received CaPre (pooled subjects), 129 subjects received placebo, and 29 subjects received Standard of Care (SoC) alone. Among these 611 subjects exposed to CaPre, 216 subjects have been exposed to 2 g/day for up to 12 weeks while 171 subjects have been exposed to 4 g/day for up to 8 weeks.

The Phase 1 PK study (CAP13-101) was conducted in the U.S. and aimed to evaluate the pharmacokinetics of CaPre following single and multiple oral doses in healthy volunteers for up to 15 days. CaPre was found to be safe and well-tolerated in healthy adult subjects when administered as multiple oral doses of 1 g/day, 2 g/day, and 4 g/day. CaPre PK appeared to be approximately dose proportional over the 1 to 4 g/day dose range. The bioavailability of CaPre did not appear to be meaningfully affected by the fat content of the meal consumed prior to dose administration. This is clinically relevant as a low-fat diet is part of the management of hypertriglyceridemic patients.

The Phase 1 Comparative bioavailability study (2016-4010) was conducted in the U.S. and aimed to establish a scientific bridge between CaPre and the marketed OM3 drug Lovaza, under fasting and fed conditions. More specifically, the study aimed to demonstrate that exposure to EPA and DHA from CaPre was not significantly higher than Lovaza under conditions of maximum exposure in the fed state, following intake of a high-fat and high-calorie meal.

Under fed conditions, the 90% confidence intervals (CIs) of the ratio of geometric means between CaPre and Lovaza for total (AUC_{0-72}) and peak (C_{max}) exposure of baseline-adjusted EPA and DHA in total lipids of plasma were each entirely contained below 125%; thereby meeting the primary objective of this study. In fasting conditions however, the total and peak exposure were each significantly enhanced following administration of CaPre compared to Lovaza as the 90% CIs of the ratio of geometric means for AUC_{0-72} and C_{max} for both analytes were entirely contained above 125%. Note that exposure levels observed under fasting conditions were still below those obtained following administration of Lovaza in the fed state and, as such, no safety concerns would be associated with these findings. Administration of OM3 drugs under fasting (empty stomach) and/or a low fat diet, which is indicated in the management patients with hypertriglyceridemia, provides least optimal conditions for EPA and DHA absorption. However, it is considered a more realistic representation of OM3 drug administration in the treatment of these patients. Finally, the impact of food on the bioavailability of Lovaza was much more pronounced compared to that following administration of CaPre, a finding that suggests less loss of exposure and perhaps efficacy when patients do not comply with the proposed product labeling of taking CaPre with a meal.

The two Phase 2 clinical studies were conducted in Canada and aimed to assess the safety and efficacy of CaPre in the treatment of mild-to-severe hypertriglyceridemia (200 mg/dL ≤ TG < 877 mg/dL), among which approximately 90% of subjects had TG levels between 200-499 mg/dL. Results gathered from a total of 675 subjects enrolled in these studies showed that CaPre was safe and well tolerated.

In the COLT (Open-Label) study, a statistically significant reduction in TG levels was demonstrated with CaPre 2 g or 4 g per day after 8 weeks of treatment compared to the standard of care (SoC) (2 g: -15.1%, p=0.06; 4 g: -14.8%, p=0.03) without deleterious effects on LDL-C (2 g: -7.6%, p=ns; 4 g: -10.4%, p=ns). In addition, beneficial effects were noted on non-HDL-C (2 g: -5.9%, p=ns; 4 g: -9.8%, p=0.036), HDL-C (2 g: +7.9%, p=0.10; 4 g: +7.7%, p=0.07) and on glycemic control (HbA1c) (2 g: -6.8%, p=ns; 4 g: -15.0%, p=0.04) primarily with CaPre administered at 4 g/day compared to the SoC.

In TRIFECTA (double-blind, placebo-controlled) study, a statistically significant reduction in TG levels was demonstrated with CaPre 1 g and 2 g/day after 12 weeks of treatment compared to placebo (1 g: -9.1%, p=0.05; 2 g: -9.8%, p=0.04) without deleterious effects on LDL-C (1

g: +2.0%, p=ns; 2 g: -0.6%, p=ns). In addition, beneficial effects were noted on non-HDL-C primarily with CaPre administered at 2 g/day compared to the placebo (1 g: -3.6%, p=ns; 2 g: -5.3%, p=0.04). There were, overall, no significant differences between treatment groups with respect to change in fasting plasma glucose, insulin, HbA1c and HOMA-IR.

In terms of safety, among all treatment-emergent adverse events (AEs) with an occurrence greater than 2% of subjects (CaPre all doses pooled) and greater than placebo or SoC, only diarrhea emerged at an incidence of 2.3%. All other AEs were reported at a frequency of less than 2%. No treatment-related AEs were reported at an incidence greater than 2% (CaPre all doses pooled) by subjects exposed to CaPre. The most frequent treatment-related AEs were gastroesophageal reflux disease (1.6%), diarrhea (1.3%), blood creatinine phosphokinase increased (1.3%) and myalgia (0.8%). These AEs were more frequent at the highest dose of CaPre (4 g/day).

Only three SAEs were reported and consisted of haemangioma, myocardial infarction and pancreatitis. All these SAEs were reported by the investigator as not related to CaPre.

Finally, a total of 9 subjects (1.2% of pooled subjects) discontinued due to AEs, among which 4 subjects following placebo or SoC and 5 subjects following CaPre (CaPre 1 g/day: n=2; CaPre 2 g/day: n=2; CaPre 4 g/day: n=1). The causality of AEs was assessed as possibly-related to the study drug for all 5 subjects who discontinued following CaPre compared to 1 subject who discontinued following placebo. Treatment-related AEs leading to discontinuation following CaPre were: abdominal distension (CaPre 1 g/day: n=1), diarrhea (CaPre 1 g/day: n=1, CaPre 2 g/day: n=1), hypersensitivity (CaPre 4 g/day: n=1), burning sensation (CaPre 4 g/day: n=1) and rash (CaPre 1 g/day: n=1, CaPre 2 g/day: n=1).

In summary, nonclinical and clinical data gathered to date are considered supportive of the proposed Phase 3 study with CaPre as an adjunctive therapy to diet in adult patients with severe hypertriglyceridemia. Please refer to the current CaPre Investigator' Brochure for further details[9].

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- The primary objective of the study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting TG levels in subjects with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by AEs, vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C after 12 weeks of treatment.

3.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol (RLP-C).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.
- To compare the proportion of patients achieving TG values below 500 mg/dL between CaPre and placebo.
- To determine the effect of CaPre, compared to placebo, on total plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations, on omega-3 (OM3) index, and on Arachidonic Acid (AA), omega-6/omega-3 and EPA/AA ratios.
- To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.
- To explore the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting serum TG levels.

- To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.
- To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.
- To determine the effect of CaPre on apo B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on FSG, insulin and on HbA1c.
- To explore the effect of CaPre on insulin resistance and beta-cell function (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on hsCRP and Lp-PLA2.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This will be a multi-center, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre or placebo 4 g/day), Phase 3 efficacy and safety study in subjects ≥18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study duration will be up to 39 weeks, consisting of an initial diet and lifestyle recommendation and medication stabilization period of 4 or 6 weeks, a 2 or 3-week TG qualifying period, a 26-week double-blind treatment period, and a 4-week contact follow-up. Approximately 653 subjects will be screened to obtain 245 randomized subjects at approximately 84 centers.

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet[10] and will be instructed to aim to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study. Appendix 2 provides information outlining the principles of NCEP-TLC dietary patterns focused on lowering cholesterol

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®,

Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects.

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1. Subjects who fail to meet the average TG inclusion level will be considered screening failure. Rescreening of these subjects will not be allowed.

After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication at a meal.

Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated with statin, CAI or PCSK9I alone or in combination).

Following randomization at Visit 4 (Week 0), subjects are to return to the study center at Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week 18) and for the last visit at Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety assessment is required 4 weeks after Final Visit (Visit 9 or early termination).

The study design is presented in Figure 1. The Schedule of Events is presented in Table 1.

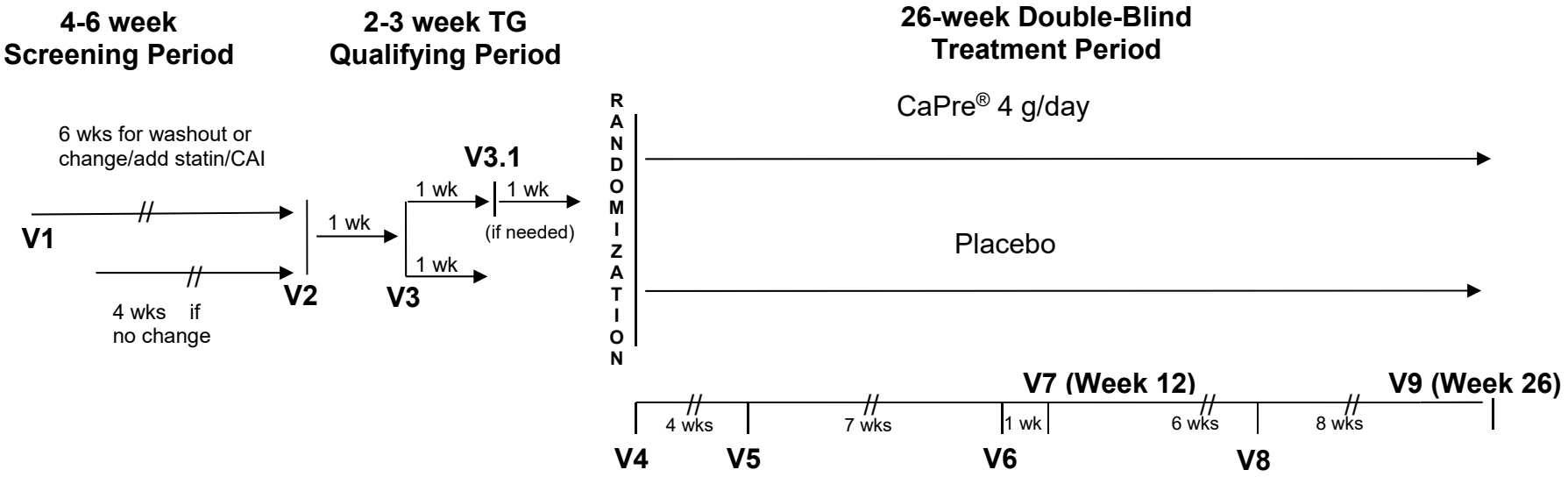

Figure 1 Schematic of Study Design

4.1.1 Screening Visit (Visit 1 [Week -8 or Week -6])

The purpose of the screening visit and the subsequent stabilization period (between V1 and Visit 2) is to allow subjects to acclimate to the dietary recommendation to consume a NCEP-TLC diet and reduce intake of added sugar, and to allow time for washout of prohibited lipid-altering agents (if necessary), stabilization following initiation or dose adjustment of a statin and/or CAI treatment at screening, or washout or dose reduction of a fibrate treatment.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, PCSK9I, CAI, such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects.

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 1:

- Signed informed consent prior to any study-related procedures.

- Review of inclusion and exclusion criteria.
- Demographic information, medical history (including tobacco and alcohol use) and concomitant medications will be recorded.
- Height and weight will be measured for calculation of BMI.
- Vital signs will be measured.
- Complete physical examination.
- The subject will provide fasting blood samples for:
  - Evaluation of eligibility (fasting lipids) to continue in the stabilization period[1]
  - Routine laboratory analysis (chemistry, hematology, coagulation)
  - HbA1c
  - Hepatitis B and C
  - Thyroid function (thyroid stimulating hormone [TSH] and thyroxine [T_4])
  - Each subject of childbearing potential (SOCBP) will provide a blood sample for pregnancy testing. A subject with a positive result must be excluded from the study as a screening failure (see Section 4.3).
- Urine sample will be collected for urinalysis.
- Recommendation to consume a NCEP-TLC diet that should be followed for the duration of the study, along with the reduction of added sugar, will be explained to the subject. Written dietary information will be available to the subject.
- Schedule the first TG Qualifying Visit (Visit 2). Visit 2 should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering agents at screening, and for subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe), PCSK9I, a fibrate, or a combination of these agents. Visit 2 should be scheduled for 6 weeks after Visit 1 for subjects who initiated or changed dose of a

[1] For randomization, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on results of the TG qualification period (see section 4.1.2); therefore TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])TG <500 mg/dL or >1500 mg/dL (<5.7 mmol/L or >17.0 mmol/L) at screening (V1) should not be considered automatically exclusionary. Investigator must use their best medical judgement when deciding whether or not a subject can continue in the study after screening depending on their evaluation of the subject's medical history, current use or washout of lipid-alterging agents, medical condition and other findings at screening.

statin and/or CAI treatment, for subjects who require washout of prohibited lipid-altering agents at screening, and for subjects who washout or reduced dose of a current fibrate treatment.

- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to aim to maintain physical activity consistent with TLC level throughout the study.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.2 TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])

At Week -2, all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's **average** TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 2 and Visit 3:

- Review of inclusion and exclusion criteria.
- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured (only at Visit 2).
- Vital signs will be measured.
- Brief physical examination (only at Visit 2).
- 12-lead electrocardiogram (ECG; only at Visit 2).

- The subject will provide fasting blood samples for evaluation of eligibility (fasting lipids) to continue in the TG qualification period[2].
- Physical activity and dietary compliance will be reviewed with the subject.
- Diet counseling.
- Schedule the next TG Qualifying Visit (Visit 3 or 3.1 (if applicable)) for 1 week after Visit 2 or 3, respectively.

  OR

  Schedule Randomization Visit 4 for 1 week after Visit 3 or 3.1 (if applicable).
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.3 Randomization Visit (Visit 4 [Week 0])

After confirmation of qualifying fasting TG values (fasting TG level ≥500 mg/dL and ≤1500 mg/dL [≥5.7 mmol/L and ≤17.0 mmol/L] based on the average [arithmetic mean] of the Visit 2 and Visit 3, or Visit 3 and Visit 3.1 values), eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), following a 2.5:1 treatment allocation ratio (CaPre:placebo), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g (4 capsules) daily, or matching placebo (4 capsules) daily. Subjects will be dispensed with adequate study medication until Visit 5.

Prior to having the blood sample drawn, subject must fast for a period of at least 9 hours and may consume only water and usual medications. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 4:

- Concomitant medications and AEs since last visit will be recorded.
- Weight and waist circumference will be measured.

[2] For randomization, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on results of the TG qualification period (see section 4.1.2); therefore TG <500 mg/dL or >1500 mg/dL (<5.7 mmol/L or >17.0 mmol/L) at V2 should not be considered automatically exclusionary. Investigator are required to use their best medical judgement when deciding whether or not a subject can continue in TG qualification period.

- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Routine laboratory analysis (chemistry, hematology, coagulation).
  - Fasting lipids.
  - Fasting insulin.
  - HbA1c.
  - Biomarkers (see Table 3).
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
  - Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk. The analysis will be considered part of this clinical protocol.
- Urine sample will be collected for urinalysis and for an optional urine pregnancy test (test strip)[3]. If the test is performed, negative pregnancy status must be confirmed before randomization.
- Physical activity and dietary compliance will be reviewed with the subject.
- Diet counseling.
- The subject will be randomized via Interactive Response Technology (IRT) to CaPre 4 g daily, or placebo.
- The subject will be supplied with study medication to be taken until Visit 5 (4 weeks), and instructed to take it once a day with a meal but not prior to attending Visit 5.
- Schedule Visit 5 for 4 weeks after Visit 4.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.

[3] Based on the Investigator's medical judgement, an optional urine pregnancy test (test strip) may be performed to confirm eligibility prior to randomizing a subject and initiate dosing with the study medication.

- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.4 Double-blind Treatment Period (Visit 5 [Week 4])

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 5:

- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Routine laboratory analysis (chemistry, hematology, coagulation).
  - Fasting lipids.
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
- Urine sample will be collected for urinalysis.
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- Previously dispensed study medication will be collected and a new supply of study medication (8 weeks) to be taken until Visit 7 (Week 12) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior to attending Visit 6 and 7. The number of capsules returned will be counted and the results will be documented.
- Schedule next study visit.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.5 Double-blind Treatment Period (Visit 6 [Week 11] and Visit 7 [Week 12])

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 6 and Visit 7:

- Concomitant medications and AEs since last visit will be recorded.
- Weight and waist circumference will be measured (only at Visit 7).
- Vital signs will be measured.
- Brief physical examination (only at Visit 7).
- 12-lead ECG (only at Visit 7).
- The subject will provide fasting blood samples for:
    - Routine laboratory analysis (chemistry, hematology, coagulation only at Visit 7).
    - Fasting lipids.
    - Fasting insulin (only at Visit 7).
    - HbA1c (only at Visit 7).
    - Biomarkers (only at Visit 7) (see Table 3).
    - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios (only at Visit 7).
    - Additional serum sample (only at Visit 7) for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.
- Urine sample will be collected for urinalysis (only at Visit 7).
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- At Visit 7 only, the previously dispensed study medication will be collected and a new supply (6 weeks) of study medication to be taken until Visit 8 (Week 18) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior

to attending Visit 8. The number of capsules returned will be counted and the results will be documented.

- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP shall be reminded to use a reliable method of birth control or remain abstinent.

4.1.6 Double-blind Treatment Period (Visit 8 [Week 18])

Subjects will be seen for Visit 8 after 18 weeks of continued double blind treatment.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 8:

- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Fasting lipids.
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- The previously dispensed study medication will be collected and a new supply of study medication (8 weeks) to be taken until Visit 9 (Week 26) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior to attending Visit 9. The number of capsules returned will be counted and the results will be documented.
- Schedule next study visit.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.

- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.7 Final Visit (Visit 9 [Week 26] or Early Termination)

Assessments for an early termination visit are essentially the same as for Visit 9 (Week 26).

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 9 or at Early Termination:

- Concomitant medications and AEs since last visit will be recorded.
- Waist circumference will be measured.
- Brief physical examination.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
    - Routine laboratory analysis (chemistry, hematology, coagulation).
    - Fasting lipids.
    - Fasting insulin.
    - HbA1c.
    - Biomarkers (see Table 3).
    - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
    - Additional serum sample (only at Visit 9, not at Early Termination Visit) for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.
- Urine sample will be collected for urinalysis.
- Physical activity level and dietary compliance will be reviewed with the subject.

- Diet counseling
- The previously dispensed study medication will be collected. The number of capsules returned will be counted and the results will be documented.
- Subject will be advised to follow up with the pre-study health care provider to have pre-study lipid management resumed and for on-going care.
- SOCBP will be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 8 weeks.
- Subject will be advised to expect a follow-up contact to assess for additional AEs and to confirm that follow-up care has been arranged for dyslipidemia.

4.1.8 Follow-up Contact

Approximately 4 weeks after the final study visit (V9 or early termination), the subject should be contacted either at a clinic visit or by any remote contact such as a telephone call or email to obtain information about possible AEs that occurred since the end of study medication. Follow-up for ongoing management of the subject's lipid disorder will be confirmed.

As well, SOCBP will be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.

Table 1 Schedule of Events

Assessments	Screening	TG Qualifying Period		26-week Double-Blind Treatment Period						Early Termination Visit	Contact follow-up[b]
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-8 or -6**	**-2**	**-1**	**0**	**4**	**11**	**12**	**18**	**26**		**30**
Visit Window (days)		**±2**	**±2**	**-1/+5**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**n/a**	**+6**
Informed consent	X										
Inclusion/exclusion criteria	X	X	X								
Demographics	X										
Medical history	X										
Withdrawal of prohibited lipid altering medication (s)	X										
Height/BMI (only at V1), weight	X	X		X	X		X	X	X	X	
Waist circumference				X			X		X	X	
Serum pregnancy test	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, temperature)	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram		X					X		X	X	
Complete physical examination	X										
Brief physical examination		X		X	X		X	X	X	X	
Chemistry, hematology and urinalysis	X			X[c]	X		X		X	X	
Coagulation	X			X	X		X		X	X	
Hepatitis B and C	X										
Thyroid function (TSH –T_4)	X										
HbA1c	X			X			X		X	X	
Fasting insulin				X			X		X	X	

Assessments	Screening	TG Qualifying Period		26-week Double-Blind Treatment Period						Early Termination Visit	Contact follow-up[b]
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-8 or -6**	**-2**	**-1**	**0**	**4**	**11**	**12**	**18**	**26**		**30**
Visit Window (days)		**±2**	**±2**	**-1/+5**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**n/a**	**+6**
Fasting lipids[d]	X	X	X	X	X	X	X	X	X	X	
Biomarkers[e]				X			X		X	X	
Total plasma EPA and DHA, OM3 index, AA, omega-6/omega-3, EPA/AA				X	X		X	X	X	X	
Serum sample for storage[f]				X			X		X		
Randomization[g]				X							
Dispense study medication				X	X		X	X			
Study medication compliance assessment					X		X	X	X	X	
Diet counseling	X	X	X	X	X	X	X	X	X	X	
Physical activity and dietary compliance assessment		X	X	X	X	X	X	X	X	X	

[a] If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

[b] A follow-up contact (either at a clinic visit or by any remote contact such as a telephone call or email) to assess for additional AEs and to confirm that follow up care has been arranged for dyslipidemia is required approximately 4 weeks after Final Visit (Visit 9 or early termination).

[c] A urine sample may be collected for an optional urine pregnancy test (test strip).

[d] Includes TG, TC, HDL-C and calculated non-HDL-C at all visits. Direct LDL-C will be obtained at all study visits Additionally, LDL-C and VLDL-C will be measured by ultracentrifugation (β quantification) at Visit 3, 4, 6, 7, and 9. RLP-C will be calculated as TC – LDL-C – HDL-C using ultracentrifugation (β quantification) measurements.

[e] Includes, Apo AI, Apo B, Apo CIII, Apo A5, hsCRP, Lp-PLA2, Lipoprotein particles concentration and size, and oxidized LDL-C.

[f] Serum samples to be stored for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.

[g] All subjects will be expected to complete all planned study assessments post randomization regardless of adherence to study medication and use of subsequent rescue therapies.

4.2 Discussion of Study Design

The study is a Phase 3, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre 4 g vs placebo), multi-center study. All subjects will take an oral, single dose of 4 g (4 capsules) a day at a meal.

A 12-week double-blind design has been previously used to characterize the efficacy and safety of other OM3 drugs (Vascepa and Epanova) in patients with severe hypertriglyceridemia and was deemed acceptable by the FDA.[11,12] In this proposed Phase 3 study, the TG change from baseline to week 12 is defined as the primary endpoint to allow comparison with other studies with OM3 drugs in severe hypertriglyceridemia; however, the double-blind period has been extended to 26 weeks to better characterize the persistence of the effect of CaPre on the TG profile.

Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- or 6-week diet,lifestyle and medication stabilization period, subjects will enter a 2- or 3-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.

Subjects with severe hypertriglyceridemia who are randomized to placebo are at risk for experiencing elevations in TG levels and at risk of developing pancreatitis. In the MARINE study (Vascepa), elevation in TG level in excess of 2000 mg/dL occurred in only 1 subject out of 76 in the placebo group and none in either the 2 or 4 g treatment groups.[13] All subjects in this study will continue to receive diet counselling.

4.3 Selection of Study Population

4.3.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Subjects ≥18 years of age.
2. Isolated hypertriglyceridemia or mixed hyperlipidemia, with TG ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated or not with a stable dose of statin, CAI, PCSK9I, fibrate, or a combination of these agents.

   If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening.

   If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of statin and/or CAI at time of screening.

If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of of a statin and/or CAI at time of screening.

3. Willingness to aim to maintain physical activity level and diet consistent with NCEP-TLC and to reduce added sugars intake throughout the study.

4. Be informed of the nature of the study and give written consent prior to any study procedure.

4.3.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. Allergy or intolerance to OM3 fatty acids, OM3-acid ethyl esters, OM3 phospholipids, fish, shellfish or any components of the study medication (HPMC, corn starch (placebo)).

2. Subjects diagnosed with Familial Chylomicronemia Syndrome (FCS).

3. Subjects with lysosomal acid lipase deficiency.

4. Body mass index (BMI) greater than 45 kg/m^2.

5. Subjects who are pregnant, lactating, and subject of childbearing potential who are either planning to become pregnant or who are not using acceptable birth control methods during study participation. Subjects of childbearing potential are subjects who have experienced menarche and do not otherwise meet the criteria for women not of childbearing potential, defined as:

   - Subjects who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation).

   or

   - Subjects who are postmenopausal, i.e., who have had a cessation of menses for at least 12 months without an alternative medical cause. A follicle stimulating hormone (FSH) test ≥40 mIU/mL may be used to confirm the post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

   Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study and for 8 weeks following the last dose of study medication.

6. Subjects taking tamoxifen, estrogens, progestins, or other medications or nutritional supplements with mechanisms modifying estrogen or progestogen pathways, who have had dosage changes within4 weeks prior to Visit 1.

7. Use of oral or injected corticosteroids or anabolic steroids within 6 weeks prior to randomization.

8. History of pancreatitis within 6 months prior to Visit 1.

9. History of symptomatic gallstone disease within the last 5 years, unless treated with cholecystectomy.

10. Diabetics requiring changes in glucose-lowering medication within 6 weeks prior to Visit 1 (other than short acting insulin dosage adjustments) or who have HbA1c greater than 9.5% at Visit 1.

11. Subjects with clinical evidence of hyperthyroidism or TSH level less than lower limit of normal (LLN) at Visit 1. Subjects diagnosed with hyperthyroidism must be treated with medication for at least 6 weeks prior to Visit 1.

12. Uncontrolled hypothyroidism or TSH level more than 1.5 × upper limit of normal (ULN) within 6 weeks prior to Visit 1.

13. Thyroid hormone replacement therapy that has not been stable for more than 6 weeks prior to Visit 1.

14. History of cancer (other than basal cell carcinoma) within 2 years prior to Visit 1.

15. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, exacerbation of congestive heart failure requiring hospitalization or a change in treatment), life-threatening arrhythmia, or revascularization procedure within 6 months prior to Visit 1.

16. Use of other prohibited drugs: weight loss prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids. Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.

17. Use of any lipid-altering drug agents, other than statins, CAI, PCSK9I or fibrate, including niacin at a dose greater than 200 mg/day, , bile acid sequestrants, OM3 drugs (e.g., Lovaza

or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued at least 8 weeks prior to randomization.

18. Resection of an aortic aneurysm or endovascular aortic repair within 6 months prior to Visit 1.

19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily.

20. Poorly controlled hypertension (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥100 mmHg). Subjects with hypertension adequately controlled with medication are eligible provided that their antihypertensive therapy has been stable for at least 4 weeks prior to Visit 1.

21. Recent history (within past 12 months prior to Visit 1) of drug abuse or alcohol abuse, or alcohol use greater than 2 units per day (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks).

22. Hepatobiliary disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × ULN; if ALT/AST is >3 × ULN, the levels must have been stable for 3 months prior to Visit 1.

23. Severe renal disease as defined by less than 30 mL/min serum creatinine clearance calculated using the Cockcroft-Gault formula.

24. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) international normalized ratio (INR) of ≥1.5. Subjects using warfarin [Coumadin®] or heparin are allowed. Subjects receiving other anticoagulants dabigatran, rivaroxaban, or apixaban are allowed. Subjects receiving acetylsalicylic acid (ASA) alone or in combination with other anti-platelet agents (e.g. clopidogrel, prasugrel, ticagrelor) are also allowed.

25. Unexplained creatine kinase concentration 3 × ULN.

26. Creatine kinase elevation owing to known hereditary or acquired muscle disease.

27. Exposure to any investigational product, within 4 weeks prior to Visit 1.

28. Presence of any other condition (such as severe pulmonary, gastrointestinal, or immunologic disease) the Investigator believes would interfere with the subject's ability to

provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

29. Any life-threatening disease expected to result in death within 2 years, require frequent hospitalizations, extensive surgery, or changes in medications or diet.

4.3.3 Subject Restrictions

The following restrictions may affect subject participation in this study:

- Availability to attend visits according to the protocol.
- Subjects must be willing to aim to maintain physical activity level and diet consistent with NCEP-TLC, and reduce intake of added sugar throughout the study.
- Concomitant medication restrictions as described in Section 5.8.1.
- Fasting for at least 9 hours prior to visits which include lipid profiles and routine safety laboratory assessments.
- Subjects of child-bearing potential must remain abstinent or must use an acceptable method of contraception during the study and for at least 8 weeks following the last dose of study medication. Acceptable methods of contraception are:
    - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
    - intrauterine device (IUD);
    - intrauterine hormone-releasing system (IUS);
    - vasectomised partner (provided that partner is the sole sexual partner and that the vasectomised partner has received medical assessment of the surgical success);
    - Any combination of male condom with either cap, diaphragm or contraceptive sponge used with spermicide (double barrier methods). The proper use of cap, diaphragm or contraceptive sponge includes the use of spermicide and is therefore considered one barrier method.
- Restricted alcohol intake (≤2 units per day) (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks).

4.3.4 Subject Withdrawal or Termination

All subjects are free to withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, specified or unspecified,and without prejudice to further treatment. Withdrawal of study medication does not mean the subject is automatically withdrawn to continue in the study. However, site personnel will discuss their reasons with subjects who express a desire to terminate participation to determine their reasons and categorize them into one of the following categories:

Non-adherers – Subjects who discontinue receiving the study medication but agree to allow some or all data collection through the planned duration of the trial. If a subject discontinues from the study medication for any reason, all efforts will be made to have them continue in the study; all visits and scheduled procedures, including efficacy and safety evaluations, should be performed unless the subject also withdraws informed consent to participate in the study (see Non-completers). If the subject does not consent to continuing with all planned study evaluations, the subject should be offered a reduced schedule of assessments with priority given to the assessments related to the primary efficacy endpoint, secondary endpoints, and safety follow-up.

If a subject who discontinues study medication does not return for a scheduled visit, every effort should be made to contact the subject. It is expected that most subjects categorized as non-adherers will allow collection of at least some follow-up efficacy and safety data, and the site should attempt to record as much follow up data as the subject will allow. Regardless of the reason, discontinuation of study medication does not mean the subject has automatically withdrawn consent to continue in the study.

Possible reasons for discontinuation of study medication are:

- The subject is unwilling to continue adherence to the study medication regimen.
- The investigator may decide to stop study medication if an intolerable AE, a clinically significant laboratory value, or other medical condition or situation such that continued intake of study medication would not be in the best interest of the subject. Appropriate medical measures are to be taken, and the Sponsor or Sponsor designee is to be notified immediately.
- The subject becomes pregnant (see Reporting of Pregnancy 6.2.1.4).

Non-completers – Non-completers are subjects who decline to continue any further study medication, study visits or to allow the site to obtain any further safety or efficacy information on their status. These subjects will have given true withdrawal of consent and are expected to be rare. Subjects who wish to discontinue from the study should have early termination

assessments performed as shown in the Schedule of Events (Table 1). Permission should be asked of the subjects to allow a final contact approximately 4 weeks later to review interval history for safety events. This may be done either at a clinic visit or by any remote contact such as a telephone call or email.

The site should continue efforts to contact subjects who are Lost to Follow-Up. Only at the end of the study should such subjects be termed "Non-completers".

Subjects who die during the study are considered to have completed the study. They are neither Non-adherers nor Non-completers. An SAE report with outcome of death is expected.

Possible reasons for discontinuation from the study are:

- The investigator may decide to terminate a subject' participation in the study if an intolerable AE, a clinically significant laboratory value, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Appropriate medical measures are to be taken accordingly, and the Sponsor or Sponsor designee is to be notified immediately.

- Complete withdrawal of informed consent for participation in the study. If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected.

- The subject becomes pregnant and termination of participation in the study is considered by either the subject or the Investigator in the best interest of the subject (see Reporting of Pregnancy 6.2.1.4).

- Subject is Lost to Follow-up. If the subject is lost to follow-up, the Investigator should attempt to contact the subject until the last scheduled visit.

- The Investigator or the Sponsor, for any reason, terminates the study.

The inclusion and exclusion criteria are to be followed explicitly. If a subject who does not respect one or the other criterion is inadvertently randomized, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator. Subjects may continue study medication if both the Medical Monitor and the Investigator agree that no undue risk is involved and the patient still has the potential for benefit. In this case, the subject will be categorized as a protocol deviation. If there is no agreement that the subject should continue in the study as planned, study medication will be discontinued and the subject will be considered a Non-adherer. Such subjects should still follow the schedule of events or, in the

least, to allow a final contact at the time of study completion, unless they elect to become Non-completers.

Subjects categorized as Non-adherers or as Non-completers of the study will not be replaced.

4.3.5 Subject Re-screening

Re-screening of certain screening failure subjects may be allowed under certain circumstances, at least 3 months after initial enrollment and only after discussion with and approval by the Medical Monitor. The following situations may give rise to re-screening:

- If a subject consents to participate, otherwise meets the eligibility criteria, but is not able to continue in the study prior to randomization due to an unforeseen change in personal situation;
- If a subject failed one or the other eligibility criterion during the stabilization or TG qualification period due to i) an acute event that has resolved ii) a medical cause or condition that has been adequately treated or for which time has sufficiently elapsed since occurrence;
- To allow time for stabilization or wash-out following initiation or dose changed of allowed or prohibited medications, as the case may be, at time of screening or during the TG qualification period;

Subject who failed to meet the eligibility criteria and do not otherwise fall into the above situations should not be considered for re-screening. Specifically, subjects who fail to meet the average TG inclusion level will be considered screening failure, and re-screening of these subjects will not be allowed. Also, subjects that are randomized and withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, are not eligible for re-screening.

In case of re-screening, all study screening procedures must be repeated, including the requirement for subjects to give new consent. Re-screened subjects will be allocated a new subject identification number. For each subject that is eligible for re-screening, only one re-screening is permitted.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Study medication will consist of HPMC capsules (size 000) that are identical in external appearance, containing 1 g of either CaPre or matching placebo (corn starch).

Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day at a meal.

5.2 Identity of Study Medication

CaPre is a krill oil-derived mixture of polyunsaturated fatty acids (PUFAs), primarily composed of OM3 fatty acids, principally EPA and DHA, present as a combination of phospholipid (PL) esters and free fatty acids (FFA).

CaPre is supplied as a 1-gram capsule (size 000) for oral administration. Each 1 gram capsule of CaPre contains approximately 310 mg of the sum of EPA and DHA (expressed as free fatty acids).

CaPre capsules also contain the following naturally occurring product-related substances and inactive ingredients:

- Other PUFAs (Omega-6 and 9), saturated and monounsaturated fatty acids, phospholipids;
- 4 mg α-tocopherol / g of total fat (added as an antioxidant);
- Components of the capsule shell (HPMC).

The matching placebo is composed of partially pregelatinized corn (maize) starch supplied as 1-gram capsule (size 000). Corn is not regarded as a source of gluten which may cause sensitivity in people with celiac disease or with non-celiac hypersensitivity. The product that is used in the composition of the placebo has not come into contact with cereals containing gluten (such as wheat, rye, barley, and oats).

Table 2 Study Medication

Study Medication	Dosage form and strength	Manufacturer
CaPre	1 g capsule	Acasti Pharma Inc.
Placebo	1 g capsule	Acasti Pharma Inc.

Study medication must be stored between 15-25°C (59-77°F). Documentation of temperature monitoring should be maintained.

5.3 Packaging and Labelling

During the double-blind period, capsules of 1 g CaPre and 1 g placebo will be provided by the Sponsor in white opaque Aclar® PVC/Aluminium blister packs, providing multiple complete daily regimens (4 capsules per day) in accordance with treatment allocation. The contents of each capsule will not be disclosed to either the subject or study center personnel (i.e. double blind).

5.4 Method of Assigning Subjects to Treatment Group

After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening (V1). At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the TG qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT. Once randomized, the site will be provided by the IRT with the corresponding study medication kit to be dispensed to the subject at Visit 4. Similarly, the corresponding study medication kit to be dispensed to the subject at subsequent study visits will be provided the study center through the IRT.

Subjects will be randomized to CaPre or placebo via stratified randomization. The randomization stratification factors are: qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI, or PCSK9I, alone or in combination, at randomization (currently treated or not currently treated with statin, CAI, or PCSK9I, alone or in combination).

The randomization code for treatment assignment will be held by the IRT vendor.

5.5 Selection of Doses in the Study

Doses selected for this study are CaPre 4 g per day compared to matching placebo. The choice of these doses is supported by work with already marketed OM3 drugs, as well as pre-clinical and clinical studies with NKPL66 (the active ingredient of CaPre capsules) showing significant reduction in TG levels and non HDL-C without deleterious effect on LDL-C primarily at 4 g a day without safety concern in patient with mild to severe HTG. (please refer to Section 2 and the CaPre Investigator's Brochure for preclinical and clinical information about CaPre).

At present, several OM3 drugs are approved in the US for severe hypertriglyceridemia: Lovaza (EPA and DHA as ethyl esters), Vascepa (EPA as ethyl esters), Epanova (EPA and DHA as FFA), Omtryg (EPA and DHA as ethyl esters), and 4 generic versions of Lovaza (EPA, DHA

as ethyl esters). All these products are approved for use at 4 g/day that provide between 3000 to 3840 mg per day of EPA alone or in mixture with DHA, except for Epanova which is also approved at 2 g/day providing 1500 mg of EPA and DHA.

5.6 Selection and Timing of Dose for Each Subject

Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I , alone or in combination at randomization (currently treated vs not currently treated).

All subjects will take four capsules, once a day, at a meal:

• CaPre Group: 4 x 1 g capsules CaPre; or

• Placebo Group: 4 x 1 g capsules placebo (corn starch).

If a subject forgets to take the capsules, they should be instructed to take them on the same day with the next meal; however, no more than one dose (4 capsules) should be taken per day.

5.7 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. CaPre and placebo capsules will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, or CRO. The treatment codes will be held by the IRT vendor.

The process for breaking the blind will be handled through the IRT. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management, and after a consultation with the Medical Monitor. Any center that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the subject in question.

The Sponsor must be notified immediately if a subject and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and electronic case report forms (eCRFs).

In addition to treatment blinding, the Investigator will also be kept blind to the fasting serum lipid assessments made during the course of the study after randomization. Except for TG (see Section 5.9), no alerts have been defined for other lipid assessments (e.g. LDL-C) due to the

short study duration and to minimize changes in lipid therapy that are not allowed post randomization .

5.8 Prior and Concomitant Treatments

5.8.1 Excluded Medications

Medications and treatments that are prohibited during the study must be discontinued at Visit 1 unless otherwise stated:

- Any lipid-altering drug agents (other than statins, CAI, PCSK9I, or fibrate alone or in combination; see below) including niacin at a dose greater than 200 mg/day, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued 8 weeks prior to randomization.

  Case of Plant sterols/stanols and Soluble Fibers:
  Because plant sterols/stanols (up to 2 grams per day) and/or soluble fibers (up to 25 grams per day) may be recommended as part of the NCEP-TLC diet, these products taken in the form of powder or supplements are allowed provided they are already consumed at a stable dose prior to screening or are initiated at screening and their intake remains stable throughout the study. Subjects should not discontinue these products during the study.

- Oral or injected corticosteroids or anabolic steroids
- Prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide.
- HIV protease inhibitors
- Cyclophosphamide
- Isotretinoin
- Investigational products must be discontinued at least 4 weeks prior to Visit 1

5.8.2 Allowed Medications

Any herbal products, dietary supplements, or medications started before the informed consent and ongoing at time of screening (V1) must be reported on the appropriate page of the eCRF. Any herbal products, dietary supplements, or medications listed in one or the other inclusion

or exclusion criterion and that was stopped during the 60 days preceding screening (V1) should also be documented.

The generic names of the herbal products, dietary supplements, or medications (or trade names for combination) must be specified along with the total daily dose and duration of treatment.

The following herbal products, dietary supplements, or medications cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:

- Statins, CAI (e.g., ezetimibe), PCSK9I or fibrate, alone or in combination:

  Subjects already regimented with a statin and/or CAI prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization

  Subjects who initiate or change dose of a statin and/or CAI treatment initiation or dose change at Visit 1 must be on stable dose at least 8 weeks prior to randomization.

  PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

  Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

- Tamoxifen, estrogens, or progestins must be stable for at least 4 weeks prior to Visit 1.
- Thyroid hormones must be at doses stable for at least 6 weeks prior to Visit 1
- Antidiabetic drugs must be at doses stable for at least 6 weeks prior to Visit 1. Short acting insulin dosage adjustments are allowed.
- Antihypertensive drugs must be at doses stable for at least 4 weeks prior to Visit 1

Wherever possible and unless deemed unsafe, subjects receiving such medication should continue with the same dose, and discontinuation during the study should be avoided.

The following herbal products, dietary supplements or medications are also allowed during the study:

- Niacin <200 mg/day

- Local, topical, inhaled, or nasal corticosteroids
- Plant sterols/stanols (up to 2 grams per day) and/or soluble fibers (up to 25 grams per day); as long as stable doses during the study (see above).

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Any changes in allowed medication being taken at the beginning of the clinical study must be recorded in the eCRF.

5.9 Rescue Medication

Due to a possible increased risk of pancreatitis, any TG value greater than 1500 mg/dL should initiate a blinded alert to the site, and require clinical and laboratory follow-up within a week. If the subject's TG level is still above 1500 mg/dL after follow up, it does not mean the subject is automatically withdrawn of study medication or to continue in the study. Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication selected by the PI or dose adjustment of fibrate (or another current medication), as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.

Consistent with Section 4.3.4, all efforts should be taken to have these subjects continue in the study; all visits and scheduled procedures, including efficacy and safety evaluations, should be performed unless the subject withdraws informed consent to participate in the study.

5.10 Treatment Compliance

The prescribed daily dose, frequency and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.

At each visit, prior to dispensing study medication, previously dispensed study medication will be retrieved by the Investigator and compliance assessed. Subjects exhibiting poor compliance, as assessed by capsule counts, should be counseled on the importance of good compliance with the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of study medication during any evaluation period (visit to visit).

After randomization, at subsequent visits 5, 6, 7, 8 and 9, subjects should be instructed not to take their daily dose before attending the visit.

5.11 Study Medication Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication. These records must be available for inspection at any time.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study medication supplies and packaging materials are to be inventoried and prepared for return or destruction by the Investigator. The Investigator is not to return or destroy unused clinical drug supplies or packaging materials without authorisation.

6.0 EFFICACY AND SAFETY ASSESSMENTS

6.1 Efficacy

6.1.1 Primary Efficacy

The primary efficacy endpoint will be the percent change in fasting TG levels from baseline to Week 12 in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L).

Baseline is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2, 3, and 4, or Visits 3, 3.1, and 4 in case an additional TG measurement was necessary during qualification). The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart that is Visit 6 (Week 11) and Visit 7 (Week 12).

6.1.2 Secondary Efficacy

The secondary efficacy endpoints for this study are (listed in order of importance for the control of type I error: :

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification)
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

6.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for this study are:

- Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and Week 12) and Week 26 in TC.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and Week 26 in RLP-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and to Week 26 in LDL-C (β-quantification) and VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 26 in non-HDL-C and HDL-C
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII, and apo A5.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (LDL, non-HDL, HDL-C, IDL and VLDL).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP and Lp-PLA2.

6.1.4 Exploratory PK Endpoints

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in OM3 Index.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in AA, omega6/omega3 and EPA/AA ratios.

6.2 Safety

6.2.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study stabilization/qualification, treatment or follow-up period.

Definition of AE: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Definition of SAE: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study medication or not) that at any dose:

- Results in death.
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia, or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, intensity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Intensity

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

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Relationship

The causal relationship between the study medication and the AE will be characterized as unrelated, unlikely related, possibly related, probably related, or related.

Events can be classified as "unrelated" if there is not a reasonable possibility that the study medication caused the AE.

An "unlikely" relationship suggests that only a remote connection exists between the study medication and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.

A "possible" relationship suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.

A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and that other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.

6.2.1.1 Reporting of Adverse Events

All AEs, regardless of intensity and whether they occurred during the study stabilization/qualification, treatment or follow-up period, are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF. The Investigator should complete all the details requested including dates of onset, intensity, action taken, outcome and relationship to study medication. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study medication, must be reported immediately (within 24 hours of the study

center's knowledge of the event) to the Sponsor or designee. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. The primary mechanism for reporting an SAE will be the electronic data collection tool, or eCRF. If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool provided by the Sponsor or designee (instructions will be provided on the paper tool). The study center will enter the SAE data into the electronic system as soon as it becomes available.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, including those ongoing after the follow-up period of 28 days planned after the final visit (or early termination) (see 4.1.8) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Non-serious AEs still ongoing after the follow-up period will not be additionally followed and the outcome at time of last contact will be reported in the study database.

The eCRF planned for this study will include programming to provide an alert to the Sponsor and study Medical Monitor for any reported SAE. The reports will be recorded in a study-specific safety database, reconciled with eCRF data, and reported in the clinical study report.

All SAEs source data will be recorded in center source documents. Criteria for documenting the relationship to study medication as well as intensity and outcome will be the same as those previously described.

6.2.1.2 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor or CRO of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or CRO. The Sponsor or CRO will ensure that the appropriate regulatory authorities are notified of all reportable SAEs.

6.2.1.3 Follow-up of Adverse Events

Any AEs observed from screening up to the end of the study will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

All SAEs that are spontaneously reported within 4 weeks of a subject's termination from the study are to be collected and reported as previously described.

6.2.1.4 Reporting of Pregnancy

If conception occurs during the study treatment period, study medication must be discontinued immediately. The Investigator must report the pregnancy by faxing the Pregnancy Notification and Outcome Form within 24 hours of the study site staff becoming aware of the pregnancy, at the country-specific fax number listed in the Study Reference Manual. With subject's consent, the investigator must report the outcome of the pregnancy to document if a congenital abnormality/birth defect in the offspring of study subjects has occurred.

6.2.2 Clinical Laboratory Evaluations

Laboratory assessments will be conducted at a central laboratory. Blood and urine samples will be taken at the times indicated in the Schedule of Events (Table 1).

The following clinical laboratory tests will be performed as specified in Table 3, in accordance with the Schedule of Events (Table 1).

Table 3 Laboratory Assessments

Hematology (Visit 1, 4, 5, 7 and 9[1])	**Clinical Chemistry** (Visit 1, 4, 5, 7 and 9[1])	**Lipids (fasting)** (All study Visits)	**Biomarkers** (Visit 4,7 and 9[1])
Hemoglobin	Albumin	Triglycerides (TG)	AA
Hematocrit	ALP	Total cholesterol (TC)	Apo AI
Erythrocyte count	ALT	non-HDL-C	Apo B
Leukocyte count	Amylase	HDL-C	Apo CIII
Leukocyte differential count (including neutrophils, lymphocytes , monocytes , eosinophils and basophils)	AST	LDL-C (direct) *	Apo A5
	GGT	IDL	Lp-PLA2
	Bilirubin, Total	VLDL-C*	hsCRP
	Lipase	RLP-C	Lipoprotein (particles concentration & size)
Platelet count	Urea Nitrogen/Urea		
MCV	Uric acid		oxidized LDL-C
MCH	Creatinine	**Urinalysis ****	omega 6 FA
MCHC	Creatine Kinase (CK)	(Visit 1, 4, 5, 7 and 9[1])	omega 3 FA
RDW	Calcium	Color	
	Chloride	Clarity/Appearance	**Pharmacokinetics**
	Magnesium	Specific gravity	DHA, EPA
Coagulation	Glucose	pH	(Visits 4, 5, 7, 8 and 9[1])
(Visit 1, 4, 5, 7 and 9[1])	Potassium	Glucose	
PT	Sodium	Blood (includes erythrocytes)	**Omega 3 Index**
INR	Bicarbonate	Protein	(Visit 4, 5, 7, 8 and 9[1])
aPTT		Leukocyte Esterase	
	Pregnancy test (SOCBP, serum testing at Visit 1)	Ketones	**Thyroid Function**
Other analytes		Nitrites	(Visit 1)
Hepatitis B and C (Visit 1)	FSH (as required for post-menopausal subjects only)	Bilirubin	TSH
		Urobilinogen	T_4
HbA1c (Visit 1,4, 7 and 9)		Creatinine	
Insulin (fasting) (Visit 4,7 and 9)	Creatinine Clearance and estimated Glomerular Filtration Rate (eGFR) (calculated at Visit 1, 4, 5, 7 and 9)	Proteinuria (estimated by urine protein/creatinine ratio - UPCR) (calculated at Visit 1)	

[1] All laboratory assessments required at visit 9 will also be made at the Early Termination Visit.
* LDL-C and VLDL-C to be also obtained via Beta (β) quantification at Visit 3,4,6,7 and 9.
**Urine Microscopy will be performed if blood, protein, leukocyte esterase, and/or urobilinogn is abnormal

TG levels will be closely monitored in all subjects throughout the treatment and safety follow-up periods. All trial personnel including site monitors, the CRO and Sponsor representatives, and site staff will be blinded to TG results throughout the trial. The central laboratory will notify the Investigator and the study Medical Monitor as soon as possible in the event that a subject's TG level is >1500 mg/dL (see Section 5.9).

Also, note that all trial personnel including site monitors, the CRO and Sponsor representatives, and site staff will be blinded to all lipids, biomarkers, Omega 3 Index and EPA, DHA results throughout the trial.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE.

An abnormal laboratory value should be deemed clinically significant, and reported as an AE, if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change dose, add or discontinue a concomitant medication, discontinuation of the study medication, close observation, more frequent follow-up assessments, or further diagnostic investigation.

6.2.2.1 Laboratory Re-testing

Request for re-testing (i.e. requiring a new blood sample) of certain clinical laboratory tests may be allowed in special circumstances and only after discussion with and approval by the Medical Monitor.

6.2.3 Vital Signs, Physical Findings, and Other Safety Assessments

6.2.3.1 Vital Signs

Vital signs evaluation should be performed before collecting laboratory samples. Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (°C) and respiratory rate for a minimum of 30 seconds will be measured at all visits. Subjects should be comfortably seated for at least 2 minutes prior to blood pressure, pulse and respiratory rate readings.

6.2.3.2 Height, MI and Weight

Height (without shoes) will be measured at Visit 1 only. Weight (light clothing, no shoes) will be measured at all visits, with the exception of Visits 3 and 6.

Body mass index (BMI) will be calculated.

6.2.3.3 Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Subjects should not hold their breath while waist circumference is being measured.

6.2.3.4 ECG

A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination. ECG assessment should be performed before collecting laboratory samples.

ECG assessment will be performed in supine position after at least 2 minutes rest. The parameters of HR, PR interval, QRS interval, and QT interval will be recorded.

No cardiac safety AEs, and in particular cardiac repolarization (significant change in QTc interval) AEs, have been previously reported by subjects on CaPre. QT intervals will be corrected and reported using both Bazett's and Fridericia's formulas. For purposes of clinical study conduct, Bazett's QT correction will be used. For purposes of data analysis, Fridericia's QT correction will be considered as primary.

Any significant change occurrence shall result in notification by the Investigator to the study Medical Monitor for immediate review of the tracings and discussion with Sponsor. Significant findings should be reported as AEs or SAEs, as appropriate.

6.2.3.5 Physical Examination

A complete physical examination (including general appearance, head, skin, neck(including thyroid), eyes/ ears,/ nose,/ throat, chest,/ lungs, heart, abdomen, back, lymph nodes, extremities and neurologic system evaluations) will be performed at Visit 1.

A brief physical examination (general appearance, lungs, heart, abdomen evaluation) will be performed at all visits with the exception of Visit 1, Visit 3/3.1, and Visit 6

6.2.4 Safety Monitoring

This study will not implement a Data Safety Monitoring Board. A Medical Monitor will be appointed to provide medical expertise to advise the study investigators and to monitor participant safety. Medical Monitoring will include :

- availability to advise the investigators on trial-related medical questions or problems (e.g. eligibility criteria, study procedures, patient continuation and discontinuation);
- routine safety monitoring of the study, including review of individual laboratory value;
- medical review of all SAEs throughout the trial;
- medical review of efficacy and safety listings (including coded listings), and patient profiles for appropriateness and consistency;
- aggregate review of blinded clinical data;

The Medical Monitor will remain blinded throughout the conduct of the clinical trial.

6.3 Pharmacokinetics

Blood samples for EPA and DHA Total Lipids will be obtained at Visit 4 (Baseline), prior to first study medication dose. Additional samples will be obtained at Visit 5 (Week 4), Visit 7 (Week 12), Visit 8 (Week 18) and Visit 9 (Week 26), and as applicable at Early Termination.

Details about the procedure will be described in the study laboratory manual. Details about the OM3 index procedure will also be described in the manual.

6.4 Health Outcomes

Not applicable.

6.5 Pharmacogenetics

Not applicable.

6.6 Appropriateness of Measurements

The efficacy and safety assessments are standard assessments and deemed to be reliable, accurate and relevant for this indication and patient population.

The primary efficacy endpoint of change in fasting TG levels is both a standard means of assessing the efficacy of treatment and is a laboratory measurement that is a direct cause of adverse outcomes, including risk of pancreatitis and cardiovascular events. To increase the

robustness of the endpoint and to minimize the natural variation in TG levels, the endpoint will be based on the average of three values at baseline and two values at the primary endpoint duration of 12 weeks.

The persistence in the TG reduction will be explored up to 26 weeks and will address the issue of durability of effect observed at 12 weeks.

The additional endpoints of change in non-HDL-C, VLDL-C, HDL-C, LDL-C, TC, and RLP-C at 12 and 26 weeks are all reflective of overall expected effect of CaPre on lipid metabolism.

The endpoint that compares the proportion of patients in each treatment group that achieve a level of fasting TG below 500 mg/dL is a categorical measure that reflects the drug effects on reducing TG below the threshold, which is generally accepted as the primary target for such therapy in patients with severe hypertriglyceridemia to prevent the risk of pancreatitis.

Other endpoints of change from baseline of different apolipoproteins (apo A1, apo A5, apo B, apo CIII, apo B/apo A1), lipoprotein particles concentration and size, inflammatory (Lp-PLA2, hs-CRP), glycemic profile (FSG, insulin, HbA1c, HOMA), and other marker (oxidized LDL) will document the effect of the study medication on a variety of biomarkers associated with the atherogenic effects of hypertriglyceridemia.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness and reliability of the data:

- Investigator meeting(s).
- Central laboratories for clinical laboratory parameters.
- Study center initiation visit.
- Early study center visits post-randomization.
- Regular study center on-site and remote monitoring during study.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, the Sponsor and/or CRO Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study centers, central laboratories, vendors, clinical database and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

An adaptive approach to clinical trial monitoring will be utilized. This is initiated by an assessment of the risk associated with the trial combined with an assessment of critical data and processes. A Risk Assessment Mitigation Plan and Integrated Project Management Plan collectively document the strategies involved with the implementation of onsite, remote and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to safety patient and data quality. Trial oversight is achieved by regular

review of a report of risk which then influences any required changes to the monitoring strategy.

The Sponsor will engage the services of a CRO to perform monitoring functions within this clinical study. The CRO's monitors will work in accordance with the CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also assess adherence to the protocol at the study center. They will verify the supply of study medication and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each study center while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification).

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of the CRO.

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain

information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records, unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events and medical histories will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary.

7.3 Quality Assurance Audit

Study centers, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or CRO on behalf of Acasti Pharma Inc. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICS

8.1 Determination of Sample Size

The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/dL; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The primary estimand in this study is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. All subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. The null hypothesis is that the percent change from baseline in fasting TG level in the CaPre 4 g group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline in fasting TG level in the active group is NOT the same as that in the placebo group.

It is anticipated that the overall treatment discontinuation rate in this study will not exceed 15% and will be approximately equal in the two treatment groups. Given that subjects may initiate subsequent rescue therapies after an early discontinuation of the study treatment and that their outcomes will be measured at Week 11 and/or 12 under the effect of rescue, the following assumptions regarding the median percent reduction in fasting TG levels from baseline to Week 12 are used in sample size calculations.

- Placebo group: 10% median reduction from baseline in subjects who complete the study on placebo and 25% median reduction from baseline in placebo subjects who discontinue the study treatment early and are rescued. This corresponds to an overall median percent reduction from baseline of approximately 12% in the placebo group based on the assumption that 85% of subjects will complete the study on placebo and 15% placebo subjects will be rescued.
- CaPre 4 g group: two scenarios will be considered with 32% and 37% median reduction from baseline, respectively. Completers and rescued subjects in the CaPre

4 g group are assumed to have a similar median percent reduction from baseline to Week 12. The two scenarios will correspond to an overall median treatment difference between the CaPre 4 g group and placebo of 20 and 25 percentage points, respectively.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a median difference of at least 20 percentage points in percent decrease from baseline to Week 12 in TG between CaPre and placebo assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05, based on a non-parametric Wilcoxon-Mann-Whitney test. The overall median treatment difference of 20 percentage is believed to be clinically relevant.

The table below shows the estimated power for four scenarios, 20 and 25 percentage points median differences between treatment groups and two settings of common standard deviation (40% and 45%), considering an unbalanced treatment allocation ratio of 2.5:1 with 175:70 subjects randomized (CaPre:placebo). These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia). Power calculations are provided under two assumptions regarding the underlying distribution of the primary variable: lognormal and normal.

Table 4 Sample Size Estimation

Sample size per group (CaPre:placebo)	Placebo-corrected treatment effect (overall median treatment difference)	Common standard deviation	Overall Type I error (two-sided)	Power (lognormal distribution)	Power (normal distribution)
175:70	20 percentage points	40%	0.05	>95%	92%
175:70	25 percentage points	40%	0.05	>95%	98%
175:70	20 percentage points	45%	0.05	>95%	87%
175:70	25 percentage points	45%	0.05	>95%	96%

Note: The sample size calculation is performed based on a Wilcoxon-Mann-Whitney test using SAS V9.4, Proc POWER.

8.2 Statistical Methods

A description of the statistical methods to be used to analyze the key efficacy and safety endpoints is outlined below. Detailed statistical methodology for the planned analyses will be provided in the Statistical Analysis Plan (SAP) that will be finalized prior to database lock and treatment unblinding. Any deviations from the planned analysis specified in the SAP will be described with justification in the final clinical study report.

Continuous data will be summarized descriptively using the number of observations, means, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. All tests of treatment effects will be

2-sided, unless otherwise specified. Individual subject data will be presented in listings. All analyses, summaries and listings will be performed using SAS® software (version 9.1 or higher).

8.2.1 Analysis Populations

The following analysis populations will be used in this trial. Classification into Safety, Per-Protocol (PP), and Intent-to-Treat (ITT) Populations will be conducted prior to the database lock.

Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) Population is defined as all randomized subjects. Following the ITT principle, subjects will be analyzed according to the treatment to which they are randomized regardless of any departures from the original assigned group.

Per-Protocol (PP) Population

The per-protocol (PP) Population is defined as all subjects from the ITT Population who did not have major protocol deviations. Major protocol violations will be defined in the statistical analysis plan prior to database lock and treatment unblinding.

Safety Population

The Safety Population is defined as all subjects who received at least 1 dose of study medication. Subjects will be analyzed according to actual treatment received.

8.2.2 Subject Disposition, Demographic and Baseline Characteristics

Subject disposition and demographics such as age, gender, race, weight, height, BMI, etc., will be summarized by treatment group using descriptive statistics. Baseline disease characteristics such as baseline statin, CAI and/or PCSK9I use, diabetes, baseline lipid profiles (including TG, TC, HDL-C, LDL-C, calculated non HDL-C, VLDL-C, RLP-C) will also be summarized.

8.2.3 Concomitant Medication

Prior and concomitant medications will each be categorized by therapeutic class and preferred term using the WHO Drug Dictionary. The number and percent of subjects using each prior and concomitant medication will be summarized by therapeutic class and preferred drug name by treatment group. Subjects who reported more than 1 medication for a particular preferred term will be counted once for each preferred term and therapeutic class.

8.2.4 Treatment Compliance and Exposure

Treatment compliance will be assessed based on the number of the actual doses taken relative to the number of doses expected and summarized by treatment group using descriptive statistics. Subject exposure to study medication will be evaluated using the first dose date and the last dose date.

8.2.5 Control of type 1 error

The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; similarly, a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before is found to be statistically significant.

The following testing order will be followed for the overall type I error control:

1. Percent change from baseline to Week 12 in TG
2. Percent change from baseline to Week 12 in non-HDL-C
3. Percent change from baseline to Week 12 in VLDL-C
4. Percent change from baseline to Week 12 in HDL-C
5. Percent change from baseline to Week 12 in LDL-C

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided). For all exploratory variables, nominal p-values will be reported in an exploratory fashion.

8.2.6 Primary Efficacy Analyses

The primary efficacy analysis will be performed on the ITT Population and the PP Population (Section 8.2.1 contains population definitions).

The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies.

All collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the primary

analysis. Subjects who withdraw consent for study participation overall and are not assessed at Week 11 and/or 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or 12.

For the primary efficacy endpoint, i.e., the percent change in fasting TG levels from baseline to Week 12, descriptive statistics will be summarized and statistical testing will be performed. The baseline value is defined as the average of the last 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification).The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12). The null hypothesis is that the percent change from baseline of fasting TG level in the active group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline of fasting TG level in the active group is NOT the same as that in the placebo group.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used to perform a hypothesis test for the primary endpoint (percent change in TG levels).

The non-parametric ANCOVA based on ranks will be performed as follows: the percent change from baseline in TG value and the TG baseline value will be transformed to modified ridit scores within stratum (qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI, PCSK9I, alone or in combination, at randomization vs. non-use). Modified ridit scores are ranks standardized for the different sample sizes per stratum. In the second step, ordinary LS regression applied to the modified ridit scores of the percent change from baseline and baseline will be performed within stratum using the model:

Percent change from baseline = baseline

In the third step, residuals from these regression models will be used. In that final step, the residuals from all strata will be included in a stratified extended Cochran-Mantel-Haenszel (CMH) test of the residuals (i.e., stratum by treatment by residual) to analyze the treatment effect. CMH test statistics obtained from each of the multiply imputed datasets will be combined using the Rubin's combination rule after applying a normalizing Wilson-Hilferty transformation for a chi-square distributed statistic.

Quantile regression, adjusting for the same baseline covariates as specified for ANCOVA model, will be used to obtain an adjusted estimate of the median treatment difference with associated two-sided 95% CI. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As supportive analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied.

8.2.7 Subgroup Analyses

The primary efficacy analysis will also be performed for the following subgroups:

- Baseline age group (≤65 years vs. >65 years)
- Race (White/Caucasian vs. Non-white/Caucasian)
- Gender (Male vs. non-Male)
- Baseline use of statin, CAI, PCSK9I, alone or in combination, at randomization (currently treated) (Yes vs. No)
- Qualifying TG levels (≤750 mg/dL vs. >750 mg/dL) (≤8.5 mmol/L vs. >8.5 mmol/L)

The models for the subgroup analyses will include all terms in the ANCOVA model used for the primary efficacy analysis plus factors for the subgroup of interest (as appropriate). The interaction between subgroup factors and treatment will be tested at a 0.10 significance level. If a significant interaction between subgroup factors and treatment is detected, the nature of the interaction will be further investigated. Descriptive statistics will be summarized for each subgroup listed above.

The primary efficacy analysis will also be carried out for the PP Population as supportive analyses. Other supportive and sensitivity analysis may be performed as appropriate.

8.2.8 Secondary Efficacy Analyses

The secondary efficacy endpoints for this study are (in order of importance):

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification).

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.

- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

Similar analyses as specified above for the primary efficacy analysis will be conducted for all of the three secondary efficacy endpoints on the ITT population.

The baseline value is defined in the same way as for the primary analysis, namely, as the average of the 3 last measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification) except for VLDL-C and LDL-C determined by β-quantification (average of Week -1 and 0 corresponding to measurements taken at Visits 3 and 4 or Visits 3.1 and 4 in case an additional TG measurement was necessary during qualification).

A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo.

8.2.9 Exploratory Efficacy Analyses

For exploratory endpoints, the change from baseline to Week 12 and/or to Week 26 will be evaluated.

The persistence of the effect of CaPre on the TG profile will be explored by comparing the percent change in fasting TG levels from Baseline to different time points. Descriptive statistics will be presented by treatment group at each visit, and will also be summarized using Graphical representation over time (from Baseline to end of study Week 26).

The relationship between baseline fasting TG levels and the change in fasting TG levels and the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting TG levels will also be explored.

Regarding the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26 week double-blind treatment period, a CMH test will be used, controlling for the two stratification factors that are used for randomization. No multiplicity adjustment will be applied to the exploratory efficacy analyses. Subjects with missing data at the analysis time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

8.2.10 Sensitivity Analysis

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the primary analyses by using other strategies for dealing with missing data.

Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed at Week 11 and/or12. This approach assumes that some subjects discontinuing the study will do so for non-treatment-related reasons and would have similar outcomes to subjects who are able to complete the treatment.

If the number of subjects who discontinue the study medication early and are assessed at Week 11 and/or12 after having started an alternative therapy is large (e.g., > 5% of all ITT subjects), then an additional sensitivity analysis will be performed where data from these subjects will be excluded from analysis and subjects will be treated as having missing data, i.e., will be imputed. This analysis will serve to assess the contribution of the alternative therapies to the estimate of the total treatment effect.

For analysis of the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26 week double-blind treatment period, a sensitivity analysis will also be performed where subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study. Other sensitivity analysis methods may be performed and will be detailed in the SAP.

More details of the proposed sensitivity analyses and possibly additional ones will be presented in the SAP.

8.2.11 Exploratory PK Analyses

The PK endpoints include exploration of:

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations;
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index;

- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in AA, in omega-6/omega-3 and in EPA/AA ratios;

8.2.12 Safety Analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be coded using the MedDRA. All treatment-emergent AEs (TEAEs) will be summarized by treatment group. TEAEs are defined as AEs that occurred on or after the first dose of study medication. The number and percentages of subjects who experienced at least 1 TEAE will be summarized by system organ class and preferred term. TEAEs will also be summarized by relationship to the study medication and by intensity. Deaths, SAEs and AEs leading to study subject early termination will be tabulated and presented in data listings. Subject level data listings of all AEs will be presented.

Clinical laboratory results (chemistry, hematology, coagulation, urinalysis, etc.) will be summarized using descriptive statistics for each visit by treatment group. Observed values at each visit and changes from baseline to each post-baseline visit will be presented. Changes from baseline in high/low/normal findings for clinical laboratory parameters for which normal ranges apply will be summarized by treatment group using shift tables. All laboratory data will be provided in subject data listings.

Vital signs and ECG parameters will be summarized by treatment group for each applicable visit. Observed values and changes from baseline values will be summarized for each visit where appropriate.

8.3 Interim Analysis

No interim analysis is planned for this study.

8.4 Level of Significance

All statistical tests will be 2-sided, and significance with respect to the primary and secondary endpoints is determined taking into account multiplicity due to multiple endpoint comparisons between CaPre vs. placebo. The family-wise Type I error rate will be controlled at a 0.05 significance level for the primary and secondary efficacy endpoints (see Section 8.2.5).

No multiplicity adjustment will be applied to the exploratory efficacy endpoints.

8.5 Missing Data Handling Rules

Missing data should be kept to a minimum. Continued efforts will be made to measure endpoints on all subjects, even those who discontinued study medication.

For the primary efficacy analyses involving fasting TG level, subjects who withdraw consent for study participation overall and are not assessed at Week 11 and/or 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or Week12. Results of the ANCOVA analysis from multiple imputed datasets will be combined using the Rubin's combination The handling of missing data for other variables will be described in the SAP.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the Informed Consent Form (ICF) and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or Sponsor's designated representative with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to Acasti Pharma Inc. or representative before enrollment of any subject into the study.

Acasti Pharma Inc. or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or Sponsor's designated representative of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject and/or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated ICF.

10.0 STUDY ADMINISTRATION

10.1 ADMINISTRATIVE STRUCTURE

Please refer to the Key Personnel and Facilities section of the protocol.

The Lead Principal Investigator, Sponsor's representative, Medical Monitor and Key CRO personnel, as needed, will meet regularly during the planning, execution, and close-out phases of the study to review the study progress.

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence and all other supporting documentation).

The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted.

Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject enrolled into the study.

The Investigator will allow the Sponsor, Sponsor's designated representative and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

10.5 Financing and Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. The terms of the insurance will be kept in the study files.

11.0 REFERENCES

[1] Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation 2011;123:292-333.

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[4] Athyros VG, Giouleme OI, Nikolaidis NL, et al. Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. J Clin Gastroenterol 2002;34:472-475.

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[8] Maki KC, Bays HE, Dicklin MR. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. J Clin Lipidol. Sep-Oct 2012;6(5):413-426.

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12.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-001

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

This protocol is a confidential communication of Acasti Pharma Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Acasti Pharma Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title and the name of the center in which the study will be conducted. Return the signed copy to Sponsor or designee and keep a copy for your records.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Investigator

Signature: _____ **Date:** _____
DD/MMM/YYYY

Printed Name: _____

Title: _____

_____

Name/Address of Center: _____

_____

_____

13.0 APPENDIX 2: NCEP-TLC DIET

1. NCEP-ATPIII Report

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) outlines the principles of therapeutic lifestyle changes (TLC) dietary patterns focused on lowering LDL. Recommended food choices for the NCEP-TLC diet are summarized in Table V.2-6 of the report[4]. Recommendations by food group include:

- Breads, cereals, pasta, whole grains, potatoes, rice, dry peas, and beans (6 or more servings per day);
- Fruits and vegetables (5 or more servings per day);
- Fat-free or 1 percent dairy products (2–3 servings per day);
- Lean meats (beef, pork, and lamb), poultry, and fish (up to 5 oz per day as 2 servings);
- Fats high in saturated fat, trans fat, and cholesterol must be limited;
- Nuts are high in fat, but in most nuts the predominant fats are unsaturated. The intake of nuts should fit within the calorie and fat goal;
- Egg yolks are high in cholesterol (~215 mg/egg) and should be limited to no more than two egg yolks per week;

Other eating tips from the report include:

- Snacks should be low in saturated fat;
- Moderate amounts of sweets and modified-fat desserts (low in saturated fat) may be chosen;
- Cooking methods that use little or no fat (steaming, baking, broiling, grilling, or stirfrying in small amounts of fat) should be used;
- Exercise caution when eating away from home;

Various TLC sample daily menus are provided in appendix B of the report[5]. This report is freely accessible online at http://circ.ahajournals.org/content/106/25/3143.long.

[4] Page 3259
[5] Pages 3287-3296

2. Your Guide To Lowering Your Cholesterol With TLC (Booklet)

The National Heart, Lung and Blood Institute (NHLBI) through the NCEP and Obesity Education Initiation has developed a guide intented for the general population that describes the TLC program for reducing high blood cholesterol.

The booklet is freely accessible online at:
https://www.nhlbi.nih.gov/files/docs/public/heart/chol_tlc.pdf

The guide contains recommended ranges of intake for the following dietary components:

Nutrient	**Recommended Intake**
Total fat	25-35% of total calories
Saturated Fatty Acids	<7% of total calories
Cholesterol	<200 mg per day
Total Calories	Depends on energy intake and expenditure to achieve optimal weight

Moreover, the TLC diet calls for other recommendations:

- Diet options for more LDL lowering
  - 2 grams per day of plant stanols or sterols;
  - 10–25 grams per day of soluble fiber;
- Only enough calories to reach or maintain a healthy weight
- Get at least 30 minutes of a moderate intensity physical activity, such as brisk walking, on most, and preferably all, days of the week.

The guide focuses on the principle that this is not a temporary diet, but rather a new way of eating that is both heart-healthy and tasty. This publication also contains TLC sample daily menus[6].

In addition, patients on this protocol will be advised to minimize their intake of added sugars (e.g., from soda, sweets, etc.) to below 10% of energy, due to their potential adverse effect on triglyercide levels and consistent with the recommendations of the 2015 Dietary Guidelines for Americans.

[6] Pages 61 to 69 of the guide.

14.0 APPENDIX 3: DETAILED REVISION HISTORY

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Page 1. Date of Protocol: 02 November 2017	Date of Protocol: **Amended Protocol 22 May 2018** **Initial** Protocol 02 November 2017	Edit to reflect amended protocol version
Page 1. Study Principal Investigator	**Lead** Principal Investigator	For consistency throughout the protocol
Page 2 Contract Research Organization (CRO) Quintiles Canada Inc. 100 Alexis Nihon, St-Laurent, Quebec, H4M 2P4	Contract Research Organization (CRO) **IQVIA RDS, Inc.** **(formerly Quintiles IMS)** **4820 Emperor** Blvd, Durham NC USA 27703	Edit to reflect change in CRO name and address.
Page 3 Version: Initial Protocol (02 November, 2017)	Version: **Amended Protocol (22 May 2018)** Initial Protocol (02 November, 2017)	Edit to reflect amended protocol version
Page 5-16 Synopis	Synopis	All changes made in the core sections of the protocol are reflected in the synopsis.
Page 31 4.1 Summary of Study design		
The study duration will be up to 39 weeks, consisting of an initial screening period of 4 to 6 weeks	The study duration will be up to 39 weeks, consisting of an initial **diet, lifestyle and medication** ~~screening~~ stabilization period of 4 ~~to~~ **or** 6	Edits to clarify study requirements for diet and physical activity
Approximately ~~615~~ 653 subjects	Approximately ~~615~~ **653** subjects	Edit to revise expected number of screened subjects
At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 to 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study.	At the screening visit (Visit 1), subjects will enter a diet **and lifestyle recommendation** and medication stabilization period that will last 4 ~~to~~ **or** 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to **aim to** maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. **Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study.**	Edits to clarify study requirements for diet and physical activity

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
The duration of this stabilization period will be 4 weeks for subjects who are not on lipid-altering or who are already receiving prior to screening a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, or a combination of these agents. The stabilization period will be 6 weeks for subjects who are required at screening to discontinue prohibited lipid-altering therapy such as fibrates, bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects. Similarly, the stabilization period for subjects who either initiate or change dose at screening of a statin and/or CAI treatment will be 6 weeks. PCSK9I treatment should not be initiated at screening.	The duration of this stabilization period **(between Visit 1 and Visit 2)** will be 4 weeks for subjects who are not ~~on~~ **currently taking any** lipid-altering **agents** or who are already receiving **prior to screening (V1)** a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, **a fibrate**, or a combination of these agents~~, prior to screening~~. **Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening. PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1).** **Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1). Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment.** The stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who are required at screening **(V1)** to discontinue prohibited lipid-altering ~~therapy~~ **agents** such as ~~fibrates,~~ bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects** ~~that may exhibit lipid-altering effects~~. Similarly, the stabilization period **(between Visit 1 and Visit 2) will be 6 weeks** for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment ~~will be 6 weeks~~.	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2; to reflect allowance of subjects taking stable dose of a fibrate; to clarify study requirements for stability of concomitant PCSK9I and Fibrate prior to the screening visit (V1)
After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication with water at a meal.	After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.
Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated).	Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated **with statin, CAI, PCSK9I, alone or in combination**).	Minot edit for clarification
Page 34 4.1.1 Screening Period (Visit 1 [Week -8 or Week -6])	4.1.1 Screening ~~Period~~ Visit (Visit 1 [Week -8 or Week -6])	

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
The purpose of the screening period is to allow subjects to acclimate to the NCEP-TLC diet, and to allow time for washout of current lipid-altering therapy (if necessary).	The purpose of the screening visit and the subsequent stabilization period **(between V1 and Visit 2)** is to allow subjects to acclimate to the **dietary recommendation to consume a** ~~the~~ NCEP-TLC ~~diet~~ **and reduce intake of added sugar**, and to allow time for washout of **prohibited** ~~current~~ lipid-altering **agents** ~~therapy~~ (if necessary), **or stabilization following initiation or dose adjustment of a statin and/or CAI treatment at screening, or washout or dose reduction of a fibrate treatment.**	Edits to clarify purpose of the stabilization period regarding diet, lifestyle and medication.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Subjects not being treated with a statin and/or CAI and/or PCSK9I at time of screening may initiate such treatment, if not contraindicated, at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement). Subjects receiving non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products) and/or any other products or supplements that may exhibit lipid-altering effects at the time of screening will be evaluated by the Investigator to determine if they can discontinue these therapies. If deemed appropriate, discontinuation is required 6 weeks prior to Visit 2 (first TG baseline qualifying measurement). If not contraindicated, these subjects may initiate a statin and/or CAI and/or PCSK9I treatment at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).	~~Subjects not being treated with a statin and/or CAI and/or PCSK9I at time of screening may initiate such treatment, if not contraindicated, at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).~~ ~~Subjects receiving non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products) and/or any other products or supplements that may exhibit lipid-altering effects at the time of screening will be evaluated by the Investigator to determine if they can discontinue these therapies. If deemed appropriate, discontinuation is required 6 weeks prior to Visit 2 (first TG baseline qualifying measurement). If not contraindicated, these subjects may initiate a statin and/or CAI and/or PCSK9I treatment at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).~~ The duration of this stabilization period **(between Visit 1 and Visit 2)** will be 4 weeks for subjects who are not ~~on~~ **currently taking any** lipid-altering **agents** or who are already receiving **prior to screening (V1)** a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), CAI such as ezetimibe, **a fibrate**, or a combination of these agents. **PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.** **Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).** The stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as~~,~~ bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects**. Similarly, the stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2; to reflect allowance of subjects taking stable dose of a fibrate; to clarify study requirements for stability of concomitant PCSK9I and Fibrate prior to the screening visit (V1)

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Determination of eligibility (fasting lipids) (see Section 4.3)	~~Determination~~ Evaluation of eligibility (fasting lipids) **to continue in the stabilization period**[1] ~~(see Section 4.3)~~	Edit and footnote added to clarify that TG values outside of the inclusion range at screening (V1) are not automatically exclusionary.
The NCEP-TLC diet that should be followed for the duration of the study will be explained to the subject. Written dietary information will also be provided to the subject.	**Recommendation to consume** a ~~The~~ NCEP-TLC diet that should be followed for the duration of the study, **along with the reduction of added sugar**, will be explained to the subject. Written dietary information **will be available** ~~also be provided~~ to the subject.	Edit to clarify dietary counselling procedures
Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to maintain current physical activity level **consistent with TLC** throughout the study.	Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to **aim to** maintain ~~current~~ physical activity level **consistent with TLC** throughout the study.	Edit to clarify physical activity counselling procedures
Schedule TG Qualifying Visit (Visit 2). The TG Qualifying Visit (Visit 2) should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering therapy at screening, subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe) or PCSK9I, alone or in combination, and subjects who initiated a stable dose of statin with or without CAI, and for 6 weeks after Visit 1 for subjects who require washout of their current non-statin, lipid-altering therapy at screening.	Schedule **the first** TG Qualifying Visit (Visit 2)[2]. ~~The TG Qualifying Visit (~~Visit 2~~)~~ should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering ~~therapy~~ **agents** at screening, **and for** subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe), PCSK9I, **a fibrate, or a combination of these agents** ~~alone or in combination~~. **Visit 2 should be scheduled for** ~~and~~ **6 weeks after Visit 1 for** subjects **who initiated or changed dose** of a ~~a stable dose of a~~ statin **and/or** ~~with or without~~ CAI **treatment**, for ~~6 weeks after Visit 1 for~~ subjects who require washout of **prohibited** ~~their current~~ non-statin, lipid-altering ~~therapy~~ **agents** at screening, **and for subjects who washout or reduced dose of a current fibrate treatment.**	Edits added to clarify dose stability requirements for lipid-altering agents prior to the first TG qualifying visit.
-	SOCBP will be reminded to use a reliable method of birth control or remain abstinent.	Edit to add reminded for SOCBP about birth control requirements
Page 35 4.1.2 TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])		
The subject will provide fasting blood samples for determination of eligibility (fasting lipids) (see Section 4.3).	The subject will provide fasting blood samples for **evaluation** ~~determination~~ of eligibility (fasting lipids) **to continue in the TG qualification period**[2]	Edit and footnote added to clarify that TG values outside of the inclusion range at V2 or V3 are not automatically exclusionary.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 36 4.1.3 Randomization Visit (Visit 4 [Week 0])		
Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk	Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk. **The analysis will be considered part of this clinical protocol.**	Minor clarification
The subject will be supplied with study medication to be taken until Visit 5 (4 weeks)	The subject will be supplied with study medication to be taken until Visit 5 (4 weeks)**, and instructed to take it once a day with a meal but not prior to attending Visit 5.**	

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Urine sample will be collected for urinalysis	Urine sample will be collected for urinalysis **and for an optional urine pregnancy test (test strip)**[3]. If the test is performed, negative pregnancy status must be confirmed before randomization.	Add optional urine pregnancy test at randomization. This test is to be conducted based on Investigator's judgement, and the subject's situation.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 38-41 4.1.4 Double-blind Treatment Period (Visit 5 [Week 4]) 4.1.5 Double-blind Treatment Period (Visit 6 [Week 11] and Visit 7 [Week 12]) 4.1.6 Double-blind Treatment Period (Visit 8 [Week 18]) 4.1.7 Final Visit (Visit 9 [Week 26] or Early Termination)		
Previously dispensed study medication will be collected and a new supply of study medication (X weeks) to be taken until Visit X (Week X) will be given to the subject. The number of capsules returned will be counted and the results will be documented.	Previously dispensed study medication will be collected and a new supply of study medication (X weeks) to be taken until Visit X (Week X) will be given to the subject. **Subject will be instructed to take it once a day with a meal but not prior to attending Visit X**. The number of capsules returned will be counted and the results will be documented.	Edit to clarify instruction for dosage administration.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 42 4.1.8 Follow-up Contact		
As well, SOCBP shall be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.	As well, SOCBP ~~shall~~ **will** be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.	Minor text edit.
Page 43 Table 1 Schedule of Events		
Visit 4 (Week 0) Visit Window (days) -1/+3	-1/~~+3~~**+5**	Edit to increase tolerance window for randomization visit
Visit 4 (Week 0) Chemistry, hematology and urinalysis X	X[c] [c]**A urine sample may be collected for an optional urine pregnancy test (test strip).**	Footnote added for optional urine pregnancy test at randomization
Page 45 Section 4.2 Discussion of Study design		
All subjects will take an oral, single dose of 4 g (4 capsules) a day with water at a meal.	All subjects will take an oral, single dose of 4 g (4 capsules) a day ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- to 6-week diet and lifestyle stabilization period, subjects will enter a 2-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.	Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- ~~to~~ **or** 6-week diet, ~~and~~ lifestyle **and medication** stabilization period, subjects will enter a 2- **or** 3-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.	Edits to clarify purpose and duration of the stabilization period.
Page 45 Section 4.3.1 Inclusion Criteria		
2. Isolated hypertriglyceridemia, with TG ≥500 mg/dL and <1500 mg/dL (≥5.7 mmol/L and <17.0 mmol/L) OR Mixed hyperlipidemia, with serum triglycerides ≥500 and <1500 mg/dL treated with a statin, CAI or PCSK9I, alone or in combination, that has been stable for 6 weeks prior to randomization. If the subject is not being treated, and not contraindicated, a statin and/or CAI treatment this may be initiated at the discretion of the Investigator at time of screening. PCSK9I treatment should not be initiated at screening.	2. Isolated hypertriglyceridemia ~~OR~~**or** Mixed hyperlipidemia, with TG ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated **or not with a stable dose** of statin, CAI, ~~or~~ PCSK9I, **fibrate, or a combination of these agents.** ~~Alone or in combination, that has been stable for 6 weeks prior to randomization.~~ **If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening.** If ~~the subject is not being treated, and~~ not contraindicated, **the investigator may prescribe new or different** ~~a~~ statin and/or CAI treatment ~~this may~~ **to be** initiated, **or change current doses of statin and/or CAI** at time of screening. ~~PCSK9I and/or fibrate treatment should not be initiated at screening.~~	Edit to clarify the same overall population of severe hypertriglyceridemia (TG ≥ 500 mg/dL), as specified in previous labels of the drug class; to allow inclusion of patients currently treated with a stable dose of fibrate; to remove specification for 6-week stability prior to randomization as this requirement is not applicable in all instances. Requirement for stability are rather clarified in other sections of the protocol (e.g. 4.1, 4.1.1, 5.8.1 and 5.8.2)
3. Willingness to maintain current physical activity level and follow the NCEP-TLC diet throughout the study.	3. Willingness to aim to maintain ~~current~~ physical activity level and **diet consistent with** ~~follow~~ the NCEP-TLC ~~diet~~ **and to reduce added sugars intake** throughout the study.	Edits to clarify study requirements for diet and physical activity
Page 46 Section 4.3.2 Exclusion Criteria		
2. Known lipoprotein lipase impairment or deficiency, or apo CII deficiency.	2. ~~Known lipoprotein lipase impairment or deficiency, or apo CII deficiency~~. **Subjects diagnosed with Familial Chylomicronemia Syndrome**	Edit to clarify exclusion criteria #2
5. …Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study or for at least 8 weeks following the last dose of study medication, whichever is longer.	5. …Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study ~~or~~ **and** for ~~at least~~ 8 weeks following the last dose of study medication. ~~, whichever is longer.~~	Edit to clarify study requirements for SOCBP
10. Diabetics requiring changes in medical therapy (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1.	10. Diabetics requiring changes in **glucose-lowering medication** ~~medical therapy~~ (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1.	Edit to clarify exclusion criteria #10

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
11. Clinical or biochemical evidence of hyperthyroidism not stable with medication for at least 6 weeks prior to Visit 1.	11. **Subjects with** clinical evidence **of hyperthyroidism** or **TSH level less than lower limit of normal (LLN) at Visit 1**. **Subjects diagnosed with hyperthyroidism must be treated** ~~biochemical evidence of hyperthyroidism not stable~~ with medication for at least 6 weeks prior to Visit 1.	Edit to clarify exclusion criteria #11
12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN)	12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN**) within 6 weeks prior to Visit 1.**	Edit to correct exclusion criteria #11 in the synopsis
16. Use of other prohibited drugs: weight loss prescription medications; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids.	16. Use of other prohibited drugs: ~~weight loss~~ prescription **or OTC** medications **specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide**; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids. **Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.**	Edit to clarify prohibited medications when specifically taken for weight loss; clarify allowance of stable dose of anabolic steroids or testosterone as replacement therapy for hypogonadism
17. Any lipid-altering drug therapy, other than statins, CAI or PCSK9I, including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects must be discontinued at least 6 weeks prior to randomization.	17. ~~Any~~ **Use** of any lipid-altering drug ~~therapy~~**agents**, other than statins, CAI, ~~or~~ PCSK9I **or fibrate**, including niacin at a dose greater than 200 mg/day~~, fibrates~~, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects**. These agents ~~that may exhibit lipid-altering effects~~ must be discontinued ~~at least 6~~ 8 weeks prior to randomization.	Edit to remove fibrate from the list of prohibited medications; to clarify washout requirements for prohibited medications prior to randomization.
19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily, pulmonary, gastrointestinal, or immunologic disease.	19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily~~, pulmonary, gastrointestinal, or immunologic disease~~.	Edit to clarify requirements for exclusion of subjects with pulmonary, gastrointestinal, or immunological disease
28. Presence of any other condition the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.	28. Presence of any other condition **(such as severe pulmonary, gastrointestinal, or immunologic disease)** the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.	
Page 48 4.3.3 Subject Restrictions		
Subjects must be willing to maintain current physical activity level and follow the NCEP-TLC diet throughout the study.	Subjects must be willing to **aim to** maintain ~~current~~ physical activity level **and diet consistent with** ~~, and follow~~ the NCEP-TLC, ~~diet~~ **and reduce intake of added sugar** throughout the study.	Edits to clarify study requirements for diet.
Subjects of child-bearing potential must remain abstinent or must use an acceptable method of contraception during the study or for at least 8 weeks following the last dose of study medication.	Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study ~~or~~ **and** for at least 8 weeks following the last dose of study medication.	Edit to clarify study requirements for SOCBP
Page 49 4.3.4 Subject Withdrawal or Termination		
The criteria for enrollment are to be followed explicitly. If a subject who does not respect enrollment criteria is inadvertently enrolled, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator.	The inclusion and exclusion criteria ~~for enrollment~~ are to be followed explicitly. If a subject who does not respect ~~enrollment~~ **one or the other** criteri~~a~~**on** is inadvertently ~~enrolled~~ **randomized**, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator.	Edit to clarify distinction between enrollment and randomization in the context of this protocol.
4.3.5 Subject Re-screening		

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
-	**Re-screening of certain screening failure subjects may be allowed under certain circumstances at least 3 months after initial enrollment and only after discussion with and approval by the Medical Monitor. The following situations may give rise to re-screening:** **• If a subject consents to participate, otherwise meets the eligibility criteria, but is not able to continue in the study prior to randomization due to an unforeseen change in personal situation ;** **• If a subject failed one or the other eligibility criterion during the stabilization or TG qualification period due to i) an acute event that has resolved ii) a medical cause or condition that has been adequately treated or for which time has sufficiently elapsed since occurrence;** **• To allow time for stabilization or wash-out following initiation or dose changed of allowed or prohibited medications, as the case may be, at time of screening or during the TG qualification period;** **Subject who failed to meet the eligibility criteria and do not otherwise fall into the above situations should not be considered for re-screening. Specifically, subjects who fail to meet the average TG inclusion level will be considered screening failure, and re-screening of these subjects will not be allowed. Also, subjects that are randomized and withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, are not eligible for re-screening.** **In case of re-screening, all study screening procedures must be repeated, including the requirement for subjects to give new consent. Re-screened subjects will be allocated a new subject identification number. For each subject that is eligible for re-screening, only one re-screening is permitted.**	New section added to clarify conditions under which the protocol allows re-screening of subjects.
Page 52 5.1 Treatments Administered		
Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day with water at a meal.	Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.
Page 53 5.4 Method of Assigning Subjects to Treatment Group		
After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening (V1). At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the TG qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT.	After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening **(V1)**. At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the **TG** qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT.	Minor text edit for consistency
Page 54 5.6 Selection and Timing of Dose for Each Subject		
Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I inhibitor, alone or in combination at randomization (currently treated vs not currently treated). All subjects will take four capsules, once a day, with water at a meal	Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I ~~inhibitor~~, alone or in combination at randomization (currently treated vs not currently treated). All subjects will take four capsules, once a day, ~~with water~~ at a meal	Minor text edit for consistency

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Page 55 5.8.1 Excluded Medications		
Any lipid-altering drug therapy (other than statins, CAI or PCSK9I, alone or in combination; see below) including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects must be discontinued at least 6 weeks prior to randomization.	Any lipid-altering drug ~~therapy~~ **agents** (other than statins, CAI, ~~or~~ PCSK9I, **or fibrate** alone or in combination; see below) including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary supplements specifically taken for their lipid-altering effects**. These agents ~~that may exhibit lipid-altering effects~~ must be discontinued ~~at least 6~~ **8** weeks prior to randomization.	Edit to remove fibrate from the list of prohibited medications; to clarify washout requirements for prohibited medications prior to randomization
Case of Plant sterols/stanols and Solube Fibers:	Case of Plant sterols/stanols and ~~Solube~~**Soluble** Fibers:	Minor text edit for consistency
Weight loss prescription medications	~~Weight loss~~ Prescription **or OTC** medications **specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide**.	Edit to clarify prohibited weight loss medications
Page 55 5.8.2 Allowed Medications		
All concomitant treatments or medications administered during the 60 days preceding the start of treatment must be reported on the appropriate page of the eCRF. The generic names of the drugs (or trade names for combination drugs) must be specified along with the total daily dose and duration of treatment. The following medications and treatments cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:	Any ~~All concomitant~~ **herbal products, dietary supplements** ~~treatments,~~ or medications **started before the informed consent and ongoing at time of screening (V1)** ~~administered during the 60 days preceding the start of treatment~~ must be reported on the appropriate page of the eCRF. **Any herbal products, dietary supplements, or medications listed in one or the other inclusion or exclusion criterion and that was stopped during the 60 days preceding screening (V1) should also be documented.** The generic names of the **herbal products, dietary supplements,** or medications ~~drugs~~ (or trade names for combination drugs) must be specified along with the total daily dose and duration of treatment. The following **herbal products, dietary supplements, or** medications ~~and treatments~~ cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:	Edit to clarify requirements for documentation of prior and concomitant herbal products, dietary supplements or medications.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Statins, CAI (e.g., Ezetimibe) or PCSK9I, alone or in combination: Subjects already regimented with statins and/or CAI and/or PCSK9I prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization; or Subjects eligible for statins and/or CAI treatment initiation or change at Visit 1 must be on stable dose at least 8 weeks prior to randomization. These subjects must continue to receive the same dose of statin and/or CAI and/or PCSK9I after randomization and must not discontinue medication during the study.	Statins, CAI (e.g., ~~E~~ezetimibe),. ~~or~~ PCSK9I **or fibrate**, alone or in combination: Subjects already regimented with a statin~~s~~ and/or CAI ~~and/or PCSK9I~~ prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization; or Subjects **who initiate or change dose** ~~eligible for~~ of a statin~~s~~ and/or CAI treatment ~~initiation or change~~ at Visit 1 must be on stable dose ~~at least~~ 8 weeks prior to randomization. **PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.** **Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).** ~~These subjects must continue to receive the same dose of statin and/or CAI and/or PCSK9I and/or fibrate after randomization and must not discontinue medication during the study.~~	Edit to allow inclusion of patients currently treated with a stable dose of fibrate; clarify study requirements for stability of dose prior to screening or randomization as the case may be.
The following medications and treatments are also allowed during the study:	The following **herbal products, dietary supplements** or medications ~~and treatments~~ are also allowed during the study:	Minor text edit for consistency
Page 57 5.9 Rescue Medication		
Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication (e.g. fibrate), as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.	Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication **selected by the PI or dose adjustment of fibrate (or another current medication)** ~~(e.g. fibrate)~~, as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.	Edit to allow dose adjustment of a current fibrate or other current medication t as part of the rescue medication
Page 57 5.10 Treatment Compliance		
The prescribed dosage, timing and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.	The prescribed daily dos~~ag~~e, **frequency** ~~timing~~ and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.	Minor edit to clarify dosage administration.
-	**After randomization, at subsequent visits 5, 6, 7, 8 and 9, subjects should be instructed not to take their daily dose before attending the visit.**	Text added to clarify study requirement pertaining to the timing of dose prior to the visit
Page 58 6.1.3 Exploratory Efficacy Endpoints		

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Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 11, Week 18 and Week 24) in TG (persistence of the effect of CaPre on TG lipid profile).	Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, ~~Week 11~~, Week 18 and Week ~~24~~26) in TG (persistence of the effect of CaPre on TG ~~lipid profile~~).	Minor edit text for consistency
Page 61 6.2.1.1 Reporting of Adverse Events		
After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.	After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs**, including those ongoing after the follow-up period of 28 days planned after the final visit (or early termination) (see 4.1.8)** will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. **Non-serious AEs still ongoing after the follow-up period will not be additionally followed and the outcome at time of last contact will be reported in the study database.**	Edit to clarify protocol requirements for AE follow-up.
Page 62 Table 3 Laboratory assessments		
Creatinine Kinase (CK)	Creati~~ni~~ne Kinase (CK)	Minor text edit
FSH (as required for SOCBP)	FSH (as required for post-menopausal subjects only ~~SOCBP~~)	Minor text edit
Glomerular Filtration Rate (eGRF)	Glomerular Filtration Rate (~~eGRF~~eGFR)	Minor text edit
6.2.2.1 Laboratory Re-testing		
-	**Request for re-testing (i.e. requiring a new blood sample) of certain clinical laboratory tests may be allowed in special circumstances and only after discussion with and approval by the Medical Monitor.**	New section added to clarify conditions under which re-testing of certain laboratory test may be allowed.
Page 65 6.2.3.1 Vital Signs		
Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (□C) and respiratory rate for a minimum of 30 seconds will be measured at all visits.	**Vital signs evaluation should be performed before collecting laboratory samples.** Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (°C) and respiratory rate for a minimum of 30 seconds will be measured at all visits.	Edit to clarify protocol expectation for timing of study procedures.
Page 66 6.2.3.4 ECG		
A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination.	A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination. **ECG assessment should be performed before collecting laboratory samples.**	Edit to clarify protocol expectation for timing of study procedures
Page 69 7.0 QUALITY CONTROL AND QUALITY ASSURANCE		
Early study center visits post-enrollment.	Early study center visits **post-randomization** ~~enrollment~~.	
Page 73 8.1 Determination of Sample Size		

<table>
<tr>
<td>The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/d; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The table below shows sample size estimation for a range of treatment effects, considering an unbalanced treatment allocation ratio of 2.5:1 (CaPre:placebo), and using step down testing procedure to adjust for multiplicity:

Table 4 Sample Size Estimation
<table>
<tr><th>Sample size per group (CaPre:placebo)</th><th>Placebo-corrected treatment effect</th><th>Common standard deviation</th><th>Overall Type I error</th><th>Power</th></tr>
<tr><td>265:106</td><td>0.15</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
<tr><td>150:60</td><td>0.20</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
<tr><td>98:39</td><td>0.25</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
</table>
Note: The sample size calculation is performed based on a 2-sample t-test using nQuery + nTerim 4.0.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a difference of at least 20 % in percent decrease from baseline in TG between CaPre and placebo (assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05), a difference that is believed to be clinically relevant. These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia).</td>
<td>The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/d;dL; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The primary estimand in this study is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. All subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. The null hypothesis is that the percent change from baseline in fasting TG level in the CaPre 4 g group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline in fasting TG level in the active group is NOT the same as that in the placebo group.
It is anticipated that the overall treatment discontinuation rate in this study will not exceed 15% and will be approximately equal in the two treatment groups. Given that subjects may initiate subsequent rescue therapies after an early discontinuation of the study treatment and that their outcomes will be measured at Week 11 and/or 12 under the effect of rescue, the following assumptions regarding the median percent reduction in fasting TG levels from baseline to Week 12 are used in sample size calculations.
• Placebo group: 10% median reduction from baseline in subjects who complete the study on placebo and 25% median reduction from baseline in placebo subjects who discontinue the study treatment early and are rescued. This corresponds to an overall median percent reduction from baseline of approximately 12% in the placebo group based on the assumption that 85% of subjects will complete the study on placebo and 15% placebo subjects will be rescued.
CaPre 4 g group: two scenarios will be considered with 32% and 37% median reduction from baseline, respectively. Completers and rescued subjects in the CaPre 4 g group are assumed to have a similar median percent reduction from baseline to Week 12. The two scenarios will correspond to an overall median treatment difference between the CaPre 4 g group and placebo of 20 and 25 percentage points, respectively.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a ~~mean~~ median difference of at least 20 ~~%~~ percentage ~~in percent decrease~~</td>
<td>Original protocol sample size calculation was based on the MEAN (parametric test). In the newer sample size calculation, the MEDIAN (non-parametric test) was used.</td>
</tr>
</table>

points in percent decrease from baseline to Week 12 in TG between CaPre and placebo ~~(~~assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05~~)~~, **based on a non-parametric Wilcoxon-Mann-Whitney test**. **The overall median treatment difference of 20 percentage points**~~, a difference that~~ is believed to be clinically relevant.

The primary analysis to test the null hypothesis of no treatment effect will be conducted using a non-parametric rank-based ANCOVA adjusting for randomization stratification factors, which is expected to be at least as powerful as the Wilcoxon-Mann-Whitney test used in sample size calculations.
The table below shows the estimated power for four scenarios, 20 and 25 percentage points median differences between treatment groups and two settings of common standard deviation (40% and 45%), considering an unbalanced treatment allocation ratio of 2.5:1 with 175:70 subjects randomized (CaPre:placebo). These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia). Power calculations are provided under two assumptions regarding the underlying distribution of the primary variable: lognormal and normal.

Table 4 Sample Size Estimation

Sample size per group (CaPre:placebo)	Placebo-corrected treatment effect (overall median treatment difference)	Common standard deviation	Overall Type I error (two-sided)	Power (lognormal distribution)	Power (normal distribution)
175:70	**20 percentage points**	**40%**	**0.05**	**>95%**	**92%**
175:70	**25 percentage points**	**40%**	**0.05**	**>95%**	**98%**
175:70	**20 percentage points**	**45%**	**0.05**	**>95%**	**87%**
175:70	**25 percentage points**	**45%**	**0.05**	**>95%**	**96%**

~~The table below shows sample size estimation for a range of treatment effects, considering an unbalanced treatment allocation ratio of 2.5:1 (CaPre:placebo), and using step-down testing procedure to adjust for multiplicity:~~

~~Table 4 Sample Size Estimation~~

<table>
<tr><th>Initial Protocol version
02 November 2017</th><th>Amended No. 1
22 May 2018</th><th>Rationale for change</th></tr>
<tr><td></td><td>
<table>
<tr><th>~~Sample size per group (CaPre:placebo)~~</th><th>~~Placebo-corrected treatment effect~~</th><th>~~Common standard deviation~~</th><th>~~Overall Type I error~~</th><th>~~Power~~</th></tr>
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</table>
~~Note: The sample size calculation is performed based on a 2-sample t-test using nQuery + nTerim 4.0.~~</td><td></td></tr>
<tr><td>Page 75
8.2.5 Control of type 1 error</td><td></td><td></td></tr>
<tr><td>The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (in terms of superiority) only if the test of the primary endpoint results in rejection of the null hypothesis in favor of the experimental drugand that a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before are found to be statistically significant.</td><td>The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; ~~(in terms of superiority) only if the test of the primary endpoint results in rejection of the null hypothesis in favor of the experimental drug and that~~ similarly, a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before ~~are~~ is found to be statistically significant.</td><td>Edit to clarify hierarchical closed testing procedure.</td></tr>
<tr><td>Page 76
8.2.6 Primary Efficacy Analyses</td><td></td><td></td></tr>
<tr><td>The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in mean percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects.</td><td>The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in ~~mean~~ median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects.</td><td>Edit to clarify that the primary estimand is based on median.</td></tr>
</table>

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
An analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used to estimate the least squares (LS) means for the primary endpoint (percent change in TG levels). The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule. Prior to performing the parametric ANCOVA analysis, the normality assumptions will be investigated with the Shapiro-Wilk test on the residuals based on observed data only. If significant departures from normality are observed, the alternative non-parametric ANCOVA based on ranks will be performed as follow:	~~An~~ **A non-parametric rank-based** analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used **to perform a hypothesis test for the primary endpoint (percent change in TG levels)** to estimate t~~he least squares (LS) means for~~ the primary endpoint (percent change in TG levels). ~~The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule.~~ ~~Prior to performing the parametric ANCOVA analysis, the normality assumptions will be investigated with the Shapiro-Wilk test on the residuals based on observed data only. If significant departures from normality are observed, the alternative a non-parametric ANCOVA based on ranks will be performed as follow:~~	Edit to clarify that the primary analysis will be based on non-parametric ANCOVA, and no testing for normality assumptions will be performed.
Quantile regression, adjusting for the same baseline covariates as specified for the primary ANCOVA analysis model, will be used to obtain an adjusted estimate of the median treatment difference. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As sensitivity analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's comination rule are not satisfied.	Quantile regression, adjusting for the same baseline covariates as specified for the ~~primary~~ ANCOVA ~~analysis~~ model, will be used to obtain an adjusted estimate of the median treatment difference **vs. placebo with associated two-sided 95% CI**. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As **supportive** ~~sensitivity~~ analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's ~~comination~~ combination rule are not satisfied. ~~The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule.~~	Edit to clarify that the primary analysis is based on non-parametric ANCOVA; clarify that Hodges-Lehman is used as supportive analysis to the primary analysis.
Page 78 8.2.8 Secondary Efficacy Analyses		
An ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo. The same normality assessment test as the primary endpoint will be performed for each secondary endpoint to select the appropriate parametric or non-parametric methods.	~~An~~ **A non-parametric rank-based** ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo. ~~The same normality assessment test as the primary endpoint will be performed for each secondary endpoint to select the appropriate parametric or non-parametric methods.~~	Edit to clarify that the secondary analysis will be based on non-parametric ANCOVA, and no testing for normality assumptions will be performed.
Page 88 8.2.10 Sensitivity Analysis		

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
-	**A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study.** Other sensitivity analysis methods may be performed and will be detailed in the SAP.	Text added to include Tipping point analysis as part of the sensitivity analyses to be performed.
More details of the two proposed sensitivity analyses and possibly additional ones will be presented in the SAP.	More details of the ~~two~~ proposed sensitivity analyses and possibly additional ones will be presented in the SAP.	Minor text edit for consistency.
Page 88 12.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR		
Version: Initial Protocol (02 November, 2017)	Version: **Amended Protocol (22 May, 2018)** Initial Protocol (02 November, 2017)	Edit to reflect amended protocol version.
14.0 APPENDIX 3: DETAILED REVISION HISTORY		
		New section added to detail to highlight all changes made to initial protocol 02 Nov 2017.

Protocol Approval Signatures

PROTOCOL TITLE: A Phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-001

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

Sponsor's representative

Signature: _____ **Date:** 22 MAY 2018
Laurent Harvey **DD/MMM/YYYY**
Vice President, Clinical and Non-Clinical

Signature: _____ **Date:** 22 MAY 2018
Jean-François Lapointe **DD/MMM/YYYY**
Director of Clinical Development

Lead Principal Investigator

Signature: _____ **Date:** _____
Dariush Mozaffarian, MD DrPH **DD/MMM/YYYY**

Clinical Study Protocol

Protocol Title:	**A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia**
Protocol Number:	**ACA-CAP-002**
Date of Protocol:	**Amended Protocol 22 May 2018** **Initial Protocol 02 November 2017**
Product:	**CaPre® (NKPL66)**
IND No.:	**104703**
EudraCT No.:	**NA**
Study Phase:	**3**
Sponsor:	**Acasti Pharma Inc.** **545, Promenade du Centropolis, Suite 100** **Laval, Québec, Canada, H7T 0A3**
Lead Principal Investigator	**Dr. Dariush Mozaffarian, MD, DrPH** **Tufts Friedman School of Nutrition Science and Policy** **150 Harrison Ave,** **Boston, MA, USA 02111**

Key Personnel and Facilities

Lead Principal Investigator	**Dariush Mozaffarian, MD DrPH** **Tufts Friedman School of Nutrition Science and Policy** **150 Harrison Ave,** **Boston, MA, USA 02111** **Office: 617-636-0876**
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Protocol Approval Signatures

PROTOCOL TITLE: A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-002

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

Sponsor's representative

Signature: **Date:**

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Vice President, Clinical and Non-Clinical

DD/MMM/YYYY

Signature: **Date:**

Jean-François Lapointe
Director of Clinical Development

DD/MMM/YYYY

Lead Principal Investigator

Signature: **Date:**

Dariush Mozaffarian, MD DrPH

DD/MMM/YYYY

Revision History

Key change(s) to the Initial Protocol dated 02 November, 2017 are summarized below:

Amendment No.	Date	Change(s)
01	22 May, 2018	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2, to allow subjects taking stable dose of fibrate, and to clarify study requirements for stability of concomitant PCSK9I and fibrate prior to the screening visit (V1). Edits and footnotes added to clarify that individual TG values outside of the study inclusion range at the screening visit (V1), or during the TG qualification period (V2 and V3) , are not automatically exclusionary as randomization of subjects is based on an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) during the TG qualification period Add optional urine pregnancy test (test strip) prior to randomization (V4). New section added to clarify conditions under which the protocol may allow re-screening of subjects. New section added to clarify conditions under which re-testing of certain laboratory test may be allowed. Edits to the statistical section of the protocol to clarify that the sample size justification and primary analysis are based on non-parametric methods.

A detailed revision history is provided in Appendix 3.

SYNOPSIS

Name of Sponsor/Company:	Acasti Pharma Inc.
Name of Finished Product:	CaPre®
Name of Active Ingredient:	NKPL66
Title of Study:	A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26- week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia.
Protocol No:	ACA-CAP-002
Investigators:	Approximately 70 Principal Investigators
Study center(s):	Approximately 45 , 15 and 10 Study Centers located in the U.S., Mexico and Canada, respectively.
Study duration: The study duration will be up to 39 weeks, consisting of an initial screening period of 4 to 6 weeks, a 2- or 3-week triglyceride (TG) qualifying period , a 26-week double-blind treatment period and a follow-up contact after 4 weeks.	**Phase:** 3

Objectives:

Primary:

- To determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting triglyceride (TG) levels in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

Secondary:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by adverse events (AEs), vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-high-density lipoprotein cholesterol (non-HDL-C), very-low-density cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) after 12 weeks of treatment.

Exploratory:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol (RLP-C).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.

- To compare between CaPre and placebo the proportion of patients achieving TG values below 500 mg/dL.
- To determine the effect of CaPre, compared to placebo, on total plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations, on omega-3 (OM3) index, and on Arachidonic Acid (AA), omega-6/omega-3 and EPA/AA ratios.
- To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.
- To explore the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting TG levels.
- To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.
- To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.
- To determine the effect of CaPre on apolipoprotein (apo) B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL, and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on fasting serum glucose (FSG), insulin, and on glycosated hemoglobin A1c (HbA1c).
- To explore the effect of CaPre on insulin resistance and beta-cell function using the homeostatic model assessment (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2).

Methodology: Please refer to Table 1 for the Schedule of Events

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to aim to maintain this diet, as well as to reduce the intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate, or a combination of these agents.

Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening. PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1).

Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1). Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment.

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects .

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values. If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made one week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1. Subjects who fail to meet the average TG inclusion level will be considered screening failure. Re-screening of these subjects will not be allowed.

After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication with meals.

Following a 2.5:1 treatment allocation ratio (CaPre:placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying fasting TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5

mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated or not currently treated with statin, CAI or PCSK9I, alone or in combination). During the double-blind treatment period, subjects are to return to the study center at Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week18) and Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety will be made 4 weeks after final visit [Week 26 or early termination].	
Planned number of subjects:	Approximately 653 subjects will be screened to obtain 245 randomized subjects, with a treatment allocation ratio of 2.5:1 (CaPre:placebo). It is planned that approximately 171 (70%), 39 (16%) and 35 (14%) subjects will be randomized from U.S, Mexican and Canadian Study Centers, respectively. Enrollment will not be blocked by country.
Diagnosis and main criteria for inclusion:	**Main Inclusion Criteria:** Subjects may be entered in the study only if they meet all of the following criteria: 1. Subjects ≥18 years of age. 2. Isolated hypertriglyceridemia or mixed hyperlipidemia, with triglycerides ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated or not with a stable dose of statin, CAI, PCSK9I, fibrate, or a combination of these agents. If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening. If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of statin and/or CAI at time of screening. 3. Willingness to aim to maintain current physical activity level and diet consistent with NCEP-TLC and to reduce added sugars intake throughout the study. 4. Be informed of the nature of the study and give written consent prior to any study procedure. **Main Exclusion Criteria:** Subjects will not be entered in the study for any of the following reasons:

	1. Allergy or intolerance to OM3 fatty acids, OM3-acid ethyl esters, OM3 phospholipids, fish, shell fish, or any component of the study medication. 2. Subjects diagnosed with Familial Chylomicronemia Syndrome (FCS). 3. Subjects with lysosomal acid lipase deficiency. 4. Body mass index greater than 45 kg/m^2. 5. Subjects who are pregnant, lactating, and subjects of childbearing potential who are either planning to become pregnant or who are not using acceptable birth control methods during study participation. Subjects of childbearing potential are subjects who have experienced menarche and do not otherwise meet the criteria for subjects not of childbearing potential, defined as: • Subjects who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation); or • Subjects who are postmenopausal, i.e., who have had a cessation of menses for at least 12 months without an alternative medical cause. A follicle stimulating hormone (FSH) test ≥40 mIU/mL may be used to confirm the post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study and for 8 weeks following the last dose of study medication. 6. Subjects taking tamoxifen, estrogens, or progestins, or other medications or nutritional supplements with mechanisms modifying estrogen or progestogen pathways, who have had dosage changes within 4 weeks prior to Visit 1. 7. Use of oral or injected corticosteroids or anabolic steroids within 6 weeks prior to randomization.

	8. History of pancreatitis within the last 6 months prior to Visit 1. 9. History of symptomatic gallstone disease within the last 5 years, unless treated with cholecystectomy. 10. Diabetics requiring changes in glucose-lowering medication (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1. 11. Subjects with clinical evidence of hyperthyroidism or TSH level less than lower limit of normal (LLN) at Visit 1. Subjects diagnosed with hyperthyroidism must be treated with medication for at least 6 weeks prior to Visit 1. 12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN) within 6 weeks prior to Visit 1. 13. Thyroid hormone replacement therapy that has not been stable for more than 6 weeks prior to Visit 1. 14. History of cancer (other than basal cell carcinoma) within 2 years prior to Visit 1. 15. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, exacerbation of congestive heart failure requiring hospitalization or a change in treatment), life-threatening arrhythmia, or revascularization procedure within 6 months prior to Visit 1. 16. Use of other prohibited drugs: prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted); or anabolic steroids. Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.

	17. Use of any lipid-altering agents other than statins, CAI, PCSK9I, or fibrate, including niacin at a dose greater than 200 mg/day, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), or any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued 8 weeks prior to randomization. 18. Resection of an aortic aneurysm or endovascular aortic repair within 6 months prior to Visit 1. 19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily. 20. Poorly controlled hypertension (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥100 mmHg). Subjects with hypertension adequately controlled with medication are eligible provided that their antihypertensive therapy has been stable for at least 4 weeks prior to Visit 1. 21. Recent history (past 12 months) of drug abuse or alcohol abuse, or alcohol use greater than 2 units per day (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks). 22. Hepatobiliary disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN; if ALT/AST is >3× ULN, the levels must have been stable for 3 months prior to Visit 1. 23. Severe renal disease as defined by less than 30 mL/min serum creatinine clearance calculated using the Cockcroft-Gault formula. 24. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) international normalized ratio (INR) of ≥1.5. Subjects using warfarin [Coumadin®] or heparin are allowed. Subjects receiving other anticoagulants dabigatran, rivaroxaban, or apixaban are allowed. Subjects receiving acetylsalicylic acid

	(ASA) alone or in combination with other anti-platelet agents (e.g., clopidogrel, prasugrel, ticagrelor) are also allowed. 25. Unexplained creatine kinase concentration 3 × ULN. 26. Creatine kinase elevation owing to known hereditary or acquired muscle disease. 27. Exposure to any investigational product, within 4 weeks prior to Visit 1. 28. Presence of any other condition (such as severe pulmonary, gastrointestinal, or immunologic disease) the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk. 29. Any life-threatening disease expected to result in death within 2 years, require frequent hospitalizations, extensive surgery or changes in medications or diet.
Test product, dose and mode of administration:	CaPre 4 g, administered orally as 1 g capsules once a day with meals.
Reference therapy, dose and mode of administration:	Matching placebo (corn starch) capsules administered orally as 1 g capsules once a day with meals.

Criteria for evaluation:

Primary Efficacy Endpoint:

- Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L).

Secondary Efficacy Endpoints:

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

The secondary efficacy endpoints are listed in order of importance for the control of the type 1 error.

Exploratory efficacy endpoints:

- Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and Week 12) and Week 26 in TC.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and to Week 26 in RLP-C.
- Percent change from baseline (average of Week -1 and 0) to Week 26 in LDL-C (β-quantification) and VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 26 in non-HDL-C and HDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII and apo A5.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (LDL, non-HDL, HDL, IDL and VLDL).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP and Lp-PLA2.

Exploratory pharmacokinetic endpoints:

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations.
- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in AA, in omega-6/omega-3 and in EPA/AA ratios.

Safety:

Adverse Events (AEs), vital signs and clinical laboratory measures.

Statistical methods:

Efficacy analyses will be based on the intent-to-treat (ITT) Population, defined as all randomized subjects. Analysis of the primary efficacy endpoint will be repeated on the per-protocol (PP) Population to test for robustness of results. The PP Population will include only those ITT subjects who have no major protocol deviations (which will be detailed in the Statistical Analysis Plan (SAP) before database lock).

The Safety Population will be used to assess safety and tolerability variables, defined as all randomized subjects who received at least 1 dose of study medication.

For the primary efficacy endpoint, i.e., the percent change in fasting TG levels from baseline to Week 12, descriptive statistics will be summarized and statistical testing will be performed. The baseline value is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification). The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of 12-weeks of double-blind treatment, approximately 1 week apart that is Visit 6 (Week 11) and Visit 7 (Week 12).

The primary estimand is the difference between the randomized treatment groups, CaPre 4 g daily and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. All collected data will be used in primary analysis.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline TG value as a covariate will be used to perform a hypothesis test for the primary endpoint (percent change in TG levels). Quantile regression, adjusting for same baseline covariates as specified for the ANCOVA model, will be used to obtain an adjusted estimate of the median treatment difference vs. placebo with associated two-sided 95% confidence intervals (CI). There is an expectation that the proportion of subjects who truly have missing data (who withdraw from study participation/data collection) will be small. Subjects who withdraw consent for study participation overall and are not assessed at Week 11 and 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or Week12. Results of the ANCOVA analysis from multiple imputed datasets will be combined using the Rubin's combination rule.

As supportive analysis, Hodges-Lehmann Estimates for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95%

CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied.

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the analyses by using other strategies for dealing with missing data. Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed Week 11 and/or 12. This approach assumes that some subjects discontinuing the study will do so for non-treatment-related reasons and would have similar outcomes to subjects who are able to complete the treatment. A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study. Other sensitivity analysis methods may be performed and will be detailed in the SAP.

For lipid parameters defined as secondary and exploratory endpoints, the percent change from baseline to Week 12 and/or to Week 26 will be evaluated. The baseline value is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2, 3 and 4 or Visits 3, 3.1, and 4 in case an additional TG measurement is necessary during qualification), except for LDL-C (beta-quantification) which baseline is defined as the average of 2 measurements (Week -1 and 0 corresponding to Visits 3 and 4 or Visits 3.1 and 4 if applicable). For all lipid endpoints, the Week 12 endpoint is defined as the average of the values obtained at Visit 6 (Week 11) and Visit 7 (Week 12), and the Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26).

Similar analyses as specified above for the primary efficacy analysis will be conducted for the secondary efficacy endpoints on the ITT population. A non-parametric rank-based ANCOVA model and quantile regression with main effects of treatment, nominal qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate, will be used to estimate the treatment effect of the CaPre dose group vs. placebo.

The experiment-wise type I error will be controlled to a maximum of two-sided 5% by using a hierarchical closed testing procedure: secondary endpoints will only be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; similarly, the later secondary endpoint in the hierarchy will be considered for statistical significance only if all former preceding secondary endpoints are found to be statistically significant.

For other exploratory efficacy endpoints, the baseline value is defined as the value obtained prior to dosing (measurement taken at Visit 4 (Week 0); Week 12 endpoint is defined as the value obtained at Visit 7 (Week 12) and Week 26 endpoint is defined as the value obtained at Visit 9 (Week 26), whenever applicable. These will be analyzed similarly as specified in the primary efficacy analysis

to be conducted on the ITT population. For exploratory endpoints, nominal p-values will be reported in an exploratory fashion.

Regarding the proportion of subjects who have a fasting TG level <500 mg/dL at the end of 12-week and 26-week double-blind treatment period, a Cochran-Mantel-Haenszel (CMH) test will be used, controlling for the stratification factors that are used for randomization. Subjects with missing data at the analysis time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis. In a sensitivity analysis, subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

All treatment-emergent AEs (TEAEs) will be summarized by treatment group. Treatment-emergent AEs will also be summarized by relationship to the study medication and by intensity. Deaths, serious adverse events (SAEs) and AEs leading to study subject early termination will be tabulated and presented in data listings. Clinical laboratory results (chemistry, hematology, coagulation, urinalysis, etc.) will be summarized using descriptive statistics for each visit by treatment group. Observed values at each visit and changes from baseline to each post-baseline visit will be presented. Vital signs and ECGs will be summarized by treatment group for each applicable visit.

Approximately 245 subjects will be randomized to this study. Subjects will be randomized to 1 of 2 treatment groups (CaPre 4 g or placebo), following a 2.5:1 (CaPre: placebo) treatment allocation ratio. Accordingly, approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. A sample size of 245 subjects will provide at least 90% power to detect a median difference of at least 20 percentage points in percent decrease from baseline to Week 12 in TG between CaPre 4 g group and placebo (assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05, based on a non-parametric Wilcoxon-Mann-Whitney test). The overall median treatment difference of 20 percentage points is believed to be clinically relevant.

These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia).

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AA	Arachidonic acid
ADR	Adverse Drug Reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CAI	Cholesterol-absorption inhibitor
CI	Confidence Interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
DHA	Docosahexaenoic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
FFA	Free fatty acid
FSG	Fasting serum glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase

Abbreviation	Definition
HbA1c	Glycosated Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HED	Human equivalent dosing
HIV	Human immunodeficiency virus
HOMA	Homeostatis model assessment
HPMC	Hydroxypropyl methyl cellulose
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IRT	Interactive Response Technology
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA2	Lipoprotein-associated phospholipase A2
LS	Least squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NCEP	National Cholesterol Education Program
NHPD	Natural Health Products Directorate
NNHPD	Natural and Non-prescription Health Products Directorate (previously NHPD)
NOAEL	No-Observed-Adverse-Effect-Level
NS	Not significant

Abbreviation	Definition
OM3	Omega-3
PCSK9I	Proprotein convertase subtilisin/kexin type 9 serine protease inhibitors
PK	Pharmacokinetics
PL	Phospholipid
PP	Per-protocol
PT	Prothrombin time
PUFA	Polyunsaturated fatty acids
RBC	Red blood cell
RDW	Red blood cell distribution width
RIDIT	Relative to an Identified Distribution Integral Transformation
RLP-C	Remnant-like particle cholesterol
RR	Respiratory Rate for Vital signs or in context Relative Risk or RR interval (time between QRS complexes) for ECG
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SoC	Standard of care
SOCBP	Subject of child-bearing potential
SOP	Standard Operating Procedures
T_4	Thyroxine
TC	Total cholesterol
TEAE	Treatment-emergent AE
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

2.0 INTRODUCTION

It is estimated that about one-third (31%) of the population aged 20 years and older in the United States (U.S.) has elevated levels of triglycerides (TG), including approximately 36 million people diagnosed with hypertriglyceridemia (TG ≥200 mg/dL) and between 1% to 2% with severe hypertriglyceridemia (TG ≥500 mg/dL) representing about 4 million people.[1] Hypertriglyceridemia is due to both genetic and environmental factors, including obesity, sedentary lifestyle and high-calorie diets and is also associated with comorbid conditions such as diabetes, chronic renal failure, pancreatitis and nephrotic syndrome.

Severe hypertriglyceridemia is associated with acute pancreatitis. While reduction in risk of recurrent pancreatitis by pharmacologic means has not been systematically studied, aggressive treatment of hypertriglyceridemia is generally believed to reduce the recurrence of pancreatitis in patients whose sole risk factor appears to be the hypertriglyceridemia.[2,3,4]

Based on data from the National Health and Nutrition Examination Surveys (NHANES) between 2001 and 2006, fewer than 4% of U.S. adults with severe hypertriglyceridemia receive prescription medication to lower their TG levels, representing a significant unmet medical need.[5] The first-line drug therapy in patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL) is often a prescription OM3, niacin or fibrates as adjunct to TLC diet. However, niacin is not well tolerated and safety, notably risk of myopathy, may be an issue with fibrates especially when used in combination with a statin [6,7]. Also, fibrates may substantially increase LDL-C in patients with more severe form of hypertriglyceridemia[8].

Lovaza (including 4 generic versions), Vascepa, Omtryg, and Epanova are prescription OM3 drugs currently approved for the treatment of severe hypertriglyceridemia in the U.S. CaPre, Acasti Pharma's prescription drug candidate, is an OM3 phospholipid concentrate derived from krill oil developed for the treatment of severe hypertriglyceridemia. Contrarily to previously approved OM3 prescription drugs in this indication, the form of OM3 found in CaPre (predominantly EPA and DHA) is a mixture of OM3 phospholipid conjugates and free fatty acids (FFA), which may offer better bioavailability over products containing OM3 in the form of ethyl esters.

The proposed indication for CaPre is as an adjunctive therapy to diet and exercise for patients with severe hypertriglyceridemia; therefore, the target population selected for the current study is adult subjects with isolated severe hypertriglyceridemia or mixed hyperlipidemia (TG ≥500 mg/dL to ≤1500 mg/dL). The main objective of the study is to show that CaPre 4 g daily, compared to placebo, is effective in lowering fasting TG levels in this patient population.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

The following paragraphs summarize background information from nonclinical and clinical studies of CaPre carried out by the Sponsor. Further details are presented in the CaPre Investigator's Brochure.

Nonclinical Data

The nonclinical program set forth to demonstrate that CaPre and more specifically its drug substance, NKPL66, can be deemed safe and tolerable for use in human clinical trials. Nonclinical studies completed so far on NKPL66 include pharmacodynamic, safety pharmacology (cardiovascular, neurological and respiratory systems), pharmacokinetic (PK), toxicology (acute, sub-chronic and chronic, as well as genotoxicity), and development and reproductive teratology (DART) in rodent and non-rodent species dosed up to 65 g/day human equivalent dose (HED) and up to 39 weeks.

Taken together, no NKPL66-related significant toxicological observations were evidenced from these nonclinical studies; results demonstrate that CaPre (NKPL66) can be considered safe and well-tolerated up to 65 g/day HED. Black (or very dark red) feces were noted in some animals treated with NKPL66. The red/black color of the feces was not due to blood but rather due to the presence of naturally-occurring carotenoid pigments contained in the NKPL66 tested. Coloration returned to normal during the recovery period.

Clinical Data

The current human exposure with CaPre consists of two Phase 1 PK clinical studies in healthy volunteers and two Phase 2 clinical studies in subjects with mild to severe hypertriglyceridemia (200 mg/dL ≤ TG <877 mg/dL).

All together, these four clinical studies included 773 subjects among which 611 subjects received CaPre (pooled subjects), 129 subjects received placebo, and 29 subjects received Standard of Care (SoC) alone. Among these 611 subjects exposed to CaPre, 216 subjects have been exposed to 2 g/day for up to 12 weeks while 171 subjects have been exposed to 4 g/day for up to 8 weeks.

The Phase 1 PK study (CAP13-101) was conducted in the U.S. and aimed to evaluate the pharmacokinetics of CaPre following single and multiple oral doses in healthy volunteers for up to 15 days. CaPre was found to be safe and well-tolerated in healthy adult subjects when administered as multiple oral doses of 1 g/day, 2 g/day, and 4 g/day. CaPre PK appeared to be approximately dose proportional over the 1 to 4 g/day dose range. The bioavailability of CaPre did not appear to be meaningfully affected by the fat content of the meal consumed prior to dose administration. This is clinically relevant as a low-fat diet is part of the management of hypertriglyceridemic patients.

The Phase 1 Comparative bioavailability study (2016-4010) was conducted in the U.S. and aimed to establish a scientific bridge between CaPre and the marketed OM3 drug Lovaza, under fasting and fed conditions. More specifically, the study aimed to demonstrate that exposure to EPA and DHA from CaPre was not significantly higher than Lovaza under conditions of maximum exposure in the fed state, following intake of a high-fat and high-calorie meal.

Under fed conditions, the 90% confidence intervals (CIs) of the ratio of geometric means between CaPre and Lovaza for total (AUC_{0-72}) and peak (C_{max}) exposure of baseline-adjusted EPA and DHA in total lipids of plasma were each entirely contained below 125%; thereby meeting the primary objective of this study. In fasting conditions however, the total and peak exposure were each significantly enhanced following administration of CaPre compared to Lovaza as the 90% CIs of the ratio of geometric means for AUC_{0-72} and C_{max} for both analytes were entirely contained above 125%. Note that exposure levels observed under fasting conditions were still below those obtained following administration of Lovaza in the fed state and, as such, no safety concerns would be associated with these findings. Administration of OM3 drugs under fasting (empty stomach) and/or a low fat diet, which is indicated in the management patients with hypertriglyceridemia, provides least optimal conditions for EPA and DHA absorption. However, it is considered a more realistic representation of OM3 drug administration in the treatment of these patients. Finally, the impact of food on the bioavailability of Lovaza was much more pronounced compared to that following administration of CaPre, a finding that suggests less loss of exposure and perhaps efficacy when patients do not comply with the proposed product labeling of taking CaPre with a meal.

The two Phase 2 clinical studies were conducted in Canada and aimed to assess the safety and efficacy of CaPre in the treatment of mild-to-severe hypertriglyceridemia (200 mg/dL ≤ TG < 877 mg/dL), among which approximately 90% of subjects had TG levels between 200-499 mg/dL. Results gathered from a total of 675 subjects enrolled in these studies showed that CaPre was safe and well tolerated.

In the COLT (Open-Label) study, a statistically significant reduction in TG levels was demonstrated with CaPre 2 g or 4 g per day after 8 weeks of treatment compared to the standard of care (SoC) (2 g: -15.1%, p=0.06; 4 g: -14.8%, p=0.03) without deleterious effects on LDL-C (2 g: -7.6%, p=ns; 4 g: -10.4%, p=ns). In addition, beneficial effects were noted on non-HDL-C (2 g: -5.9%, p=ns; 4 g: -9.8%, p=0.036), HDL-C (2 g: +7.9%, p=0.10; 4 g: +7.7%, p=0.07) and on glycemic control (HbA1c) (2 g: -6.8%, p=ns; 4 g: -15.0%, p=0.04) primarily with CaPre administered at 4 g/day compared to the SoC.

In TRIFECTA (double-blind, placebo-controlled) study, a statistically significant reduction in TG levels was demonstrated with CaPre 1 g and 2 g/day after 12 weeks of treatment compared to placebo (1 g: -9.1%, p=0.05; 2 g: -9.8%, p=0.04) without deleterious effects on LDL-C (1

g: +2.0%, p=ns; 2 g: -0.6%, p=ns). In addition, beneficial effects were noted on non-HDL-C primarily with CaPre administered at 2 g/day compared to the placebo (1 g: -3.6%, p=ns; 2 g: -5.3%, p=0.04). There were, overall, no significant differences between treatment groups with respect to change in fasting plasma glucose, insulin, HbA1c and HOMA-IR.

In terms of safety, among all treatment-emergent adverse events (AEs) with an occurrence greater than 2% of subjects (CaPre all doses pooled) and greater than placebo or SoC, only diarrhea emerged at an incidence of 2.3%. All other AEs were reported at a frequency of less than 2%. No treatment-related AEs were reported at an incidence greater than 2% (CaPre all doses pooled) by subjects exposed to CaPre. The most frequent treatment-related AEs were gastroesophageal reflux disease (1.6%), diarrhea (1.3%), blood creatinine phosphokinase increased (1.3%) and myalgia (0.8%). These AEs were more frequent at the highest dose of CaPre (4 g/day).

Only three SAEs were reported and consisted of haemangioma, myocardial infarction and pancreatitis. All these SAEs were reported by the investigator as not related to CaPre.

Finally, a total of 9 subjects (1.2% of pooled subjects) discontinued due to AEs, among which 4 subjects following placebo or SoC and 5 subjects following CaPre (CaPre 1 g/day: n=2; CaPre 2 g/day: n=2; CaPre 4 g/day: n=1). The causality of AEs was assessed as possibly-related to the study drug for all 5 subjects who discontinued following CaPre compared to 1 subject who discontinued following placebo. Treatment-related AEs leading to discontinuation following CaPre were: abdominal distension (CaPre 1 g/day: n=1), diarrhea (CaPre 1 g/day: n=1, CaPre 2 g/day: n=1), hypersensitivity (CaPre 4 g/day: n=1), burning sensation (CaPre 4 g/day: n=1) and rash (CaPre 1 g/day: n=1, CaPre 2 g/day: n=1).

In summary, nonclinical and clinical data gathered to date are considered supportive of the proposed Phase 3 study with CaPre as an adjunctive therapy to diet in adult patients with severe hypertriglyceridemia. Please refer to the current CaPre Investigator' Brochure for further details[9].

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- The primary objective of the study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting TG levels in subjects with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To determine the safety and tolerability of CaPre 4 g daily as assessed by AEs, vital signs and clinical laboratory measures.
- To determine the effect of CaPre 4 g daily, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C after 12 weeks of treatment.

3.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- To determine the effect of CaPre, compared to placebo, on non-HDL-C, VLDL-C, HDL-C, and LDL-C over 26 weeks of treatment.
- To determine the effect of CaPre compared to placebo on total cholesterol (TC) and on remnant-like particle cholesterol (RLP-C).
- To explore the persistence of the effect of CaPre on the TG profile over 26 weeks of treatment.
- To compare the proportion of patients achieving TG values below 500 mg/dL between CaPre and placebo.
- To determine the effect of CaPre, compared to placebo, on total plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations, on omega-3 (OM3) index, and on Arachidonic Acid (AA), omega-6/omega-3 and EPA/AA ratios.
- To explore the relationship between baseline fasting TG levels and the change in fasting TG levels.
- To explore the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting serum TG levels.

- To explore the relationship between demographic and baseline characteristics and the changes in total plasma EPA, DHA and OM3 Index.
- To explore the relationship between demographic and baseline characteristics and the change in fasting TG levels.
- To determine the effect of CaPre on apo B, apo AI, apo B/apo A1 ratio, apo CIII, and apo A5.
- To explore the effect of CaPre on lipoprotein particles concentration and size (LDL, HDL, non-HDL, IDL and VLDL).
- To explore the effect of CaPre on oxidized LDL-C.
- To explore the effect of CaPre on FSG, insulin and on HbA1c.
- To explore the effect of CaPre on insulin resistance and beta-cell function (HOMA-IR and HOMA-β).
- To explore the effect of CaPre on hsCRP and Lp-PLA2.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This will be a multi-center, multi-national, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre or placebo 4 g/day), Phase 3 efficacy and safety study in subjects ≥18 years old, with severe hypertriglyceridemia defined by having fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). The study duration will be up to 39 weeks, consisting of an initial diet and lifestyle recommendation and medication stabilization period of 4 or 6 weeks, a 2 or 3-week TG qualifying period, a 26-week double-blind treatment period, and a 4-week contact follow-up. Approximately 653 subjects will be screened to obtain 245 randomized subjects at approximately 84 centers.

At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 or 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet[10] and will be instructed to aim to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study. Appendix 2 provides information outlining the principles of NCEP-TLC dietary patterns focused on lowering cholesterol

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®,

Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects.

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

At Visit 2 (4 or 6 weeks after the initial screening visit), all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1. Subjects who fail to meet the average TG inclusion level will be considered screening failure. Rescreening of these subjects will not be allowed.

After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication at a meal.

Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated with statin, CAI or PCSK9I alone or in combination).

Following randomization at Visit 4 (Week 0), subjects are to return to the study center at Visit 5 (Week 4), Visit 6 (Week 11), Visit 7 (Week 12), Visit 8 (Week 18) and for the last visit at Visit 9 (Week 26) for efficacy and safety evaluations. A follow-up contact for safety assessment is required 4 weeks after Final Visit (Visit 9 or early termination).

The study design is presented in Figure 1. The Schedule of Events is presented in Table 1.

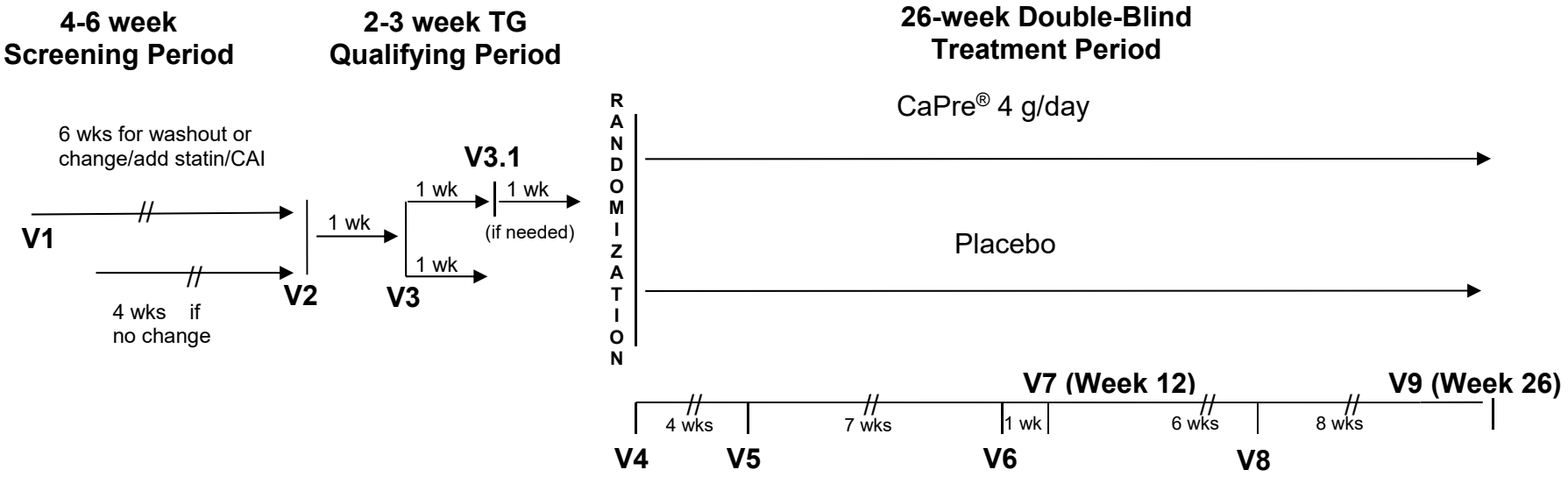

Figure 1 Schematic of Study Design

4.1.1 Screening Visit (Visit 1 [Week -8 or Week -6])

The purpose of the screening visit and the subsequent stabilization period (between V1 and Visit 2) is to allow subjects to acclimate to the dietary recommendation to consume a NCEP-TLC diet and reduce intake of added sugar, and to allow time for washout of prohibited lipid-altering agents (if necessary), stabilization following initiation or dose adjustment of a statin and/or CAI treatment at screening, or washout or dose reduction of a fibrate treatment.

The duration of this stabilization period (between Visit 1 and Visit 2) will be 4 weeks for subjects who are not currently taking any lipid-altering agents or who are already receiving prior to screening (V1) a stable dose of statins, PCSK9I, CAI, such as ezetimibe, a fibrate or a combination of these agents.

PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects.

Similarly, the stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 1:

- Signed informed consent prior to any study-related procedures.

- Review of inclusion and exclusion criteria.
- Demographic information, medical history (including tobacco and alcohol use) and concomitant medications will be recorded.
- Height and weight will be measured for calculation of BMI.
- Vital signs will be measured.
- Complete physical examination.
- The subject will provide fasting blood samples for:
  - Evaluation of eligibility (fasting lipids) to continue in the stabilization period[1]
  - Routine laboratory analysis (chemistry, hematology, coagulation)
  - HbA1c
  - Hepatitis B and C
  - Thyroid function (thyroid stimulating hormone [TSH] and thyroxine [T_4])
  - Each subject of childbearing potential (SOCBP) will provide a blood sample for pregnancy testing. A subject with a positive result must be excluded from the study as a screening failure (see Section 4.3).
- Urine sample will be collected for urinalysis.
- Recommendation to consume a NCEP-TLC diet that should be followed for the duration of the study, along with the reduction of added sugar, will be explained to the subject. Written dietary information will be available to the subject.
- Schedule the first TG Qualifying Visit (Visit 2). Visit 2 should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering agents at screening, and for subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe), PCSK9I, a fibrate, or a combination of these agents. Visit 2 should be scheduled for 6 weeks after Visit 1 for subjects who initiated or changed dose of a

[1] For randomization, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on results of the TG qualification period (see section 4.1.2); therefore TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])TG <500 mg/dL or >1500 mg/dL (<5.7 mmol/L or >17.0 mmol/L) at screening (V1) should not be considered automatically exclusionary. Investigator must use their best medical judgement when deciding whether or not a subject can continue in the study after screening depending on their evaluation of the subject's medical history, current use or washout of lipid-alterging agents, medical condition and other findings at screening.

statin and/or CAI treatment, for subjects who require washout of prohibited lipid-altering agents at screening, and for subjects who washout or reduced dose of a current fibrate treatment.

- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to aim to maintain physical activity consistent with TLC level throughout the study.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.2 TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])

At Week -2, all eligible subjects will enter the TG qualifying period. Subjects will have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 26-week double-blind treatment period, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values.

If a subject's **average** TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 2 and Visit 3:

- Review of inclusion and exclusion criteria.
- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured (only at Visit 2).
- Vital signs will be measured.
- Brief physical examination (only at Visit 2).
- 12-lead electrocardiogram (ECG; only at Visit 2).

- The subject will provide fasting blood samples for evaluation of eligibility (fasting lipids) to continue in the TG qualification period[2].
- Physical activity and dietary compliance will be reviewed with the subject.
- Diet counseling.
- Schedule the next TG Qualifying Visit (Visit 3 or 3.1 (if applicable)) for 1 week after Visit 2 or 3, respectively.

  OR

  Schedule Randomization Visit 4 for 1 week after Visit 3 or 3.1 (if applicable).
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.3 Randomization Visit (Visit 4 [Week 0])

After confirmation of qualifying fasting TG values (fasting TG level ≥500 mg/dL and ≤1500 mg/dL [≥5.7 mmol/L and ≤17.0 mmol/L] based on the average [arithmetic mean] of the Visit 2 and Visit 3, or Visit 3 and Visit 3.1 values), eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), following a 2.5:1 treatment allocation ratio (CaPre:placebo), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g (4 capsules) daily, or matching placebo (4 capsules) daily. Subjects will be dispensed with adequate study medication until Visit 5.

Prior to having the blood sample drawn, subject must fast for a period of at least 9 hours and may consume only water and usual medications. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 4:

- Concomitant medications and AEs since last visit will be recorded.
- Weight and waist circumference will be measured.

[2] For randomization, subjects must have an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) based on results of the TG qualification period (see section 4.1.2); therefore TG <500 mg/dL or >1500 mg/dL (<5.7 mmol/L or >17.0 mmol/L) at V2 should not be considered automatically exclusionary. Investigator are required to use their best medical judgement when deciding whether or not a subject can continue in TG qualification period.

- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Routine laboratory analysis (chemistry, hematology, coagulation).
  - Fasting lipids.
  - Fasting insulin.
  - HbA1c.
  - Biomarkers (see Table 3).
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
  - Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk. The analysis will be considered part of this clinical protocol.
- Urine sample will be collected for urinalysis and for an optional urine pregnancy test (test strip)[3]. If the test is performed, negative pregnancy status must be confirmed before randomization.
- Physical activity and dietary compliance will be reviewed with the subject.
- Diet counseling.
- The subject will be randomized via Interactive Response Technology (IRT) to CaPre 4 g daily, or placebo.
- The subject will be supplied with study medication to be taken until Visit 5 (4 weeks), and instructed to take it once a day with a meal but not prior to attending Visit 5.
- Schedule Visit 5 for 4 weeks after Visit 4.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.

[3] Based on the Investigator's medical judgement, an optional urine pregnancy test (test strip) may be performed to confirm eligibility prior to randomizing a subject and initiate dosing with the study medication.

- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.4 Double-blind Treatment Period (Visit 5 [Week 4])

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 5:

- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Routine laboratory analysis (chemistry, hematology, coagulation).
  - Fasting lipids.
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
- Urine sample will be collected for urinalysis.
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- Previously dispensed study medication will be collected and a new supply of study medication (8 weeks) to be taken until Visit 7 (Week 12) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior to attending Visit 6 and 7. The number of capsules returned will be counted and the results will be documented.
- Schedule next study visit.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.5 Double-blind Treatment Period (Visit 6 [Week 11] and Visit 7 [Week 12])

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 6 and Visit 7:

- Concomitant medications and AEs since last visit will be recorded.
- Weight and waist circumference will be measured (only at Visit 7).
- Vital signs will be measured.
- Brief physical examination (only at Visit 7).
- 12-lead ECG (only at Visit 7).
- The subject will provide fasting blood samples for:
    - Routine laboratory analysis (chemistry, hematology, coagulation only at Visit 7).
    - Fasting lipids.
    - Fasting insulin (only at Visit 7).
    - HbA1c (only at Visit 7).
    - Biomarkers (only at Visit 7) (see Table 3).
    - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios (only at Visit 7).
    - Additional serum sample (only at Visit 7) for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.
- Urine sample will be collected for urinalysis (only at Visit 7).
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- At Visit 7 only, the previously dispensed study medication will be collected and a new supply (6 weeks) of study medication to be taken until Visit 8 (Week 18) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior

to attending Visit 8. The number of capsules returned will be counted and the results will be documented.

- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.
- SOCBP shall be reminded to use a reliable method of birth control or remain abstinent.

4.1.6 Double-blind Treatment Period (Visit 8 [Week 18])

Subjects will be seen for Visit 8 after 18 weeks of continued double blind treatment.

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 8:

- Concomitant medications and AEs since last visit will be recorded.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
  - Fasting lipids.
  - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
- Physical activity level and dietary compliance will be reviewed with the subject.
- Diet counseling.
- The previously dispensed study medication will be collected and a new supply of study medication (8 weeks) to be taken until Visit 9 (Week 26) will be given to the subject. Subject will be instructed to take it once a day with a meal but not prior to attending Visit 9. The number of capsules returned will be counted and the results will be documented.
- Schedule next study visit.
- Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit.

- SOCBP will be reminded to use a reliable method of birth control or remain abstinent.

4.1.7 Final Visit (Visit 9 [Week 26] or Early Termination)

Assessments for an early termination visit are essentially the same as for Visit 9 (Week 26).

Subject must fast for a period of at least 9 hours and may consume only water and usual medications prior to having the blood sample drawn. If the subject has not fasted, the study visit must be rescheduled as soon as possible.

The following procedures will be performed at Visit 9 or at Early Termination:

- Concomitant medications and AEs since last visit will be recorded.
- Waist circumference will be measured.
- Brief physical examination.
- Weight will be measured.
- Vital signs will be measured.
- Brief physical examination.
- The subject will provide fasting blood samples for:
    - Routine laboratory analysis (chemistry, hematology, coagulation).
    - Fasting lipids.
    - Fasting insulin.
    - HbA1c.
    - Biomarkers (see Table 3).
    - EPA, DHA, OM3 index, AA, omega-6/omega-3 and EPA/AA ratios.
    - Additional serum sample (only at Visit 9, not at Early Termination Visit) for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.
- Urine sample will be collected for urinalysis.
- Physical activity level and dietary compliance will be reviewed with the subject.

- Diet counseling
- The previously dispensed study medication will be collected. The number of capsules returned will be counted and the results will be documented.
- Subject will be advised to follow up with the pre-study health care provider to have pre-study lipid management resumed and for on-going care.
- SOCBP will be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 8 weeks.
- Subject will be advised to expect a follow-up contact to assess for additional AEs and to confirm that follow-up care has been arranged for dyslipidemia.

4.1.8 Follow-up Contact

Approximately 4 weeks after the final study visit (V9 or early termination), the subject should be contacted either at a clinic visit or by any remote contact such as a telephone call or email to obtain information about possible AEs that occurred since the end of study medication. Follow-up for ongoing management of the subject's lipid disorder will be confirmed.

As well, SOCBP will be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.

Table 1 Schedule of Events

Assessments	Screening	TG Qualifying Period		26-week Double-Blind Treatment Period						Early Termination Visit	Contact follow-up[b]
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-8 or -6**	**-2**	**-1**	**0**	**4**	**11**	**12**	**18**	**26**		**30**
Visit Window (days)		**±2**	**±2**	**-1/+5**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**n/a**	**+6**
Informed consent	X										
Inclusion/exclusion criteria	X	X	X								
Demographics	X										
Medical history	X										
Withdrawal of prohibited lipid altering medication (s)	X										
Height/BMI (only at V1), weight	X	X		X	X		X	X	X	X	
Waist circumference				X			X		X	X	
Serum pregnancy test	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, temperature)	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram		X					X		X	X	
Complete physical examination	X										
Brief physical examination		X		X	X		X	X	X	X	
Chemistry, hematology and urinalysis	X			X[c]	X		X		X	X	
Coagulation	X			X	X		X		X	X	
Hepatitis B and C	X										
Thyroid function (TSH –T_4)	X										
HbA1c	X			X			X		X	X	
Fasting insulin				X			X		X	X	

Assessments	Screening	TG Qualifying Period		26-week Double-Blind Treatment Period						Early Termination Visit	Contact follow-up[b]
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-8 or -6**	**-2**	**-1**	**0**	**4**	**11**	**12**	**18**	**26**		**30**
Visit Window (days)		**±2**	**±2**	**-1/+5**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**-2/+3**	**n/a**	**+6**
Fasting lipids[d]	X	X	X	X	X	X	X	X	X	X	
Biomarkers[e]				X			X		X	X	
Total plasma EPA and DHA, OM3 index, AA, omega-6/omega-3, EPA/AA				X	X		X	X	X	X	
Serum sample for storage[f]				X			X		X		
Randomization[g]				X							
Dispense study medication				X	X		X	X			
Study medication compliance assessment					X		X	X	X	X	
Diet counseling	X	X	X	X	X	X	X	X	X	X	
Physical activity and dietary compliance assessment		X	X	X	X	X	X	X	X	X	

[a] If a subject's average TG level from Visit 2 to Visit 3 falls outside the required range for entry into the study, an additional TG measurement can be made 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study is to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

[b] A follow-up contact (either at a clinic visit or by any remote contact such as a telephone call or email) to assess for additional AEs and to confirm that follow up care has been arranged for dyslipidemia is required approximately 4 weeks after Final Visit (Visit 9 or early termination).

[c] A urine sample may be collected for an optional urine pregnancy test (test strip).

[d] Includes TG, TC, HDL-C and calculated non-HDL-C at all visits. Direct LDL-C will be obtained at all study visits Additionally, LDL-C and VLDL-C will be measured by ultracentrifugation (β quantification) at Visit 3, 4, 6, 7, and 9. RLP-C will be calculated as TC – LDL-C – HDL-C using ultracentrifugation (β quantification) measurements.

[e] Includes, Apo AI, Apo B, Apo CIII, Apo A5, hsCRP, Lp-PLA2, Lipoprotein particles concentration and size, and oxidized LDL-C.

[f] Serum samples to be stored for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk.

[g] All subjects will be expected to complete all planned study assessments post randomization regardless of adherence to study medication and use of subsequent rescue therapies.

4.2 Discussion of Study Design

The study is a Phase 3, randomized, double-blind, placebo-controlled, 2-arm parallel group (CaPre 4 g vs placebo), multi-center study. All subjects will take an oral, single dose of 4 g (4 capsules) a day at a meal.

A 12-week double-blind design has been previously used to characterize the efficacy and safety of other OM3 drugs (Vascepa and Epanova) in patients with severe hypertriglyceridemia and was deemed acceptable by the FDA.[11,12] In this proposed Phase 3 study, the TG change from baseline to week 12 is defined as the primary endpoint to allow comparison with other studies with OM3 drugs in severe hypertriglyceridemia; however, the double-blind period has been extended to 26 weeks to better characterize the persistence of the effect of CaPre on the TG profile.

Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- or 6-week diet,lifestyle and medication stabilization period, subjects will enter a 2- or 3-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.

Subjects with severe hypertriglyceridemia who are randomized to placebo are at risk for experiencing elevations in TG levels and at risk of developing pancreatitis. In the MARINE study (Vascepa), elevation in TG level in excess of 2000 mg/dL occurred in only 1 subject out of 76 in the placebo group and none in either the 2 or 4 g treatment groups.[13] All subjects in this study will continue to receive diet counselling.

4.3 Selection of Study Population

4.3.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Subjects ≥18 years of age.
2. Isolated hypertriglyceridemia or mixed hyperlipidemia, with TG ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated or not with a stable dose of statin, CAI, PCSK9I, fibrate, or a combination of these agents.

   If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening.

   If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of statin and/or CAI at time of screening.

If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of of a statin and/or CAI at time of screening.

3. Willingness to aim to maintain physical activity level and diet consistent with NCEP-TLC and to reduce added sugars intake throughout the study.

4. Be informed of the nature of the study and give written consent prior to any study procedure.

4.3.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. Allergy or intolerance to OM3 fatty acids, OM3-acid ethyl esters, OM3 phospholipids, fish, shellfish or any components of the study medication (HPMC, corn starch (placebo)).

2. Subjects diagnosed with Familial Chylomicronemia Syndrome (FCS).

3. Subjects with lysosomal acid lipase deficiency.

4. Body mass index (BMI) greater than 45 kg/m^2.

5. Subjects who are pregnant, lactating, and subject of childbearing potential who are either planning to become pregnant or who are not using acceptable birth control methods during study participation. Subjects of childbearing potential are subjects who have experienced menarche and do not otherwise meet the criteria for women not of childbearing potential, defined as:

   - Subjects who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation).

   or

   - Subjects who are postmenopausal, i.e., who have had a cessation of menses for at least 12 months without an alternative medical cause. A follicle stimulating hormone (FSH) test ≥40 mIU/mL may be used to confirm the post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

   Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study and for 8 weeks following the last dose of study medication.

6. Subjects taking tamoxifen, estrogens, progestins, or other medications or nutritional supplements with mechanisms modifying estrogen or progestogen pathways, who have had dosage changes within4 weeks prior to Visit 1.

7. Use of oral or injected corticosteroids or anabolic steroids within 6 weeks prior to randomization.

8. History of pancreatitis within 6 months prior to Visit 1.

9. History of symptomatic gallstone disease within the last 5 years, unless treated with cholecystectomy.

10. Diabetics requiring changes in glucose-lowering medication within 6 weeks prior to Visit 1 (other than short acting insulin dosage adjustments) or who have HbA1c greater than 9.5% at Visit 1.

11. Subjects with clinical evidence of hyperthyroidism or TSH level less than lower limit of normal (LLN) at Visit 1. Subjects diagnosed with hyperthyroidism must be treated with medication for at least 6 weeks prior to Visit 1.

12. Uncontrolled hypothyroidism or TSH level more than 1.5 × upper limit of normal (ULN) within 6 weeks prior to Visit 1.

13. Thyroid hormone replacement therapy that has not been stable for more than 6 weeks prior to Visit 1.

14. History of cancer (other than basal cell carcinoma) within 2 years prior to Visit 1.

15. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, exacerbation of congestive heart failure requiring hospitalization or a change in treatment), life-threatening arrhythmia, or revascularization procedure within 6 months prior to Visit 1.

16. Use of other prohibited drugs: weight loss prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids. Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.

17. Use of any lipid-altering drug agents, other than statins, CAI, PCSK9I or fibrate, including niacin at a dose greater than 200 mg/day, , bile acid sequestrants, OM3 drugs (e.g., Lovaza

or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued at least 8 weeks prior to randomization.

18. Resection of an aortic aneurysm or endovascular aortic repair within 6 months prior to Visit 1.

19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily.

20. Poorly controlled hypertension (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥100 mmHg). Subjects with hypertension adequately controlled with medication are eligible provided that their antihypertensive therapy has been stable for at least 4 weeks prior to Visit 1.

21. Recent history (within past 12 months prior to Visit 1) of drug abuse or alcohol abuse, or alcohol use greater than 2 units per day (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks).

22. Hepatobiliary disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × ULN; if ALT/AST is >3 × ULN, the levels must have been stable for 3 months prior to Visit 1.

23. Severe renal disease as defined by less than 30 mL/min serum creatinine clearance calculated using the Cockcroft-Gault formula.

24. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) international normalized ratio (INR) of ≥1.5. Subjects using warfarin [Coumadin®] or heparin are allowed. Subjects receiving other anticoagulants dabigatran, rivaroxaban, or apixaban are allowed. Subjects receiving acetylsalicylic acid (ASA) alone or in combination with other anti-platelet agents (e.g. clopidogrel, prasugrel, ticagrelor) are also allowed.

25. Unexplained creatine kinase concentration 3 × ULN.

26. Creatine kinase elevation owing to known hereditary or acquired muscle disease.

27. Exposure to any investigational product, within 4 weeks prior to Visit 1.

28. Presence of any other condition (such as severe pulmonary, gastrointestinal, or immunologic disease) the Investigator believes would interfere with the subject's ability to

provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

29. Any life-threatening disease expected to result in death within 2 years, require frequent hospitalizations, extensive surgery, or changes in medications or diet.

4.3.3 Subject Restrictions

The following restrictions may affect subject participation in this study:

- Availability to attend visits according to the protocol.
- Subjects must be willing to aim to maintain physical activity level and diet consistent with NCEP-TLC, and reduce intake of added sugar throughout the study.
- Concomitant medication restrictions as described in Section 5.8.1.
- Fasting for at least 9 hours prior to visits which include lipid profiles and routine safety laboratory assessments.
- Subjects of child-bearing potential must remain abstinent or must use an acceptable method of contraception during the study and for at least 8 weeks following the last dose of study medication. Acceptable methods of contraception are:
    - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
    - intrauterine device (IUD);
    - intrauterine hormone-releasing system (IUS);
    - vasectomised partner (provided that partner is the sole sexual partner and that the vasectomised partner has received medical assessment of the surgical success);
    - Any combination of male condom with either cap, diaphragm or contraceptive sponge used with spermicide (double barrier methods). The proper use of cap, diaphragm or contraceptive sponge includes the use of spermicide and is therefore considered one barrier method.
- Restricted alcohol intake (≤2 units per day) (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks).

4.3.4 Subject Withdrawal or Termination

All subjects are free to withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, specified or unspecified,and without prejudice to further treatment. Withdrawal of study medication does not mean the subject is automatically withdrawn to continue in the study. However, site personnel will discuss their reasons with subjects who express a desire to terminate participation to determine their reasons and categorize them into one of the following categories:

Non-adherers – Subjects who discontinue receiving the study medication but agree to allow some or all data collection through the planned duration of the trial. If a subject discontinues from the study medication for any reason, all efforts will be made to have them continue in the study; all visits and scheduled procedures, including efficacy and safety evaluations, should be performed unless the subject also withdraws informed consent to participate in the study (see Non-completers). If the subject does not consent to continuing with all planned study evaluations, the subject should be offered a reduced schedule of assessments with priority given to the assessments related to the primary efficacy endpoint, secondary endpoints, and safety follow-up.

If a subject who discontinues study medication does not return for a scheduled visit, every effort should be made to contact the subject. It is expected that most subjects categorized as non-adherers will allow collection of at least some follow-up efficacy and safety data, and the site should attempt to record as much follow up data as the subject will allow. Regardless of the reason, discontinuation of study medication does not mean the subject has automatically withdrawn consent to continue in the study.

Possible reasons for discontinuation of study medication are:

- The subject is unwilling to continue adherence to the study medication regimen.
- The investigator may decide to stop study medication if an intolerable AE, a clinically significant laboratory value, or other medical condition or situation such that continued intake of study medication would not be in the best interest of the subject. Appropriate medical measures are to be taken, and the Sponsor or Sponsor designee is to be notified immediately.
- The subject becomes pregnant (see Reporting of Pregnancy 6.2.1.4).

Non-completers – Non-completers are subjects who decline to continue any further study medication, study visits or to allow the site to obtain any further safety or efficacy information on their status. These subjects will have given true withdrawal of consent and are expected to be rare. Subjects who wish to discontinue from the study should have early termination

assessments performed as shown in the Schedule of Events (Table 1). Permission should be asked of the subjects to allow a final contact approximately 4 weeks later to review interval history for safety events. This may be done either at a clinic visit or by any remote contact such as a telephone call or email.

The site should continue efforts to contact subjects who are Lost to Follow-Up. Only at the end of the study should such subjects be termed "Non-completers".

Subjects who die during the study are considered to have completed the study. They are neither Non-adherers nor Non-completers. An SAE report with outcome of death is expected.

Possible reasons for discontinuation from the study are:

- The investigator may decide to terminate a subject' participation in the study if an intolerable AE, a clinically significant laboratory value, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Appropriate medical measures are to be taken accordingly, and the Sponsor or Sponsor designee is to be notified immediately.

- Complete withdrawal of informed consent for participation in the study. If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected.

- The subject becomes pregnant and termination of participation in the study is considered by either the subject or the Investigator in the best interest of the subject (see Reporting of Pregnancy 6.2.1.4).

- Subject is Lost to Follow-up. If the subject is lost to follow-up, the Investigator should attempt to contact the subject until the last scheduled visit.

- The Investigator or the Sponsor, for any reason, terminates the study.

The inclusion and exclusion criteria are to be followed explicitly. If a subject who does not respect one or the other criterion is inadvertently randomized, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator. Subjects may continue study medication if both the Medical Monitor and the Investigator agree that no undue risk is involved and the patient still has the potential for benefit. In this case, the subject will be categorized as a protocol deviation. If there is no agreement that the subject should continue in the study as planned, study medication will be discontinued and the subject will be considered a Non-adherer. Such subjects should still follow the schedule of events or, in the

least, to allow a final contact at the time of study completion, unless they elect to become Non-completers.

Subjects categorized as Non-adherers or as Non-completers of the study will not be replaced.

4.3.5 Subject Re-screening

Re-screening of certain screening failure subjects may be allowed under certain circumstances, at least 3 months after initial enrollment and only after discussion with and approval by the Medical Monitor. The following situations may give rise to re-screening:

- If a subject consents to participate, otherwise meets the eligibility criteria, but is not able to continue in the study prior to randomization due to an unforeseen change in personal situation;
- If a subject failed one or the other eligibility criterion during the stabilization or TG qualification period due to i) an acute event that has resolved ii) a medical cause or condition that has been adequately treated or for which time has sufficiently elapsed since occurrence;
- To allow time for stabilization or wash-out following initiation or dose changed of allowed or prohibited medications, as the case may be, at time of screening or during the TG qualification period;

Subject who failed to meet the eligibility criteria and do not otherwise fall into the above situations should not be considered for re-screening. Specifically, subjects who fail to meet the average TG inclusion level will be considered screening failure, and re-screening of these subjects will not be allowed. Also, subjects that are randomized and withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, are not eligible for re-screening.

In case of re-screening, all study screening procedures must be repeated, including the requirement for subjects to give new consent. Re-screened subjects will be allocated a new subject identification number. For each subject that is eligible for re-screening, only one re-screening is permitted.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Study medication will consist of HPMC capsules (size 000) that are identical in external appearance, containing 1 g of either CaPre or matching placebo (corn starch).

Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day at a meal.

5.2 Identity of Study Medication

CaPre is a krill oil-derived mixture of polyunsaturated fatty acids (PUFAs), primarily composed of OM3 fatty acids, principally EPA and DHA, present as a combination of phospholipid (PL) esters and free fatty acids (FFA).

CaPre is supplied as a 1-gram capsule (size 000) for oral administration. Each 1 gram capsule of CaPre contains approximately 310 mg of the sum of EPA and DHA (expressed as free fatty acids).

CaPre capsules also contain the following naturally occurring product-related substances and inactive ingredients:

- Other PUFAs (Omega-6 and 9), saturated and monounsaturated fatty acids, phospholipids;
- 4 mg α-tocopherol / g of total fat (added as an antioxidant);
- Components of the capsule shell (HPMC).

The matching placebo is composed of partially pregelatinized corn (maize) starch supplied as 1-gram capsule (size 000). Corn is not regarded as a source of gluten which may cause sensitivity in people with celiac disease or with non-celiac hypersensitivity. The product that is used in the composition of the placebo has not come into contact with cereals containing gluten (such as wheat, rye, barley, and oats).

Table 2 Study Medication

Study Medication	Dosage form and strength	Manufacturer
CaPre	1 g capsule	Acasti Pharma Inc.
Placebo	1 g capsule	Acasti Pharma Inc.

Study medication must be stored between 15-25°C (59-77°F). Documentation of temperature monitoring should be maintained.

5.3 Packaging and Labelling

During the double-blind period, capsules of 1 g CaPre and 1 g placebo will be provided by the Sponsor in white opaque Aclar® PVC/Aluminium blister packs, providing multiple complete daily regimens (4 capsules per day) in accordance with treatment allocation. The contents of each capsule will not be disclosed to either the subject or study center personnel (i.e. double blind).

5.4 Method of Assigning Subjects to Treatment Group

After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening (V1). At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the TG qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT. Once randomized, the site will be provided by the IRT with the corresponding study medication kit to be dispensed to the subject at Visit 4. Similarly, the corresponding study medication kit to be dispensed to the subject at subsequent study visits will be provided the study center through the IRT.

Subjects will be randomized to CaPre or placebo via stratified randomization. The randomization stratification factors are: qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI, or PCSK9I, alone or in combination, at randomization (currently treated or not currently treated with statin, CAI, or PCSK9I, alone or in combination).

The randomization code for treatment assignment will be held by the IRT vendor.

5.5 Selection of Doses in the Study

Doses selected for this study are CaPre 4 g per day compared to matching placebo. The choice of these doses is supported by work with already marketed OM3 drugs, as well as pre-clinical and clinical studies with NKPL66 (the active ingredient of CaPre capsules) showing significant reduction in TG levels and non HDL-C without deleterious effect on LDL-C primarily at 4 g a day without safety concern in patient with mild to severe HTG. (please refer to Section 2 and the CaPre Investigator's Brochure for preclinical and clinical information about CaPre).

At present, several OM3 drugs are approved in the US for severe hypertriglyceridemia: Lovaza (EPA and DHA as ethyl esters), Vascepa (EPA as ethyl esters), Epanova (EPA and DHA as FFA), Omtryg (EPA and DHA as ethyl esters), and 4 generic versions of Lovaza (EPA, DHA

as ethyl esters). All these products are approved for use at 4 g/day that provide between 3000 to 3840 mg per day of EPA alone or in mixture with DHA, except for Epanova which is also approved at 2 g/day providing 1500 mg of EPA and DHA.

5.6 Selection and Timing of Dose for Each Subject

Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I , alone or in combination at randomization (currently treated vs not currently treated).

All subjects will take four capsules, once a day, at a meal:

• CaPre Group: 4 x 1 g capsules CaPre; or

• Placebo Group: 4 x 1 g capsules placebo (corn starch).

If a subject forgets to take the capsules, they should be instructed to take them on the same day with the next meal; however, no more than one dose (4 capsules) should be taken per day.

5.7 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. CaPre and placebo capsules will be identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor, or CRO. The treatment codes will be held by the IRT vendor.

The process for breaking the blind will be handled through the IRT. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management, and after a consultation with the Medical Monitor. Any center that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the subject in question.

The Sponsor must be notified immediately if a subject and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and electronic case report forms (eCRFs).

In addition to treatment blinding, the Investigator will also be kept blind to the fasting serum lipid assessments made during the course of the study after randomization. Except for TG (see Section 5.9), no alerts have been defined for other lipid assessments (e.g. LDL-C) due to the

short study duration and to minimize changes in lipid therapy that are not allowed post randomization .

5.8 Prior and Concomitant Treatments

5.8.1 Excluded Medications

Medications and treatments that are prohibited during the study must be discontinued at Visit 1 unless otherwise stated:

- Any lipid-altering drug agents (other than statins, CAI, PCSK9I, or fibrate alone or in combination; see below) including niacin at a dose greater than 200 mg/day, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued 8 weeks prior to randomization.

  Case of Plant sterols/stanols and Soluble Fibers:
  Because plant sterols/stanols (up to 2 grams per day) and/or soluble fibers (up to 25 grams per day) may be recommended as part of the NCEP-TLC diet, these products taken in the form of powder or supplements are allowed provided they are already consumed at a stable dose prior to screening or are initiated at screening and their intake remains stable throughout the study. Subjects should not discontinue these products during the study.

- Oral or injected corticosteroids or anabolic steroids
- Prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide.
- HIV protease inhibitors
- Cyclophosphamide
- Isotretinoin
- Investigational products must be discontinued at least 4 weeks prior to Visit 1

5.8.2 Allowed Medications

Any herbal products, dietary supplements, or medications started before the informed consent and ongoing at time of screening (V1) must be reported on the appropriate page of the eCRF. Any herbal products, dietary supplements, or medications listed in one or the other inclusion

or exclusion criterion and that was stopped during the 60 days preceding screening (V1) should also be documented.

The generic names of the herbal products, dietary supplements, or medications (or trade names for combination) must be specified along with the total daily dose and duration of treatment.

The following herbal products, dietary supplements, or medications cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:

- Statins, CAI (e.g., ezetimibe), PCSK9I or fibrate, alone or in combination:

  Subjects already regimented with a statin and/or CAI prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization

  Subjects who initiate or change dose of a statin and/or CAI treatment initiation or dose change at Visit 1 must be on stable dose at least 8 weeks prior to randomization.

  PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.

  Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).

- Tamoxifen, estrogens, or progestins must be stable for at least 4 weeks prior to Visit 1.
- Thyroid hormones must be at doses stable for at least 6 weeks prior to Visit 1
- Antidiabetic drugs must be at doses stable for at least 6 weeks prior to Visit 1. Short acting insulin dosage adjustments are allowed.
- Antihypertensive drugs must be at doses stable for at least 4 weeks prior to Visit 1

Wherever possible and unless deemed unsafe, subjects receiving such medication should continue with the same dose, and discontinuation during the study should be avoided.

The following herbal products, dietary supplements or medications are also allowed during the study:

- Niacin <200 mg/day

- Local, topical, inhaled, or nasal corticosteroids
- Plant sterols/stanols (up to 2 grams per day) and/or soluble fibers (up to 25 grams per day); as long as stable doses during the study (see above).

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Any changes in allowed medication being taken at the beginning of the clinical study must be recorded in the eCRF.

5.9 Rescue Medication

Due to a possible increased risk of pancreatitis, any TG value greater than 1500 mg/dL should initiate a blinded alert to the site, and require clinical and laboratory follow-up within a week. If the subject's TG level is still above 1500 mg/dL after follow up, it does not mean the subject is automatically withdrawn of study medication or to continue in the study. Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication selected by the PI or dose adjustment of fibrate (or another current medication), as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.

Consistent with Section 4.3.4, all efforts should be taken to have these subjects continue in the study; all visits and scheduled procedures, including efficacy and safety evaluations, should be performed unless the subject withdraws informed consent to participate in the study.

5.10 Treatment Compliance

The prescribed daily dose, frequency and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.

At each visit, prior to dispensing study medication, previously dispensed study medication will be retrieved by the Investigator and compliance assessed. Subjects exhibiting poor compliance, as assessed by capsule counts, should be counseled on the importance of good compliance with the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of study medication during any evaluation period (visit to visit).

After randomization, at subsequent visits 5, 6, 7, 8 and 9, subjects should be instructed not to take their daily dose before attending the visit.

5.11 Study Medication Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication. These records must be available for inspection at any time.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study medication supplies and packaging materials are to be inventoried and prepared for return or destruction by the Investigator. The Investigator is not to return or destroy unused clinical drug supplies or packaging materials without authorisation.

6.0 EFFICACY AND SAFETY ASSESSMENTS

6.1 Efficacy

6.1.1 Primary Efficacy

The primary efficacy endpoint will be the percent change in fasting TG levels from baseline to Week 12 in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L).

Baseline is defined as the average of the 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to Visits 2, 3, and 4, or Visits 3, 3.1, and 4 in case an additional TG measurement was necessary during qualification). The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart that is Visit 6 (Week 11) and Visit 7 (Week 12).

6.1.2 Secondary Efficacy

The secondary efficacy endpoints for this study are (listed in order of importance for the control of type I error: :

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification)
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

6.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for this study are:

- Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 18 and Week 26) in TG (persistence of the effect of CaPre on TG).
- Proportion of subjects with a fasting TG level below 500 mg/dL (<5.7 mmol/L) at Week 12 and at Week 26

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and Week 12) and Week 26 in TC.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and Week 26 in RLP-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) and to Week 26 in LDL-C (β-quantification) and VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 26 in non-HDL-C and HDL-C
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in apo B, apo A1, apo B/apo A1 ratio, apo CIII, and apo A5.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in lipoprotein particles concentration and size (LDL, non-HDL, HDL-C, IDL and VLDL).
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in oxidized LDL-C.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in FSG, insulin and HbA1c.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in HOMA-IR and HOMA-β.
- Percent change from baseline (Week 0) to Week 12 and to Week 26 in hs-CRP and Lp-PLA2.

6.1.4 Exploratory PK Endpoints

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in OM3 Index.
- Change and percent change from baseline (Week 0) to Week 12 and to Week 26 in AA, omega6/omega3 and EPA/AA ratios.

6.2 Safety

6.2.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study stabilization/qualification, treatment or follow-up period.

Definition of AE: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Definition of SAE: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study medication or not) that at any dose:

- Results in death.
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia, or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

Each AE is to be evaluated for duration, intensity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Intensity

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

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Relationship

The causal relationship between the study medication and the AE will be characterized as unrelated, unlikely related, possibly related, probably related, or related.

Events can be classified as "unrelated" if there is not a reasonable possibility that the study medication caused the AE.

An "unlikely" relationship suggests that only a remote connection exists between the study medication and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.

A "possible" relationship suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.

A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and that other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.

6.2.1.1 Reporting of Adverse Events

All AEs, regardless of intensity and whether they occurred during the study stabilization/qualification, treatment or follow-up period, are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF. The Investigator should complete all the details requested including dates of onset, intensity, action taken, outcome and relationship to study medication. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study medication, must be reported immediately (within 24 hours of the study

center's knowledge of the event) to the Sponsor or designee. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. The primary mechanism for reporting an SAE will be the electronic data collection tool, or eCRF. If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool provided by the Sponsor or designee (instructions will be provided on the paper tool). The study center will enter the SAE data into the electronic system as soon as it becomes available.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, including those ongoing after the follow-up period of 28 days planned after the final visit (or early termination) (see 4.1.8) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Non-serious AEs still ongoing after the follow-up period will not be additionally followed and the outcome at time of last contact will be reported in the study database.

The eCRF planned for this study will include programming to provide an alert to the Sponsor and study Medical Monitor for any reported SAE. The reports will be recorded in a study-specific safety database, reconciled with eCRF data, and reported in the clinical study report.

All SAEs source data will be recorded in center source documents. Criteria for documenting the relationship to study medication as well as intensity and outcome will be the same as those previously described.

6.2.1.2 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor or CRO of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or CRO. The Sponsor or CRO will ensure that the appropriate regulatory authorities are notified of all reportable SAEs.

6.2.1.3 Follow-up of Adverse Events

Any AEs observed from screening up to the end of the study will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

All SAEs that are spontaneously reported within 4 weeks of a subject's termination from the study are to be collected and reported as previously described.

6.2.1.4 Reporting of Pregnancy

If conception occurs during the study treatment period, study medication must be discontinued immediately. The Investigator must report the pregnancy by faxing the Pregnancy Notification and Outcome Form within 24 hours of the study site staff becoming aware of the pregnancy, at the country-specific fax number listed in the Study Reference Manual. With subject's consent, the investigator must report the outcome of the pregnancy to document if a congenital abnormality/birth defect in the offspring of study subjects has occurred.

6.2.2 Clinical Laboratory Evaluations

Laboratory assessments will be conducted at a central laboratory. Blood and urine samples will be taken at the times indicated in the Schedule of Events (Table 1).

The following clinical laboratory tests will be performed as specified in Table 3, in accordance with the Schedule of Events (Table 1).

Table 3 Laboratory Assessments

Hematology (Visit 1, 4, 5, 7 and 9[1])	**Clinical Chemistry** (Visit 1, 4, 5, 7 and 9[1])	**Lipids (fasting)** (All study Visits)	**Biomarkers** (Visit 4,7 and 9[1])
Hemoglobin	Albumin	Triglycerides (TG)	AA
Hematocrit	ALP	Total cholesterol (TC)	Apo AI
Erythrocyte count	ALT	non-HDL-C	Apo B
Leukocyte count	Amylase	HDL-C	Apo CIII
Leukocyte differential count (including neutrophils, lymphocytes , monocytes , eosinophils and basophils)	AST	LDL-C (direct) *	Apo A5
	GGT	IDL	Lp-PLA2
	Bilirubin, Total	VLDL-C*	hsCRP
	Lipase	RLP-C	Lipoprotein (particles concentration & size)
Platelet count	Urea Nitrogen/Urea		
MCV	Uric acid		oxidized LDL-C
MCH	Creatinine	**Urinalysis ****	omega 6 FA
MCHC	Creatine Kinase (CK)	(Visit 1, 4, 5, 7 and 9[1])	omega 3 FA
RDW	Calcium	Color	
	Chloride	Clarity/Appearance	**Pharmacokinetics**
	Magnesium	Specific gravity	DHA, EPA
Coagulation	Glucose	pH	(Visits 4, 5, 7, 8 and 9[1])
(Visit 1, 4, 5, 7 and 9[1])	Potassium	Glucose	
PT	Sodium	Blood (includes erythrocytes)	**Omega 3 Index**
INR	Bicarbonate	Protein	(Visit 4, 5, 7, 8 and 9[1])
aPTT		Leukocyte Esterase	
	Pregnancy test (SOCBP, serum testing at Visit 1)	Ketones	**Thyroid Function**
Other analytes		Nitrites	(Visit 1)
Hepatitis B and C (Visit 1)	FSH (as required for post-menopausal subjects only)	Bilirubin	TSH
		Urobilinogen	T_4
HbA1c (Visit 1,4, 7 and 9)		Creatinine	
Insulin (fasting) (Visit 4,7 and 9)	Creatinine Clearance and estimated Glomerular Filtration Rate (eGFR) (calculated at Visit 1, 4, 5, 7 and 9)	Proteinuria (estimated by urine protein/creatinine ratio - UPCR) (calculated at Visit 1)	

[1] All laboratory assessments required at visit 9 will also be made at the Early Termination Visit.
* LDL-C and VLDL-C to be also obtained via Beta (β) quantification at Visit 3,4,6,7 and 9.
**Urine Microscopy will be performed if blood, protein, leukocyte esterase, and/or urobilinogn is abnormal

TG levels will be closely monitored in all subjects throughout the treatment and safety follow-up periods. All trial personnel including site monitors, the CRO and Sponsor representatives, and site staff will be blinded to TG results throughout the trial. The central laboratory will notify the Investigator and the study Medical Monitor as soon as possible in the event that a subject's TG level is >1500 mg/dL (see Section 5.9).

Also, note that all trial personnel including site monitors, the CRO and Sponsor representatives, and site staff will be blinded to all lipids, biomarkers, Omega 3 Index and EPA, DHA results throughout the trial.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE.

An abnormal laboratory value should be deemed clinically significant, and reported as an AE, if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change dose, add or discontinue a concomitant medication, discontinuation of the study medication, close observation, more frequent follow-up assessments, or further diagnostic investigation.

6.2.2.1 Laboratory Re-testing

Request for re-testing (i.e. requiring a new blood sample) of certain clinical laboratory tests may be allowed in special circumstances and only after discussion with and approval by the Medical Monitor.

6.2.3 Vital Signs, Physical Findings, and Other Safety Assessments

6.2.3.1 Vital Signs

Vital signs evaluation should be performed before collecting laboratory samples. Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (°C) and respiratory rate for a minimum of 30 seconds will be measured at all visits. Subjects should be comfortably seated for at least 2 minutes prior to blood pressure, pulse and respiratory rate readings.

6.2.3.2 Height, MI and Weight

Height (without shoes) will be measured at Visit 1 only. Weight (light clothing, no shoes) will be measured at all visits, with the exception of Visits 3 and 6.

Body mass index (BMI) will be calculated.

6.2.3.3 Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Subjects should not hold their breath while waist circumference is being measured.

6.2.3.4 ECG

A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination. ECG assessment should be performed before collecting laboratory samples.

ECG assessment will be performed in supine position after at least 2 minutes rest. The parameters of HR, PR interval, QRS interval, and QT interval will be recorded.

No cardiac safety AEs, and in particular cardiac repolarization (significant change in QTc interval) AEs, have been previously reported by subjects on CaPre. QT intervals will be corrected and reported using both Bazett's and Fridericia's formulas. For purposes of clinical study conduct, Bazett's QT correction will be used. For purposes of data analysis, Fridericia's QT correction will be considered as primary.

Any significant change occurrence shall result in notification by the Investigator to the study Medical Monitor for immediate review of the tracings and discussion with Sponsor. Significant findings should be reported as AEs or SAEs, as appropriate.

6.2.3.5 Physical Examination

A complete physical examination (including general appearance, head, skin, neck(including thyroid), eyes/ ears,/ nose,/ throat, chest,/ lungs, heart, abdomen, back, lymph nodes, extremities and neurologic system evaluations) will be performed at Visit 1.

A brief physical examination (general appearance, lungs, heart, abdomen evaluation) will be performed at all visits with the exception of Visit 1, Visit 3/3.1, and Visit 6

6.2.4 Safety Monitoring

This study will not implement a Data Safety Monitoring Board. A Medical Monitor will be appointed to provide medical expertise to advise the study investigators and to monitor participant safety. Medical Monitoring will include :

- availability to advise the investigators on trial-related medical questions or problems (e.g. eligibility criteria, study procedures, patient continuation and discontinuation);
- routine safety monitoring of the study, including review of individual laboratory value;
- medical review of all SAEs throughout the trial;
- medical review of efficacy and safety listings (including coded listings), and patient profiles for appropriateness and consistency;
- aggregate review of blinded clinical data;

The Medical Monitor will remain blinded throughout the conduct of the clinical trial.

6.3 Pharmacokinetics

Blood samples for EPA and DHA Total Lipids will be obtained at Visit 4 (Baseline), prior to first study medication dose. Additional samples will be obtained at Visit 5 (Week 4), Visit 7 (Week 12), Visit 8 (Week 18) and Visit 9 (Week 26), and as applicable at Early Termination.

Details about the procedure will be described in the study laboratory manual. Details about the OM3 index procedure will also be described in the manual.

6.4 Health Outcomes

Not applicable.

6.5 Pharmacogenetics

Not applicable.

6.6 Appropriateness of Measurements

The efficacy and safety assessments are standard assessments and deemed to be reliable, accurate and relevant for this indication and patient population.

The primary efficacy endpoint of change in fasting TG levels is both a standard means of assessing the efficacy of treatment and is a laboratory measurement that is a direct cause of adverse outcomes, including risk of pancreatitis and cardiovascular events. To increase the

robustness of the endpoint and to minimize the natural variation in TG levels, the endpoint will be based on the average of three values at baseline and two values at the primary endpoint duration of 12 weeks.

The persistence in the TG reduction will be explored up to 26 weeks and will address the issue of durability of effect observed at 12 weeks.

The additional endpoints of change in non-HDL-C, VLDL-C, HDL-C, LDL-C, TC, and RLP-C at 12 and 26 weeks are all reflective of overall expected effect of CaPre on lipid metabolism.

The endpoint that compares the proportion of patients in each treatment group that achieve a level of fasting TG below 500 mg/dL is a categorical measure that reflects the drug effects on reducing TG below the threshold, which is generally accepted as the primary target for such therapy in patients with severe hypertriglyceridemia to prevent the risk of pancreatitis.

Other endpoints of change from baseline of different apolipoproteins (apo A1, apo A5, apo B, apo CIII, apo B/apo A1), lipoprotein particles concentration and size, inflammatory (Lp-PLA2, hs-CRP), glycemic profile (FSG, insulin, HbA1c, HOMA), and other marker (oxidized LDL) will document the effect of the study medication on a variety of biomarkers associated with the atherogenic effects of hypertriglyceridemia.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness and reliability of the data:

- Investigator meeting(s).
- Central laboratories for clinical laboratory parameters.
- Study center initiation visit.
- Early study center visits post-randomization.
- Regular study center on-site and remote monitoring during study.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, the Sponsor and/or CRO Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study centers, central laboratories, vendors, clinical database and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

An adaptive approach to clinical trial monitoring will be utilized. This is initiated by an assessment of the risk associated with the trial combined with an assessment of critical data and processes. A Risk Assessment Mitigation Plan and Integrated Project Management Plan collectively document the strategies involved with the implementation of onsite, remote and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to safety patient and data quality. Trial oversight is achieved by regular

review of a report of risk which then influences any required changes to the monitoring strategy.

The Sponsor will engage the services of a CRO to perform monitoring functions within this clinical study. The CRO's monitors will work in accordance with the CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also assess adherence to the protocol at the study center. They will verify the supply of study medication and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each study center while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification).

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of the CRO.

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain

information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records, unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events and medical histories will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary.

7.3 Quality Assurance Audit

Study centers, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or CRO on behalf of Acasti Pharma Inc. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICS

8.1 Determination of Sample Size

The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/dL; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The primary estimand in this study is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. All subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. The null hypothesis is that the percent change from baseline in fasting TG level in the CaPre 4 g group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline in fasting TG level in the active group is NOT the same as that in the placebo group.

It is anticipated that the overall treatment discontinuation rate in this study will not exceed 15% and will be approximately equal in the two treatment groups. Given that subjects may initiate subsequent rescue therapies after an early discontinuation of the study treatment and that their outcomes will be measured at Week 11 and/or 12 under the effect of rescue, the following assumptions regarding the median percent reduction in fasting TG levels from baseline to Week 12 are used in sample size calculations.

- Placebo group: 10% median reduction from baseline in subjects who complete the study on placebo and 25% median reduction from baseline in placebo subjects who discontinue the study treatment early and are rescued. This corresponds to an overall median percent reduction from baseline of approximately 12% in the placebo group based on the assumption that 85% of subjects will complete the study on placebo and 15% placebo subjects will be rescued.
- CaPre 4 g group: two scenarios will be considered with 32% and 37% median reduction from baseline, respectively. Completers and rescued subjects in the CaPre

4 g group are assumed to have a similar median percent reduction from baseline to Week 12. The two scenarios will correspond to an overall median treatment difference between the CaPre 4 g group and placebo of 20 and 25 percentage points, respectively.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a median difference of at least 20 percentage points in percent decrease from baseline to Week 12 in TG between CaPre and placebo assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05, based on a non-parametric Wilcoxon-Mann-Whitney test. The overall median treatment difference of 20 percentage is believed to be clinically relevant.

The table below shows the estimated power for four scenarios, 20 and 25 percentage points median differences between treatment groups and two settings of common standard deviation (40% and 45%), considering an unbalanced treatment allocation ratio of 2.5:1 with 175:70 subjects randomized (CaPre:placebo). These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia). Power calculations are provided under two assumptions regarding the underlying distribution of the primary variable: lognormal and normal.

Table 4 Sample Size Estimation

Sample size per group (CaPre:placebo)	Placebo-corrected treatment effect (overall median treatment difference)	Common standard deviation	Overall Type I error (two-sided)	Power (lognormal distribution)	Power (normal distribution)
175:70	20 percentage points	40%	0.05	>95%	92%
175:70	25 percentage points	40%	0.05	>95%	98%
175:70	20 percentage points	45%	0.05	>95%	87%
175:70	25 percentage points	45%	0.05	>95%	96%

Note: The sample size calculation is performed based on a Wilcoxon-Mann-Whitney test using SAS V9.4, Proc POWER.

8.2 Statistical Methods

A description of the statistical methods to be used to analyze the key efficacy and safety endpoints is outlined below. Detailed statistical methodology for the planned analyses will be provided in the Statistical Analysis Plan (SAP) that will be finalized prior to database lock and treatment unblinding. Any deviations from the planned analysis specified in the SAP will be described with justification in the final clinical study report.

Continuous data will be summarized descriptively using the number of observations, means, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. All tests of treatment effects will be

2-sided, unless otherwise specified. Individual subject data will be presented in listings. All analyses, summaries and listings will be performed using SAS® software (version 9.1 or higher).

8.2.1 Analysis Populations

The following analysis populations will be used in this trial. Classification into Safety, Per-Protocol (PP), and Intent-to-Treat (ITT) Populations will be conducted prior to the database lock.

Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) Population is defined as all randomized subjects. Following the ITT principle, subjects will be analyzed according to the treatment to which they are randomized regardless of any departures from the original assigned group.

Per-Protocol (PP) Population

The per-protocol (PP) Population is defined as all subjects from the ITT Population who did not have major protocol deviations. Major protocol violations will be defined in the statistical analysis plan prior to database lock and treatment unblinding.

Safety Population

The Safety Population is defined as all subjects who received at least 1 dose of study medication. Subjects will be analyzed according to actual treatment received.

8.2.2 Subject Disposition, Demographic and Baseline Characteristics

Subject disposition and demographics such as age, gender, race, weight, height, BMI, etc., will be summarized by treatment group using descriptive statistics. Baseline disease characteristics such as baseline statin, CAI and/or PCSK9I use, diabetes, baseline lipid profiles (including TG, TC, HDL-C, LDL-C, calculated non HDL-C, VLDL-C, RLP-C) will also be summarized.

8.2.3 Concomitant Medication

Prior and concomitant medications will each be categorized by therapeutic class and preferred term using the WHO Drug Dictionary. The number and percent of subjects using each prior and concomitant medication will be summarized by therapeutic class and preferred drug name by treatment group. Subjects who reported more than 1 medication for a particular preferred term will be counted once for each preferred term and therapeutic class.

8.2.4 Treatment Compliance and Exposure

Treatment compliance will be assessed based on the number of the actual doses taken relative to the number of doses expected and summarized by treatment group using descriptive statistics. Subject exposure to study medication will be evaluated using the first dose date and the last dose date.

8.2.5 Control of type 1 error

The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; similarly, a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before is found to be statistically significant.

The following testing order will be followed for the overall type I error control:

1. Percent change from baseline to Week 12 in TG
2. Percent change from baseline to Week 12 in non-HDL-C
3. Percent change from baseline to Week 12 in VLDL-C
4. Percent change from baseline to Week 12 in HDL-C
5. Percent change from baseline to Week 12 in LDL-C

The statistical comparisons will be done using a comparison-wise type I error of 5% (2-sided). For all exploratory variables, nominal p-values will be reported in an exploratory fashion.

8.2.6 Primary Efficacy Analyses

The primary efficacy analysis will be performed on the ITT Population and the PP Population (Section 8.2.1 contains population definitions).

The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. In order to estimate this estimand, all subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies.

All collected data, including those from subjects who discontinue the study medication early but remain on study and are assessed at Week 11 and/or 12, will be included in the primary

analysis. Subjects who withdraw consent for study participation overall and are not assessed at Week 11 and/or 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or 12.

For the primary efficacy endpoint, i.e., the percent change in fasting TG levels from baseline to Week 12, descriptive statistics will be summarized and statistical testing will be performed. The baseline value is defined as the average of the last 3 measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification).The Week 12 endpoint is defined as the average of the 2 measurements obtained at the end of the 12-week double-blind treatment period, approximately 1 week apart, that is Visit 6 (Week 11) and Visit 7 (Week 12). The null hypothesis is that the percent change from baseline of fasting TG level in the active group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline of fasting TG level in the active group is NOT the same as that in the placebo group.

A non-parametric rank-based analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used to perform a hypothesis test for the primary endpoint (percent change in TG levels).

The non-parametric ANCOVA based on ranks will be performed as follows: the percent change from baseline in TG value and the TG baseline value will be transformed to modified ridit scores within stratum (qualifying TG category [≤750 mg/dL vs. >750 mg/dL] and use of statin, CAI, PCSK9I, alone or in combination, at randomization vs. non-use). Modified ridit scores are ranks standardized for the different sample sizes per stratum. In the second step, ordinary LS regression applied to the modified ridit scores of the percent change from baseline and baseline will be performed within stratum using the model:

Percent change from baseline = baseline

In the third step, residuals from these regression models will be used. In that final step, the residuals from all strata will be included in a stratified extended Cochran-Mantel-Haenszel (CMH) test of the residuals (i.e., stratum by treatment by residual) to analyze the treatment effect. CMH test statistics obtained from each of the multiply imputed datasets will be combined using the Rubin's combination rule after applying a normalizing Wilson-Hilferty transformation for a chi-square distributed statistic.

Quantile regression, adjusting for the same baseline covariates as specified for ANCOVA model, will be used to obtain an adjusted estimate of the median treatment difference with associated two-sided 95% CI. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As supportive analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's combination rule are not satisfied.

8.2.7 Subgroup Analyses

The primary efficacy analysis will also be performed for the following subgroups:

- Baseline age group (≤65 years vs. >65 years)
- Race (White/Caucasian vs. Non-white/Caucasian)
- Gender (Male vs. non-Male)
- Baseline use of statin, CAI, PCSK9I, alone or in combination, at randomization (currently treated) (Yes vs. No)
- Qualifying TG levels (≤750 mg/dL vs. >750 mg/dL) (≤8.5 mmol/L vs. >8.5 mmol/L)
- Country (U.S. vs. Mexico vs. Canada)

The models for the subgroup analyses will include all terms in the ANCOVA model used for the primary efficacy analysis plus factors for the subgroup of interest (as appropriate). The interaction between subgroup factors and treatment will be tested at a 0.10 significance level. If a significant interaction between subgroup factors and treatment is detected, the nature of the interaction will be further investigated. Descriptive statistics will be summarized for each subgroup listed above.

The primary efficacy analysis will also be carried out for the PP Population as supportive analyses. Other supportive and sensitivity analysis may be performed as appropriate.

8.2.8 Secondary Efficacy Analyses

The secondary efficacy endpoints for this study are (in order of importance):

- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C.

- Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification).
- Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C.
- Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification).

Similar analyses as specified above for the primary efficacy analysis will be conducted for all of the three secondary efficacy endpoints on the ITT population.

The baseline value is defined in the same way as for the primary analysis, namely, as the average of the 3 last measurements obtained prior to dosing (average of Week -2, -1 and 0 corresponding to measurements taken at Visits 2, 3, and 4 or Visits 3, 3.1 and 4 in case an additional TG measurement was necessary during qualification) except for VLDL-C and LDL-C determined by β-quantification (average of Week -1 and 0 corresponding to measurements taken at Visits 3 and 4 or Visits 3.1 and 4 in case an additional TG measurement was necessary during qualification).

A non-parametric rank-based ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo.

8.2.9 Exploratory Efficacy Analyses

For exploratory endpoints, the change from baseline to Week 12 and/or to Week 26 will be evaluated.

The persistence of the effect of CaPre on the TG profile will be explored by comparing the percent change in fasting TG levels from Baseline to different time points. Descriptive statistics will be presented by treatment group at each visit, and will also be summarized using Graphical representation over time (from Baseline to end of study Week 26).

The relationship between baseline fasting TG levels and the change in fasting TG levels and the relationship between changes in total plasma EPA, DHA and OM3 Index and the change in fasting TG levels will also be explored.

Regarding the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26 week double-blind treatment period, a CMH test will be used, controlling for the two stratification factors that are used for randomization. No multiplicity adjustment will be applied to the exploratory efficacy analyses. Subjects with missing data at the analysis

time points of interest will be handled using the same multiple imputation-based approaches as specified for the primary analysis.

8.2.10 Sensitivity Analysis

Sensitivity analyses will be performed to assess the impact of assumptions on the results of the primary analyses by using other strategies for dealing with missing data.

Subjects who withdraw from the study overall and are not assessed at Week 11 and/or 12 will be imputed using the MI methodology with the imputation model estimated from all subjects in their treatment group, including both those who completed treatment through Week 12 and those who discontinued study medication early but were assessed at Week 11 and/or12. This approach assumes that some subjects discontinuing the study will do so for non-treatment-related reasons and would have similar outcomes to subjects who are able to complete the treatment.

If the number of subjects who discontinue the study medication early and are assessed at Week 11 and/or12 after having started an alternative therapy is large (e.g., > 5% of all ITT subjects), then an additional sensitivity analysis will be performed where data from these subjects will be excluded from analysis and subjects will be treated as having missing data, i.e., will be imputed. This analysis will serve to assess the contribution of the alternative therapies to the estimate of the total treatment effect.

For analysis of the proportion of subjects who have a fasting TG level below 500 mg/dL at the end of 12-week and 26 week double-blind treatment period, a sensitivity analysis will also be performed where subjects with missing data at the analysis time point will be considered as not having a fasting TG level <500 mg/dL.

A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study. Other sensitivity analysis methods may be performed and will be detailed in the SAP.

More details of the proposed sensitivity analyses and possibly additional ones will be presented in the SAP.

8.2.11 Exploratory PK Analyses

The PK endpoints include exploration of:

- Change and percent change from baseline (Week 0) to Week 4, Week 12, Week 18 and Week 26 in Total plasma EPA and DHA concentrations;

- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in OM3 Index;

- Change and percent change from baseline (Week 0) to Week 12 and Week 26 in AA, in omega-6/omega-3 and in EPA/AA ratios;

8.2.12 Safety Analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be coded using the MedDRA. All treatment-emergent AEs (TEAEs) will be summarized by treatment group. TEAEs are defined as AEs that occurred on or after the first dose of study medication. The number and percentages of subjects who experienced at least 1 TEAE will be summarized by system organ class and preferred term. TEAEs will also be summarized by relationship to the study medication and by intensity. Deaths, SAEs and AEs leading to study subject early termination will be tabulated and presented in data listings. Subject level data listings of all AEs will be presented.

Clinical laboratory results (chemistry, hematology, coagulation, urinalysis, etc.) will be summarized using descriptive statistics for each visit by treatment group. Observed values at each visit and changes from baseline to each post-baseline visit will be presented. Changes from baseline in high/low/normal findings for clinical laboratory parameters for which normal ranges apply will be summarized by treatment group using shift tables. All laboratory data will be provided in subject data listings.

Vital signs and ECG parameters will be summarized by treatment group for each applicable visit. Observed values and changes from baseline values will be summarized for each visit where appropriate.

8.3 Interim Analysis

No interim analysis is planned for this study.

8.4 Level of Significance

All statistical tests will be 2-sided, and significance with respect to the primary and secondary endpoints is determined taking into account multiplicity due to multiple endpoint comparisons between CaPre vs. placebo. The family-wise Type I error rate will be controlled at a 0.05 significance level for the primary and secondary efficacy endpoints (see Section 8.2.5).

No multiplicity adjustment will be applied to the exploratory efficacy endpoints.

8.5 Missing Data Handling Rules

Missing data should be kept to a minimum. Continued efforts will be made to measure endpoints on all subjects, even those who discontinued study medication.

For the primary efficacy analyses involving fasting TG level, subjects who withdraw consent for study participation overall and are not assessed at Week 11 and/or 12 will be imputed using the Multiple Imputation (MI) methodology with the imputation model estimated from subjects in their treatment group who discontinued study medication early but were assessed at Week 11 and/or Week12. Results of the ANCOVA analysis from multiple imputed datasets will be combined using the Rubin's combination The handling of missing data for other variables will be described in the SAP.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the Informed Consent Form (ICF) and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or Sponsor's designated representative with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to Acasti Pharma Inc. or representative before enrollment of any subject into the study.

Acasti Pharma Inc. or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or Sponsor's designated representative of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject and/or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated ICF.

10.0 STUDY ADMINISTRATION

10.1 ADMINISTRATIVE STRUCTURE

Please refer to the Key Personnel and Facilities section of the protocol.

The Lead Principal Investigator, Sponsor's representative, Medical Monitor and Key CRO personnel, as needed, will meet regularly during the planning, execution, and close-out phases of the study to review the study progress.

10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence and all other supporting documentation).

The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted.

Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject enrolled into the study.

The Investigator will allow the Sponsor, Sponsor's designated representative and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

10.5 Financing and Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. The terms of the insurance will be kept in the study files.

11.0 REFERENCES

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12.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-002

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

This protocol is a confidential communication of Acasti Pharma Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Acasti Pharma Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title and the name of the center in which the study will be conducted. Return the signed copy to Sponsor or designee and keep a copy for your records.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Investigator

Signature: _____ **Date:** _____
DD/MMM/YYYY

Printed Name: _____

Title: _____

_____

Name/Address of Center: _____

_____

_____

13.0 APPENDIX 2: NCEP-TLC DIET

1. NCEP-ATPIII Report

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) outlines the principles of therapeutic lifestyle changes (TLC) dietary patterns focused on lowering LDL. Recommended food choices for the NCEP-TLC diet are summarized in Table V.2-6 of the report[4]. Recommendations by food group include:

- Breads, cereals, pasta, whole grains, potatoes, rice, dry peas, and beans (6 or more servings per day);
- Fruits and vegetables (5 or more servings per day);
- Fat-free or 1 percent dairy products (2–3 servings per day);
- Lean meats (beef, pork, and lamb), poultry, and fish (up to 5 oz per day as 2 servings);
- Fats high in saturated fat, trans fat, and cholesterol must be limited;
- Nuts are high in fat, but in most nuts the predominant fats are unsaturated. The intake of nuts should fit within the calorie and fat goal;
- Egg yolks are high in cholesterol (~215 mg/egg) and should be limited to no more than two egg yolks per week;

Other eating tips from the report include:

- Snacks should be low in saturated fat;
- Moderate amounts of sweets and modified-fat desserts (low in saturated fat) may be chosen;
- Cooking methods that use little or no fat (steaming, baking, broiling, grilling, or stirfrying in small amounts of fat) should be used;
- Exercise caution when eating away from home;

Various TLC sample daily menus are provided in appendix B of the report[5]. This report is freely accessible online at http://circ.ahajournals.org/content/106/25/3143.long.

[4] Page 3259
[5] Pages 3287-3296

2. Your Guide To Lowering Your Cholesterol With TLC (Booklet)

The National Heart, Lung and Blood Institute (NHLBI) through the NCEP and Obesity Education Initiation has developed a guide intented for the general population that describes the TLC program for reducing high blood cholesterol.

The booklet is freely accessible online at:
https://www.nhlbi.nih.gov/files/docs/public/heart/chol_tlc.pdf

The guide contains recommended ranges of intake for the following dietary components:

Nutrient	**Recommended Intake**
Total fat	25-35% of total calories
Saturated Fatty Acids	<7% of total calories
Cholesterol	<200 mg per day
Total Calories	Depends on energy intake and expenditure to achieve optimal weight

Moreover, the TLC diet calls for other recommendations:

- Diet options for more LDL lowering
  - 2 grams per day of plant stanols or sterols;
  - 10–25 grams per day of soluble fiber;
- Only enough calories to reach or maintain a healthy weight
- Get at least 30 minutes of a moderate intensity physical activity, such as brisk walking, on most, and preferably all, days of the week.

The guide focuses on the principle that this is not a temporary diet, but rather a new way of eating that is both heart-healthy and tasty. This publication also contains TLC sample daily menus[6].

In addition, patients on this protocol will be advised to minimize their intake of added sugars (e.g., from soda, sweets, etc.) to below 10% of energy, due to their potential adverse effect on triglyercide levels and consistent with the recommendations of the 2015 Dietary Guidelines for Americans.

[6] Pages 61 to 69 of the guide.

14.0 APPENDIX 3: DETAILED REVISION HISTORY

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Page 1. Date of Protocol: 02 November 2017	Date of Protocol: **Amended Protocol 22 May 2018** **Initial** Protocol 02 November 2017	Edit to reflect amended protocol version
Page 1. Study Principal Investigator	**Lead** Principal Investigator	For consistency throughout the protocol
Page 2 Contract Research Organization (CRO) Quintiles Canada Inc. 100 Alexis Nihon, St-Laurent, Quebec, H4M 2P4	Contract Research Organization (CRO) Quintiles Canada Inc. **16720 Rte Transcanadienne, suite 100** **Kirkland, Quebec H9H 5M3**	Edit to reflect change in CRO name and address.
Page 3 Version: Initial Protocol (02 November, 2017)	Version: **Amended Protocol (22 May 2018)** Initial Protocol (02 November, 2017)	Edit to reflect amended protocol version
Page 5-16 Synopis	Synopis	All changes made in the core sections of the protocol are reflected in the synopsis.
Page 31 4.1 Summary of Study design		
The study duration will be up to 39 weeks, consisting of an initial screening period of 4 to 6 weeks	The study duration will be up to 39 weeks, consisting of an initial **diet, lifestyle and medication** ~~screening~~ stabilization period of 4 ~~to~~ **or** 6	Edits to clarify study requirements for diet and physical activity
Approximately ~~615~~ 653 subjects	Approximately ~~615~~ **653** subjects	Edit to revise expected number of screened subjects
At the screening visit (Visit 1), subjects will enter a diet, lifestyle and medication stabilization period that will last 4 to 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to maintain the diet, as well as to reduce intake of added sugar, for the duration of the study.	At the screening visit (Visit 1), subjects will enter a diet **and lifestyle recommendation** and medication stabilization period that will last 4 ~~to~~ **or** 6 weeks. Subjects will be provided with information regarding the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will be instructed to **aim to** maintain the diet, as well as to reduce intake of added sugar, for the duration of the study. **Subjects will also be instructed to aim to maintain physical activity level consistent with TLC for the duration of the study.**	Edits to clarify study requirements for diet and physical activity

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
The duration of this stabilization period will be 4 weeks for subjects who are not on lipid-altering or who are already receiving prior to screening a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, or a combination of these agents. The stabilization period will be 6 weeks for subjects who are required at screening to discontinue prohibited lipid-altering therapy such as fibrates, bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects. Similarly, the stabilization period for subjects who either initiate or change dose at screening of a statin and/or CAI treatment will be 6 weeks. PCSK9I treatment should not be initiated at screening.	The duration of this stabilization period **(between Visit 1 and Visit 2)** will be 4 weeks for subjects who are not ~~on~~ **currently taking any** lipid-altering **agents** or who are already receiving **prior to screening (V1)** a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), cholesterol-absorption inhibitors (CAI) such as ezetimibe, **a fibrate**, or a combination of these agents~~, prior to screening~~. **Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening. PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1).** **Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1). Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment.** The stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who are required at screening **(V1)** to discontinue prohibited lipid-altering ~~therapy~~ **agents** such as ~~fibrates,~~ bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects** ~~that may exhibit lipid-altering effects~~. Similarly, the stabilization period **(between Visit 1 and Visit 2) will be 6 weeks** for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment ~~will be 6 weeks~~.	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2; to reflect allowance of subjects taking stable dose of a fibrate; to clarify study requirements for stability of concomitant PCSK9I and Fibrate prior to the screening visit (V1)
After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication with water at a meal.	After confirmation of qualifying fasting TG values, eligible subjects will enter a 26-week randomized, double-blind treatment period. At Visit 4 (Week 0), subjects will be randomly assigned to one of the following treatment groups: CaPre 4 g daily, or placebo daily. Subjects will receive instructions to take the study medication ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.
Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated).	Following a 2.5:1 treatment allocation ratio (CaPre: placebo), approximately 175 subjects are to be randomized in the CaPre 4 g group and approximately 70 subjects in the placebo group. Stratification will be based on qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin, CAI or PCSK9I, alone or in combination, at randomization (currently treated vs not currently treated **with statin, CAI, PCSK9I, alone or in combination**).	Minot edit for clarification
Page 34 4.1.1 Screening Period (Visit 1 [Week -8 or Week -6])	4.1.1 Screening ~~Period~~ Visit (Visit 1 [Week -8 or Week -6])	

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
The purpose of the screening period is to allow subjects to acclimate to the NCEP-TLC diet, and to allow time for washout of current lipid-altering therapy (if necessary).	The purpose of the screening visit and the subsequent stabilization period **(between V1 and Visit 2)** is to allow subjects to acclimate to the **dietary recommendation to consume a** ~~the~~ NCEP-TLC ~~diet~~ **and reduce intake of added sugar**, and to allow time for washout of **prohibited** ~~current~~ lipid-altering **agents** ~~therapy~~ (if necessary), **or stabilization following initiation or dose adjustment of a statin and/or CAI treatment at screening, or washout or dose reduction of a fibrate treatment.**	Edits to clarify purpose of the stabilization period regarding diet, lifestyle and medication.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Subjects not being treated with a statin and/or CAI and/or PCSK9I at time of screening may initiate such treatment, if not contraindicated, at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement). Subjects receiving non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products) and/or any other products or supplements that may exhibit lipid-altering effects at the time of screening will be evaluated by the Investigator to determine if they can discontinue these therapies. If deemed appropriate, discontinuation is required 6 weeks prior to Visit 2 (first TG baseline qualifying measurement). If not contraindicated, these subjects may initiate a statin and/or CAI and/or PCSK9I treatment at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).	~~Subjects not being treated with a statin and/or CAI and/or PCSK9I at time of screening may initiate such treatment, if not contraindicated, at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).~~ ~~Subjects receiving non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products) and/or any other products or supplements that may exhibit lipid-altering effects at the time of screening will be evaluated by the Investigator to determine if they can discontinue these therapies. If deemed appropriate, discontinuation is required 6 weeks prior to Visit 2 (first TG baseline qualifying measurement). If not contraindicated, these subjects may initiate a statin and/or CAI and/or PCSK9I treatment at the discretion of the Investigator and maintain a stable regimen for ≥6 weeks prior to Visit 2 (first TG baseline qualifying measurement).~~ The duration of this stabilization period **(between Visit 1 and Visit 2)** will be 4 weeks for subjects who are not ~~on~~ **currently taking any** lipid-altering **agents** or who are already receiving **prior to screening (V1)** a stable dose of statins, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors (PCSK9I), CAI such as ezetimibe, **a fibrate**, or a combination of these agents. **PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.** **Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue fibrate treatment. The stabilization period (between Visit 1 and Visit 2) will be 6 weeks for subjects who reduce dose or discontinue fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).** The stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who are required at screening (V1) to discontinue prohibited lipid-altering agents such as~~,~~ bile acid sequestrants, niacin >200 mg/day, and OM3 drugs (e.g., Lovaza® or its generics,Vascepa®, Epanova®, Omtryg®), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects**. Similarly, the stabilization period **(between Visit 1 and Visit 2)** will be 6 weeks for subjects who either initiate or change dose at screening (V1) of a statin and/or CAI treatment.	Edits to clarify duration of the medication stabilization between screening visit (V1) and V2; to reflect allowance of subjects taking stable dose of a fibrate; to clarify study requirements for stability of concomitant PCSK9I and Fibrate prior to the screening visit (V1)

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Determination of eligibility (fasting lipids) (see Section 4.3)	~~Determination~~ Evaluation of eligibility (fasting lipids) **to continue in the stabilization period**[1] ~~(see Section 4.3)~~	Edit and footnote added to clarify that TG values outside of the inclusion range at screening (V1) are not automatically exclusionary.
The NCEP-TLC diet that should be followed for the duration of the study will be explained to the subject. Written dietary information will also be provided to the subject.	**Recommendation to consume** a ~~The~~ NCEP-TLC diet that should be followed for the duration of the study, **along with the reduction of added sugar**, will be explained to the subject. Written dietary information **will be available** ~~also be provided~~ to the subject.	Edit to clarify dietary counselling procedures
Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to maintain current physical activity level **consistent with TLC** throughout the study.	Subject will be reminded that they are to fast for at least 9 hours and may consume only water and usual medications prior to the next study visit. Subject will also be instructed to **aim to** maintain ~~current~~ physical activity level **consistent with TLC** throughout the study.	Edit to clarify physical activity counselling procedures
Schedule TG Qualifying Visit (Visit 2). The TG Qualifying Visit (Visit 2) should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering therapy at screening, subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe) or PCSK9I, alone or in combination, and subjects who initiated a stable dose of statin with or without CAI, and for 6 weeks after Visit 1 for subjects who require washout of their current non-statin, lipid-altering therapy at screening.	Schedule **the first** TG Qualifying Visit (Visit 2)[2]. ~~The TG Qualifying Visit (~~Visit 2~~)~~ should be scheduled for 4 weeks after Visit 1 for subjects not taking any lipid-altering ~~therapy~~ **agents** at screening, **and for** subjects receiving prior to screening a stable dose of statin, CAI (such as ezetimibe), PCSK9I, **a fibrate, or a combination of these agents** ~~alone or in combination~~. **Visit 2 should be scheduled for** ~~and~~ **6 weeks after Visit 1 for** subjects **who initiated or changed dose** of a ~~a stable dose of a~~ statin **and/or** ~~with or without~~ CAI **treatment**, for ~~6 weeks after Visit 1 for~~ subjects who require washout of **prohibited** ~~their current~~ non-statin, lipid-altering ~~therapy~~ **agents** at screening, **and for subjects who washout or reduced dose of a current fibrate treatment.**	Edits added to clarify dose stability requirements for lipid-altering agents prior to the first TG qualifying visit.
-	SOCBP will be reminded to use a reliable method of birth control or remain abstinent.	Edit to add reminded for SOCBP about birth control requirements
Page 35 4.1.2 TG Qualifying Period (Visit 2 [Week -2] and Visit 3 [Week -1])		
The subject will provide fasting blood samples for determination of eligibility (fasting lipids) (see Section 4.3).	The subject will provide fasting blood samples for **evaluation** ~~determination~~ of eligibility (fasting lipids) **to continue in the TG qualification period**[2]	Edit and footnote added to clarify that TG values outside of the inclusion range at V2 or V3 are not automatically exclusionary.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 36 4.1.3 Randomization Visit (Visit 4 [Week 0])		
Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk	Additional serum sample for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular risk. **The analysis will be considered part of this clinical protocol.**	Minor clarification
The subject will be supplied with study medication to be taken until Visit 5 (4 weeks)	The subject will be supplied with study medication to be taken until Visit 5 (4 weeks)**, and instructed to take it once a day with a meal but not prior to attending Visit 5.**	

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Urine sample will be collected for urinalysis	Urine sample will be collected for urinalysis **and for an optional urine pregnancy test (test strip)**[3]. If the test is performed, negative pregnancy status must be confirmed before randomization.	Add optional urine pregnancy test at randomization. This test is to be conducted based on Investigator's judgement, and the subject's situation.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 38-41 4.1.4 Double-blind Treatment Period (Visit 5 [Week 4]) 4.1.5 Double-blind Treatment Period (Visit 6 [Week 11] and Visit 7 [Week 12]) 4.1.6 Double-blind Treatment Period (Visit 8 [Week 18]) 4.1.7 Final Visit (Visit 9 [Week 26] or Early Termination)		
Previously dispensed study medication will be collected and a new supply of study medication (X weeks) to be taken until Visit X (Week X) will be given to the subject. The number of capsules returned will be counted and the results will be documented.	Previously dispensed study medication will be collected and a new supply of study medication (X weeks) to be taken until Visit X (Week X) will be given to the subject. **Subject will be instructed to take it once a day with a meal but not prior to attending Visit X**. The number of capsules returned will be counted and the results will be documented.	Edit to clarify instruction for dosage administration.
-	**SOCBP will be reminded to use a reliable method of birth control or remain abstinent.**	Edit to remind SOCBP about birth control requirements
Page 42 4.1.8 Follow-up Contact		
As well, SOCBP shall be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.	As well, SOCBP ~~shall~~ **will** be reminded to agree to use a reliable method of birth control or remain abstinent for an additional 4 weeks.	Minor text edit.
Page 43 Table 1 Schedule of Events		
Visit 4 (Week 0) Visit Window (days) -1/+3	-1/~~+3~~**+5**	Edit to increase tolerance window for randomization visit
Visit 4 (Week 0) Chemistry, hematology and urinalysis X	X[c] [c]**A urine sample may be collected for an optional urine pregnancy test (test strip).**	Footnote added for optional urine pregnancy test at randomization
Page 45 Section 4.2 Discussion of Study design		
All subjects will take an oral, single dose of 4 g (4 capsules) a day with water at a meal.	All subjects will take an oral, single dose of 4 g (4 capsules) a day ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- to 6-week diet and lifestyle stabilization period, subjects will enter a 2-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.	Subjects in this proposed study will have severe hypertriglyceridemia with fasting serum TG levels ≥500 mg/dL and ≤1500 mg/dL). After a 4- ~~to~~ **or** 6-week diet, ~~and~~ lifestyle **and medication** stabilization period, subjects will enter a 2- **or** 3-week TG qualifying period, where eligible subjects will be required to have an average fasting TG level of ≥500 and ≤1500 mg/dL to enter the 26-week double-blind treatment period.	Edits to clarify purpose and duration of the stabilization period.
Page 45 Section 4.3.1 Inclusion Criteria		
2. Isolated hypertriglyceridemia, with TG ≥500 mg/dL and <1500 mg/dL (≥5.7 mmol/L and <17.0 mmol/L) OR Mixed hyperlipidemia, with serum triglycerides ≥500 and <1500 mg/dL treated with a statin, CAI or PCSK9I, alone or in combination, that has been stable for 6 weeks prior to randomization. If the subject is not being treated, and not contraindicated, a statin and/or CAI treatment this may be initiated at the discretion of the Investigator at time of screening. PCSK9I treatment should not be initiated at screening.	2. Isolated hypertriglyceridemia ~~OR~~**or** Mixed hyperlipidemia, with TG ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated **or not with a stable dose** of statin, CAI, ~~or~~ PCSK9I, **fibrate, or a combination of these agents.** ~~Alone or in combination, that has been stable for 6 weeks prior to randomization.~~ **If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening.** If ~~the subject is not being treated, and~~ not contraindicated, **the investigator may prescribe new or different** ~~a~~ statin and/or CAI treatment ~~this may~~ **to be** initiated, **or change current doses of statin and/or CAI** at time of screening. ~~PCSK9I and/or fibrate treatment should not be initiated at screening.~~	Edit to clarify the same overall population of severe hypertriglyceridemia (TG ≥ 500 mg/dL), as specified in previous labels of the drug class; to allow inclusion of patients currently treated with a stable dose of fibrate; to remove specification for 6-week stability prior to randomization as this requirement is not applicable in all instances. Requirement for stability are rather clarified in other sections of the protocol (e.g. 4.1, 4.1.1, 5.8.1 and 5.8.2)
3. Willingness to maintain current physical activity level and follow the NCEP-TLC diet throughout the study.	3. Willingness to aim to maintain ~~current~~ physical activity level and **diet consistent with** ~~follow~~ the NCEP-TLC ~~diet~~ **and to reduce added sugars intake** throughout the study.	Edits to clarify study requirements for diet and physical activity
Page 46 Section 4.3.2 Exclusion Criteria		
2. Known lipoprotein lipase impairment or deficiency, or apo CII deficiency.	2. ~~Known lipoprotein lipase impairment or deficiency, or apo CII deficiency~~. **Subjects diagnosed with Familial Chylomicronemia Syndrome**	Edit to clarify exclusion criteria #2
5. …Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study or for at least 8 weeks following the last dose of study medication, whichever is longer.	5. …Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study ~~or~~ **and** for ~~at least~~ 8 weeks following the last dose of study medication. ~~,~~ ~~whichever is longer.~~	Edit to clarify study requirements for SOCBP
10. Diabetics requiring changes in medical therapy (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1.	10. Diabetics requiring changes in **glucose-lowering medication** ~~medical therapy~~ (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1.	Edit to clarify exclusion criteria #10

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
11. Clinical or biochemical evidence of hyperthyroidism not stable with medication for at least 6 weeks prior to Visit 1.	11. **Subjects with** clinical evidence **of hyperthyroidism** or **TSH level less than lower limit of normal (LLN) at Visit 1**. **Subjects diagnosed with hyperthyroidism must be treated** ~~biochemical evidence of hyperthyroidism not stable~~ with medication for at least 6 weeks prior to Visit 1.	Edit to clarify exclusion criteria #11
12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN)	12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN**) within 6 weeks prior to Visit 1.**	Edit to correct exclusion criteria #11 in the synopsis
16. Use of other prohibited drugs: weight loss prescription medications; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids.	16. Use of other prohibited drugs: ~~weight loss~~ prescription **or OTC** medications **specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide**; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted), or anabolic steroids. **Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.**	Edit to clarify prohibited medications when specifically taken for weight loss; clarify allowance of stable dose of anabolic steroids or testosterone as replacement therapy for hypogonadism
17. Any lipid-altering drug therapy, other than statins, CAI or PCSK9I, including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects must be discontinued at least 6 weeks prior to randomization.	17. ~~Any~~ **Use** of any lipid-altering drug ~~therapy~~**agents**, other than statins, CAI, ~~or~~ PCSK9I **or fibrate**, including niacin at a dose greater than 200 mg/day~~, fibrates~~, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary** supplements **specifically taken for their lipid-altering effects**. These agents ~~that may exhibit lipid-altering effects~~ must be discontinued ~~at least 6~~ 8 weeks prior to randomization.	Edit to remove fibrate from the list of prohibited medications; to clarify washout requirements for prohibited medications prior to randomization.
19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily, pulmonary, gastrointestinal, or immunologic disease.	19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily~~, pulmonary, gastrointestinal, or immunologic disease~~.	Edit to clarify requirements for exclusion of subjects with pulmonary, gastrointestinal, or immunological disease
28. Presence of any other condition the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.	28. Presence of any other condition **(such as severe pulmonary, gastrointestinal, or immunologic disease)** the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.	
Page 48 4.3.3 Subject Restrictions		
Subjects must be willing to maintain current physical activity level and follow the NCEP-TLC diet throughout the study.	Subjects must be willing to **aim to** maintain ~~current~~ physical activity level **and diet consistent with** ~~, and follow~~ the NCEP-TLC, ~~diet~~ **and reduce intake of added sugar** throughout the study.	Edits to clarify study requirements for diet.
Subjects of child-bearing potential must remain abstinent or must use an acceptable method of contraception during the study or for at least 8 weeks following the last dose of study medication.	Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study ~~or~~ **and** for at least 8 weeks following the last dose of study medication.	Edit to clarify study requirements for SOCBP
Page 49 4.3.4 Subject Withdrawal or Termination		
The criteria for enrollment are to be followed explicitly. If a subject who does not respect enrollment criteria is inadvertently enrolled, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator.	The inclusion and exclusion criteria ~~for enrollment~~ are to be followed explicitly. If a subject who does not respect ~~enrollment~~ **one or the other** criteri~~a~~**on** is inadvertently ~~enrolled~~ **randomized**, the Medical Monitor must be contacted and the subject evaluated in conjunction with the Investigator.	Edit to clarify distinction between enrollment and randomization in the context of this protocol.
4.3.5 Subject Re-screening		

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
-	**Re-screening of certain screening failure subjects may be allowed under certain circumstances at least 3 months after initial enrollment and only after discussion with and approval by the Medical Monitor. The following situations may give rise to re-screening:** **• If a subject consents to participate, otherwise meets the eligibility criteria, but is not able to continue in the study prior to randomization due to an unforeseen change in personal situation ;** **• If a subject failed one or the other eligibility criterion during the stabilization or TG qualification period due to i) an acute event that has resolved ii) a medical cause or condition that has been adequately treated or for which time has sufficiently elapsed since occurrence;** **• To allow time for stabilization or wash-out following initiation or dose changed of allowed or prohibited medications, as the case may be, at time of screening or during the TG qualification period;** **Subject who failed to meet the eligibility criteria and do not otherwise fall into the above situations should not be considered for re-screening. Specifically, subjects who fail to meet the average TG inclusion level will be considered screening failure, and re-screening of these subjects will not be allowed. Also, subjects that are randomized and withdraw from study medication or completely withdraw consent for participation in the study at any time, for any reason, are not eligible for re-screening.** **In case of re-screening, all study screening procedures must be repeated, including the requirement for subjects to give new consent. Re-screened subjects will be allocated a new subject identification number. For each subject that is eligible for re-screening, only one re-screening is permitted.**	New section added to clarify conditions under which the protocol allows re-screening of subjects.
Page 52 5.1 Treatments Administered		
Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day with water at a meal.	Subjects will be instructed to take 4 capsules (i.e. 4 g) of the study medication once per day ~~with water~~ at a meal.	Edit to provide flexibility for dosage administration.
Page 53 5.4 Method of Assigning Subjects to Treatment Group		
After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening (V1). At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the TG qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT.	After completing the informed consent process, subjects will be assigned an identification number by interactive response technology (IRT) at screening **(V1)**. At Visit 4, once the subject satisfies inclusion and exclusion criteria at the end of the **TG** qualifying period, the study center will request a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre:placebo) using IRT.	Minor text edit for consistency
Page 54 5.6 Selection and Timing of Dose for Each Subject		
Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I inhibitor, alone or in combination at randomization (currently treated vs not currently treated). All subjects will take four capsules, once a day, with water at a meal	Subjects will be randomized in a 2.5:1 ratio to one of two treatments: CaPre 4 g daily, or matching placebo. Randomization will be stratified by qualifying TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of a statin, CAI or PCSK9I ~~inhibitor~~, alone or in combination at randomization (currently treated vs not currently treated). All subjects will take four capsules, once a day, ~~with water~~ at a meal	Minor text edit for consistency

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Page 55 5.8.1 Excluded Medications		
Any lipid-altering drug therapy (other than statins, CAI or PCSK9I, alone or in combination; see below) including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other products or supplements that may exhibit lipid-altering effects must be discontinued at least 6 weeks prior to randomization.	Any lipid-altering drug ~~therapy~~ **agents** (other than statins, CAI, ~~or~~ PCSK9I, **or fibrate** alone or in combination; see below) including niacin at a dose greater than 200 mg/day, fibrates, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), and any other **herbal** products or **dietary supplements specifically taken for their lipid-altering effects**. These agents ~~that may exhibit lipid-altering effects~~ must be discontinued ~~at least 6~~ **8** weeks prior to randomization.	Edit to remove fibrate from the list of prohibited medications; to clarify washout requirements for prohibited medications prior to randomization
Case of Plant sterols/stanols and Solube Fibers:	Case of Plant sterols/stanols and ~~Solube~~**Soluble** Fibers:	Minor text edit for consistency
Weight loss prescription medications	~~Weight loss~~ Prescription **or OTC** medications **specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide**.	Edit to clarify prohibited weight loss medications
Page 55 5.8.2 Allowed Medications		
All concomitant treatments or medications administered during the 60 days preceding the start of treatment must be reported on the appropriate page of the eCRF. The generic names of the drugs (or trade names for combination drugs) must be specified along with the total daily dose and duration of treatment. The following medications and treatments cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:	Any ~~All concomitant~~ **herbal products, dietary supplements** ~~treatments,~~ or medications **started before the informed consent and ongoing at time of screening (V1)** ~~administered during the 60 days preceding the start of treatment~~ must be reported on the appropriate page of the eCRF. **Any herbal products, dietary supplements, or medications listed in one or the other inclusion or exclusion criterion and that was stopped during the 60 days preceding screening (V1) should also be documented.** The generic names of the **herbal products, dietary supplements,** or medications ~~drugs~~ (or trade names for combination drugs) must be specified along with the total daily dose and duration of treatment. The following **herbal products, dietary supplements, or** medications ~~and treatments~~ cannot be started after randomization but are allowed during the study provided that subjects are on stable doses prior to randomization:	Edit to clarify requirements for documentation of prior and concomitant herbal products, dietary supplements or medications.

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
Statins, CAI (e.g., Ezetimibe) or PCSK9I, alone or in combination: Subjects already regimented with statins and/or CAI and/or PCSK9I prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization; or Subjects eligible for statins and/or CAI treatment initiation or change at Visit 1 must be on stable dose at least 8 weeks prior to randomization. These subjects must continue to receive the same dose of statin and/or CAI and/or PCSK9I after randomization and must not discontinue medication during the study.	Statins, CAI (e.g., ~~E~~ezetimibe),. ~~or~~ PCSK9I **or fibrate**, alone or in combination: Subjects already regimented with a statin~~s~~ and/or CAI ~~and/or PCSK9I~~ prior to Visit 1 must be on stable dose for at least 6 weeks prior to randomization; or Subjects **who initiate or change dose** ~~eligible for~~ of a statin~~s~~ and/or CAI treatment ~~initiation or change~~ at Visit 1 must be on stable dose ~~at least~~ 8 weeks prior to randomization. **PCSK9I treatment must not be initiated or the dose changed at the screening visit (V1). Subjects taking PCSK9I should be on a stable dose at least 12 weeks prior to screening.** **Fibrate treatment must not be initiated or the dose increased at the screening visit (V1). At screening (V1) or upon review of the subject's TG value following the screening visit, if not contraindicated, at the discretion of the Investigator, subjects may reduce dose or discontinue from fibrate treatment. Subjects taking fibrate who do not reduce or discontinue from treatment should be on a stable dose 12 weeks prior to the screening visit (V1).** ~~These subjects must continue to receive the same dose of statin and/or CAI and/or PCSK9I and/or fibrate after randomization and must not discontinue medication during the study.~~	Edit to allow inclusion of patients currently treated with a stable dose of fibrate; clarify study requirements for stability of dose prior to screening or randomization as the case may be.
The following medications and treatments are also allowed during the study:	The following **herbal products, dietary supplements** or medications ~~and treatments~~ are also allowed during the study:	Minor text edit for consistency
Page 57 5.9 Rescue Medication		
Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication (e.g. fibrate), as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.	Rather, a discussion between the Medical Monitor and the Investigator is required, which may include decision to continue study medication or initiate an alternative treatment, including rescue medication **selected by the PI or dose adjustment of fibrate (or another current medication)** ~~(e.g. fibrate)~~, as deemed appropriate by the Investigator after consultation with the patient's primary physician/care giver, as the case may be.	Edit to allow dose adjustment of a current fibrate or other current medication t as part of the rescue medication
Page 57 5.10 Treatment Compliance		
The prescribed dosage, timing and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.	The prescribed daily dos~~ag~~e, **frequency** ~~timing~~ and mode of administration for study medication may not be changed. Departures from the intended regimen will be reported as protocol non-compliance.	Minor edit to clarify dosage administration.
-	**After randomization, at subsequent visits 5, 6, 7, 8 and 9, subjects should be instructed not to take their daily dose before attending the visit.**	Text added to clarify study requirement pertaining to the timing of dose prior to the visit
Page 58 6.1.3 Exploratory Efficacy Endpoints		

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Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, Week 11, Week 18 and Week 24) in TG (persistence of the effect of CaPre on TG lipid profile).	Percent change from baseline (average of Week -2, -1, and 0) to all measured visits other than Week 12 (Week 4, ~~Week 11~~, Week 18 and Week ~~24~~26) in TG (persistence of the effect of CaPre on TG ~~lipid profile~~).	Minor edit text for consistency
Page 61 6.2.1.1 Reporting of Adverse Events		
After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.	After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs**, including those ongoing after the follow-up period of 28 days planned after the final visit (or early termination) (see 4.1.8)** will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. **Non-serious AEs still ongoing after the follow-up period will not be additionally followed and the outcome at time of last contact will be reported in the study database.**	Edit to clarify protocol requirements for AE follow-up.
Page 62 Table 3 Laboratory assessments		
Creatinine Kinase (CK)	Creati~~ni~~ne Kinase (CK)	Minor text edit
FSH (as required for SOCBP)	FSH (as required for post-menopausal subjects only ~~SOCBP~~)	Minor text edit
Glomerular Filtration Rate (eGRF)	Glomerular Filtration Rate (~~eGRF~~eGFR)	Minor text edit
6.2.2.1 Laboratory Re-testing		
-	**Request for re-testing (i.e. requiring a new blood sample) of certain clinical laboratory tests may be allowed in special circumstances and only after discussion with and approval by the Medical Monitor.**	New section added to clarify conditions under which re-testing of certain laboratory test may be allowed.
Page 65 6.2.3.1 Vital Signs		
Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (□C) and respiratory rate for a minimum of 30 seconds will be measured at all visits.	**Vital signs evaluation should be performed before collecting laboratory samples.** Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, body temperature (°C) and respiratory rate for a minimum of 30 seconds will be measured at all visits.	Edit to clarify protocol expectation for timing of study procedures.
Page 66 6.2.3.4 ECG		
A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination.	A complete standard 12-lead ECG recording will be performed at Visits 2, 7, 9, and as applicable at early termination. **ECG assessment should be performed before collecting laboratory samples.**	Edit to clarify protocol expectation for timing of study procedures
Page 69 7.0 QUALITY CONTROL AND QUALITY ASSURANCE		
Early study center visits post-enrollment.	Early study center visits **post-randomization** ~~enrollment~~.	
Page 73 8.1 Determination of Sample Size		

<table>
<tr>
<td>The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/d; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The table below shows sample size estimation for a range of treatment effects, considering an unbalanced treatment allocation ratio of 2.5:1 (CaPre:placebo), and using step down testing procedure to adjust for multiplicity:

Table 4 Sample Size Estimation
<table>
<tr><th>Sample size per group (CaPre:placebo)</th><th>Placebo-corrected treatment effect</th><th>Common standard deviation</th><th>Overall Type I error</th><th>Power</th></tr>
<tr><td>265:106</td><td>0.15</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
<tr><td>150:60</td><td>0.20</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
<tr><td>98:39</td><td>0.25</td><td>0.4</td><td>0.05</td><td>90%</td></tr>
</table>
Note: The sample size calculation is performed based on a 2-sample t-test using nQuery + nTerim 4.0.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a difference of at least 20 % in percent decrease from baseline in TG between CaPre and placebo (assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05), a difference that is believed to be clinically relevant. These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia).</td>
<td>The determination of the sample size is based on the results from the two completed Phase 2 studies in subjects with TG between 200-877 mg/d;dL; TRIFECTA (double-blind) and COLT (open label). For TRIFECTA study, the estimated treatment difference between CaPre 2 g (the highest dose tested) and placebo group in decrease from baseline to Week 12 was 10%, with a standard deviation ranging from 33% to 40%. For COLT open label study, the estimated treatment difference between CaPre 4 g (the highest dose tested) and SoC in percent decrease from baseline to Week 8 in TG was 15%, with a standard deviation ranging from 22% to 36%.

For the current Phase 3 trial, it is anticipated that the treatment effects of CaPre 4 g will be larger in severe hypertriglyceridemia subjects (500 mg/dL≤ TG ≤1500 mg/dL), as it has been observed in other clinical studies with OM3 drugs.

The primary estimand in this study is the difference between the randomized treatment groups, CaPre 4 g and placebo, in median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects. All subjects will be expected to complete all planned study assessments regardless of adherence to study medication and use of subsequent rescue therapies. The null hypothesis is that the percent change from baseline in fasting TG level in the CaPre 4 g group is the same as that in the placebo group. The alternative hypothesis is that the change from baseline in fasting TG level in the active group is NOT the same as that in the placebo group.
It is anticipated that the overall treatment discontinuation rate in this study will not exceed 15% and will be approximately equal in the two treatment groups. Given that subjects may initiate subsequent rescue therapies after an early discontinuation of the study treatment and that their outcomes will be measured at Week 11 and/or 12 under the effect of rescue, the following assumptions regarding the median percent reduction in fasting TG levels from baseline to Week 12 are used in sample size calculations.
• Placebo group: 10% median reduction from baseline in subjects who complete the study on placebo and 25% median reduction from baseline in placebo subjects who discontinue the study treatment early and are rescued. This corresponds to an overall median percent reduction from baseline of approximately 12% in the placebo group based on the assumption that 85% of subjects will complete the study on placebo and 15% placebo subjects will be rescued.
CaPre 4 g group: two scenarios will be considered with 32% and 37% median reduction from baseline, respectively. Completers and rescued subjects in the CaPre 4 g group are assumed to have a similar median percent reduction from baseline to Week 12. The two scenarios will correspond to an overall median treatment difference between the CaPre 4 g group and placebo of 20 and 25 percentage points, respectively.

Approximately 175 subjects are to be randomized in the CaPre 4 g group and 70 subjects in the placebo group, for a total of 245 subjects randomized to this study following a 2.5:1 treatment allocation ratio (CaPre:placebo). Such a sample size would provide at least 90% power to detect a <s>mean</s> median difference of at least 20 <s>%</s> percentage</td>
<td>Original protocol sample size calculation was based on the MEAN (parametric test). In the newer sample size calculation, the MEDIAN (non-parametric test) was used.</td>
</tr>
</table>

points in percent decrease from baseline to Week 12 in TG between CaPre and placebo ~~(~~assuming a common standard deviation in percentage change of 40% and a two-sided α at 0.05~~)~~, **based on a non-parametric Wilcoxon-Mann-Whitney test**. **The overall median treatment difference of 20 percentage points**~~, a difference that~~ is believed to be clinically relevant.

The primary analysis to test the null hypothesis of no treatment effect will be conducted using a non-parametric rank-based ANCOVA adjusting for randomization stratification factors, which is expected to be at least as powerful as the Wilcoxon-Mann-Whitney test used in sample size calculations.
The table below shows the estimated power for four scenarios, 20 and 25 percentage points median differences between treatment groups and two settings of common standard deviation (40% and 45%), considering an unbalanced treatment allocation ratio of 2.5:1 with 175:70 subjects randomized (CaPre:placebo). These assumptions are comparable to those from Phase 3 trials with other OM3 drugs conducted in the target indication (severe hypertriglyceridemia). Power calculations are provided under two assumptions regarding the underlying distribution of the primary variable: lognormal and normal.

Table 4 Sample Size Estimation

Sample size per group (CaPre:placebo)	Placebo-corrected treatment effect (overall median treatment difference)	Common standard deviation	Overall Type I error (two-sided)	Power (lognormal distribution)	Power (normal distribution)
175:70	**20 percentage points**	**40%**	**0.05**	**>95%**	**92%**
175:70	**25 percentage points**	**40%**	**0.05**	**>95%**	**98%**
175:70	**20 percentage points**	**45%**	**0.05**	**>95%**	**87%**
175:70	**25 percentage points**	**45%**	**0.05**	**>95%**	**96%**

~~The table below shows sample size estimation for a range of treatment effects, considering an unbalanced treatment allocation ratio of 2.5:1 (CaPre:placebo), and using step down testing procedure to adjust for multiplicity:~~

~~Table 4 Sample Size Estimation~~

<table>
<tr><th>Initial Protocol version
02 November 2017</th><th>Amended No. 1
22 May 2018</th><th>Rationale for change</th></tr>
<tr><td></td><td>
<table>
<tr><th>~~Sample size per group (CaPre:placebo)~~</th><th>~~Placebo-corrected treatment effect~~</th><th>~~Common standard deviation~~</th><th>~~Overall Type I error~~</th><th>~~Power~~</th></tr>
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</table>
~~Note: The sample size calculation is performed based on a 2-sample t-test using nQuery + nTerim 4.0.~~</td><td></td></tr>
<tr><td>Page 75
8.2.5 Control of type 1 error</td><td></td><td></td></tr>
<tr><td>The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (in terms of superiority) only if the test of the primary endpoint results in rejection of the null hypothesis in favor of the experimental drugand that a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before are found to be statistically significant.</td><td>The experiment-wise type I error will be controlled to a maximum of two-sided 5%. A hierarchical closed testing procedure will be employed such that secondary endpoints will be considered for statistical significance (according to a predetermined hierarchy) if the test of the primary endpoint is statistically significant at one-sided 2.5% level in favor of experimental treatment; ~~(in terms of superiority) only if the test of the primary endpoint results in rejection of the null hypothesis in favor of the experimental drug and that~~ similarly, a secondary endpoint will be considered for statistical significance only if the secondary endpoint ordered before ~~are~~ is found to be statistically significant.</td><td>Edit to clarify hierarchical closed testing procedure.</td></tr>
<tr><td>Page 76
8.2.6 Primary Efficacy Analyses</td><td></td><td></td></tr>
<tr><td>The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in mean percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects.</td><td>The primary estimand is the difference between the randomized treatment groups, CaPre 4 g and placebo, in ~~mean~~ median percent change in fasting TG levels from baseline to Week 12 due to study medication and any subsequent rescue therapy regardless of treatment adherence in all ITT subjects.</td><td>Edit to clarify that the primary estimand is based on median.</td></tr>
</table>

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
An analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used to estimate the least squares (LS) means for the primary endpoint (percent change in TG levels). The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule. Prior to performing the parametric ANCOVA analysis, the normality assumptions will be investigated with the Shapiro-Wilk test on the residuals based on observed data only. If significant departures from normality are observed, the alternative non-parametric ANCOVA based on ranks will be performed as follow:	~~An~~ **A non-parametric rank-based** analysis of covariance (ANCOVA) model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCSK9I, alone or in combination vs. non-use at randomization, and baseline TG value as a covariate will be used **to perform a hypothesis test for the primary endpoint (percent change in TG levels)** to estimate t~~he least squares (LS) means for~~ the primary endpoint (percent change in TG levels). ~~The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule.~~ ~~Prior to performing the parametric ANCOVA analysis, the normality assumptions will be investigated with the Shapiro-Wilk test on the residuals based on observed data only. If significant departures from normality are observed, the alternative a non-parametric ANCOVA based on ranks will be performed as follow:~~	Edit to clarify that the primary analysis will be based on non-parametric ANCOVA, and no testing for normality assumptions will be performed.
Quantile regression, adjusting for the same baseline covariates as specified for the primary ANCOVA analysis model, will be used to obtain an adjusted estimate of the median treatment difference. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As sensitivity analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's comination rule are not satisfied.	Quantile regression, adjusting for the same baseline covariates as specified for the ~~primary~~ ANCOVA~~ analysis~~ model, will be used to obtain an adjusted estimate of the median treatment difference **vs. placebo with associated two-sided 95% CI**. Rubin's combination rule will be used to combine the estimates from multiply imputed datasets. As **supportive** ~~sensitivity~~ analysis, Hodges-Lehmann estimate for the median of the treatment difference and a corresponding 95% bootstrap CI will also be provided as an estimate of the treatment effect magnitude without adjustment for covariates. Bootstrap will be used for the computation of the 95% CI for the Hodges-Lehmann median treatment difference estimate based on the multiply imputed data because the assumptions of the Rubin's ~~comination~~ combination rule are not satisfied. ~~The LS mean for the treatment vs. placebo comparisons from the model will be presented for the contrast at 12 weeks, with the two-sided 95% confidence interval (CI) and p-values. This ANCOVA analysis will be performed on each of the multiple imputed datasets and the results will be combined using the Rubin's combination rule.~~	Edit to clarify that the primary analysis is based on non-parametric ANCOVA; clarify that Hodges-Lehman is used as supportive analysis to the primary analysis.
Page 78 8.2.8 Secondary Efficacy Analyses		
An ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo. The same normality assessment test as the primary endpoint will be performed for each secondary endpoint to select the appropriate parametric or non-parametric methods.	~~An~~ **A non-parametric rank-based** ANCOVA model with main effects of treatment, baseline TG category (≤750 mg/dL vs. >750 mg/dL) use of statin, CAI or PCSK9I, alone or in combination, vs. non-use at randomization, and baseline value as covariate will be used to estimate the treatment effect of CaPre 4 g vs. placebo. ~~The same normality assessment test as the primary endpoint will be performed for each secondary endpoint to select the appropriate parametric or non-parametric methods.~~	Edit to clarify that the secondary analysis will be based on non-parametric ANCOVA, and no testing for normality assumptions will be performed.
Page 88 8.2.10 Sensitivity Analysis		

Initial Protocol version 02 November 2017	Amended No. 1 22 May 2018	Rationale for change
-	**A tipping point approach will also be used to assess robustness of the primary analysis under alternative assumptions about missing data, i.e., assuming that subjects who withdraw from the study participation have worse outcomes compared to subjects who remain in the study.** Other sensitivity analysis methods may be performed and will be detailed in the SAP.	Text added to include Tipping point analysis as part of the sensitivity analyses to be performed.
More details of the two proposed sensitivity analyses and possibly additional ones will be presented in the SAP.	More details of the ~~two~~ proposed sensitivity analyses and possibly additional ones will be presented in the SAP.	Minor text edit for consistency.
Page 88 12.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR		
Version: Initial Protocol (02 November, 2017)	Version: **Amended Protocol (22 May, 2018)** Initial Protocol (02 November, 2017)	Edit to reflect amended protocol version.
14.0 APPENDIX 3: DETAILED REVISION HISTORY		
		New section added to detail to highlight all changes made to initial protocol 02 Nov 2017.

Protocol Approval Signatures

PROTOCOL TITLE: A Phase 3, multi-center, multi-national, placebo-controlled, randomized, double-blind 26-week study to assess the safety and efficacy of CaPre® in patients with severe hypertriglyceridemia

PROTOCOL NO: ACA-CAP-002

VERSION: Amended Protocol (22 May, 2018)
Initial Protocol (02 November, 2017)

Sponsor's representative

Signature: _____ **Date:** 22 MAY 2018
Laurent Harvey **DD/MMM/YYYY**
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Signature: _____ **Date:** 22 MAY 2018
Jean-François Lapointe **DD/MMM/YYYY**
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Lead Principal Investigator

Signature: _____ **Date:** _____
Dariush Mozaffarian, MD DrPH **DD/MMM/YYYY**