Official Protocol Title:	A Phase III, Randomized, Active Comparator-controlled, Clinical Trial to Study the Efficacy and Safety of MK-0653H in Japanese Patients With Hypercholesterolemia.
NCT number:	NCT02741245
Document Date:	20-Sep-2016

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TITLE:

A Phase III, Randomized, Active Comparator-controlled, Clinical Trial to Study the Efficacy and Safety of MK-0653H in Japanese Patients with Hypercholesterolemia.

EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.1.3	Ongoing Clinical Trials	Phase III long-term safety study in Japanese hypercholesterolemia patients is on-going.	Reflect the current status.
5.1.3	Subject Exclusion #14	Subject is currently taking medications restricted by labeling as below. ● Cyclosporine ● Systemically administered azole antifungals(e.g., ketoconazole, itraconazole and fluconazole) ● Macrolide antibiotics (e.g., clarithromycin, erythromycin and telithromycin) ● Antacid (e.g., aluminum hydroxide/magnesium hydroxide) ● Protease inhibitors (e.g., Lopinavir/Ritonavir, Atazanavir+Ritonavir, Darunavir+Ritonavir, concomitant use with elbasvir and grazoprevir) ● Simeprevir ● Eltrombopag	New information
5.1.3	Subject Exclusion #28	Subject has taken lipid-lowering agents (except probucol) including fish oils, Cholestin™, bile acid sequestrants, statins, Ezetimibe, fibrates or niacin (>200 mg/day) within 6 weeks prior to Visit 2. Subject has taken probucol or protein convertase subtilisin/kexin type 9 (PCSK 9) inhibitor within 10 weeks prior to Visit 2.	PCSK9 inhibitor has been launched in Japan.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
11.0	list of references #10	Crestor 2.5 mg, Crestor 5 mg label(Revised: Jun/2016, version 13)	New information

1.0 TRIAL SUMMARY

Abbreviated Title	MK-0653H Phase III Factorial Study in Japanese Hypercholesterolemic Patients
Sponsor Product Identifiers	MK-0653H
Trial Phase	III
Clinical Indication	Hypercholesterolemia, Familial Hypercholesterolemia
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Ezetimibe 10 mg Rosuvastatin 2.5 mg Rosuvastatin 5 mg MK-0653H (EZ 10 mg+Ros 2.5 mg) MK-0653H (EZ 10 mg+Ros 5 mg)
Number of trial subjects	Approximately 306 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 9 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial up to 22 weeks from the time the subject signs the Informed Consent Form (ICF) through the final visit. After a screening/washout phase of up to 6 weeks followed by a placebo run-in period of 2 weeks, each subject will be receiving assigned treatment for 12 weeks. After the end of treatment each subject will be followed for 14 days.
Randomization Ratio	Subject will be randomized into 1 of the 5 treatment groups including Ezetimibe 10 mg, Rosuvastatin 2.5 mg, Rosuvastatin 5 mg, MK-0653H (EZ 10 mg + Ros 2.5 mg), MK-0653H (EZ 10 mg + Ros 5 mg) in an allocation ratio of 1:2:2:2:2. NOTE: MK-0653H (EZ 10mg + Ros 2.5mg) is co-administration with a tablet of Ezetimibe 10 mg and a capsule of Rosuvastatin 2.5 mg and a capsule of matching placebo. MK-0653H (EZ 10 mg + Ros 5 mg) is co-administration with a tablet of Ezetmibe 10 mg and 2 capsules of Rosuvastatin 2.5 mg.

A list of abbreviations used in this document can be found in Appendix 12.2.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Randomized, active-controlled, parallel-group, multi- site, double-blind trial of MK-0653H in subjects with hypercholesterolemia to be conducted in conformance with Good Clinical Practices.

The study consists of a screening period, a placebo run-in period, a treatment period, and follow up, and the total duration of each subject is 17 to 22 weeks, depending on the length of the screening period, which is according to subjects' prior lipid-lowering therapy. For subjects on lipid-lowering therapy, this screening period will be 6 weeks and during this period, subject washoff prior lipid lowering therapy. In patients on a lipid lowering therapy (ie., statin) at Visit 1, investigators should consider the patients LDL-C level on the statin to assess whether the patient is likely to qualify for entry at Visit 2 after the wash-out of statin therapy. For subjects not on lipid-lowering therapy, it will be 1-6 weeks depending on the state of prior pharmacotherapy other than lipid-lowering agents in each subject. Subjects who meet all of the eligibility criteria will be enrolled in 12 weeks of treatment period following a 2-week placebo run-in period. Subjects will be randomized to one of the 5 treatment groups [Ezetimibe monotherapy at 10 mg, Rosuvastatin calcium (hereafter Rosuvastatin or Ros) monotherapy at 2.5 mg or 5 mg, MK-0653H (EZ 10 mg + Ros 2.5 mg), or MK-0653H (EZ 10 mg + Ros 5 mg)] in an allocation ratio of 1:2:2:2:2. Three hundreds six subjects will be randomized to ensure 279 completers. Subjects will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Subjects who complete the study or prematurely discontinue during the study will receive a 14-day follow-up phone call to assess for serious adverse events.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

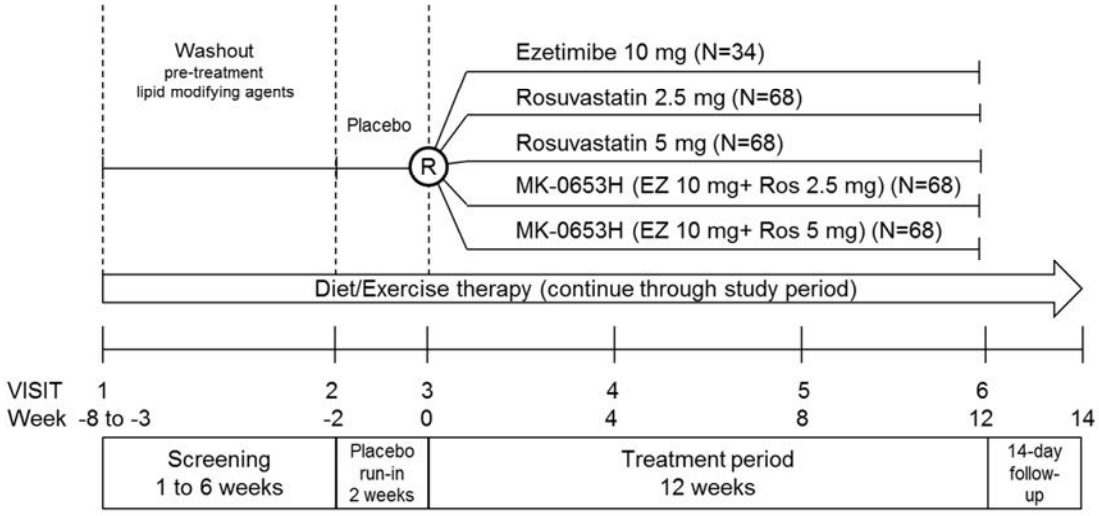

Figure 1 Study Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective:

In Japanese patients with hypercholesterolemia,

1) To evaluate the percent change from baseline in LDL-C of MK-0653H (EZ 10 mg + Ros 2.5 mg) compared to Ezetimibe 10 mg and compared to Rosuvastatin 2.5 mg at Week 12.
2) To evaluate the percent change from baseline in LDL-C of MK-0653H (EZ 10 mg + Ros 5 mg) compared to Ezetimibe 10 mg and compared to Rosuvastatin 5 mg at Week 12.
3) To evaluate the safety and tolerability of MK-0653H (EZ 10 mg + Ros 2.5 mg) and MK-0653H (EZ 10 mg + Ros 5 mg) once daily dosing through 12 weeks.

Hypothesis:

1) MK-0653H (EZ 10 mg + Ros 2.5 mg) is superior to Ezetimibe 10 mg and is superior to Rosuvastatin 2.5 mg in percent reduction from baseline in LDL-C after 12 weeks of treatment.
2) MK-0653H (EZ 10 mg + Ros 5 mg) is superior to Ezetimibe 10 mg and is superior to Rosuvastatin 5 mg in percent reduction from baseline in LDL-C after 12 weeks of treatment.

There are two families each with 2 primary hypotheses and the overall success is determined by a success in at least one family of hypotheses.

3.2 Secondary Objective(s) & Hypothesis(es)

No secondary objectives or hypotheses are planned for this protocol.

3.3 Exploratory Objectives

In Japanese patients with hypercholesterolemia,

1) To evaluate the percent change from baseline in LDL-C at Weeks 4 and 8 based on the following;

- MK-0653H (EZ 10 mg + Ros 2.5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 2.5 mg
- MK-0653H (EZ 10 mg + Ros 5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 5 mg

2) To evaluate the percent change from baseline in total cholesterol (TC), HDL-C, non-HDL-C, triglyceride (TG), Apoprotein (Apo) B and hs-CRP at Week 12 based on the following;

- MK-0653H (EZ 10 mg + Ros 2.5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 2.5 mg

- MK-0653H (EZ 10 mg + Ros 5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 5 mg

3) To evaluate the proportion of patients who achieve LDL-cholesterol goal (refer to Appendix 12.4) at Week 12 based on the following;

- MK-0653H (EZ 10 mg + Ros 2.5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 2.5 mg

- MK-0653H (EZ 10 mg + Ros 5 mg) compared to single entity, Ezetimibe 10 mg and Rosuvastatin 5 mg

4) To evaluate the percent change from baseline in LDL-C at Week 12 based on the following;

- MK-0653H (EZ 10 mg + Ros 5 mg) compared to MK-0653H (EZ 10 mg + Ros 2.5 mg)

4.0 BACKGROUND & RATIONALE

4.1 Background

MK-0653H is a fixed dose combination drug containing Ezetimibe, a Niemann-Pick Cl Like 1 (NPC1L1) inhibitor, and Rosuvastatin, a HMG-CoA reductase inhibitor, as active ingredients. The active ingredients are Ezetimibe 10 mg and Rosuvastatin 2.5 mg or 5 mg.

Refer to the Investigator's Brochure (IB)/approved labeling of Zetia® or Crestor® for detailed background information on Ezetimibe, Rosuvastatin or MK-0653H.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Pathophysiology and Epidemiology

Atherosclerosis and coronary heart disease (CHD), stroke and peripheral arterial disease caused by atherosclerosis are quite significant burdens to medical care in advanced countries. Approximately 0.4 million and 75,000 people die of CHD each year in the United States [1)] and Japan[2)], respectively. This number is expected to grow further in the next quarter of a century with increases in the morbidity of obesity and diabetes mellitus as well as the rapid aging of the population in Japan unequaled anywhere in the world.

Based on the results of many epidemiological surveys including the Framingham study, a correlation between serum lipid levels and the CHD risk has been well known [3), 4), 5)]. Epidemiological surveys in Japan such as the NIPPON DATA 80 have also demonstrated that serum lipid levels correlate with the CHD risk[6)]. Main large-scale clinical interventional studies of statins on serum lipid levels have shown that decreases in LDL-C levels are effective for the prevention of cardiovascular events, and statins are recommended to be first line therapy for the treatment of hyper-LDL-cholesterolaemia (2012 Japan Atherosclerosis

Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases [JAS2012][7]). Nonetheless, statin can decrease the relative risk of cardiovascular events only by approximately 20 to 40% so that the majority (approximately 70%) of cardiovascular events including myocardial infarction, coronary death, coronary revascularization and stroke are not actually prevented[8), 9)]. Ezetimibe is recommended to be added-on to statin high risk hyper-LDL-cholesterolemia in patient who is uncontrolled with statin in the JAS2012[7)]. Furthermore, a combination of statin monotherapy and another lipid-lowering drug to sufficiently lower LDL-C levels is suggested to be an approach for reducing the risk of cardiovascular events.

4.1.1.2 Significance of the Development of Fixed Dose Combination Tablet (FDC) for Therapy of Hyper-LDL-cholesterolemia

Mode of action

Ezetimibe inhibits the intestinal absorption of cholesterol and structurally-related phytosterols by blocking their passage across the intestinal wall. The molecular target of Ezetimibe action has been identified as the putative cholesterol transporter NPC1L1. This blockade results in decreased absorption of dietary and biliary cholesterol without effects on the absorption of other lipids (e.g., triglyceride), lipid derivatives (e.g., bile acids) or lipid-soluble nutrients or vitamins.

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis taken into liver actively, and the biosynthesis of cholesterol is restrained strongly. As a result, cholesterol level in liver decrease so that the expression of LDL-receptor is induced to support this decrease. Through LDL receptor, promote the synthesis of LDL receptors and decrease serum LDL-C. Rosuvastatin is mainly taken into liver via active transportation system. Because lipid affinity is relatively low, Rosuvastatin is not taken into other organs which don't have active transportation system. Therefore Rosuvastatin is a liver-specific HMG-CoA reductase. [10)].

Ezetimibe reduces hepatic cholesterol stores by inhibiting the absorption of cholesterol in the small intestine, but compensatory increased cholesterol biosynthesis occurs in the liver. Coadministration of Ezetimibe and an HMG-CoA reductase inhibitor which inhibits cholesterol biosynthesis was shown to complementarily lower cholesterol in studies in dogs and in non-Japanese hypercholesterolemic patients.[11)]

2012 Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (JAS2012)[7)]

For drug therapy for patients with hyper-LDL-cholesterolemia, statin treatment is recommended. If the therapeutic target goal for dyslipidemia are not achieved with statin monotherapy, then increasing the dose or combination therapy with other class anti-hyperlipidemia drugs can be considered. Combination therapies that have been proven to be effective in improving serum lipid profiles in Japanese populations include the administration of statins in combination with Ezetimibe or resins is theoretically the most effective means of decreasing the LDL-C level. Furthermore, statin and Ezetimibe exerts TG-lowering and HDL-C increasing effect.

Adherence

In a recent survey on adherence to statin treatment revealed a decrease in adherence with time; thus, statin treatment adherence is estimated to be about 50% in long-term therapy[12]. In addition, data on other diseases show that the treatment compliance rate is correlated with the number of tablets (capsules) prescribed[13), 14)]. Therefore, a combination drug with a good tolerability profile in combination therapy for hyper-LDL-cholesterolemia may well be an important alternative as a treatment drug that can improve patients' treatment adherence and may be anticipated to display more reliable therapeutic efficacy.

Consequently, concomitant administration of Ezetimibe and statin is assumed to more effectively improve hyper-LDL-cholesterolaemia based on their different mechanisms of actions.

4.1.2 Pre-clinical and Clinical Trials

Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Rosuvastatin in Healthy Hypercholesterolemic Subjects (P03317)

A randomized, investigator/evaluator blind, placebo-controlled, single-center, multi-dose, parallel-group study in healthy hypercholesterolemic subjects (N=39 completers; for PK N=12 Ezetimibe+Rosuvastatin , N=11 Rosuvastatin alone, N=8 Ezetimibe alone and N=8 placebo) for 14 days. The data on metabolism of Ezetimibe and Rosuvastatin are also consistent with the lack of pharmacokinetic interaction between Ezetimibe and Rosuvastatin in this study. The findings of the study demonstrate that the co-administration of Ezetimibe and Rosuvastatin was well tolerated, with no evidence of increased incidence of adverse events or increases in clinical laboratory tests indicative of liver or skeletal muscle toxicity.

A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate the Efficacy and Safety of Ezetimibe Added On to Rosuvastatin Versus Up Titration of Rosuvastatin in Patients with Hypercholesterolemia at Risk for Coronary Heart Disease (P139)

440 subjects at moderately high/high risk of coronary heart disease with LDL cholesterol levels failing to reach their LDL C goal (100 mg/dL [<2.6 mmol/L] or 70 mg/dL [<1.8 mmol/L] depending on baseline characteristics) were stratified to treatment with Rosuvastatin 5 mg or 10 mg for 4-5 weeks. Patients were then randomized to either doubling of their Rosuvastatin dose (to 10 mg or 20 mg) or adding Ezetimibe 10 mg to their Rosuvastatin (5 or 10 mg) therapy for 6 additional weeks.

Patients taking Ezetimibe 10 mg+Rosuvastatin 5 mg or 10 mg achieved significantly greater LDL C reductions compared to patients doubling the initial dose of Rosuvastatin (to 10 mg or 20 mg) ($p < 0.001$). The LS mean percent change in LDL C from baseline to the study end was 21.0% when Ezetimibe 10 mg was added to Rosuvastatin and -5.71% when the original Rosuvastatin dose was doubled (data pooled across the Rosuvastatin 5 mg and 10 mg strata). The LS mean treatment difference was -15.3% with a 95% CI (-19.9, -10.6).

The overall safety profile appeared generally comparable between treatment groups. Pooled across strata, there were no clinically relevant differences between Rosuvastatin (5 or 10 mg) + Ezetimibe 10 mg and Rosuvastatin (10 or 20 mg) in the proportion of patients with clinical adverse experiences, serious adverse experiences, drug-related adverse experiences, serious and drug-related adverse experiences, or adverse experiences leading to discontinuation.

There was no significant difference between Rosuvastatin (5 or 10 mg) + Ezetimibe 10 mg and Rosuvastatin (10 or 20 mg) with respect to the percentage of patients with gastrointestinal-related, allergic events or rash, and hepatitis-related clinical adverse experiences.

Post-marketing survey of Ezetimibe (Zetia®) in Japan

Specific drug use survey of Ezetimibe for hyperlipidemia (52 weeks long term treatment) was performed from June 2007 to February 2011. The objective is to confirm the safety and efficacy of long-term use of Ezetimibe as monotherapy and combination therapy with other lipid lowering drugs (statins and non-statins) in the routine clinical practice.Total 1640 patients were analyzed and the incidence of drug-related adverse events (AE) were 204 patients (12.44%)[15]. 168 patients of them were co-administered with Ros and the incidence of drug-related AE were 9 patients (5.36%). This survey shows that the incidence of drug-related AE of total and co-administered with Ros group are lower than that of Ezetimibe approved in Japan, 18.85%.

The most commonly reported drug-related AE in total is Blood creatine phosphokinase increased (2.26%), Hepatic function abnormal (1.40%), Diarrhoea (0.79%), Gamma-glutamyltransferase increased (0.61%). The most commonly reported drug-related AE in co-administered with Ros group is Hepatic function abnormal (1.79%), Alanine aminotransferase increased and Gamma-glutamyltransferase increased (1.19%).

The incidence of side effects was similar in total and Ros co-administration group and As for the effectiveness, LDL-C was reduced both in total and Ros co-administration group (-26.06%) and no attenuation of clinical effect was observed in the long term administration.

4.1.3 Ongoing Clinical Trials

A phase III, clinical trial to assess the long term safety and tolerability of MK-0653H in japanese patients with hypercholesterolemia(P833) is ongoing.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Since the dosage and administration of this FDC is expected second-line therapy, FDC will be administered when patients are uncontrolled with monotherapy. Therefore, this study will be conducted to demonstrate the additional effect by comparing the efficacy between monotherapy and FDC.

The target population of this study is patients with hypercholesterolemia in whom the lipid management target value of LDL-C as per their coronary artery disease (CAD)-risk category based on JAS2012 has not been achieved, that is, patients meeting any of the following conditions, judging from the results of laboratory tests at the start of the placebo administration period and the presence/absence of CAD history.

For the hyperlipidemia patient with history of coronary artery disease (CAD), it is assumed that most of the patients are treated with lipid lowering agent based on the recommendation of JAS2012. And considering the safety of the patients, the patients who has a history of CAD or CAD-equivalent disease will be excluded from PN832 because it is considered not

appropriate to stop the lipid lowering therapy for a patient with a history of CAD, and to ensure that subjects are not placed on lipid lowering therapy with lower potency than they usually receive.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The dosage of Ezetimibe is 10 mg once daily. The results of the Japanese Phase II study of Ezetimibe (JPC-00-335-21) revealed that the LDL-C lowering rate practically reached the maximum at a dose of 10 mg and there was no increase in the incidence of adverse events with increases in the dose. The dosage of Ezetimibe in foreign countries is 10 mg once daily as in Japan, and the Ezetimibe dose combined in its combination drug with simvastatin approved in foreign countries is 10 mg. In Japan, Ezetimibe at a dose of 10 mg has been approved since 2007; thus, it has an abundance of clinical use experience both as monotherapy and combination therapy in Japanese patients. Consequently, we have chosen to examine Ezetimibe to be combined in MK-0653H at 10 mg.

The starting dose of Rosuvastatin in Japanese patients is 2.5 mg once a day, which can be titrated to 10 mg and 20 mg (where available). Furthermore, according to the survey of Japan Medical Data Center (JMDC) prescription receipt data from January 2013, out of the subjects who were coadministered Rosuvastatin and Ezetimibe (estimated number of patients is 0.2 million including familial cholesterolemia), the ratio of subjects who were administered the daily dose of Rosuvastatin 2.5mg and 5 mg were 54.5% and 35.3%, respectively, and these two doses accounted for 90% of the total subjects.[16)]. In consideration of the efficacy and safety profiles of Rosuvastatin, the prescription status of Rosuvastatin, and the clinical position of MK-0653H, we have found that 2.5 or 5 mg is an appropriate dose to be combined for Rosuvastatin.

Subject will receive one tablet of Ezetimibe 10 mg active or placebo and two capsules of Rosuvastatin 2.5 mg active or placebo under double-blind in this trial.

4.2.2.1 Rationale for The Use of Comparator/Placebo

Placebo run-in period: in order to confirm the subject's adherence, all subjects will receive placebo for 2 weeks under single blind.

Treatment period: In order to demonstrate the efficacy of MK-0653H comparing with single entity, this study has Ezetimibe 10 mg, Rosuvastatin 2.5 mg or 5 mg as parallel comparator. In addition, because the exploratory objective is to compare the efficacy between MK-0653H (EZ 10 mg + Ros 2.5 mg) and MK-0653H (EZ 10 mg + Ros 5 mg), this study is parallel study with 5 arms.

4.2.2.2 Efficacy Endpoints

In this study, the percent change in LDL-C at Week 12 from baseline will be used as the primary variable.

Results of many epidemiological surveys in Japan and overseas have shown that the incidence rate of CAD or the mortality rate increases with increasing level of LDL-C, and results of many large-scale clinical studies have confirmed that LDL-C lowering therapy is effective for the primary and secondary prevention of CAD[3) 4) 5) 6)]. In Japan and overseas,

LDL-C level is positioned as an important index for lipid management, and is used as an important variable for the development of lipid-improving drugs. LDL-C level is an index which has been established from the viewpoint of the prevention of arteriosclerotic diseases and lipid management, and the efficacy evaluation has been performed with the percent change in LDL-C as the primary variable in the previous clinical studies of Ezetimibe. Meanwhile, it is considered that other lipid parameters (TC, HDL-C, non HDL-C, TG and Apo-B) and hs-CRP should be sufficiently evaluated similarly to the LDL-C lowering effect, and therefore it is planned that those parameters will be analyzed as exploratory variables.

As shown above, the percent changes in TC, HDL-C, non HDL-C, TG, Apo-B and hs-CRP will be used as exploratory variables to evaluate the efficacy of MK-0653H.

4.2.2.3 Safety Endpoints

The safety will be evaluated with clinical and laboratory safety assessments conducted throughout the study.

Clinical measurements to assess the safety and tolerability of MK-0653H include monitoring of AEs and clinical evaluation (including vital signs and physical examination).

Laboratory safety assessments include chemistry, hematology and urinalysis, performed at specific study visits. All determinations will be performed by the central laboratory.

Gastrointestinal related AEs, gallbladder-related AEs, allergic reaction or rash AEs, hepatitis-related AEs, consecutive elevations in ALT and/or AST ≥3xULN, ALT and/or AST elevation ≥5xULN, ALT and/or AST elevation ≥10xULN, Potential Hy's Law Condition (defined as serum ALT or serum AST elevations >3xULN, with serum alkaline phosphatase <2xULN and total bilirubin (TBL) ≥2xULN), elevations in CK ≥10xULN, elevations in CK ≥10xULN with muscle symptoms and elevations in CK ≥10xULN with muscle symptoms that are considered drug-related are determined as safety events of special interest (Tier1 events) and will be evaluated.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Because the primary objective of this study is to evaluate the efficacy in parallel study under double-blind, in order to wash-off the prior medication's effect, subject is not allow to use lipid lowering agents 8 weeks prior to randomization (Visit 3) and see the values of lipid panels during treatment period. On the other hand, since there is no placebo arm during treatment period, subject is assigned to active arm only.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with hypercholesterolemia between the ages of 20 and 80 years (inclusive) will be enrolled in this trial.

Subjects with screening one value/finding outside the range described in the inclusion or exclusion criteria may, at the discretion of the investigator, have one repeat determination performed and if the repeat value satisfies the criterion, they may continue in the screening process. Only one specific out of range value/finding should be repeated (not entire panel).

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

<Visit 1: Screening, Week -8~ -3>

1. Japanese male or female and between ≥ 20 and ≤ 80 years of age on the day of signing informed consent.
2. Subject understands the study procedures alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
3. Outpatient with hypercholesterolemia.
4. Subject is a male or female subject who is of reproductive potential agrees about contraception, or a female subject who is not of reproductive potential.

   Female subject who is of reproductive potential has to agree to remain abstinent or use (or partner use) two acceptable methods of birth control from date of signed informed consent to the 14 days after the last dose of study drug. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, condom, and vasectomy.

   A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as: one who has either 1) reached natural menopause defined as age 46 or older with 12 months of spontaneous amenorrhea, 2) 6 weeks post surgical bilateral oophorectomy or hysterectomy, or 3) bilateral tubal ligation.
5. Subject will maintain a stable diet that is consistent with the Japan Atherosclerosis Society Guideline 2012 (JAS 2012) for prevention of atherosclerotic cardiovascular diseases for the duration of the study.

<Visit 2: Placebo run-in , Week -2>

6. Subject has TG value < 400 mg/dL at Visit 1.
7. Subject has CK (CPK) value ≤ 3 x upper limit of normal (ULN) [per central laboratory reference ranges] at Visit 1.

8. Subject has ALT and AST value ≤ 2 x ULN [per central laboratory reference ranges] at Visit 1.

<Visit 3: Randomization>

9. Subject meets any of the following criteria.

   Category will be assessed based on Section 12.3. (JAS2012).

   LDL-C value will be calculated by Friedewald method at Visit 2.

   Friedewald method : LDL-C = Total cholesterol – HDL-cho – TG/5.

   (1) Subject is categorized "Category I" and has LDL-C value ≥160 mg/dL to <220 mg/dL

   (2) Subject is categorized "Category II" and has LDL-C value ≥140 mg/dL to <190 mg/dL

   (3) Subject is categorized "Category III" and has LDL-C value ≥120 mg/dL to <160 mg/dL

10. Subject able to follow the instruction for drug administration and is greater than 75% compliant with study medication during the single-blind placebo run-in period.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

<Visit 1: Screening, Week -8~ -3>

Prohibited medical conditions

1. Subject has uncontrolled hypertension (treated or untreated) with systolic blood pressure >160 mmHg or diastolic >100 mmHg at Visit 1.
2. Subject has uncontrolled type 1 or type 2 diabetes mellitus (treated or untreated, HbA_{1C} ≥8.0% at Visit 1 or newly diagnosed within 3 months).
3. Subject has chronic heart failure defined by New York Heart Association (NYHA) Classes III or IV.
4. Subject has uncontrolled cardiac arrhythmias or recent significant abnormality in the subject's electrocardiogram as takes within 6 months prior to Visit 1 in the opinion of the investigator.
5. Subject has a history of coronary artery disease (CAD), CAD-equivalent disease [e.g., peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease transient ischemic attack, stroke].
6. Subject has familial hypercholesterolemia or has undergone LDL apheresis.

7. Subject has uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia, e.g., hyper- or hypothyroidism, Cushing's syndrome).

   Note: Definitions of hyper- and hypothyroidism are as follows:

   Hyperthyroidism: TSH below the central laboratory's LLN.

   Hypothyroidism: TSH >20% above the central laboratory's ULN.

   For subjects receiving thyroid hormone, there is no lower TSH threshold for entry (Visit 1) and the subject must be on a stable dose for ≥6 weeks before the randomization visit (Visit 3). One redraw will be allowed if the original TSH value is less than 40% above or below the reference range, but the subject must meet the criterion upon redraw.

8. Subject has estimated glomerular filtration rate (eGFR) < 30 mL/min /1.73 m^2 based on the below equation, nephrotic syndrome or other clinically significant renal disease at Visit 1.

   Male eGFR [mL/min/1.73m^2] =194 x Cr[mg/dL] $^{-1.094}$ x age [yr] $^{-0.287}$

   Female eGFR[mL/min/1.73m^2]=194 x Cr[mg/dL] $^{-1.094}$ x age [yr] $^{-0.287}$ x 0.739

9. Subject has had a gastrointestinal tract bypass, or other significant intestinal melabsorption.

10. Subject has a history of cancer within the past 5 years from Visit 1 (except for successfully treated dermatological basal cell or squamous cell carcinoma or in situ cervical cancer).

11. Subject who is known HIV positive (as assessed by medical history).

12. Subject has a history of drug/ alcohol abuse within the past 5 years from Visit 1, or psychiatric illness no adequately controlled and stable on pharmacotherapy.

13. Subject has a condition or situation, which described as contraindication in labeling of Zetia® or Crestor® (i.e., Patients with diminished liver metabolism capacity due to the following conditions: Acute hepatitis, acute exacerbation of chronic hepatitis, hepatic cirrhosis, liver cancer, or jaundice.) or may interfere with participation in the study in the opinion of the investigator.

Prohibited therapies

14. Subject is currently taking medications restricted by labeling as below.

    - Cyclosporine
    - Systemically administered azole antifungals(e.g., ketoconazole, itraconazole and fluconazole)
    - Macrolide antibiotics (e.g., clarithromycin, erythromycin and telithromycin)
    - Antacid (e.g., aluminum hydroxide/magnesium hydroxide)
    - Protease inhibitors (e.g., Lopinavir/Ritonavir, Atazanavir+Ritonavir, Darunavir +Ritonavir, concomitant use with elbasvir and grazoprevir)

- Simeprevir
- Eltrombopag

15. Subject is receiving treatment with systemic corticosteroids (intravenous, intramuscular and oral steroids).

    NOTE1: If subject has been treated with a stable regimen of oral corticosteroids used as replacement therapy for pituitary/adrenal disease as well as inhaled steroid therapy for ≥ 8 weeks prior to Visit 3 and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

    NOTE2: Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are acceptable.

16. Subject is taking any cyclical hormones (e.g., cyclical oral contraceptives, cyclical hormone replacement), including the combination of ethinyl estradiol and norethisterone within 8 weeks prior to Visit 3.
17. Subject is receiving non-cyclical hormone therapy (including non-cyclical hormone replacement therapy or any estrogen antagonist/agonist).

    Note: If subject has been treated with a stable regimen for ≥ 8 weeks prior to Visit 3 and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

18. Subject is treated with psyllium, other fiber-based laxatives, phytosterol margarine, herbal medicine and/or over the counter (OTC) therapies that are known to affect serum lipids.

    Note: If subject has been treated with a stable regimen for ≥ 8 weeks prior to Visit 3 and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

19. Subject is treated with an anti-obesity drug (e.g. mazindol) within 3 months (12 weeks) prior to Visit 1.
20. Subject is newly treated with warfarin and/or warfarin-like anticoagulants at Visit 1, or subject has not been on a stable dose with a stable International Normalized Ratio (INR) for at least 6 weeks prior to Visit 1.

General

21. Subject consumes more than 25 g of alcohol per day. (Refer to Appendix 12.5)
22. Subject who currently follows an excessive weight reduction diet in the opinion of the investigator.
23. Subject currently engages in a vigorous exercise regimen (e.g.; marathon training, body building training etc.) or intends to start training during the study.
24. Subject has hypersensitivity or intolerance to Ezetimibe or Rosuvastatin.
25. Subject has a history of myopathy or rhabdomyolysis with Ezetimibe or any statin.
26. Subject is currently pregnant or lactating.

27. Subject is taking any other investigational drugs and/or has taken any investigational drugs within 30 days prior to the day of signing informed consent, unless pharmacokinetics necessitates a longer washout.

<Visit 2: Placebo run-in , Week -2>

28. Subject has taken lipid-lowering agents (except probucol) including fish oils, Cholestin™, bile acid sequestrants, statins, Ezetimibe, fibrates or niacin (>200 mg/day) within 6 weeks prior to Visit 2. Subject has taken probucol or protein convertase subtilisin/kexin type 9 (PCSK 9) inhibitor within 10 weeks prior to Visit 2.

<Visit 1 to 3>

29. Subject has developed a new medical condition, suffered a change in status of an established medical condition or required a new tratement or medication, which meets any previously described study exclusion criteria.
30. The subject who is considered inappropriate for participation in the study by the investigator for any other reason.
31. Subject Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatment(s)to be used in this trial is outlined below in Table 1.

Table 1 Trial Treatment

Treatment group	Study Drug Containers Dispensed		
	Bottle A	Blister card B	Blister card C
Placebo run-in period (single-blind)	Ezetimibe Placebo tablet	Rosuvastatin Placebo capsule	Rosuvastatin Placebo capsule
Treatment period (double-blind)			
Ezetimibe 10 mg	Ezetimibe 10 mg tablet	Rosuvastatin Placebo capsule	Rosuvastatin Placebo capsule
Rosuvastatin 2.5 mg	Ezetimibe Placebo tablet	Rosuvastatin 2.5 mg capsule	Rosuvastatin Placebo capsule
Rosuvastatin 5 mg	Ezetimibe Placebo tablet	Rosuvastatin 2.5 mg capsule	Rosuvastatin 2.5 mg capsule
MK-0653H (EZ 10 mg+Ros 2.5 mg)	Ezetimibe 10 mg tablet	Rosuvastatin 2.5 mg capsule	Rosuvastatin Placebo capsule
MK-0653H (EZ 10 mg+Ros 5 mg)	Ezetimibe 10 mg tablet	Rosuvastatin 2.5 mg capsule	Rosuvastatin 2.5 mg capsule

The first dose of trial treatment will be administered at the trial site at Visit 2. Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

Study drug will be administered orally once daily after meal. As there is no recommended time for the dosage, subject should take their treatment at a consistent time each day to promote compliance. On the visit day, subject should take the medication after all procedure is completed. The scheduled last study drug is a day before Visit6.

5.2.3 Trial Blinding

A single-blinding technique will be used. In Placebo Run-in period, Ezetimibe 10 mg matching placebo tablet and Rosuvastatin 2.5 mg matching placebo capsule will be packaged identically so that blind/masking is maintained. The subject will not know the treatment they are administered, however the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be aware of the group assignments.

A double-blinding technique will be used. In treatment period, Ezetimibe 10 mg tablet and Rosuvastatin 2.5 mg capsule will be packaged identically relative to their matching placebos so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 5 treatment arms. Subjects will be assigned randomly in a 1:2:2:2:2 ratio to Ezetimibe 10 mg, Rosuvastatin 2.5 mg, Rosuvastatin 5 mg, MK-0653H (EZ 10 mg+Ros 2.5 mg) and MK-0653H (EZ 10 mg+Ros 5 mg), respectively.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

To achieve balance across treatment groups, randomization will be stratified according to the risk category determined at Visit 3.

1. Category I
2. Category II
3. Category III

5.5 Concomitant Medications/Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Concurrent antihypertensive, and antihyperglycemic medications are permitted. It is preferable that doses of these medications remain stable throughout the study.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should be instructed on JAS2012 diet or a similar diet at Visit 1. Please refer to Appendix 12.5 for details on the diet regimen.

At each subsequent study visit, the dietary compliance will be monitored and sites should reinstruct subjects who are not compliant. This monitoring is particularly important in an effort to minimize any diet-related lipid changes.

5.7.2 Activity

Subjects should continue any activity he/she was accustomed to prior to entering the study (including smoking), but should refrain from engaging in a vigorous exercise regimen and initiating smoking during the study. Subjects should be instructed the activity by investigator based on JAS2012 guideline. Subject also should keep exclusion criterion #22 and #23. (Subject does not follow excessive weight reduction diet from study duration, and does not engage in a vigorous exercise regimen or start training) during the study.

5.7.3 Alcohol Intake

Subjects should not consume more than the 25 g alcohol per day, and should not have any alcohol within 24 hours prior to scheduled visit.

Subjects will not be permitted in the study if they consistently consume excessive amounts of alcohol. Subjects should be encouraged not to make major changes in their alcohol consumption for the duration of the study. Please refer to Appendix 12.5 for reference volume of alcohol.

5.7.4 Contraception

Women of reproductive potential can be entered in the study (see inclusion criteria #4) and must agree to use 2 acceptable methods of contraception during sexual activity with a male partner. These contraceptive methods must be used throughout the study. Acceptable methods of contraception are either 2 barrier methods to prevent pregnancy. The following are considered acceptable barrier methods of contraception: intrauterine device (IUD), diaphragm with spermicides, condoms, partner or vasectomy. Contraception medications are restricted in exclusion criteria #16 and #17.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures are provided in Section 7.1.4 – Other Procedures.

Table 2 provides reasons why a subject must be discontinued from treatment but may continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 2 Discontinuation Scenarios

Reason for Discontinuation Scenario	***Action***
The subject or legal representative (such as a parent or legal guardian) withdraws consent.	Discontinuation from Treatment and Trial
The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center..	Discontinuation from Treatment and Trial
Consecutive (2 or more measurements) elevations in ALT and/or AST ≥3 x ULN	Discontinuation from Treatment and Trial
Consecutive elevations in CK ≥10 x ULN with or without muscle symptoms.	Discontinuation from Treatment and Trial
Consecutive elevations in CK ≥5 to <10 x ULN with muscle symptoms.	Discontinuation from Treatment and Trial
Subject requiring any treatment with cyclosporine or fibrates.	Discontinuation from Treatment and Trial
Pregnancy (Positive serum pregnancy test): A positive urine pregnancy test requires immediate interruption of study drug while awaiting results of serum pregnancy (β-hCG) test.	Discontinuation from Treatment and Trial
Any subject who is unblinded to treatment regimen during study. (The subject's treatment assignment has been unblinded by subject him/herself.)	Discontinuation from Treatment and Trial
Adverse experiences: Subject may be withdrawn from the study in the event that the investigator	Discontinuation from Treatment and Trial

Reason for Discontinuation Scenario	*Action*
assesses that administration of the study drug should be discontinued due to the occurrence of adverse experiences which would interfere with study continuation.	
Serious deviation from the protocol: It becomes inappropriate to continue study treatment as a result of a significant protocol deviation.	Discontinuation from Treatment and Trial
Lost to follow up: When a subject stops visiting a site after initiation study drug, he/she will be contacted via a letter or telephone call to confirm the reason for missed visits, dosing of study drug and the subsequent courses as much as possible.	Discontinuation from Treatment and Trial
Moved (or relocated): When subject has either moved or relocated and is no longer able to participate in the study.	Discontinuation from Treatment and Trial
The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.	Discontinuation from Treatment and Trial

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Phase		Screening (1~6 weeks)	Placebo run-in (2 weeks)	Treatment (12 weeks)				Follow up
Week		Week -8~ -3[1]	Week -2	Week 0	Week 4	Week 8	Week 12/ Discontinuation	14 days after last dosing
Visit number		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Visit window permitted (Day)[2]		N/A	7~42+7	14+/-3	28+/-7	28+/-7	28+/-7	
Administrative procedure								
Obtain Informed Consent[3]		X						
Collect Medical History		X						
Review Inclusion/Exclusion criteria		X	X	X				
Review Prior/Concomitant Therapies		X	X	X	X	X	X	
Contact Patient Registration Center		X	X	X	X	X	X	
Risk assessment [4]		X	X	X				
Review Diet/Exercise and Instruct on JAS Guidelines		X						
Monitor Dietary/Exercise Compliance			X	X	X	X	X	
Dispense Study Drug[5]			X	X	X	X		
Randomized (assignment of randomization number)				X				
Monitor Medication compliance/patient diary				X	X	X	X	
Safety assessment								
Review adverse event		X	X	X	X	X	X	X [15]
Perform Physical Examination [6]			X				X	
Vital sign	Height/Weight[7]	X		X			X	
	Sitting Blood Pressure/Pulse	X	X	X	X	X	X	
ECG			X					
Laboratory test[8]								
Lipid Panel A[9]		X	X	X	X	X	X	
hs CRP				X			X	
Apo protein (Apo) B				X	X	X	X	
Blood Chemistry [10]		X	X	X	X	X	X	
Hematology[11]		X					X	
TSH		X						
$HbA1_C$[12]		X					X	
Urinalysis[13]		X		X			X	
Pregnancy test[14]		X	X	X	X	X	X	

1. Interval between Visit 1 and Visit 2 is determined depending on the presence of the prior treatments. Subjects washing out lipid-lowering therapy will have Visit 1 at -6 weeks from Visit 2; subjects not requiring washout will have Visit 1 at -1~-6 weeks from Visit 2 depending on the state of prior pharmacotherapy other than lipid-lowering agents in each subject.
2. Visit window is relative to previous Visit.
3. Informed consent must be obtained before any protocol-related study procedures are performed. It is allowable to obtain informed consent before Visit 1. After obtaining informed consent, subject will be given a unique screening number (refer to 7.1.1.6) and a subject identification card (refer to 7.1.1.3).
4. Subject's risk category assessment is determined at Visit 3 according to the Japan Atherosclerosis Society (JAS) Guideline 2012 based on the results obtained at Visit 1 and 2 (refer to Appendix 12.3).
5. First dose of study drug should be taken on the day of the visit; last dose between each visit should be taken on the day before the next scheduled visit.
6. Auscultation and palpation and interview of condition will be conducted for physical examination.
7. Weight will be measured at Visit 1, 3, 6. Height will be measured only at Visit 1.
8. All laboratory draws for the study will be conducted after at least 10-hour fast.
9. Lipid panel A: LDL-C, total cholesterol (TC), HDL-C, non-HDL-C, and Triglyceride (TG)
10. Chemistry: Glucose, ALT, AST, ALP, uric acid, total bilirubin, BUN, CK (CPK), creatinine, Cl, potassium, sodium, γ-glutamyl transferase
11. Hematology: hemoglobin, platelet count, red blood cell count, white blood cell count, hematocrit
12. Subjects who have diagnosed with diabetes only may have their sample collected.
13. Urinalysis: pH, glucose (qualitative), protein (qualitative)
14. Urine pregnancy test (urine hCG) will be measured only in female subjects who have reproductive potential as specified in inclusion criteria #4. Urine pregnancy test (urine hCG) will be determined locally, serum β-hCG test is determined by central lab if urine pregnancy performed at the site is positive.
15. Post study phone call will be conducted 14 days after administration of the last dose of study drug.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 8 weeks before the randomization (Visit 3). Please note that the prior medications for hypercholesterolemia just before washout must be reported to eCRF.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

Randomization number will be allocated at Week 0 (Visit 3) via interactive voice response system / integrated web response system (IVRS/IWRS).

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Adherence to study medication will be assessed by subject report by patient diary recorded by subject every day.

Interruptions from the protocol specified compliance <= 75% at each visit require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication at Visit 2 will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

In order to minimize variability, it is preferred that the same individual perform the same procedure (s)/ evaluation (s) for all subjects at each trial site. All procedures will be performed at Visits outlined in the study flow chart (Section 6.0).

7.1.2.1 Physical Examination

Physical examination (auscultation, palpation, and interview of condition) will be performed by investigator. The investigator will determine if the results are clinically significant prior to Week 0 (Visit 3), any physical examination abnormalities will be recorded as part of the subject's medical history.

7.1.2.2 Vital Sign

7.1.2.2.1 Height

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows should be moved or removed from the top of the head before the measurement is taken.

7.1.2.2.2 Weight

Weight must be measured after at least 10 hours of fasting after voiding, with shoes and socks off, wearing only underwear, or a clinic vest or light clothing to reduce variability and to maintain consistency. Subjects should not be weighed while wearing sweaters, coats, or other heavy clothing.

7.1.2.2.3 Sitting Blood pressure/ pulse

Sitting blood pressure (SiDBP) and pulse will be measured by automated sphygmomanometer provided by the SPONSOR. Throughout the study, the measurement should be conducted with a consistent arm for a given person.

1. The subject will remain in the sitting position for at least 10 minutes before any blood pressure readings are recorded.

2. Situate the individual in a quiet environment with the arm resting at heart level.

3. Select the appropriately sized cuff.

4. Systolic and diastolic blood pressures will be determined by averaging 2 replicate measurements obtained 1 to 2 minutes apart.

5. The mean BP value is calculated from 2 readings by omitting the figures below the first decimal place.

6. None of the 2 consecutive SiDBP readings can be >5 mm Hg from the calculated average of the 2 readings. Additional readings must be done until this is achieved.

7. Assessment should be used average of 2 readings.

Note: A pulse rate evaluates 2 consecutive readings measured simultaneously with blood pressure and assessment should be used average of 2 readings.

7.1.2.2.4 ECG

12-lead ECG will be performed at the respective study sites and recorded. The investigator or sub-investigator will determine if the results are clinically significant and they meet the eligibility criteria. Any ECG abnormalities will be recorded as part of the subject's medical history. ECG readings reported to Sponsor will be diagnosed by the investigator or sub-investigator.

7.1.2.3 Monitor Medication compliance

Subjects should be instructed to record date and the number of tablet/capsule that administered the study drug at home to the provided patient diary during treatment period. The site staff should confirm and collect the diary at each visit.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 3.

Table 3 Laboratory Tests

Category	Test
Lipid Panel A	LDL-C, total cholesterol (TC), HDL-C, non-HDL-C, and Triglyceride (TG)
hs-CRP	
Apo protein (Apo) B	
Blood Chemistry	Glucose, ALT, AST, ALP, uric acid, total bilirubin, BUN, CK (CPK), creatinine, Cl, potassium, sodium, γ-glutamyl transferase
Hematology	hemoglobin, platelet count, red blood cell count, white blood cell count, hematocrit
TSH	
$HbA1_C$	NOTE: Subjects who have diagnosed with diabetes only
Urinalysis	pH, glucose (qualitative), protein (qualitative)
Pregnancy test	Urine pregnancy test (urine hCG) will be determined at the site. Serum β-hCG test is determined by central lab if urine pregnancy performed is positive. NOTE: female subjects who have reproductive potential Only

Laboratory safety tests will be performed after at least a 10-hour fast.

Fasting blood samples will be drawn as outlined in the Study Flow Chart. The central laboratory will perform all laboratory test determinations. LDL-C will be calculated using the Friedewald method when TG≤400 mg/dL and beta quantification ultracentrifugation when TG>400 mg/dL. All Lipid Panel A, Apo B and hs-CRP data will be blinded once the subject is centrally randomized. Once a subject is randomized (Visit 3), no attempts should be made on the part of the investigator or subject to have a local evaluation of the subject's lipid values (Lipid Panel A, Apo B and hs-CRP).

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit (Visit 6) should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity, relationship to the study medications and reason etc., of the adverse experiences observed, their relation to study

drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed. Subjects whose treatment assignment has been unblinded must be discontinued from study drug.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Auto sphygmomanometer

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening (Visit 1)

Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. A signed informed consent will be obtained prior to performing any protocol study procedures.

Screening procedures may be repeated after consultation with the Sponsor. In case of re-screening, all procedure listed at screening visit including informed consent should be performed.

Screening visit will be performed 1 to 6 weeks prior to Visit 2. Subject must discontinue the prior medication (except probucol) for hypercholesterolemia [fish oils, Cholestin™, bile acid sequestrants, statins, Ezetimibe, fibrates or niacin (>200 mg/day)] at least 6 weeks prior to Visit 2. If subject has taken probucol, probucol must be discontinued from at least 10 weeks prior to Visit 2. If a subject is eligible for study participation, a 10 hour fasting blood sample will be drawn.

Subject will be instructed on the JAS2012 diet and exercise, and will agree to maintain the diet/exercise regimen throughout the study.

7.1.5.2 Placebo run-in (Visit 2)

Visit 2 will be performed 2 weeks prior to randomization (Visit 3).

Visit 1 lab results must be reviewed and subject must meet all eligibility criteria at Visit 1 prior to performing any procedures at Visit 2. If a subject is eligible for study participation, a 10 hour fasting blood sample will be drawn. After initiating study drug (placebo) administration, subject who is determined to be not appropriate by the investigator will be excluded the study as screen failed. If a subject is not eligible for study participation, the investigator should contact with the subject, stop dosing study drug and performing the study immediately. NOTE: it is not necessary for screen failed subject to perform examination at discontinuation visit.

Subject will be instructed to take one tablet from a bottle and 1 capsule from each blister card and record medication compliance in a patient diary by following instruction. In principle, the day before scheduled visit should be administered study drug after dinner since blood sample is obtained at trough. All subjects will be asked to bring the bottle, blister cards and patient diary to their next scheduled clinic visit for compliance assessment.

7.1.5.3 Treatment Period (Visits 3 to 6)

If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the site will perform all procedures for Visit 3 and the subject will be randomized.

Blood sample will be obtained after at least 10 hour fasting and prior to administrating the study medication. After the all procedures have been completed, the study drugs will be dispensed to the subject and his/her will take them.

All lipid evaluations will be blinded once the subject is centrally randomized. No attempts could be made to have local evaluation of the subject's lipid levels once they have been issued active therapy. The investigator will not be blinded to laboratory safety results.

7.1.5.4 Discontinuation

After performing Visit 3, subject who is determined to be not appropriate by the investigator will be discontinued from the study. The investigator should contact with the subject to perform the examination listed at Visit 6 (12w/Discon) immediately, and be discontinued from the study.

7.1.5.5 Post-Trial (follow up telephone contact)

14 days after the last dose of study drug and thereafter, a follow up contact will be conducted via telephone to collect all adverse events that might have occurred within the 14 days.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than 1 tablet/capsule from either bottle or blister card per day during the study.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic

reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. Myopathy or Rhabdomyolysis are to be reported as ECI because of their association with lipid-lowering treatments. If a subject is reported as having myopathy, rhabdomyolysis, or if the CPK criterion necessitating study medication discontinuation is met, this constitutes an ECI. ECIs will be recorded in the database, monitored by the SPONSOR and reported in the clinical study report.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 4. The investigator's assessment of causality is required for each adverse event. Refer to Table 4 for instructions in evaluating adverse events.

Table 4 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to unblinding, changes are made to the primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	MK-0653H Phase III Factorial Study in Japanese Hypercholesterolemic Patients
Treatment Assignment	Subjects will be randomized to the following 5 arms in a 1:2:2:2:2 ratio. • EZ 10 mg • Ros 2.5 mg • Ros 5 mg • MK-0653H (EZ 10 mg + Ros 2.5 mg) • MK-0653H (EZ 10 mg + Ros 5 mg) The study will be conducted as a double-blind study.
Analysis Populations	Efficacy Full Analysis Set (FAS) population, defined as all randomized subjects who: • received at least one dose of double-blind study treatment • have baseline or post-baseline data • have baseline data for those analyses that require baseline data. Safety All Subject as Treated (ASaT) population, defined as all randomized subjects who received at least one dose of double-blind study treatment.
Primary Endpoint	Percent change from baseline in LDL-C at Week 12
Statistical Methods for Key Efficacy Analyses	Percent change from baseline in LDL-C at Week 12 will be analyzed using a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger[17] . The model will include terms for treatment, time, risk category, interactions of treatment by time and time by risk category. The primary hypotheses will be evaluated by comparing MK-0653H (EZ 10 mg + Ros 2.5 mg) to EZ 10 mg and to Ros 2.5 mg, as well as MK-0653H (EZ 10 mg + Ros 5 mg) to EZ 10 mg and to Ros 5 mg, based on the above model.

Statistical Methods for Key Safety Analyses	Safety events of special interest such as elevations in liver function tests will be pre-specified as Tier 1 events. (Refer to Section 8.6.2 for a full list of events.) The Tier 2 events are as follows. • AE • drug-related AE • serious AE (SAE) • drug-related SAE • discontinuation due to AE • discontinuation due to drug-related AE • discontinuation due to SAE • discontinuation due to drug-related SAE • specific AEs and system organ classes (SOCs) with incidence ≥4 subjects in at least one treatment group The percentage of subjects experiencing respective Tier 1 and Tier 2 events will be analyzed using the Miettinen and Nurminen method[18]. p-Values for treatment comparisons (Tier 1 only) and 95% confidence intervals (CIs) for treatment differences (Tier 1 and Tier 2) will be provided.
Interim Analyses	No interim analyses are planned.
Multiplicity	The study has two families of primary hypotheses, each comparing one arm of MK-0653H to the corresponding monotherapy components [i.e., EZ 10 mg and Ros (2.5 or 5 mg)]. Successful demonstration of a family of primary hypotheses requires superiority of MK-0653H to both EZ and Ros, and hence, no adjustment for multiplicity within a family of primary hypotheses is required. Multiplicity across the two families of primary hypotheses will be adjusted by the Hochberg procedure.
Sample Size and Power	With 31 subjects for EZ 10 mg and 62 subjects for each of the other 4 arms, the study will have a power of approximately 97% to successfully demonstrate both of the two families of primary hypotheses (α=0.05, two-sided). This calculation is based on the true percent change from baseline in LDL-C of -15% for EZ 10 mg, -34% for Ros 2.5 mg, -40% for Ros 5 mg, -46% for MK-0653H (EZ 10 mg + Ros 2.5 mg) and -52% for MK-0653H (EZ 10 mg + Ros 5 mg), and a true standard deviation (SD) of 16%. To account for discontinuation, a total of 306 subjects will be randomized.

8.2 Responsibility for Analyses / In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will

not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment.

8.3 Hypotheses / Estimation

The study has the following two families of primary hypotheses in terms of percent reduction from baseline in LDL-C at Week 12.

(1) MK-0653H (EZ 10 mg + Ros 2.5 mg) is superior to Ezetimibe 10 mg and is superior to Rosuvastatin 2.5 mg in percent reduction from baseline in LDL-C after 12 weeks of treatment.

(2) MK-0653H (EZ 10 mg + Ros 5 mg) is superior to Ezetimibe 10 mg and is superior to Rosuvastatin 5 mg in percent reduction from baseline in LDL-C after 12 weeks of treatment.

Successful demonstration of a family of primary hypotheses requires superiority of MK-0653H (EZ 10 mg + Ros 2.5 mg, or EZ 10 mg + Ros 5 mg) to both of the corresponding monotherapy components [i.e., EZ 10 mg and Ros (2.5 or 5 mg)]. Successful demonstration of at least one family of primary hypotheses is required to declare study success.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below. For each of the efficacy and safety parameters, the baseline value is defined as the last available measurement prior to randomization, which typically corresponds to the measurement obtained at Visit 3.

8.4.1 Efficacy Endpoints

The primary efficacy endpoint is percent change from baseline in LDL-C at Week 12. The exploratory endpoints include percent change from baseline in LDL-C at Weeks 4 and 8, proportion of subjects achieving LDL-C goal at Week 12, as well as percent change from baseline in the other efficacy parameters (refer to Section 4.2.3.1) at Week 12.

8.4.2 Safety Endpoints

Refer to Section 4.2.3.2 for a list of safety endpoints.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The FAS population will serve as the population for the analyses of efficacy data in this study. The FAS population consists of all randomized subjects who:

- received at least one dose of double-blind study treatment
- have baseline or post-baseline data
- have baseline data for those analyses that require baseline data.

Even though no Per-Protocol analysis is planned, major deviations from the protocol that may substantially affect the results of the primary efficacy endpoint will be identified and documented in a separate memo prior to unblinding. Such major deviations include:

- off-drug periods during the treatment period
- noncompliance
- concomitant use of prohibited medications with presumed lipid lowering efficacy
- errors in assigned study medication during the study.

Subjects will be included in the treatment group to which they are randomized for analyses of efficacy data.

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of double-blind study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of double-blind study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary objectives. Methods related to the exploratory objectives will be described in the sSAP.

The primary endpoint, percent change from baseline in LDL-C at Week 12, will be analyzed using a cLDA model proposed by Liang and Zeger. The model will include terms for treatment, time, risk category, and the interactions of treatment by time and time by risk category. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values (percent change) observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion. The treatment difference in terms of mean percent change from baseline to Week 12 will be estimated and tested from this model to address the primary hypotheses. Sensitivity analysis will be performed to assess the robustness of the results to the assumptions about missing data. The details will be described in sSAP.

The above analysis based on restricted maximum likelihood (REML) assumes that the vector of model-based residuals follows a multivariate normal distribution. Under severe departures from normality, the REML-based analysis can be inefficient or potentially

misleading. Accordingly, the residuals from the REML-based analysis, scaled by the inverse Cholesky root of the marginal variance-covariance matrix, will be subjected to a test for normality. If normality is not rejected at the α=0.001 level, then the above REML-based analysis will serve as the primary analysis. However, if normality is rejected, then the primary analysis will be conducted using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression approach that uses M-estimation. The model will include factors for treatment and risk category, and baseline value as a covariate. Of note, the 0.001 level for the normality test was chosen so that the default REML-based analysis is abandoned only under a clear departure from normality; moreover, this choice guarantees that there is no material inflation in the type I error rate for the treatment effect comparison due to a potential correlation between the test statistics for the treatment effect and the normality test.

The strategy to address multiplicity issues with regard to multiple treatment comparisons is described in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. The treatment comparisons or treatment differences in this section pertain to the MK-0653H (EZ 10 mg + Ros 2.5 mg, or EZ 10 mg + Ros 5 mg) versus corresponding monotherapy components [i.e., EZ 10 mg and Ros (2.5 or 5 mg)].

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values for treatment comparisons as well as point estimates and corresponding 95% CIs for between-group differences. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates and corresponding 95% CIs provided for between-group differences; only point estimates by treatment group are provided for Tier 3 safety parameters.

AEs (specific terms as well as SOC terms) that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of subjects who experiences the events. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other AEs will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

Continuous measures such as changes from baseline in laboratory and vital signs parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Refer to Table 5 for a list of safety endpoints by tier.

p-Values (Tier 1 only) for treatment comparisons and 95% CIs for between-treatment differences in the percentage of subjects with respective Tier 1 and Tier 2 events will be

calculated using the Miettinen and Nurminen method. The analysis will not be stratified by risk category.

Table 5 Analysis Strategy for Safety Parameters

Safety tier	Safety endpoint†	p-Value	95% CI for treatment difference	Descriptive statistics
Tier 1	• gastrointestinal related AEs • gallbladder-related AEs • allergic reaction or rash AEs • hepatitis-related AEs • consecutive elevations in ALT ≥3x ULN • consecutive elevations in AST ≥3x ULN • consecutive elevations in ALT or AST ≥3x ULN • ALT elevations ≥5x ULN • AST elevations ≥5x ULN • ALT or AST elevations ≥5x ULN • ALT elevations ≥10 xULN • AST elevations ≥10x ULN • ALT or AST elevations ≥10x ULN • potential Hy's Law condition (ALT or AST elevations >3x ULN, with ALP <2x ULN and TBL ≥2x ULN) • CK elevations ≥10x ULN • CK elevations ≥10x ULN with muscle symptoms • CK elevations ≥10x ULN with muscle symptoms that are considered drug-related	X	X	X
Tier 2	• AE • drug-related AE • SAE • drug-related SAE • discontinuation due to AE • discontinuation due to drug-related AE • discontinuation due to SAE • discontinuation due to drug-related SAE • specific AEs, SOCs (incidence ≥4 subjects in at least one treatment group)		X	X
Tier 3	• Specific AEs, or SOCs‡ (incidence <4 subjects in all treatment groups) • Change from baseline results (laboratory, and vital signs)			X

† AE references refer to both clinical and laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or Tier 2 endpoints.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

No interim analyses are planned for the study.

8.8 Multiplicity

The study has two families of primary hypotheses, each comparing one arm of MK-0653H (i.e., EZ 10 mg + Ros 2.5 mg, or EZ 10 mg + Ros 5 mg) to the corresponding monotherapy components [i.e., EZ 10 mg and Ros (2.5 or 5 mg)]. Successful demonstration of a family of primary hypotheses requires superiority of MK-0653H to both EZ and Ros, and hence, no adjustment for multiplicity within a family of primary hypotheses is required. Multiplicity across the two families of primary hypotheses will be adjusted by the Hochberg procedure, which is implemented as follows.

Let p_{1E} and p_{1R} be the p-values associated with the treatment comparisons of EZ 10 mg + Ros 2.5 mg to EZ 10 mg and to Ros 2.5 mg, respectively, and p_{1max} be the larger of p_{1E} and p_{1R}. Define p_{2E}, p_{2R} and p_{2max} similarly for the treatment comparisons of EZ 10 mg + Ros 5 mg to EZ 10 mg and to Ros 5 mg.

Let p_{Fmax} and p_{Fmin} be the larger and smaller of p_{1max} and p_{2max}, respectively. Then the conclusions of the study will be as follows, depending on the values of p_{Fmax} and/or p_{Fmin}:

- if $p_{Fmax} \leq 0.05$, then both of the two families of primary hypotheses are considered successfully demonstrated
- if $p_{Fmax} > 0.05$ and $p_{Fmin} \leq 0.025$, then only the family of primary hypotheses associated with p_{Fmin} is considered successfully demonstrated but the other family is not
- otherwise, neither of the two families of primary hypotheses is considered successfully demonstrated.

A schematic display of multiplicity adjustment is shown in Figure 2 below.

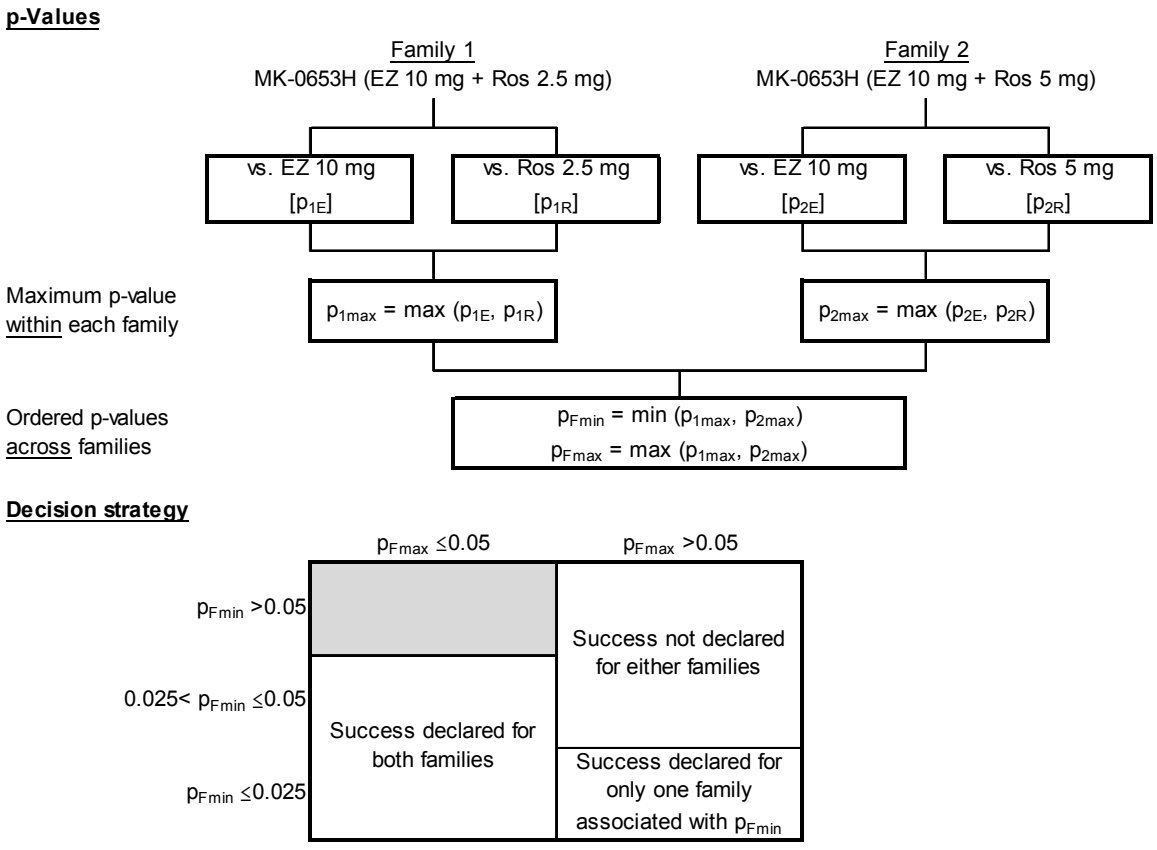

Figure 2 Schematic Display of Multiplicity Adjustment

8.9 Sample Size and Power Calculations

A total of 306 subjects will be randomized in a ratio of 1:2:2:2:2 to the following 5 arms: EZ 10 mg, Ros 2.5 mg, Ros 5 mg, MK-0653H (EZ 10 mg + Ros 2.5 mg), MK-0653H (EZ 10 mg + Ros 5 mg). Assuming that valid LDL-C measurements can be obtained at Week 12 from 31 subjects in the EZ 10 mg arm and from 62 subjects in each of the other 4 arms, the study will have a power of approximately 97% to successfully demonstrate both of the two families of primary hypotheses at α=0.05, two-sided. For each of the two families of primary hypotheses, the study will have a power of approximately 97% that the family of primary hypotheses can be demonstrated at α=0.025, two-sided. The study will have a probability of approximately 98% to show a numerically greater LDL-C percent reduction at Week 12 with MK-0653H (EZ 10 mg + Ros 5 mg) compared with MK-0653H (EZ 10 mg + Ros 2.5 mg). These calculations were performed using simulations. Power calculations for pairwise comparisons are shown in Table 6 below.

Table 6 Power Calculations for Pairwise Comparisons

Endpoint	N_1	N_2	Minimum detectable difference with 90% power [α=0.05 (0.025), two-sided]	Half-width of 95 (97.5) % CI	SD
LDL-C % change	62	62	9.4 (10.2) %	5.7 (6.5) %	16%
	62	31	11.5 (12.6) %	7.0 (8.0) %	16%

The calculations shown in Table 6, and the calculations above performed using simulations, are based on the assumptions on the true percent change from baseline in LDL-C at Week 12 for each treatment arm as shown in Table 7, and a true SD of 16%. These are conservative estimates from previously conducted factorial studies with EZ 10 mg and statins, as well as placebo-controlled monotherapy studies with EZ 10 mg or Rosuvastatin.

Table 7 Assumptions on True LDL-C Percent Change from Baseline by Treatment

Ezetimibe	Rosuvastatin		
	0 mg	2.5 mg	5 mg
0 mg	--	-34%	-40%
10 mg	-15%	-46%	-52%

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of each subgroup.

- age category (<65 years, ≥65 years)
- gender (male, female)
- prior lipid-lowering agent therapy [none, treatment with a statin (with or without other lipid-lowering agent therapies), treatment without a statin]
- diabetes mellitus (yes, no)
- hypertension (yes, no)
- baseline LDL-C (≤ or > median)
- risk category (category I, category II, category III)

The consistency of the treatment effect will be assessed using the same model as the primary efficacy analysis model.

8.11 Compliance (Medication Adherence)

A day within the study will be considered an "On-Therapy" day if the subject takes one tablet / capsule each from Bottle A and Blister cards B and C. For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the day of randomization to the last scheduled day for treatment administration for that subject. For a patient who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from the day of randomization to the date of the last dose of study medication.

For each subject, percent compliance will be calculated using the following formula:

(Number of Days on Therapy / Number of Days Should be on Therapy) x 100.

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

8.12 Extent of Exposures

The dose level and treatment duration will be summarized for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Ezetimibe 10 mg or matching placebo	Tablet
Rosuvastatin Calcium 2.5 mg or matching placebo	Capsule

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

In the placebo run-in period, subjects will receive one (1) single blinded bottle of Ezetimibe 10 mg matching placebo and two (2) single blinded blister card of Rosuvastatin Calcium 2.5 mg matching placebo. In the treatment period, subjects will receive one (1) blinded bottle of Ezetimibe 10 mg or matching placebo and two (2) blinded blister card of Rosuvastatin Calcium 2.5 mg or matching placebo every four (4) weeks.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment allocation/randomization schedule for the trial to unblind subjects and to unmask treatment identity . The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her

knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results

until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

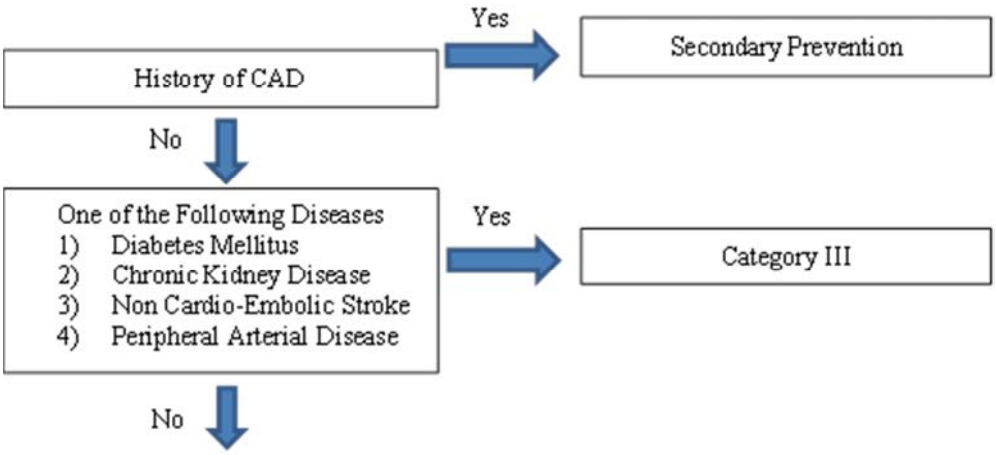
* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 List of Abbreviations

Abbreviation	Details
EZ	Ezetimibe
Rosuvastatin Ros	Rosuvastatin calcium
EZ 10 mg+Ros 2.5 mg	Co-administration of Ezetimibe 10 mg and Rosuvastatincalcium 2.5 mg
EZ 10 mg+Ros 5 mg	Co-administration of Ezetimibe 10 mg and Rosuvastatincalcium 5 mg
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
CHD	Coronary heart disease
CAD	Coronary artery disease
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
JAS2012	2012 Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases

12.3 Category Assessment for Each Patient

Subjects will be assessed using following chart based on JAS 2012.



Baseline Risk		No. of Risk Factors	Category
Gender	Age	1) Hypertension 2) Smoking 3) Hypo HDL cholesterolemia (HDL-C < 40 mg/dL) 4) Family history of premature CAD in first-degree relatives (a man aged < 55 years or a woman aged < 65 years) 5) Impaired glucose tolerance	
Male	40's	0	Category I
		1-2	Category II
		≥ 3	Category III
	50's	0	Category II
		1	Category II
		≥ 2	Category III
	60's (up to 74 years)	0	Category II
		≥ 1	Category III
Female	40's and 50's	0-1	Category I
		≥ 2	Category II
	60's (up to 74 years)	0-1	Category II
		≥ 2	Category III

[Instruction for this study]

· Smoking should be counted as 1 risk if patient have had ≥ 1 cigarette within last month.

· Patient who is ≥ 75 years old should be assessed based on the criteria of 60's for each gender.

· Male patients who are under 40's should be assessed based on the criteria of males of 40's. Female patients who are under 40's should be assessed based on the criteria of females of 40's and 50's.

[Definition of CAD by events, procedures, symptoms or imaging]

1. Event:

· Myocardial infarction (MI) (e.g., subendocardial myocardial infarction, non-Q wave MI, unstable angina, acute coronary syndrome)

2. Procedure:

· Percutaneous Transluminal Coronary Angioplasty (PTCA).

· Coronary Stenting

· Coronary Artery Bypass Graft (CABG)

3. Symptoms:

· Angina (chest pain deemed to be of cardiac origin)

4. Imaging:

· Angiography with evidence of CAD

· Stress test using treadmill, echocardiography or nuclear testing consistent with CAD

Note: The above lists are not all inclusive. If your patient has a medical/physical condition and you are unsure if the condition excludes them from participation in the study, please contact the SPONSOR.

12.4 Lipid Management Goals Based on Risk Assessment

Principle of the Therapeutic Strategy	Category	Absolute Risk†	Additional Risk‡	Lipid Control Target Values (mg/dL)	
				LDL-C	HDL-C
Primary prevention (No history of CAD) Drug treatment should be considered after first improving the patient's lifestyle.	I	< 0.5%	No	< 160	≥ 40
	II	< 0.5%	Yes	< 140	
		≥ 0.5%, < 2.0%	No		
	III	≥ 0.5%, < 2.0%	Yes	< 120	
		≥ 2.0%	No/ Yes		
Secondary prevention (History of CAD) Drug treatment should be considered, together with improving the patient's lifestyle.	History of CAD			< 100	
†Absolute Risk is defined as Probability of death form CAD in 10 years based on NIPPON DATA 80 ‡ Additional Risk are defined as 1) Hypo HDL-cholesterolemia (HDL-C < 40 mg/dL), 2) Family history of premature CAD in first-degree relatives (a man aged < 55 years or a woman aged < 65 years), 3) Impaired glucose tolerance. Patient who has diabetes mellitus, chronic kidney disease (CKD), non cardio-embolic stroke or peripheral arterial disease (PAD) are definded as category III					

Revised JAS Guidelines, 2012 version (The Japan Atherosclerosis Society)

12.5 Diet and Alcohol

Diet

Patient should follow the nutrient recommendation provided by the JAS2012 for prevention of atherosclerotic cardiovascular diseases throughout this study.

1) with consideration for energy intake and amount of physical examination, maintain normal body weight ($[Height(m)]^2 \times 22$)
2) control energy rate of fat 20 to 25%, unsaturated fatty acid 4.5% to not more than 7%, and amount of cholesterol intake, <200 mg/day
3) increase n-3 poly unsaturated fatty acids intake
4) control energy rate of carbonhydrates 50 to 60%, and increase fiber intake
5) control salt intake 6 g/day
6) limit alcohol intake <25 g/day

Alcohol

The amount of 25 g alcohol is defined as follows:

Alcohol	25 g/day
Beer	1 bottle (633 ml/bottle)
Sake	180 ml
Whiskey / Brandy	2.5 glasses (Single)
Distilled spirit	90 ml
Wine	2 glasses

12.6 Standard Operating Procedure for Liver and Muscle Enzyme Evaluations

Every increase in ALT, AST, and/or CK above the limits described in the protocol (i.e., ALT/AST ≥3 times the upper limit of normality [ULN], and CK ≥5 times ULN), the central laboratory will alert the investigators/ coordinators and the SPONSOR clinical personnel. The study and central laboratory SOP calls for immediate repeat testing within 3 days every time these tests reach these limits or are otherwise questionable.

Under these circumstances, the investigators/coordinators must recall the subject and attempt to identify the cause of the elevation. This evaluation should include:

A. For CK Increases

1. Patients should return to the center within 3 days after result available for the following (history can be obtained over the phone in the interim):

   · A search for potential drug interactions with known inhibitors or substrate of cytochrome P-450 CYP3A4.

   · Rule out myocardial ischemia as a cause for the elevation.

   · Documentation of unusual and/or strenuous physical activities, recent trauma, or IM injections preceding the blood testing.

2. Actions

   · Patients with persistent (2 or more) CK elevations between 5 and <10 times the ULN and muscle symptoms will also be discontinued .

   · Patients with persistent (2 or more) CK elevations between 5 and <10 times the ULN without symptoms may remain on drug (at the discretion of the SPONSOR medical monitor) with more intensive monitoring (as agreed to by the monitor and investigator). These patients should remain on drug until repeat labs are obtained.

   · Patients with persistent (i.e., 2 consecutive measurements), unexplained 10 fold elevation in CK with or without symptoms will be discontinued from the study.

     NOTE: All discontinued patients should be monitored and have repeat lab draws completed until critical elevations have resolved.

B. For ALT or AST Increases

1. Patients should return to the center within 3 days after results available for the evaluations listed below (history can be obtained over the phone in the interim). In cases where the ALT and/or AST value is ≥3-fold ULN patients should generally remain on drug until the follow-up visit.

   · Careful questioning of recent alcohol consumption. Recent change in pattern.

   · Search for iatrogenic causes of hepatitis and liver injuries (acetaminophen, amiodarone, aspirin, chlorpromazine, dantrolene, erythromycin, halothane, isoniazid, methyldopa, nitrofurantoin, oxyphenisatin, perhexiline maleate, phenytoin, propylthiouracil, rifampin, sulfonamides, tetracyclines).

- Search for alternative medical causes such as cholelithiasis and ascending cholangitis, viral illnesses, hepatitis, or potential exposure to viral hepatitis (transfusion).

2. Action

   - Values of ALT or AST ≥3 X ULN at any visit will result in mandatory retest within 3 days. Persistent (2 consecutive measurements) 3-fold elevations in ALT or AST will result in withdrawal of the patient from the study.

12.7 Clinical Study Conduct System

Clinical study conduct system in Japan is provided by Japanese language.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	