Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

MHICC

# STATISTICAL ANALYSIS PLAN

Protocol number: PROJ1601

## A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY TO COMPARE THE EFFICACY AND SAFETY OF HIGH-MEDIUM MOLECULAR WEIGHT BETA-GLUCAN IN SUBJECTS WITH HYPERLIPIDEMIA WITH OR WITHOUT STATIN THERAPY

## THE BETAVENA STUDY

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|---|---|
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# Revision History

| Version | Date (DD-MMM-YYYY) | Author | Summary of Changes |
|---|---|---|---|
| Final | 24-SEP-2021 | Sylvie Levesque | Initial version |
| Amendment 1 | 14-OCT-2021 | Sylvie Levesque | Section 6.3.6: Modification of the formula to calculate compliance to account for missing information.<br><br>Section 6.4.4.1: Addition of a sensitivity analysis on a modified PP population with compliance criteria set to 70%. |
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse Event |
| **ALT** | Alanine Aminotransferase |
| **ANCOVA** | Analysis of Covariance |
| **apo B** | Apolipoprotein B |
| **AST** | Aspartate Aminotransferase |
| **BLQ** | Below Limit of Quantification |
| **CPK** | Creatine Phosphokinase |
| **CRF** | Case Report Form |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic Case Report Form |
| **EENT** | Ears, Eyes, Nose, Throat |
| **EtOH** | Ethyl Alcohol or Alcohol |
| **HbA1c** | Hemoglobin A1C, Glycated Hemoglobin or Glycosylated Hemoglobin |
| **hCG** | Human Chorionic Gonadotropin |
| **HDL-C** | High-Density Lipoprotein Cholesterol |
| **hsCRP** | High Sensitivity C-Reactive Protein |
| **ITT** | Intent To Treat |
| **LDH** | Lactate Dehydrogenase |
| **LDL-C** | Low Density Lipoprotein-Cholesterol |
| **LP(a)** | Lipoprotein (a) |
| **MedDRA** | Medical Dictionary for Regulatory Activity |
| **MHI** | Montreal Heart Institute |
| **MHICC** | Montreal Health Innovations Coordinating Center |
| **PP** | Per Protocol |
| **RBC** | Red Blood Cell |
| **SAE** | Serious Adverse Event |
| **SAP** | Statistical Analysis Plan |
| **TC** | Total Cholesterol |
| **TG** | Triglycerides |
| **TID** | Three Times a Day |
| **VLDL-C** | Very Low-Density Lipoprotein Cholesterol |
| **WBC** | White Blood Cell |
| **WHO** | World Health Organization |

# 1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the final analysis of CEAPRO Inc. protocol PROJ1601. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. It is based on the protocol version 2.1 dated 23JAN2020 and on the annotated case report form (CRF) version 2.0. In case of differences in terms of descriptions or explanations between the SAP and the clinical protocol, the SAP will supersede the protocol. Any deviation to this SAP would be reported in the statistical report.

# 2 STUDY DESCRIPTION

## 2.1 Study Design

This is a Phase 2, double-blind, randomized, multicenter, 12-week comparative study of beta-glucan versus placebo, in subjects with an elevated LDL–C >3.37mmol/L (130 mg/dL) treated with a stable dose of statin for at least 6 weeks or not treated with a statin.

Following signature of informed consent, approximately 264 subjects (66 subjects per beta-glucan treatment group and 22 subjects per matching placebo group) meeting all inclusion criteria and no exclusion criteria will be randomized to receive one of the three doses of beta-glucan (1.5 g, 3 g or 6 g daily) TID or a matching placebo.

The subjects will be assigned to the three different doses of beta-glucan or placebo in a tiered fashion as follows:

- The first set of 88 subjects randomized will receive either 1.5 g beta-glucan (1 tablet of 500 mg TID) or a matching placebo in a 3:1 ratio,
- The next set of 88 subjects randomized will receive either 3 g of beta-glucan (2 tablets of 500 mg TID) or a matching placebo in a 3:1 ratio,
- The last set of 88 subjects randomized will receive either 6 g of beta-glucan (4 tablets of 500 mg TID) or a matching placebo in a 3:1 ratio.

The duration of treatment is twelve weeks with beta-glucan 1.5 g, beta-glucan 3 g, beta-glucan 6 g (total daily dose) or matching placebo. Each subject is expected to participate for about 15 weeks (up to 1 week of screening, 12-weeks of treatment and follow-up call 2 weeks after last dose taken).

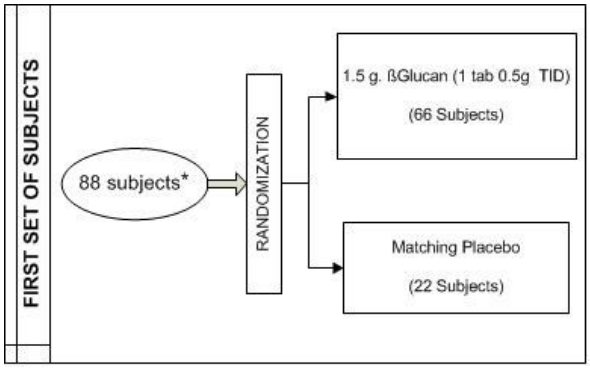
At baseline Visit (Week 0), the subjects should be already on a standard cholesterol lowering diet (American Heart Association Guidelines) and they should maintain it throughout the study. Subjects are encouraged to pursue a healthy lifestyle. The subjects must abstain from/minimize alcohol (EtOH) intake and keep stable any other variables that may alter serum lipid levels (e.g., strenuous exercise, weight loss programs, drugs including over the counter preparations that may alter serum lipid levels).

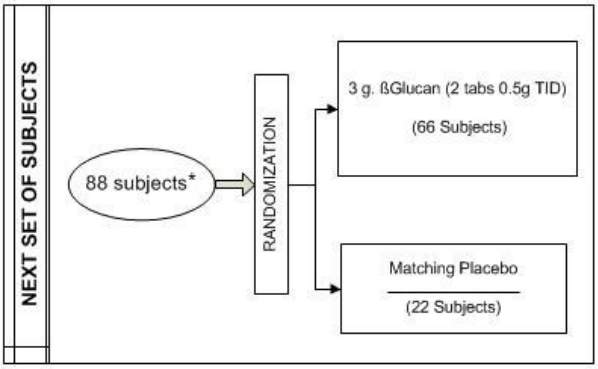
During the treatment period, subjects will return to the study site at Visit 3 (Week 6) and at the End of Treatment Visit (Week 12) for laboratory tests and clinical assessments, including for Adverse Events (AEs), dietary guidance and IP compliance. At the Safety Follow-up Visit (Week 14), subjects will be contacted via telephone for an assessment of Adverse Events (AEs). Time window for the Visit 3 (Week 6), Final Visit (Week 12) and Safety Follow-up Visit is ± 5 days.

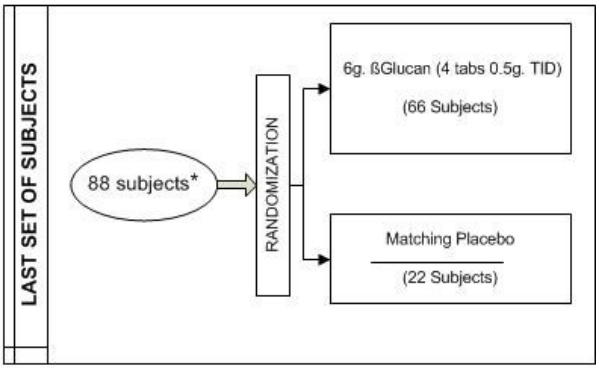
Laboratory tests and clinical assessments will be performed as noted in the schedule of visits (Appendix 1).

Safety and tolerability assessment will include AEs, hematology, biochemistry, physical examination, vital signs and electrocardiogram (ECG).

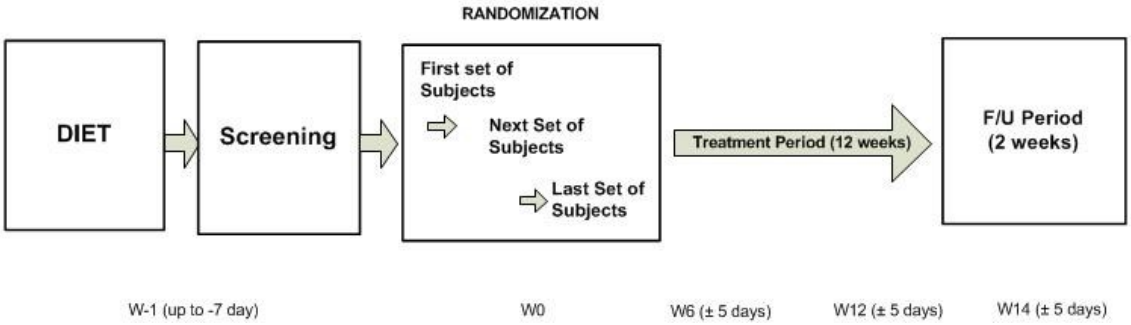
The study design is presented in the following figure.




* Subjects treated or not with a statin at baseline



### 2.2 Study Objectives

The overall aim of this study is to evaluate the effects of beta-glucan (1.5 g, 3 g or 6 g daily) administered three times a day (TID) in divided doses compared to placebo on heart disease lipid risk factors.

The primary objective is to evaluate the effects of beta-glucan on the direct-measured Low-Density Lipoprotein Cholesterol (LDL-C) level compared to placebo after 12 weeks of treatment in subjects with LDL-C > 3.37 mmol/L (130 mg/dL).

The secondary objectives are to evaluate:

- The effects of beta-glucan on Total Cholesterol (TC), small LDL-C subclass particle concentration, high sensitivity C-reactive protein (hsCRP), non-High Density Lipoprotein Cholesterol (HDL-C), Apolipoprotein B (apo B) and Very Low Density Lipoprotein Cholesterol (VLDL-C) levels compared to placebo after 12 weeks of treatment.
- The safety profile of beta-glucan.

The exploratory objectives are to evaluate the effects of beta-glucan on HDL-C, Triglyceride (TG), Lipoprotein a (Lp(a)) and glycated hemoglobin (HbA1c) levels compared to placebo after 12 weeks of treatment.

## 3 DATASETS ANALYZED

Subjects who were not eligible for randomization but who have been erroneously randomized into the study will be excluded from all datasets analyzed, if they did not take study medication. All populations of analysis will be approved by the sponsor prior to unblinding.

### 3.1 Intent-To-Treat (ITT) Population

All patients randomized will be included in the ITT population (i.e. subjects having a randomization number on the Randomization Form of the electronic case report form (eCRF)). In the ITT population, subjects allocated to a treatment group by randomization will be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

### 3.2 Per-Protocol Population

The per-protocol population will include all subjects randomized, excluding subjects who were not compliant to IP and who had major protocol deviation. Subjects will be assigned to treatment groups as randomized for analysis purposes. Specific requirements are:

- Compliance of at least 80%. The compliance will be taken from the Drug Accountability Form of the eCRF.
- Absence of any major protocol deviations that could affect the primary endpoint. Those major protocol deviations are defined as:
    - "Incorrect investigational product kit administrated to subject" on Protocol Deviation Form of the eCRF

- "Subject received another investigational product" on Protocol Deviation Form of the eCRF
- Inclusion criteria "Subjects with hyperlipidemia treated with stable dose of statin for at least 6 weeks; either atorvastatin (10 mg to 20 mg daily) or equivalent dose of another statin at the time of informed consent and with LDL-C level >3.37 mmol/L (130 mg/dL) in fasting conditions at screening." not met on Inclusion/Exclusion Criteria Form of the eCRF version previous 2.1.
- Inclusion criteria "Subjects with hyperlipidemia with LDL-C level >3.37 mmol/L (130 mg/dL) in fasting conditions at screening, treated with a stable dose of statin for at least 6 weeks or not treated with a statin at the time of informed consent." not met on Inclusion/Exclusion Criteria Form of the eCRF version 2.1.
- Any other protocol deviations considered as major as per the sponsor.

### 3.3 Safety Population

The safety population will include all randomized subjects who received at least one dose of IP (i.e. subjects with at least one non missing Investigational Product treatment period start date (variable EXSTDAT or a comment indicating unknown date of first dose) on Investigational Product Use Form of the eCRF). Subjects will be assigned to treatment groups as per actual treatment received for analysis purposes.

## 4 EFFICACY ENDPOINTS

### 4.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from Week 0 to Week 12 in direct-measured LDL-C.

### 4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the changes from Week 0 to Week 12 in:

- TC
- non-HDL-C
- small LDL subclass particle concentration
- hsCRP
- VLDL-C
- Apo B

### 4.3 Exploratory Endpoints

Exploratory endpoints will include changes from Week 0 to Week 12 in:

- HDL-C
- TG
- Lp(a)
- HbA1c

# 5 SAFETY PARAMETERS

Safety will be assessed by adverse events (AEs) and serious adverse events (SAEs), physical examination results, vital signs, ECG and laboratory parameters (hematology, biochemistry).

## 5.1 Adverse Events

As per Natural Health Products Regulations SOR/2003-196, an AE is any adverse occurrence in the health of a clinical trial subject who is administered a natural health product that may or may not be caused by the administration of the natural health product, and includes an adverse reaction, a serious adverse reaction and a serious unexpected adverse reaction.

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition is to be reported as AE. Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concurrent medication are to be reported as AEs.

Medical or surgical procedures (e.g. endoscopy, appendectomy) are not to be reported as AEs; the medical condition that leads to the procedure is an AE. For each adverse event, start and stop dates, action taken, outcome, intensity and relationship to IP (causality) must be documented by the investigator. If an AE changes in frequency or intensity during a study, an update of the event must be made on the eCRF.

Treatment-emergent adverse events will be defined as adverse events with a start date on or after the first dose of study product (which will be derived as the earliest date of variable EXSTDAT on Investigational Product Use Form of the eCRF).

## 5.2 Serious Adverse Events

A serious adverse event is a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization that causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

SAEs will be collected from the time of consent through to 2 weeks after the last dose of study product.

## 5.3 Physical Examination

Physical examinations will include examination of the following body systems: general appearance, skin (including hair and nails), EENT (ears, eyes, nose, throat), neck/thyroid, chest/lungs, cardiovascular, gastrointestinal, genito-urinary (optional), neurological, lymphatic and musculoskeletal systems. Height and body weight will also be measured and recorded at Screening, and weight at the Week 12.

Any new clinically significant finding identified upon physical examination that meets the definition of an AE or SAE must be documented as such.

## 5.4 Vital Signs

Blood pressure and pulse will be recorded after at least 5-minute rest in the sitting position. Two measurements should be made for each blood pressure measurement and the average recorded. Vital sign checks will be performed at Screening, Baseline, Week 6 and Week 12.

### 5.5 Electrocardiogram

All ECGs will be obtained in the decubitus position following a 10-minute rest time. The following parameters PQ (PR), QRS, QT, RR, QTcB (calculated according to Bazett's formula) and the heart rate will be measured automatically and recorded in the eCRF at Screening and Week 12.

### 5.6 Laboratory Parameters

A full clinical laboratory profile including hematology, biochemistry, lipids and other analyses will be performed during the study. Laboratory data will be transferred electronically by the Dynacare central lab. Blood samples are to be collected at Screening, Baseline, Week 6, Week 12 and at some unscheduled visits if it is necessary to repeat testing following abnormal laboratory results. Here is the list of the collected laboratory assessment:

**Screening (Visit 1)**: The following screening laboratory assessments are to be performed during the screening period for the determination of study eligibility and the patient's current medical state at the time of study entry:

| | Determinations | |
|---|---|---|
| Hematology | RBC<br>Hemoglobin<br>Hematocrit<br>WBC<br>Platelet Count | |
| | Differential<br>(to be performed only<br>if WBC is abnormal) | Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Biochemistry | AST<br>ALT<br>Bilirubin<br>Creatinine<br>eGFR | |
| Lipids | Triglycerides<br>Total cholesterol<br>LDL-Cholesterol<br>HDL-Cholesterol | |
| Urine (only for females of childbearing potential) | Human chorionic gonadotropin (hCG) urine pregnancy test | |

**Baseline and Treatment Period (Visits 2, 3, and 4)**

| | Determinations | |
|---|---|---|
| Hematology | RBC<br>Hemoglobin<br>Hematocrit<br>WBC<br>Platelet Count | |
| | Differential<br>(to be performed only<br>if WBC is abnormal) | Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Biochemistry | AST<br>ALT<br>LDH<br>CPK<br>Creatinine<br>eGFR<br>Glucose (fasting) (at visit 2 and 4 only)<br>Insulin (fasting) (at visit 2 and 4 only)<br>HbA1c (at visit 2 and 4 only)<br>hs-CRP (at visit 2 and 4 only) | |
| Lipids / Other | Triglycerides<br>Total cholesterol<br>LDL-Cholesterol (direct-measured)<br>HDL-Cholesterol<br>VLDL Cholesterol<br>Apolipoprotein B (apo B)<br>Lipoprotein (a) [Lp(a)]<br>Non-HDL-C<br>small low-density lipoprotein (LDL) subclass particle concentration | |
| Urine (only for females of childbearing potential) | Human chorionic gonadotropin (hCG) urine pregnancy test (Visit 2 only) | |

Female patients of childbearing potential will have a urine pregnancy test performed at the Screening visit and at Baseline.

# 6 STATISTICAL METHODOLOGY

## 6.1 Determination of Sample Size

Sample size computation was based on the change in LDL-cholesterol. Based on previous literature, we are expecting a mean decrease from baseline to follow-up in LDL-C of -0.30 mmol/L (11.6 mg/dl) in the placebo group and we are aiming to show that the addition of beta-glucan, either at 1.5 g, 3 g or 6 g, will further reduce LDL-C by -0.30 mmol/L, leading to an expected difference in change in LDL-C of 0.30

mmol/L between the placebo group and at least one of the active groups. The expected standard deviation of the change in LDL-C is 0.50 mmol/L (19.3 mg/dl). To reach a power of 80% in detecting this 0.30 mmol/L difference with a two-tailed significance level of 0.0167 (to account for three main comparisons (placebo vs. beta-glucan 1.5 g, placebo vs. beta-glucan 3 g and placebo vs. beta-glucan 6 g), 60 subjects per group were needed for a total of 240 subjects. To account for approximately 9% lost to follow-up, 264 subjects (66 subjects per treatment group) were randomized.

Sample size was calculated with nQuery + nTerim 2.0.

### 6.2 Statistical Considerations

This is a randomized, parallel study with four treatment groups (placebo, beta-glucan 1.5 g, beta-glucan 3 g and beta-glucan 6 g). The statistical analysis will focus on the comparisons of the three active groups vs. placebo.

Descriptive statistics of all study variables will be presented overall and broken down by treatment group. Number of observations, mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Count and proportion will be displayed for categorical variables.

Basic assumptions of the proposed analyses will be checked and data transformation or other analyses could be done if appropriate. For example, as some endpoints are likely to be skewed (ex. triglycerides, hsCRP), log-transformation might be used, in which case descriptive statistics would also include geometric means.

Laboratory parameters will be assigned to visits based on number of days from randomization and not based on scheduled visit at which the measurement was made. The time windows that will be used to assign measurements to visits are given in Appendix 2.

Values entered as less than a specified value will be considered as the specified value divided by 2 (e.g. entered value <0.2 will be analyzed as 0.1). Values entered as BLQ (Below Limit of Quantification) will be considered as the limit of quantification divided by 2. Values entered as more than a specified value will be considered as the specified value.

All statistical tests will be two-sided. Tests involving the comparisons of the active groups vs. placebo for the primary endpoint will be conducted at the 0.0167 significance level. All other tests will be considered secondary or exploratory and will be conducted at the 0.05 significance level.

No interim analysis on efficacy endpoints is planned for this study.

Statistical analyses will be done using SAS version 9.4 or higher.

#### 6.2.1 Handling of Missing Data

For efficacy laboratory endpoints, the screening value will be taken if the baseline value is missing.

In addition, the proposed statistical analysis will account for all available data and will not disregard subjects with missing data at either Week 6 or Week 12. However, in subjects who will only have a baseline measurement, the last observation carried forward approach will be used.

## 6.3 Study Subjects

### 6.3.1 Subject Disposition

Number of subjects screened, number of subjects randomized, number of subjects who took at least one dose of study medication, number of randomized subjects who complete all study visits and reasons if not will be summarized overall and by treatment group. A listing of subject disposition will be provided. Subject disposition will also be presented with a flow chart.

### 6.3.2 Protocol Deviations

Protocol deviations, as collected on the Protocol Deviation Form of the eCRF, will be summarized overall and by treatment group for the ITT population. A listing will also be provided.

### 6.3.3 Datasets Analyzed

The number of subjects in each datasets will be summarized overall and by treatment group. A listing, including reason for being excluded from a given dataset, will be provided as well.

### 6.3.4 Demographic and Baseline Characteristics

Demographic data and baseline characteristics such as medical history will be summarized using descriptive statistics, overall and by treatment group for the ITT population. A listing will be presented for demographic data.

### 6.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded with respect to indication and generic name using the WHO Drug dictionary (version C March 2018).

Frequency of use of medications at randomization will be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

A medication will be flagged as being ongoing at the time of randomization if:

- Medication start date < randomization date
  AND
- Medication end date ≥ randomization date OR Medication is ongoing

In case of missing or incomplete medication start / end dates, the following rules will be applied:

- If 1) the medication start date is completely missing or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same as the randomization month/year, then the medication will be assumed to have started before randomization.
- If 1) the medication end date is completely missing or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same

as the randomization month/year, then the medication will be assumed to have ended after randomization.

- Otherwise, partial medication start / end dates will be compared to the randomization date and the medication will be classified accordingly.

Frequency of use of prior and concomitant medications will also be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

### 6.3.6 Treatment Compliance

An overall compliance calculation will be performed using primarily the study administration intake recorded on the Drug Accountability Form of the eCRF or on the Investigational Product Use Form of the eCRF if information regarding study medication returned/lost is missing. Compliance for the whole study is derived as follows:

| | | |
|---|---|---|
| Compliance overall (%) | Pill counts (%) | [sum of caplets dispensed – sum of caplets returned – sum of caplets lost] x 100<br>[# caplets to take per day x (date last scheduled visit – date rando)] |
| | Days on treatment (%) | If # of caplets dispensed ≠ missing<br>AND<br>If information regarding study medication returned is missing (i.e. # of caplets returned is missing and/or # of caplets lost is missing)<br><br>[date of last dose – date of first dose] x 100<br>[date last scheduled visit – date rando] |
| | NA | If # of caplets dispensed = missing<br>OR<br>If last scheduled visit = baseline |

Where

- Cohort 1 (rando number 001 à 280): Number of tablets dispensed = 147 (# caplets per day = 3)
- Cohort 2 (rando number 281 à 563): Number of tablets dispensed = 294 (# caplets per day = 6)
- Cohort 3 (rando number 564 à 997): Number of tablets dispensed = 588 (# caplets per day = 12)

Compliance will also be categorized as follow: < 80%, [80%-120%] or >120% and summarized accordingly using frequencies and percentages, by treatment arm, for the subjects of the ITT population.

## 6.4 Efficacy Analysis

Unless otherwise specified, all efficacy analyses will be conducted on the ITT population.

### 6.4.1 Primary Analysis

The primary endpoint is the change from Week 0 to Week 12 in direct-measured LDL-C. The changes, as well as the LDL-C values at each study visit, will be summarized with descriptive statistics.

The primary endpoint will be compared between treatment groups using a repeated measures analysis of covariance (ANCOVA) model.. More specifically, the dependent variable will be the change from Week 0 in LDL-C (change calculated as post Week 0 level – Week 0 level) the model will include treatment group, time (Week 6 and Week 12) and treatment group x time interaction as well as the covariates of Week 0 value of LDL-C and Week 0 value of LDL-C x time interaction. An unstructured covariance structure will be

used to model the within-patient errors and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Contrasts under this model will allow for the three main comparisons: placebo vs. beta-glucan 1.5 g, placebo vs. beta-glucan 3 g and placebo vs. beta-glucan 6 g. More specifically, the following hypotheses will be tested:

$$H0: \Delta_{W12,placebo} = \Delta_{W12,1.5g} \quad vs. \quad H1: \Delta_{W12,placebo} \neq \Delta_{W12,1.5g}$$

$$H0: \Delta_{W12,placebo} = \Delta_{W12,3g} \quad vs. \quad H1: \Delta_{W12,placebo} \neq \Delta_{W12,3g}$$

$$H0: \Delta_{W12,placebo} = \Delta_{W12,6g} \quad vs. \quad H1: \Delta_{W12,placebo} \neq \Delta_{W12,6g}$$

where $\Delta_{W12,placebo}$, $\Delta_{W12,1.5g}$, $\Delta_{W12,3g}$ and $\Delta_{W12,6g}$ are respectively the mean change from Week 0 to Week 12 in LDL-C in the placebo, beta-glucan 1.5 g, beta-glucan 3 g and beta-glucan 6 g group.

All sets of hypotheses will be tested at the 0.0167 significance level to maintain the overall type I error to 0.05 for the primary endpoint. These tests will be considered as the primary analysis of the study.

For illustrative purposes, changes within groups will be tested at the 0.05 significance level. Estimates of the changes within groups and of the between-group differences will also be presented along with 95% confidence intervals.

The same ANCOVA model will also allow for the examination of the change from Week 0 to Week 6 in LDL-C. In other words, the hypotheses described above will also be tested at Week 6 at the 0.05 significance level for illustrative purposes.

Because the SAS procedure PROC MIXED will be used, subjects with missing data at a given study visit will not be excluded from the analysis.

### 6.4.2 Secondary Analysis

Secondary endpoints are expressed as change from Week 0 to Week 12. Those that are measured at baseline (Week 0), Week 6 and Week 12 will be analyzed as the primary endpoint, with the exception that tests will be conducted at the 0.05 significance level. Those measured at baseline (Week 0) and Week 12 only will be analyzed with an analysis of covariance (ANCOVA) model including treatment group and baseline value. Because it is expected that the distribution of hsCRP will be skewed, a log-transformation will be applied to hsCRP data prior to analysis. Geometric mean and geometric mean percent change will be added to the descriptive statistics that will be presented.

### 6.4.3 Exploratory Analysis

Similarly, exploratory endpoints are expressed as change from Week 0 to Week 12. Those that are measured at baseline (Week 0), Week 6 and Week 12 will be analyzed as the primary endpoint, with the exception that tests will be conducted at the 0.05 significance level. Those measured at baseline (Week 0) and Week 12 only will be analyzed with an ANCOVA model including treatment group and baseline value. Because it is expected that the distribution of triglycerides will be skewed, a log-transformation will be applied to triglycerides data prior to analysis. Geometric mean and geometric mean percent change will be added to the descriptive statistics that will be presented.

### 6.4.4 Sensitivity Analysis

#### 6.4.4.1 Per-Protocol Analysis

The analysis of the primary endpoint described in section 6.4.1 will be repeated on the PP population. The tests will be conducted at the 0.05 significance level.

To better understand the impact of compliance, the same analysis will be repeated on a modified version of the PP population where the compliance criteria will be set to 70%. In other word, the analysis of the primary endpoint will be conducted in patients who had a compliance of at least 70% and no major protocol deviations that could affect the primary endpoint.

#### 6.4.4.2 Dose-Response Analysis

In order to visualize the dose-response relationship, a regression model including linear and quadratic terms will be used to characterize the relationship between dose level (considered as a continuous variable) and the change from Week 0 to Week 12 in direct-measured LDL-C. More specifically, the model will be:

$$Y_j = \beta_0 + \beta_1 d_j + \beta_2 d_j^2 + \varepsilon_j$$

where $Y_j$ is the change from Week 0 to Week 12 of the $j^{th}$ patient, $\beta_0$ is the intercept, $\beta_1$ is the coefficient of the linear dose term, $\beta_2$ is the coefficient of the quadratic dose term, $d_j$ is the dose level (0g, 1.5g, 3g, 6g) and $\varepsilon_j$ is the error term. A test of the null hypothesis $H_0$: $\beta_2 = 0$ versus the alternative hypothesis $H_1$: $\beta_2 \neq 0$ will be performed at the 0.05 significance level. Non rejection of the null hypothesis will result in dropping the quadratic term from the model and concluding that a linear relationship provides a better fit. Otherwise, the quadratic term will be kept in the model. A plot of the predicted dose-response curve with 95% CIs will be provided to visualize the dose response relationship, along with the estimate of the coefficients $\beta_1$ and $\beta_2$ (if applicable) with associated 95% CI and p-values.

### 6.4.5 Subgroup Analysis

The following subgroup analyses are planned for the primary endpoint:

- Hypercholesterolemia according to median of direct-measured LDL-C at baseline,
- Hypercholesterolemia according to quartiles of direct-measured LDL-C at baseline,
- Male vs female,
- Diabetic vs non-diabetic,
- Hypertensive vs non-hypertensive,
- Age < 65 years old vs. age ≥ 65 years old,
- Age according to quartiles,
- Treated with a statin at baseline vs. not treated with a statin at baseline (based on variable DS_STATIN on the Randomization Form of the electronic case report form (eCRF)).

For subgroup analyses, ANCOVA models on the change from Week 0 to Week 12 in LDL-C will be used. These models will include a factor for the Week 0 value of LDL-C, as well as factors for the treatment

group, the subgroup variable and the treatment group x subgroup variable interaction. This interaction term will determine the impact of the subgroup on the treatment effect. For illustrative purposes, estimates of treatment effect will be presented within each subgroup. The tests will be conducted at the 0.05 level for the ITT population.

## 6.5 Safety Analysis

The safety analyses described in this section will be conducted on the safety population. No formal statistical testing is planned for the safety parameters.

### 6.5.1 Treatment Exposure

Duration of exposure will be defined as number of days on treatment (computed as date of last dose – date of first dose + 1) for each subject. Date of last dose of study drug will be derived as the latest date of variable EXENDAT and date of first dose of study drug will be derived as the earliest date of variable EXSTDAT both on Investigational Product Use Form. In subjects with a comment indicating unknown date of first dose, randomization date will be used. In addition, if the date of last dose is missing the minimum of Week 12 visit date or study completion date will be used. Duration of exposure will be summarized overall and by treatment group. Duration of exposure will also be categorized according to 14 days intervals ([1-14], [15-28], [29-42], etc.) and summarized accordingly using frequencies and percentages, overall and by treatment group. Summary of study treatment discontinuation will also be presented overall and by treatment group.

### 6.5.2 Adverse Events and Serious Adverse Events

#### 6.5.2.1 Adverse Events

AEs will be coded by system organ class and body system according to the MedDRA dictionary (version 22.0).

The total number of TEAEs reported, the number and proportion of subjects experiencing at least one TEAE, at least one severe TEAE, at least one TEAE related to the study treatment, and at least one TEAE leading to drug withdrawal will be presented. In addition, number and proportion of subjects experiencing a treatment-emergent AE will be presented by system organ class and preferred term overall and for each treatment group.

A treatment-emergent AE will be defined as an AE with onset date on or after the date of first dose. If it is not possible to assess the timing of the start of the AE to the date of first dose due to incomplete AE onset date and/or incomplete date of first dose, the event will be assumed to be treatment-emergent.

All AEs will be listed but only treatment-emergent AEs will be summarized.

#### 6.5.2.2 Serious Adverse Events

Serious adverse events will be presented in a manner similar to that described for adverse events.

### 6.5.3 Physical Examination

Physical examinations will include examination of various body systems and will be summarized by visit (Screening, Week 12) using frequencies and percentages, overall and by treatment group.

### 6.5.4 Vital Signs

Vital signs will be summarized by visit (Screening, Baseline, Week 6, Week 12) using descriptive statistics, overall and by treatment group.

### 6.5.5 Electrocardiogram

ECGs parameters will be summarized by visit (Screening, Week 12) using descriptive statistics, overall and by treatment group.

### 6.5.6 Laboratory Parameters

Laboratory parameters, more specifically hematology and biochemistry parameters, will be summarized using descriptive statistics and presented by study visit (Screening, Baseline, Week 6 and Week 12) and treatment group.

All laboratory results will be listed.

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## 8 REFERENCES

Not applicable.

# 9 APPENDICES

## 9.1 Appendix 1 - Schedule of visits

| Procedure/Visit | Screening Period (V1) | Randomization Baseline Visit (V2) | Visit 3 (V3) | End of Treatment Visit (V4) | Safety Follow-up Visit (V5) (telephone) |
|---|---|---|---|---|---|
| | Week -1 Up to 7 days | Week 0 | Week 6 ( ± 5 days) | Week 12 ( ± 5 days) | Week 14 (± 5 days) |
| Informed consent form | X | | | | |
| Inclusion & Exclusion criteria | X | X | | | |
| Medical History | X | X | | | |
| Demographics | X | | | | |
| Physical examination | X | | | X | |
| Vital signs (blood pressure, pulse) | X | X | X | X | |
| Height | X | | | | |
| Weight | X | | | X | |
| Dietary counselling including alcohol consumption, and timing of statin vs. IP intake | X | X | X | | |
| Check compliance on statin and IP | | | X | X | |
| 12-Lead ECG | X | | | X | |
| Hematology | X | X | X | X | |
| AST, ALT, Creatinine | X | X | X | X | |
| Bilirubin | X | | | | |
| LDH, CPK | | X | X | X | |
| TG, TC, LDL-C, HDL-C | X | X | X | X | |
| LDL-C (direct-measured), VLDL-C, apo-B, Lp(a), non-HDL-C, small low-density lipoprotein (LDL) subclass particle concentration | | X | X | X | |
| HbA1c, Insulin, Glucose and hsCRP | | X | | X | |
| Concomitant medication | X | X | X | X | |
| Pregnancy test* | X* | X* | | | |
| Randomization | | X | | | |
| IP dispensing | | X | X | | |
| Adverse Events | X** | X** | X** | X** | X** |

*Female patients of childbearing potential will have a urine pregnancy test performed at the screening visit and at randomization (visit 2)
**Serious Adverse Events (SAEs) are captured from the time of consent through to week 14 safety Follow up phone call. AEs are captured between the time of randomization up to the last dose IP taken.

## 9.2 Appendix 2 - Reporting windows for laboratory parameters

Number of days between a laboratory assessment and randomization will be calculated (date of assessment – date of randomization + 1 day), compared to the lab reporting window below, and the assessment will be assigned to the corresponding visit.

| VISIT | SCHEDULED VISIT | SCHEDULED DAY | SCHEDULED WINDOW (± DAYS) | SCHEDULED WINDOW (DAYS) | LAB REPORTING WINDOW (DAYS) |
|---|---|---|---|---|---|
| V1 | Screening | | Up to 7 days before randomization | <1 | <1 |
| V2 | Baseline (randomization) | 1 | | 1 | 1 to 2 |
| V3 | Week 6 | 42 | ±5 | 37 to 47 | 3 to 63 |
| V4 | Week 12 | 84 | ±5 | 79 to 89 | ≥64 |

**Notes:**
The algorithm chooses the mid-point between consecutive scheduled visits and so achieves that no gaps between reporting windows occur, and that reporting windows correspond to the schedule of assessments.

In cases where more than one non missing assessment falls within the same window, the closest assessment will be chosen.

The LAB reporting window for baseline visit include day 2 because some subjects were randomized on scheduled day 1 but laboratory parameters were taken only the next day, where day 2 is the day of first dose.