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.

Protocol Number/Protocol Name: PROJ1601 / BetAvena

Product Code: CP105F

Sponsor name: CEAPRO Inc.

CEAPRO
Nature Enhancing Life®

Version number: Version 2.1

23-Jan-2020

Signature Approval Page

By signing below, I indicate that I have reviewed the Clinical Protocol in its entirety and approve its contents.

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INVESTIGATOR'S STATEMENT AND SIGNATURE

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.

Protocol Number/Protocol Name: PROJ1601/BetAvena

Product Code: CP105F

Version Date: 23-Jan-2020

I have read the protocol described herein and I agree to comply with all applicable laws and regulations in accordance with Good Clinical Practice, and in accordance with the ethics principles outlined in the Declaration of Helsinki, and conduct this clinical study as described in this protocol.

By signing below, I hereby declare that I am not debarred, disqualified, or otherwise restricted by any agency from conducting research studies.

Principal Investigator:

Print/Type Name: _____

Signature: _____ Date: _____

SYNOPSIS OF PROTOCOL NUMBER / NAME: PROJ1601

Sponsor: CEAPRO Inc.	Name of Study Product: CP105F (Oat beta-glucan)	Date: 23-Jan-2020

Title of Study: 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.

Principal Investigator: Jean-Claude Tardif, MD

Study Sites: Up to twelve (12) study sites in Canada

Treatment duration: 12 weeks	**Phase of Development**: 2

Objective: The objective 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 on heart disease lipid risk factors.

Methodology:

Male and female subjects ≥ 18 years of age with an elevated LDL–C > 3.37 mmol/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) administered TID in divided doses or a matching placebo.

The subjects will be assigned to the 3 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 daily (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 daily (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 daily (4 tablets of 500 mg TID) or a matching placebo in a 3:1 ratio.

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 Adverse Events (AEs), dietary guidance and study product compliance. At the Safety Follow-up Visit (Week 14), subjects will be contacted via telephone for an assessment of AEs.

Number of Subjects:

Planned: Approximately 310 subjects screened to randomize approximately 264 subjects (66 per treatment group and 22 per matching placebo group).

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 18 years of age with an elevated LDL–C > 3.37 mmol/L (130 mg/dL) treated with a stable dose of statin for at least 6 weeks or not treated with a statin.

Test Product, Dose/Strength/Concentration, Mode of Administration:

Test product: Oat beta-glucan tablet is a natural health product of high-medium molecular weight produced through CEAPRO's proprietary and patented Pressurized Gas eXpanded technology.

Dose: 1.5 g or 3 g or 6 g daily

Mode of administration: oral

Duration of Treatment:

Twelve weeks of treatment with beta-glucan 1.5 g, beta-glucan 3 g, beta-glucan 6 g (total daily dose) or a 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).

Criteria for Evaluation:

Efficacy:

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

The secondary efficacy endpoints will be changes from Week 0 to Week 12 in total cholesterol (TC), non-High-density lipoprotein cholesterol (non-HDL-C), small low-density lipoprotein (LDL) subclass particle concentration, high sensitivity C-reactive protein (hsCRP), very low-density lipoprotein cholesterol (VLDL-C), and apo B.

Exploratory endpoints will include changes in HDL-C, triglycerides, Lipoprotein (a) (Lp(a)) and glycated hemoglobin (HbA1c).

Safety:

Safety will be assessed by adverse events, physical examination, vital signs, ECG, and laboratory analyses (hematology, biochemistry).

Statistical Methods:

Sample Size:

Sample size computation is based on the change in LDL-C. 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 control 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 control 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 the 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 are required for a total of 240 subjects. To account for approximately 9% lost to follow-up, 264 subjects (66 subjects per treatment group) will be randomized.

Efficacy:

The primary dataset for efficacy analyses will be the set of all randomized subjects (ITT Population).

For the primary, secondary and exploratory endpoints, the values at each study visit and the changes from Week 0 to follow-up visits (week 6 and week 12) will be summarized for each treatment group using descriptive statistics. The changes will be compared between treatment groups using repeated measures analysis of covariance (ANCOVA) models adjusting for the Week 0 value. Contrasts under these models 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. For the primary endpoint, these comparisons will be done at the 0.0167 significance level. The significance level will be set to 0.05 for all other analyses.

Safety:

The primary dataset for safety analyses will be the set of all randomized subjects who received at least one dose of investigational product (IP) (Safety Population).

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary. Treatment-emergent adverse events will be summarized for each treatment group.

Treatment-emergent adverse events will be defined as adverse events with a start date on or after the first dose of study product.

For all study visits as well as for the changes from Week 0 to follow-up visits (week 6 and week 12) when applicable, safety laboratory parameter and other safety assessments, including physical examination, vital signs and ECG, will be summarized for each treatment group using descriptive statistics.

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GLOSSARY OF ABBREVIATIONS

• ACC	• American College of Cardiology
• AE	• Adverse Event
• AHA	• American Heart Association
• ALT	• Alanine aminotransferase
• ANCOVA	• Analysis of Covariance
• apo B	• apolipoprotein B
• AST	• Aspartate aminotransferase
• BMI	• Body mass index
• β-glucan	• beta-glucan
• CABG	• Coronary artery bypass graft
• CAD	• Coronary artery disease
• CHD	• Coronary Heart Disease
• CI	• Confidence interval
• COR	• Class of Recommendation
• CPK	• Creatine phosphokinase
• CRA	• Clinical Research Associate
• CRF	• Case Report Form(s)
• CQ	• Critical Question
• CVD	• Cardiovascular Disease
• DASH	• Dietary Approaches to Stop Hypertension
• dL	• deciliter

GLOSSARY OF ABBREVIATIONS

• DSMC	• Data Safety Monitoring Committee
• EAS	• European Atherosclerosis Society
• ECG	• Electrocardiogram
• EENT	• Ears, eyes, nose, throat
• EFSA	• European Food Safety Authority
• eCRF	• Electronic case report form(s)
• ES	• Evidence Statement
• ESC	• European Society of Cardiology
• EtOH	• Ethyl alcohol or alcohol
• FDA	• Food and Drug Administration
• G	• Gram
• GCP	• Good Clinical Practice
• GFR	• Glomerular filtration rate
• HbA1c	• Hemoglobin A1C, glycated hemoglobin or glycosylated hemoglobin
• Hb	• Hemoglobin
• HDL-C	• High-density lipoprotein cholesterol
• HMG-CoA	• 3-hydroxy-3-methyl-glutaryl-co-enzyme A
• hsCRP	• High sensitivity C-reactive protein
• ICF	• Information and Consent Form
• ICH	• International Council for Harmonisation
• IEC	• Independent Ethics Committee
• IDL-C	• Intermediate-density lipoprotein cholesterol
• IP	• Investigational Product
• IRB	• Institutional Review Board
• ITT	• Intention to Treat
• Kg	• Kilogram
• LDL-C	• Low density lipoprotein-cholesterol
• LOE	• Level of Evidence
• LP(a)	• Lipoprotein (a)
• MedDRA	• Medical Dictionary for Regulatory Activity
• Mg	• Milligram
• MHI	• Montreal Heart Institute
• MHICC	• Montreal Health Innovations Coordinating Center
• NCEP	• National Cholesterol Education Program
• NHLBI	• National Heart, Lung and Blood Institute
• Non-HDL-C	• Non-High-density lipoprotein cholesterol
• NYHA	• New York Heart Association
• PGX	• Pressurized Gas Expanded

GLOSSARY OF ABBREVIATIONS

• PCI	• Percutaneous coronary intervention
• SAE	• Serious Adverse Event
• SAP	• Statistical analysis plan
• SC	• Steering committee
• SUSAR	• Suspected unexpected serious adverse reaction
• TC	• Total cholesterol
• TDD	• Total daily dose
• TIA	• Transient ischemic attack
• TID	• Three times a day
• TLC	• Therapeutic Lifestyle Changes
• TG	• Triglycerides
• ULN	• Upper limit of normal
• USDA	• US Department of Agriculture
• VLDL-C	• Very low-density lipoprotein cholesterol
• WBC	• White blood cell

1 BACKGROUND AND RATIONALE

Hyperlipidemia is a potent risk factor for atherosclerosis and, implicitly for Cardiovascular Disease (CVD). CVD is one of the leading causes of death and disability in Canada and worldwide. Atherosclerotic coronary artery disease (CAD), the most common form of CVD, is characterised by plaque build-up inside the arteries. The plaque, or atheroma, is formed of fatty deposits, calcium and cells. The fatty deposits thicken the arteries and promote the accumulation of calcium and cells, leading to the formation of plaques. The plaque can then rupture diminishing the downstream blood flow by the formation of superimposed luminal thrombosis, which leads to either a heart attack or stroke depending on the artery affected. [1, 2, 3]

Lipid-related risk factors for atherosclerotic CAD include elevated levels of total cholesterol (TC), non-HDL cholesterol, very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B or B-100), intermediate-density lipoprotein cholesterol (IDL-C), lipoprotein(a) and reduced concentrations of high-density lipoprotein cholesterol (HDL-C).[4,5,6]

LDL-Cholesterol makes up to 60-70% of the total serum cholesterol and the LDL particle has been identified as being the major atherosclerotic lipoprotein. The studies across different populations have shown that there is a positive relationship between serum LDL-C levels and the development of the first or subsequent attacks of Coronary Heart Diseases (CHD). [4]

LDL-Cholesterol is the primary target of treatment in clinical lipid management. The therapeutic goal is achieved in many persons by using therapeutic lifestyle changes (TLC), including LDL-lowering dietary options (plant stanols/sterols and increased viscous fibre). Lifestyle changes include smoking cessation, an overall healthy eating pattern, with maintenance of appropriate body weight, and controlled blood pressure and diabetes. Nonetheless, the LDL-C goal currently often requires LDL-lowering drugs in patients at risk for CHD.[4] Clinical lipid management consists predominantly of HMG-CoA reductase inhibitors (statins), but also includes non-statin therapies such as bile acid sequestrants, ezetimibe and soluble/viscous fibre.[4, 7]

Non-HDL-Cholesterol and apo B are considered alternate therapeutic targets. Ho *et al*. have shown in a systematic review that there is a high correlation between CVD risk and both Non-HDL-C and apo B. [8]

The regulatory agencies US Food and Drug Administration (FDA), Health Canada and European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies, approved claims for soluble fibre, as part of a diet low in saturated fat and cholesterol. [5, 9, 10]

Soluble/viscous fibre is found in whole oat food (oat bran, rolled oats, whole oat flour) and in barley foods. The National Cholesterol Education Program (NCEP) Expert Panel recommends, as part of the TLC, that the diet be enriched by foods containing at least 5–10 grams of viscous fiber daily. Intakes of 10–25 grams per day can be beneficial, being one of the therapeutic options for lowering LDL-C.[4] According to an ACC Expert Consensus, the mean TC and LDL-C levels were decreased relative to control by 9.7 and 11.6 mg/dL respectively with an intake of 3.0-12.4 g/day.[7] European guidelines for the management of

dyslipidemia notes that a consumption of 5-15 g/day of soluble fibre from oat product may be beneficial in reducing the CVD risk.[11] Health Authorities' approvals are based on a diet containing at least 3 g oat beta-glucan per day.[12]

Health Canada approval recognizes the relation between the increased oats (*Avena sativa*)-soluble fibre consumption and the reduction in total serum cholesterol level, and the reduction of the risk of CAD. The main active food component responsible for the hypocholesterolaemic property of oats is beta-glucan. [9, 12]

Beta-glucan is a highly viscous soluble fibre composed of D-glucose monomers linked by a combination of β -(1 to 4) and β -(1 to 3) glycosidic bonds. It is thought that beta-glucan reduces TC and LDL-C by forming a viscous mass in the small intestine, thus limiting intestinal absorption of dietary cholesterol as well as the re-absorption of bile acids.[9] In a randomized, single-blinded, controlled crossover study, it has been shown that gut microbiota were modulated in response to beta-glucan consumption on a molecular weight-dependent manner. The shift in gut microbiota might be one of the underlying mechanisms responsible for the physiological benefits of beta-glucan and this was correlated with reduced CVD risk factors. [13]

The EFSA Panel assumes that the target population is the general population and that the claimed effects refer to the maintenance of normal blood LDL-C concentrations, increasing in satiety which leads to a reduction in energy intake, reduction of post-prandial glycaemic response and improvement of the digestive function. [10]

A systematic review of 16 studies conducted by Q. Hou *et al*. has shown that oat intake reduced the concentrations of TC and LDL-C. It is thought that the cholesterol-lowering effect might be due to beta-glucan binding with bile acids which leads to decreased cholesterol absorption, increased expression of hepatic LDL-C receptor, and increased faecal bile acid excretion. The effect of beta-glucan on HDL-C has varied in those studies.

Hou *et al*. have also demonstrated that oat intake has a moderately beneficial effect on glycaemic control and lipid profile in patients with type 2 diabetes. The beneficial effect on blood lipids and glycaemia have been found to be linked to the increased viscosity of the food bolus, delayed gastric emptying, lengthened intestinal transit time, slowed absorption of nutrients especially carbohydrates, and enhanced satiety. The authors have also shown that the effects on health depend on the dosage, chemical structure, molecular weight, solubility and viscosity of the oat. No evidence has been found linking oat consumption and allergic reactions or disease; however, the authors recommend using pure oats without wheat contamination in wheat hypersensitive patients. [14]

CEAPRO's beta-glucan is a high-medium molecular weight soluble fibre obtained by a Pressurized Gas eXpanded® (PGX) method, which is a novel drying technique for processing water-soluble biopolymers. The use of high-medium molecular weight beta-glucan, obtained by the PGX method, for 12 weeks may significantly reduce the level of LDL-C and contribute to reducing the cardiovascular disease risk.

This phase II trial is indicated in the context of substantial scientific evidence on the cholesterol lowering effect of beta-glucan, the existence of a beta-glucan monograph published by Health Canada and the need to better delineate the effective dosage of the new formulation of CEAPRO's beta-glucan [15], [16].

2 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.

2.1 Primary Objective

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).

2.2 Secondary Objectives

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

2.3 Exploratory Objectives

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 STUDY DESIGN AND ENDPOINTS

3.1 Study Design and Dosing Regimen

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. (Figure 1)

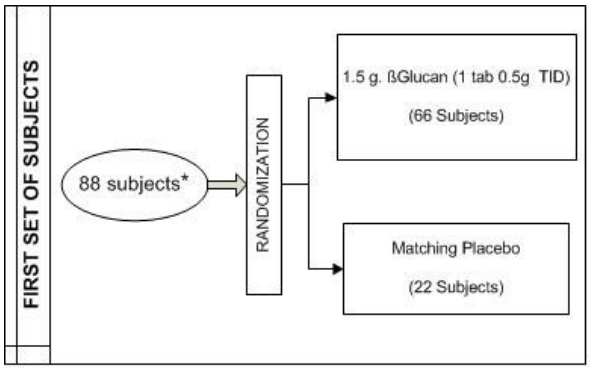
At baseline Visit (Week 0), the subjects should be already on a standard cholesterol lowering diet (American Heart Association Guidelines) (Appendix 1) and they should maintain it throughout the study. Subjects are encouraged to pursue a healthy lifestyle. The subjects must abstain from/minimize alcohol (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).

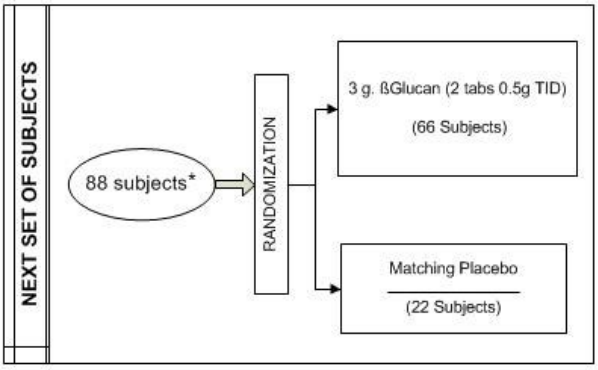
During the treatment period, subjects will return to the study site at Visit 3 (Week 6) and at the End of Treatment Visit (Week 12) for laboratory tests and clinical assessments, including for Adverse Events (AEs), dietary guidance and IP compliance. At the Safety Follow-up Visit (Week 14), subjects 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.

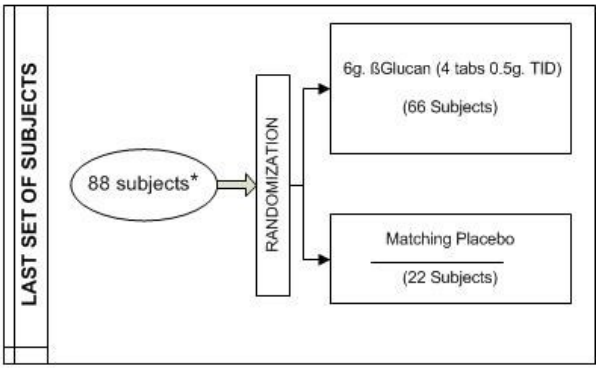
Laboratory tests and clinical assessments will be performed as noted in the schedule of visits (Appendix 2) and section 3.1

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

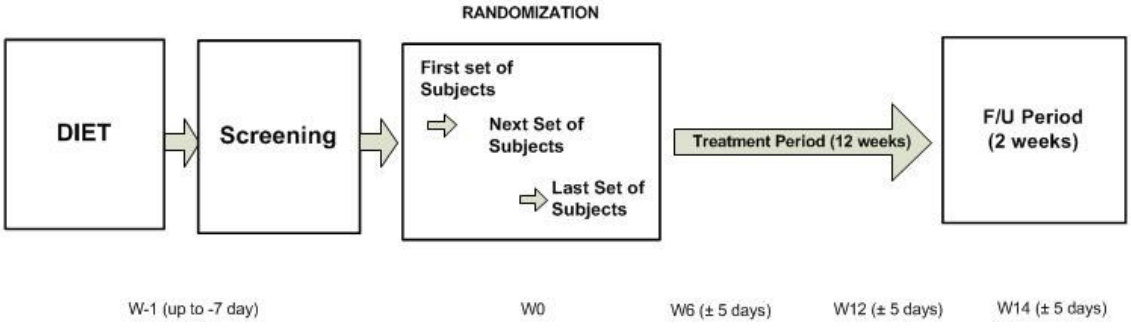
The study design is presented in Figure 1 below.







* Subjects treated or not with a statin at baseline



3.2 Study endpoints

3.2.1 Primary Endpoint

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

3.2.2 Secondary 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

3.2.3 Exploratory Endpoints

Exploratory endpoints will include changes in HDL-C, TG, Lp(a) and HbA1c from Week 0 to Week 12.

3.2.4 Safety

Safety will be assessed by adverse events, physical examination, vital signs, ECG and laboratory analyses (hematology, biochemistry).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

The target population will consist of subjects who are diagnosed with hyperlipidemia. In order to be included into the trial, subjects must fulfill all the inclusion and not meet any of the exclusion criteria listed below.

4.1 Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria in order to be eligible for this study**:**

1. Male or female ≥18 years of age

2. 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.

3. Subjects willing to maintain stable standard cholesterol lowering diet (Appendix 1) and physical activity level throughout the study

4. Female of childbearing potential must have a negative urine pregnancy test at screening and randomization baseline Visit 2

Women are considered not of childbearing potential if they:

a. Have had a hysterectomy, a bilateral oophorectomy or tubal ligation prior to Baseline Visit.

b. Are postmenopausal defined as no menses for at least 1 year and have a serum FSH level of 40 IU/L.

Women of childbearing potential must agree to use an effective method of birth control throughout the study. Acceptable means of birth control include: implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, male or female condoms with spermicide, abstinence, or a sterile sexual partner

5. Ability and willingness to give written informed consent and to comply with the requirements of the study

4.2 Exclusion Criteria

A subject who meets any of the following criteria will NOT be eligible to the study:

1. Use of any other lipid modifying drugs including but not limited to:
   a. Niacin (nicotinic acid) or niacinamide (nicotinamide)
   b. Bile acid sequestrants including cholestyramine, colesevelam, colestipol
   c. Ezetimibe
   d. PCSK9 inhibitors
   e. Systemic corticosteroids

2. Use of any other lipid modifying supplements within the last 30 days, including but not limited to (a 30-day wash out period is permitted):
   a. Beta-glucan supplements other than the investigational product
   b. Omega-3 fatty acids
   c. Supplements containing flaxseed, fish oil, or algal oil
   d. Sterol/stanol products
   e. Red yeast rice supplements or soy isoflavone supplements
   f. Dietary fiber supplements including > 2 teaspoonful of Metamucil® or psyllium containing supplements per day
   g. Supplements containing oats, oatmeal and oat bran.

3. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of acetylsalicylic acid (ASA) at a concentration of up to 325 mg twice a day and occasional/intermittent use for the symptomatic control of minor acute ailments (e.g. headaches).

4. BMI ≥ 40 kg/m^2

5. Female who is pregnant, planning to become pregnant during the study, or breast feeding

6. Subject who is not willing to keep stable the exercise level during the study

7. History of poorly controlled diabetes within the last 3 months (HbA1C >10%)

8. Subjects with poorly controlled blood pressure defined as a sustained mean systolic blood pressure >160 or <100 mmHg and/or diastolic blood pressure >100 or <60 mmHg at screening

9. History of unstable angina, myocardial infarction, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, or transient ischemic attack (TIA) within 6 months prior to screening

10. History of heart failure NYHA III-IV within 12 months prior to screening

11. Subjects with clinically significant electrocardiographic abnormalities

12. Subjects with history of clinically significant endocrine disease known to influence serum lipids

13. Subjects with evidence of hepatic disease (ALT and/or AST greater than 2X ULN, total bilirubin greater than 1.5X ULN, or cirrhosis) at screening

14. Renal dysfunction defined as glomerular filtration rate (GFR) ≤45 mL/min/1.73 m^2 at screening

15. Subjects who suffer from inflammatory bowel disease or irritable bowel syndrome

16. Known allergies or intolerance to oats

17. History of malignancy, except subjects who have been disease-free for > 3 yrs or resected basal or squamous cell skin carcinoma or cervical carcinoma in situ

18. Consumption of > 14 alcoholic drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1.5 oz hard liquor at screening). Counseling should be given to encourage the subject to maintain consumption at or below this level throughout the study

19. History of drug abuse

20. Participation in another clinical trial within 30 days of signing the Information and Consent Form (ICF)

21. Any condition or therapy that the investigator believes might pose a risk to the subject or makes participation in the study not in the subject's best interest

4.3 Subject Withdrawal or Termination

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue temporarily or permanently the IP for a subject in the event of an intercurrent illness, adverse event (AE), or other reasons.

An excessive rate of study withdrawal would diminish the informative value of the study data; therefore, unnecessary withdrawal of subjects should be avoided.

The reason for the subject's premature discontinuation from the study must be fully documented in the source documents and electronic Case Report Form (eCRF).

Subjects who discontinue IP but who consent to remain in the study will continue to comply with study visits and assessments. See section 6.6.

Subjects prematurely discontinued from the study will not be replaced.

4.4 Screen Failure

Subjects who sign the ICF and who are discontinued or withdraw from the study before they are randomized are defined as screen failures. Date of the visit, date of consent, demographic information as well as the reason for screen failure will be collected in the eCRF for screen failure subjects.

5 STUDY PRODUCT

5.1 Study Product and Control Description

5.1.1 Acquisition

The investigational product (IP) beta-glucan and placebo are shipped to the investigator's pharmacy or suitable storage area by the sponsor's packaging contractor. The IP is prepared according to the randomization algorithm provided by the MHICC and is supplied in a double-blind fashion. Each subject kit contains a 6-week (± 5 days for visit window) supply of therapy, i.e. either beta-glucan or placebo for dispensing of one kit at the randomization baseline Visit 2 and one kit at Week 6 (Visit 3).

The IP is to be dispensed only to subjects included in the study and per the Investigator's instructions. The Investigator is the person responsible for the distribution of the IP, and he/she or his/her delegate will record the distribution of the IP. Instructions will be given to Investigators regarding the return or destruction of remaining IP and any other clinical trial supplies after the end of the study.

5.1.2 Formulation, Appearance, Packaging, and Labeling

CEAPRO's CP105F is supplied as enteric coated 500 mg oral tablets or matching placebo. The batch number is filed at CEAPRO Inc. (7824 – 51 Avenue, Edmonton, AB T6E 6W2).

Each CP105F tablet contains oat beta-glucan concentrate, other oat dietary fibers, oat proteins, food grade salts, and oat lipids. Each placebo tablet resembling CP105F contains Mannitol 100SD, Prosolv SMCC HD90, Copovidone S-630, Crospovidone XL-10, Sodium starch glycolate, Mg St MF-2-V, Opadry II White85F18422.

IP label is designed to comply with the Regulations of the country where the clinical trial will be conducted: in Canada this is the Natural Health Products Regulations, Part 4, Sponsor's Obligations, Labelling Sections 75-76 and the following information shall be included on labels in both official languages:

a) a statement indicating that the natural health product is an investigational natural health product to be used only by a qualified investigator;
b) the brand name or code of the natural health product;
c) the expiry date of the natural health product;
d) the recommended storage conditions for the natural health product, if any;
e) the lot number of the natural health product;
f) the name and address of the manufacturer;
g) the name and address of the sponsor; and
h) the protocol code or identification.

Additional components of the label may include:

- A space to complete the subject number
- A space to complete the dispensing date of the kit
- Identification of the group: 1.5 g, 3 g, or 6 g TDD CP105F or placebo, whether by text or colour-code or other means of identification

5.1.3 Investigational Product Storage and Stability

Product stability data on file at the sponsor indicate exposure to temperatures between -15 and 40 °C (5 to 104 °F) does not affect the active ingredient.

Investigational Product (IP) should be stored at room temperature in a dry environment.

5.1.4 Preparation

No special preparation is required. The IP kit label (subject number and dispensing date, as applicable) and log(s) are to be completed by the investigator's delegate at the time of dispensing to subjects.

5.1.5 Dosing and Administration

CEAPRO's CP105F (oat beta-glucan) 1.5 g, 3 g, or 6 g daily or matching placebo are to be given as 500 mg tablets taken 3 times daily in the morning before breakfast, at mid-day before lunch and before supper time. The product should not be taken at the same time as statins (for subjects who are taking statins) which should be taken in the evening or at least 2 hours after the last dose of IP.

Subject should be instructed on administration of the IP:

IP tablets should be taken whole (not cut or crushed) with plenty of liquid (>350 ml or 1½ c.), preferably with warm or hot water before the meal. It is best not to consume alcohol immediately after ingesting the tablet, as beta-glucan is not soluble in alcohol. If a dose is missed, the next regularly scheduled dose should be taken. Unused tablets and empty containers (bottles and kit box) returned to the site at the next study visit.

5.1.6 Route of Administration

IP is to be administered orally per dosing and administration instructions in section 5.1.5.

5.1.7 Duration of Treatment

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).

5.1.8 Tracking of Dose

A dosing schedule will be provided to each subject. A product intake card will be maintained by the subject to help with compliance and will be returned to the site along with remaining IP tablets and containers.

5.2 Blinding and Unblinding

This is a double-blind study. With the exception of the study unblinded statistician who generates and provides the randomization algorithm for the Interactive Web Response System (IWRS) all site staff and study subjects will remain blinded until study completion and database closure.

Unblinding of the treatment assignment for a subject may be necessary due to a medical emergency, a Serious Adverse Event (SAE) that is unexpected and for which a causal relationship to the IP cannot be ruled out or any other significant medical event.

Details for unblinding will be provided under a separate cover.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the treatment assignment for the affected subject will be unblinded
- Treatment assignment will be provided to the investigator
- The investigator will notify Sponsor and /or designee immediately that the subject has been unblinded

5.3 Assessment of Compliance

At each visit, all unused tablets and empty containers (bottles and kit box) should be returned by the subjects to the investigator or designee as a measure of compliance. Compliance is defined as consumption of at least 80% of the required dosage.

Accountability will be assessed by maintaining adequate IP dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

If for any reason the IP is not administered or partially administered it should be reported in the eCRF and the reason for this must also be clearly reported in the eCRF. If this is due to occurrence of an AE the details of the event must be collected in the eCRF.

5.4 Investigational Product Accountability

The investigator is responsible for the control of products/drugs under investigation. Adequate records of the receipt (e.g., IP Receipt Record(s) and Master IP Log or equivalent) and disposition (e.g., IP Dispensing Log or equivalent) of the IP must be maintained. The IP Dispensing Log must be kept current and should contain the following information:

- Documentation of IP shipments received from the sponsor (date received and quantity)
- Disposition of unused IP not dispensed to study participants
- The identification of the study participant to whom the IP was dispensed (for example, a unique subject number of other study participant identifier)
- The date(s), quantity of the IP dispensed to the study participant
- The identification of the person who dispensed the IP

All records and IP supplies must be available for inspection by the Clinical Research Associate (CRA) and any other sponsor representatives. When the study is completed, the investigator will return any unused IP and containers (i.e., empty, partially used, and unused containers) to CEAPRO Inc. or designee unless alternate destruction has been authorized by CEAPRO Inc. or designee, or required by local or institutional requirements. The investigator's copy of the IP Return Record(s) or equivalent must accurately document the return of all IP supplies to CEAPRO Inc.

5.5 Interruption or Discontinuation of Investigational Product

Study participants may be interrupted or discontinued from the IP if any of the following occur:

1. A IP-related adverse event or other reason which, in the investigator's opinion, will jeopardize the subject's participation in the study or the interpretation of study data (e.g., severe intercurrent illness requiring additional care measures or preventing further dosing)
2. Significant tolerability issues
3. Participant's decision

At the time of IP interruption, the study site will document in the eCRF the reason for IP discontinuation. The study participant should continue to be followed for all other study related procedures and visits, and clinical study outcomes and evaluation.

5.6 Destruction of the Investigational Product

IP must be returned or destroyed locally following CRA authorization.

Written authorization of local IP destruction must be obtained from the sponsor or delegate before destruction occurs.

Written documentation of destruction must contain the following:

- Identity [batch numbers or subject numbers] of IP [and placebo] destroyed
- Quantity of IP destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person [or company] who destroyed IP.

6 STUDY ASSESSMENTS AND PROCEDURES

The schedule of visits for this study is outlined in Appendix 2, however, a subject may be seen at any time for safety reasons.

6.1 Screening Assessments

All subjects must provide written informed consent before any study-specific assessments or procedures are performed including 10-hour fasting for labs.

Screening procedures (Visit 1, up to 7 days prior to Baseline Visit 2) to assess eligibility include medical history, height, weight, physical examination, vital signs, ECG, concomitant medications, and lab blood draw per Appendix 3.

Urine pregnancy test is performed in females of childbearing potential.

Subjects who fail to meet inclusion/exclusion criteria may not be re-screened for study entry.

Subjects taking supplements defined in the exclusion criterion #2 and who accept to stop taking these supplements, may be randomized after a 30-day wash out period. If during the screening period it is determined that a subject is taking an excluded supplement, it is permissible to extend the 7-day screening period to allow for a 30-day washout in these exceptional circumstances.

Any clinically significant AE occurring prior to subject randomization is to be reported in the Medical History, and if serious, should be recorded as a SAE.

6.2 Randomization and Treatment Procedures

Urine pregnancy test is repeated in females of childbearing potential at the randomization Visit 2.

Subjects considered by the investigator to meet all entry criteria are scheduled for randomization at Week 0 (Visit 2) where subject receives either CP105F (1.5 g, 3 g or 6 g) or matching placebo in a double-blinded fashion. Dietary counselling per Appendix 1, and IP and statin (for subjects who are taking statins) administration instructions are reviewed with the subject at each dispensing visit (Visits 2 and 3), and IP and statin (for subjects who are taking statins) compliance is assessed at subsequent visits (Visits 3 and 4):

- IP administration: 1, 2 or 4 tablets (based on the dosing arm currently recruiting) taken TID in the morning before breakfast, at mid-day before lunch and before supper time preferably at the same times every day. Subjects should be clearly instructed that if a dose is missed, the next regularly scheduled dose should be taken and unused tablets returned at the next study visit.
- Statin administration (for subjects who are taking statins): in the evening or least 2 hours after the last dose of IP.

During the 12-week treatment period, visits will take place at Weeks 6 and 12 (Visit 3 and 4 respectively, ± 5 days), followed by a Safety Follow up (Visit 5, ± 5 days) at Week 14.

Subjects will continue to receive dietary counselling throughout the course of the treatment period and have labs measured as outlined in Appendices 2 and 3. Subjects will be assessed for compliance to IP through pill counts (see section 5.3). At each visit, subjects will be questioned in a non-specific manner for the occurrence of Adverse Events.

Safety assessments may be done at any time during the subject's participation in the study. Follow-up phone call will be performed 2 weeks after last dose taken for capturing any AEs.

6.3 Medical History:

Medical History will consist of detailed information, with particular attention to identify factors that would exclude a patient, including: age, race, sex, current medications, drug sensitivities or any adverse reactions to medications, history of hepatic, renal, or cardiovascular disease,

smoking history, alcohol intake, drug abuse, prior hospitalizations, surgeries, interventions, and serious illnesses

6.4 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 Visit (V1), and weight at the End of Treatment Visit (V4).

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

6.5 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 according to the schedule summarized in Appendix 3.

6.6 Electrocardiogram

All ECGs will be obtained in the decubitus position following a 10-minute rest time.

All ECG recordings must be performed using a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. Digital ECG recording is recommended.

For safety monitoring purposes, the investigator or physician delegate must review, sign and date all ECG tracings. Paper copies will be kept at the study center with the subject's clinical file as part of the permanent record. The ECG intervals and interpretation will be recorded on the eCRF

The following parameters PQ (PR), QRS, QT and QTcB (calculated according to Bazett's formula) and the heart rate will be measured automatically and recorded in the eCRF. In addition, any observed abnormality will be reported and documented.

6.7 Laboratory Analyses

A full clinical laboratory profile including hematology, biochemistry, lipids and other analyses will be performed during the study as outlined in Appendix 3.

All lab tests are performed in the 10-hour fasting state (water allowed). If a subject has not adhered to the 10-hour fast, the visit can be rescheduled within approximately 1-3 days (maximum visit window is +/- 5-days). Urine samples will be analysed and destroyed. Blood samples will be retained during the study and for up to 6 months following completion of the trial to facilitate complete analysis and for the potential analysis of additional lipid, or lipoprotein or biomarker analyses.

6.8 Concomitant and Prohibited Medications

The investigator or designee will review the concomitant medications being taken by the subject. Any AE that leads to the administration of any new concomitant medications will be reported as an AE.

The use of medications or supplements which may have a possibility of altering lipid levels (see Exclusion #1 and #2) should be avoided until after end of treatment or ideally, study completion at Week 14. Oral or parenteral hormonal contraceptive agents should be stabilized prior to study entry and maintained stable throughout the course of the trial. Use of NSAIDs is prohibited with the exception of acetylsalicylic acid (ASA) at a concentration of up to 325 mg twice a day and occasional/intermittent use for the symptomatic control of minor acute ailments (e.g. headaches).

In the course of the study, patients will be receiving standard medical care at the discretion of the treating physician. During the treatment period, the investigators will carefully monitor and consider adjusting the dose in patients who are taking concomitant medications known to have hypotensive properties such as immunosuppressants, antihypertensive drugs or natural health products (e.g. andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lyceum, stinging nettle, theanine).

6.9 Adverse Events

Adverse events (serious and non-serious) will be collected throughout the study from randomization to last dose of IP taken. SAEs will be collected from the time of consent through to 2 weeks after the last dose of study product. At each visit, the investigator or designated qualified study site staff will ask the subject if any untoward medical event occurred since the last visit. For each event, the date of onset and end, severity, relationship to IP, outcome and treatments administered for the event will be recorded in the eCRF.

6.10 Unscheduled Visit

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

The following information will be collected at any unscheduled visit:

- New/change in concomitant medications
- AEs

Details of these visits will be recorded as appropriate.

6.11 Early Termination Visit

Any subject terminating from the study early during the treatment period will, at the time of withdrawal, be encouraged to complete all Visit 4 (Week 12) procedures if possible.

6.12 Efficacy Assessments

6.12.1 Primary Efficacy Assessment

The primary efficacy assessment is direct-measured of LDL-cholesterol.

6.12.2 Secondary Efficacy Assessment

The secondary efficacy assessments include TC, non-HDL-C, small LDL subclass particle concentration, hsCRP, apo B, and VLDL-C.

6.13 Exploratory Assessments

Exploratory assessments include HDL-C, TG, Lp(a) and HbA1c.

6.14 Safety Assessments

Safety will be assessed by adverse events, physical examination, ECG, vital signs, and laboratory analyses (hematology and biochemistry).

6.15 End of Study

The end of the study is defined as the date of the last visit of the last subject. Last visit of the last subject is either the date of the last visit of the last participant to complete the study, or the date at which the last data point from the last subject, which was required for statistical analysis (i.e. key safety and efficacy results for decision making), was received, whichever is the later date.

6.16 Dietary and Concomitant Medications Restrictions

At the screening visit subjects should be already on a standard cholesterol lowering diet 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 control 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).

7 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)/SAFETY INSTRUCTIONS AND GUIDANCE

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided

in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7.1 Definition of Adverse Event (AE)

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.

7.2 Definition of Serious Adverse Event

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.

7.2.1 Follow-up of AEs/SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each study participant and provide further information on the study participant's condition.

All AEs/SAEs documented at a previous visit or contact and designated as ongoing, will be reviewed at subsequent visit or contacts. All AEs/SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the study participant is lost to follow-up.

The appropriate AE/SAE eCRF page(s) will be completed and updated with follow-up information. Follow-up will include any supplemental investigations carried out to elucidate the nature and /or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological investigations, or consultation with other health care physicians.

7.3 Laboratory Test Abnormalities and other abnormal assessments as AEs or SAEs

Abnormal laboratory findings (e.g. clinical biochemistry, hematology) or other abnormal assessments (e.g. ECG, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 7.1, or SAE as defined in Section 7.2.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in IP (permanent or temporary discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of IP, which falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria (which will be analysed and reported as laboratory abnormalities) or those which are a result of an AE which has already been reported.

7.3.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

7.4 Time Period, Frequency, and Method of Detecting AEs and SAEs

All serious adverse events (SAEs) will be captured from the time of consent through to week 14 safety Follow up phone call. All AEs will be captured between the time of randomization up to the last dose IP taken. Each study participant will be monitored by the investigator and study staff for AEs/SAEs occurring throughout the study. The investigator or designee will enquire about AEs/SAEs in a non-specific manner through the study at all visits.

7.5 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE into the eCRF. It is

not acceptable for the investigator to send photocopies of the study participant's medical records to the MHICC in lieu of completion of the appropriate AE/SAE eCRF pages. However, there may be instances when copies of medical records for certain cases will be requested by the MHICC Medical Reviewer. In this instance, all study participant identifiers (subject number is acceptable) will be blinded on the copies of the medical records prior to submission to MHICC Medical Reviewer.

For each adverse event, start and stop dates, action taken, outcome, intensity and relationship to IP (causality) must be documented. If an AE changes in frequency or intensity during a study, an update of the event must be made on the eCRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented.

All details of any treatments initiated due to the AE should be recorded in the study participant's clinic notes and the eCRF.

7.6 Prompt Reporting of SAEs

This study adheres to the definition and reporting requirements of Natural Health Products Regulations SOR/2003-196.

Once an investigator becomes aware that an SAE has occurred in a study participant, he/she will immediately notify the MHICC Medical Reviewer by completing the study-specific eCRF SAE form. The SAE form must be completed as thoroughly as possible with all available details of the event, within 24 hours of first becoming aware of the event.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before completing the eCRF SAE form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report. If data obtained after the initial report, indicate that the assessment of causality is incorrect, the SAE form may be appropriately amended by the investigator, and resubmitted to sponsor or delegate.

The investigator must also notify their ethics committee, whether local or central.

7.7 Expeditable Events (SUSAR's)

During the course of a clinical trial, the sponsor / or delegate shall notify the regulatory authorities of any serious unexpected adverse reaction to the natural health product that has occurred inside or outside Canada as follows:

a) if it is neither fatal nor life threatening, the regulatory authorities should be notified immediately if possible, and no later 15 days after the sponsor becomes aware of the information; and

b) if it is fatal or life threatening, the regulatory authorities should be notified immediately if possible and no later than seven days after the sponsor becomes aware of the information.

c) Within eight days after having informed the regulatory authorities of a serious unexpected adverse reaction to the natural health product, the sponsor must submit a report as complete as possible that includes an assessment of the importance and implication of any findings. The final report should include relevant previous experience with the same or similar health products.

A serious adverse reaction is a serious adverse event that is **CAUSALLY** related to the investigational product.

Serious expected adverse reactions could qualify for an expedited reporting if there is a clinically significant increase in the rate of its occurrence within the study population. Appropriate scientific and medical judgment should be applied.

7.8 Evaluating AEs and SAEs

7.8.1 Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The severity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort, requiring minimal or no treatment and not interfering with everyday activities.

Moderate: An event that results in a low level of inconvenience or concern with the therapeutic measures. Moderate event may cause some interference with the normal everyday activities.

Severe: An event which interrupts a participant's everyday activities and may require systemic drug therapy or other treatment. Severe event is usually potentially life-threatening or incapacitating.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as described in Section 7.2 "Definition of Serious Adverse Events".

7.8.2 Assessment of Causality

The investigator is obligated to assess the relationship between IP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

Not Related: The adverse event is completely independent of IP administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, a definitive etiology documented by the clinician.

Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The adverse event occurs in a plausible time relationship to IP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response on dechallenge of the IP should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

7.8.3 Assessment of Expectedness

The sponsor (or delegate) will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

7.9 Pregnancy

A female subject must be instructed to immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor. The investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy.

8 CLINICAL MONITORING

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this the protocol, ICH guidelines for Good Clinical Practice [16] and the applicable regulatory requirements. The Investigator agrees to provide reliable data and all information requested by the protocol in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor and its delegates.

The sponsor of this clinical trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the Monitoring Team (CRA and MHICC Medical Reviewer) is to help the Investigator and the sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (e.g., subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

A separate Monitoring Plan will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

9 STUDY COMMITTEES

Not Applicable

9.1 Steering Committee: Not applicable

9.2 Data and Safety Monitoring Board (DSMB): Not applicable

10 STATISTICAL CONSIDERATIONS

10.1 Analysis Datasets

10.1.1 Intent-to-Treat Population

The intent-to treat (ITT) population will include all randomized subjects. Subjects will be assigned to treatment groups as randomized for analysis purposes.

10.1.2 Per-Protocol Population

The per-protocol (PP) population will include all randomized subjects who were compliant to IP and who were not subject to major protocol deviation. Subjects will be assigned to treatment groups as randomized for analysis purposes.

10.1.3 Safety Population

The safety population will include all randomized subjects who received at least one dose of IP. Subjects will be assigned to treatment groups as per actual treatment received for analysis purposes.

10.2 General Statistical Approach

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.

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.

A statistical analysis plan (SAP) will be written to fully describe the statistical analyses that will be done. The SAP will be finalized prior to database lock and unblinding.

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

10.3 Efficacy Analyses

All efficacy analyses will be conducted on the ITT population. However, as a sensitivity analysis, the analysis of the primary endpoint described in section 10.3.1 will be repeated on the PP population.

10.3.1 Analysis of the Primary Efficacy Endpoint

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 adjusting for the Week 0 value of LDL-C. 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 factors. 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:

H_0: $\square_{W12,placebo} = \square_{W12,1.5g}$ vs. H_1: $\square_{W12,placebo} \neq \square_{W12,1.5g}$

H_0: $\square_{W12,placebo} = \square_{W12,3g}$ vs. H_1: $\square_{W12,placebo} \neq \square_{W12,3g}$

H_0: $\square_{W12,placebo} = \square_{W12,6g}$ vs. H_1: $\square_{W12,placebo} \neq \square_{W12,6g}$

where $\square_{W12,placebo}$, $\square_{W12,1.5g}$, $\square_{W12,3g}$ and $\square_{W12,6g}$ 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.

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.

10.3.2 Analysis of the Secondary Endpoints

Secondary endpoints are expressed as change from Week 0 to Week 12 and will be analysed as the primary endpoint, with the exception that tests will be conducted at the 0.05 significance level.

10.3.3 Analysis of the Exploratory Endpoints

Similarly, exploratory endpoints are expressed as change from Week 0 to Week 12 and will be analysed as the primary endpoint, with the exception that tests will be conducted at the 0.05 significance level.

10.3.4 Subgroup Analyses

The following subgroup analyses are planned for the primary endpoint: mild vs severe hypercholesterolemia, male vs female, diabetic vs non-diabetic, hypertensive vs non-hypertensive, age < 65 years old vs. age ≥ 65 years old and treated with a statin at baseline vs. not treated with a statin at baseline.

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.

10.4 Safety Analyses

Safety will be assessed by adverse events, physical examination, vital signs, ECG, and laboratory analyses (hematology, biochemistry).

No formal statistical testing will be done for the safety endpoints. Statistical analysis will be mainly descriptive, broken down by treatment group, and conducted on the safety population.

10.4.1 Adverse Events

Adverse events will be coded by body system as defined by the latest version of the MedDRAs, following classification of investigator assessments into MedDRA preferred terms.

Treatment-emergent adverse events, defined as adverse events with a start date on or after the first dose of IP will be tabulated by preferred term, body system, severity and treatment group.

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

10.4.2 Laboratory Data

All laboratory parameters will be summarized using descriptive statistics and presented by study visit and treatment group. Changes from Week 0 to post Week 0 visits will also be summarized.

10.4.3 Other safety assessments

Other safety assessments, including physical examination, vital signs and ECG, will be summarized using descriptive statistics and presented by study visit and treatment group. When applicable, changes from Week 0 to post Week 0 visits will also be summarized.

10.5 Planned Interim Analyses

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

10.6 Sample Size Calculation

Sample size computation is 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 are needed for a total of 240 subjects. To account for approximately 9% lost to follow-up, 264 subjects (66 subjects per treatment group) will be randomized.

Sample size was calculated with nQuery + nTerim 2.0.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator (s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory.

11.2. Ethical Review

It is the understanding of the Sponsor that this protocol (and any amendment) as well as appropriate consent procedures, will be reviewed and approved by a Research Ethics Board / an Institutional Review Board (REB/IRB). This Board must operate in accordance with the currently applicable regulations. For sites with local ethics committee, a letter or certification

of approval will be sent by the Investigator to the Sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

11.3. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment or any new information that may affect willingness to continue to participate, the consent form should if necessary be reviewed and updated by the REB/IRB. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study per local requirements. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject. A notation that written informed consent has been obtained will be made on the participant's eCRF.

11.4. Ethics Review Committee

The protocol will be submitted for approval to the REB/IRB, and a written approval will be obtained before study participants are recruited and enrolled in this study. The Investigators will receive from the MHICC all the documentation needed for submitting the clinical study to the Ethics Committee. A copy of the respective approval letters will be forwarded to the MHICC and to the sponsor if applicable before starting to recruit study participants in this study. The composition of the Ethics Committee must also be provided to the MHICC as part of the essential documents. If approval is suspended or terminated by the local ethics, the Investigator will notify the MHICC immediately.

It is the responsibility of the Investigator to report study progress to the local Ethics Committee as required or at intervals not greater than one year.

The Principal Investigator, or his/her delegate, will be responsible for reporting any serious adverse events to the local Ethics Committee and as soon as possible, and in accordance with local regulatory requirements.

11.5. Confidentiality

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should only be identified by their initials (or coded initials if required by institutional policy) and a subject identification number on eCRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (e.g., signed ICF, subject identity log) must be kept in strict confidence.

The subject's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

12. FINANCIAL DISCLOSURE

Financial disclosure is provided as a separate agreement**.**

13. INVESTIGATOR RESPONSIBILITY

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this study protocol and on the eCRFs refers to the Principal Investigator or an appropriately qualified member of the clinical staff that the Principal Investigator designates to perform specified duties of the study Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

Each Investigator will comply with the local regulations regarding clinical studies and the Investigator responsibilities outlined in the ICH GCP guidelines.

14. PROTOCOL COMPLIANCE

The instructions and procedures specified in this protocol require diligent attention to their execution. Should there be questions or consideration of deviation from the protocol, clarification will be sought from the study team. Any study participant treated in a manner that deviates from the protocol, or who is admitted into the study but is not qualified according to the protocol, may be ineligible for analysis and thereby compromise the study.

Only when an emergency occurs that requires a departure from the protocol for an individual will there be such a departure. The nature and reasons for the protocol violation/deviation shall be recorded in the eCRF and the investigator should notify the sponsor and the Ethics Committee.

The Investigator and designees will comply with all applicable federal, provincial and local laws.

15. PROTOCOL AMENDMENT

The Investigator may recommend changes to the protocol. The sponsor will decide if an amendment to the original protocol is warranted. Protocol modifications that impact on study participant safety or the validity of the study will be reviewed and approved by the Ethics Committee prior to implementation.

It is the responsibility of the Investigator to submit the amendment to the Ethics Committee for their approval; written approval must be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority

must be notified of the protocol change. Completed and signed protocol amendments will be circulated to all those who were on the circulation list for the original protocol.

16. PUBLICATIONS

All information and data regarding the IP obtained in connection with the conduct of this study are considered confidential. Accordingly, the sponsor retains the right to review manuscripts, abstracts, and presentation material related to this protocol and its amendments/addenda prior to presentation or submission to a journal. This review will not restrict publication of facts or opinions formulated by the investigator.

17. RETENTION OF RECORDS AND ARCHIVING

All source documents, eCRFs and study documentation will be kept by the Investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP.

18. REFERENCES

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19. APPENDICES

19.1. Appendix 1: Standard Cholesterol Lowering Diet

DIET
1. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats. a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus). b. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.
2. Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat.
3. Reduce percent of calories from saturated fat.
4. Reduce percent of calories from *trans* fat.

*Refer to 2013 Blood Cholesterol Guideline ([17], [18])

19.2. Appendix 2. 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.

19.3. Appendix 3. Clinical Laboratory Parameters

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	
	Hemoglobin	
	Hematocrit	
	WBC	
	Platelet Count	
	Differential (to be performed only if WBC is abnormal)	Neutrophils
		Lymphocytes
		Monocytes
		Eosinophils
		Basophils
Biochemistry	AST	
	ALT	
	Bilirubin	
	Creatinine	
Lipids	Triglycerides	
	Total cholesterol	
	LDL-Cholesterol	
	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	
	Hemoglobin	
	Hematocrit	
	WBC	
	Platelet Count	
	Differential (to be performed only if WBC is abnormal)	Neutrophils
		Lymphocytes
		Monocytes
		Eosinophils
		Basophils
Biochemistry	AST	
	ALT	
	LDH	
	CPK	
	Creatinine	
	Glucose (fasting) (at visit 2 and 4 only)	
	Insulin (fasting) (at visit 2 and 4 only)	
	HbA1c (at visit 2 and 4 only)	
	hs-CRP (at visit 2 and 4 only)	
Lipids / Other	Triglycerides	
	Total cholesterol	
	LDL-Cholesterol (direct-measured)	
	HDL-Cholesterol	
	VLDL Cholesterol	
	Apolipoprotein B (apo B)	
	Lipoprotein (a) [Lp(a)]	
	Non-HDL-C	
	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 randomization (visit 2).