TITLE PAGE

Protocol Title: A phase 4, multicenter, randomized, open-label, active-controlled study to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

Protocol Number: OG-KORATO-001

Amendment Number: Protocol OG-KORATO-001 ver.4.1

Compound: ezetimibe/atorvastatin, atorvastatin

Brief Title: Effectiveness and safety study of early add-on of ezetimibe with atorvastatin in very high-risk patients

Study Phase: Phase 4

Sponsor Name: Organon Korea Co. Ltd

Legal Registered Address: 50, Jong-ro 1-gil, Jongno-gu, Seoul, Republic of Korea

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STATEMENT OF CONFIDENTIALITY

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

Signature of Sponsor

PROTOCOL TITLE: A phase 4, multicenter, randomized, open-label, active-controlled study to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

PROTOCOL NO: OG-KORATO-001

VERSION: 4.1 dated 27-Jun-2024

Reviewed and Approved by:

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PPD			

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PPD			

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase 4, multicenter, randomized, open-label, active-controlled study to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

Rationale:

The 2019 dyslipidemia management guidelines from the European Society of Cardiology set an LDL-C target for very high-risk patients of less than 55 mg/dL (as well as at least a 50% cut from baseline), a class I recommendation. Accordingly, the Korean Society of Lipid and Atherosclerosis has also updated the treatment guidelines in 2022. However, the 2021 EAS practical guidance says that the new LDL-C goals for high and very-high risk group patients with dyslipidema are more demanding; in real-world practice, only 1/3 patients reach the LDL-C target (Averna M 2021). Therefore, this study aims to confirm the effectiveness of ezetimibe add-on therapy on LDL-C levels compared to atorvastatin monotherapy, especially in very high-risk patients. We intend to lay the foundation for a standard treatment for these patients through ezetimibe add on lipid-lowering therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effectiveness of early add-on of ezetimibe with atorvastatin in very high-risk patients	• Percentage change in LDL-C from baseline to week 6
Secondary	
• To evaluate the clinical effectiveness of early add-on of ezetimibe with atorvastatin in very high-risk patients.	• Proportion of patients achieving LDL-C goal of <55 mg/dL after 6 weeks and 12 weeks of treatment • Proportion of patients achieving LDL-C goal of <70 mg/dL after 6 weeks and 12 weeks of treatment • Percentage change in LDL-C from baseline to week 12 • Percentage change in HDL-C, non-HDL-C, triglycerides, and total cholesterol from baseline to week 6 and week 12
• To evaluate the safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.	• Treatment-emergent adverse events (TEAEs) at 6 weeks and 12 weeks

	• Dropout rate due to TEAEs at 6 weeks and 12 weeks

Abbreviations: LDL-C=Low-density lipoprotein cholesterol; HDL-C= High-density lipoprotein cholesterol

Overall Design:

This is Phase 4, multicenter, randomized, open-label, active-controlled study. The study has been designed to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

In Visit 1, screening is conducted for patients in the very high-risk group. LDL-C needs to be above 70 mg/dL in patients (a) who failed to achieve their target LDL-C goals with mild to moderate intensity statin; (b) who are statin-naive or have not been on a stable statin regimen for at least 4 weeks prior to enrollment. However, by tracking the registration status of patients, (b) patients should be enrolled not to exceed 40% of each group. All laboratory tests are performed in the local laboratory and the Visit 1 results may be substituted if available within 2 weeks prior to the screening visit. The study participation is determined through the inclusion/exclusion criteria based on the test results conducted for Visit 1. In the case of the lipid parameter, Visit 1 results are used as the baseline. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

In Visit 2, randomization is performed on patients who meet the inclusion criteria and do not meet any of the exclusion criteria and will be distributed 1:1 between test group (arm Eze/Ato) and control group (arm Ato). The results of laboratory tests at the Visit 2 are used as baseline except lipid parameters. Visit 1 and Visit 2 may be conducted on the same date.

In Visit 2 and Visit 3, the appropriate investigational medical product (IMP) is given to each group. In principle, IMPs are administered orally once a day from the day of distribution.

For participants whose LDL-C value has reached the target (LDL-C < 55 mg/dL) according to the lipid indicator test at Visit 3, they will continue treatment with the same dose for 6 weeks. If the LDL-C level has not reached target, the dose of atorvastatin should be increased to ezetimibe/atorvastatin 10/80 mg or atorvastatin 80 mg according to the group assigned. In principle, a morning visit is recommended so that the laboratory test results can be checked and the IMP can be prescribed and taken on the same day. However, if the test results are not confirmed on the same day and a participant has enough IMP to take until the next visit, IMP compliance is checked, and the same dose of IMP (ezetimibe/atorvastatin 10/40mg or atorvastatin 40mg) is continued. An additional visit is made within 1 week to return the remaining IMP and receive new IMP. If the test results are not confirmed on the same day and a participant does not have remaining IMP, the investigator prescribes the same dose of IMP (ezetimibe/atorvastatin 10/40mg or atorvastatin 40mg) that the participant was taking

previously, and an additional visit is made within 1 week to receive new IMP. Visit 4 is the end of study visit, and tests for effectiveness and safety are conducted.

Number of Participants:

The number of patients in each treatment group is about 57 under the assumption of two-sided significance level $\alpha = 0.05$, power $1-\beta = 0.80$ with a randomization ratio $\lambda = 1$. Considering the dropout rate of 10%, 63 patients for each group and thus, a total of 126 patients will be randomized in this study.

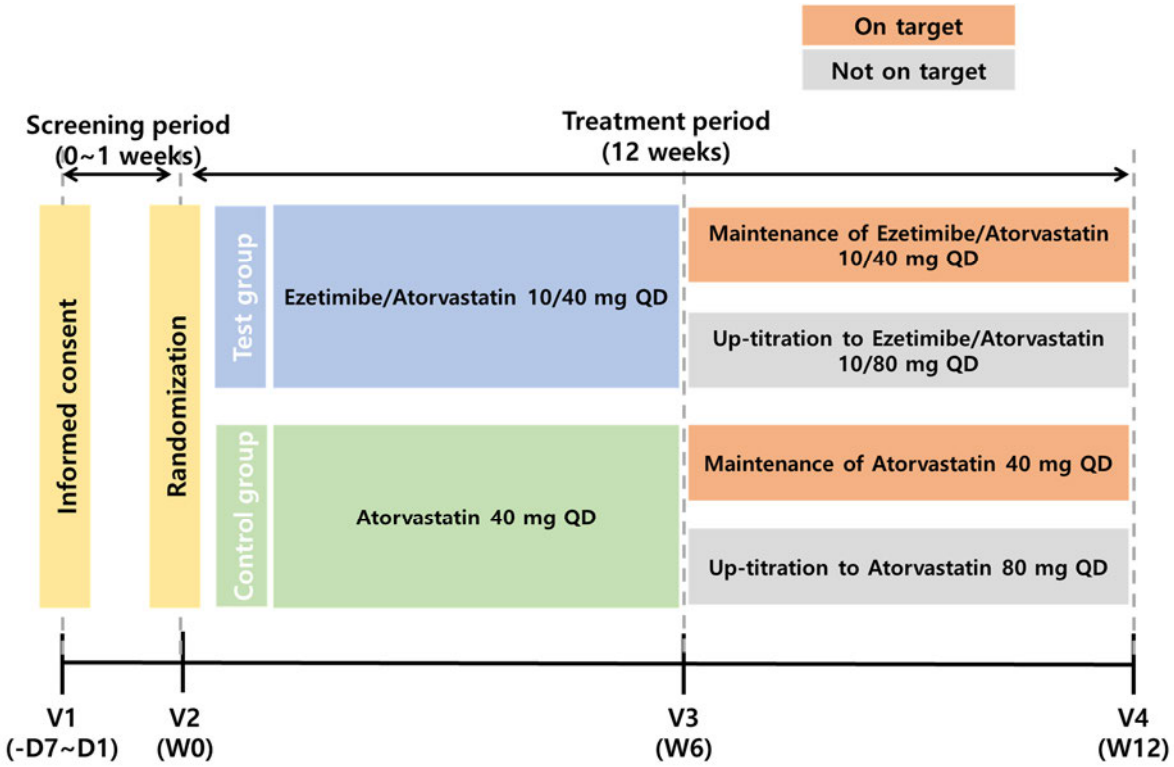
Intervention Groups and Duration:

Arm Title	Eze/Ato	Ato
Arm Type	Experimental	Active comparator
[Arm Description]	Participants will receive ezetimibe/atorvastatin 10/40 mg QD from Visit 2 (Day 1) to Visit 3 (Week 6). If the LDL-C target is reached (LDL-C < 55 mg/dL) at Visit 3, maintain the dose to Visit 4 (Week 12). If the LDL-C target level is not reached at Visit 3, dose is increased to ezetimibe/atorvastatin 10/80 mg QD from Visit 3 to Visit 4.	Participants will receive atorvastatin 40 mg QD from Visit 2 (Day 1) to Visit 3 (Week 6). If the LDL-C target is reached (LDL-C < 55 mg/dL) at Visit 3, maintain the dose to Visit 4 (Week 12). If the LDL-C target is not reached at Visit 3, dose is increased to atorvastatin 80 mg QD from Visit 3 to Visit 4.
Associated Intervention Labels	Ezetimibe/Atorvastatin	Atorvastatin

Abbreviation: QD = once a day

1.2 Schema

Figure 1-1 Study Schema



1.3 Schedule of Activities

Table 1–1 presents the schedule of activities (SoA).

Table 1–1 Schedule of Activities

Procedure	Screening [a]	Intervention Period			E/D
	-D7~D1	W0	W6	W12/EOS	
	V1	V2	V3	V4	
Visit window			± 7 days	± 7 days	
Informed consent [b]	X				
Inclusion and exclusion criteria	X				
Demographics	X				
Physical examination (height, weight) [c]	X	X	X	X	X
Medical history related to dyslipidemia	X				
General medical history	X	X			
Prior medication [d]	X				
Serum or urine pregnancy test (WOCBP only)	X	X	X	X	X
12-lead ECG	X	X	X	X	X
Vital signs [e]	X	X	X	X	X
TLC [f]	X	X	X	X	X
Randomization		X			
IMP distribution and return [g]		X	X	X	
Concomitant therapy		X	X	X	X
Lipid parameter laboratory tests [h]	X	X	X	X	X
General laboratory tests	X	X	X	X	X

Procedure	Screening [a)]	Intervention Period			E/D
	-D7~D1	W0	W6	W12/EOS	
	V1	V2	V3	V4	
Visit window			± 7 days	± 7 days	
AE/SAE review		X	X	X	X

Abbreviations: AE = adverse event; D = day; ECG = electrocardiogram; EOS = end of study; E/D = early discontinuation; IMP = investigational medical product; SAE = serious adverse event; TLC = therapeutic lifestyle change; V = visit; W = week; WOCBP = women of childbearing potential.

a) Screening test (Visit 1) will be performed in the local laboratory and results may be substituted if available within 2 weeks prior to the screening visit. The Visit 1 and Visit 2 may be conducted on the same day.
b) All procedures related to clinical trials must be carried out after obtaining written consent, and screening numbers are assigned in the order of written consent.
c) Height is measured at screening only and body weight will be measured at each visit.
d) Prior medication up to 1 month prior to enrollment will be collected.
e) Heart rate and blood pressure will be assessed. Vital signs will be measured in a relax position after 5 minutes rest.
f) Participants will receive education on TLC methods and perform during the clinical trial period.
g) IMPs are distributed at Visit 2 and Visit 3, and the remaining IMPs are returned at Visit 3 and Visit 4, respectively.
h) All tests will be performed in the local laboratory.

2.0 STUDY RATIONALE AND BACKGROUND

Dyslipidemia is characterized by elevated total cholesterol, low density lipoprotein-cholesterol (LDL-C), triglyceride, and reduced high-density lipoprotein cholesterol (HDL-C), and is classified into hypercholesterolemia, hypertriglyceridemia and mixed dyslipidemia. Dyslipidemia is also a major risk factor that can lead to cardiovascular disease (CVD) along with smoking, hypertension, diabetes, and obesity (Keys A 1972). Therefore, it is important to manage blood lipids in these patients. Treatment methods for dyslipidemia include non-drug therapy and drug therapy (Rhee EJ 2019). Since the blood lipid, which is the target for the primary treatment of dyslipidemia, is affected by dietary factors such as excessive intake of saturated fatty acids or cholesterol, overeating, and drinking, an appropriate diet should be the basis. In addition, regular exercise not only reduces lipid levels but also affects body fat reduction, so it is effective to combine exercise therapy with it. Therefore, when managing dyslipidemia, a therapeutic lifestyle change (TLC) is essential, and it is important to treat optimal drug therapy in consideration of LDL-C and other risk factors (Rhee EJ 2019).

According to the 2018 guideline for the management of dyslipidemia in Korea, patients with CVD are classified as a very high-risk group, and the treatment goal is to lower LDL-C levels to <70 mg/dL or by >50% from the baseline level for secondary prevention (Rhee EJ 2019). However, in a large-scale observational study of 10,661 patients in the Dyslipidemia International Study (DYSIS), only 29.4% and 18.9% patients with coronary heart disease and acute coronary syndrome respectively were under target LDL-C levels. (Gitt AK 2012).

Statin is currently recommended as the first-line pharmacologic agent among other therapeutic agents, as it has relatively few adverse effects and clearly is beneficial for reducing CVD by lowering LDL-C (Rhee EJ 2019; Mihaylova B 2012). Therefore, for very high-risk patients, administration of statins is also recommended, and ezetimibe should be added if the target LDL-C goal is not met even with maximum tolerable dose of statin. Ezetimibe is commonly combined with statin therapy, as it lowers LDL-C by inhibiting cholesterol reabsorption in the small intestine. Although ezetimibe is also used alone, many studies have been conducted on its benefits when combined with statins.

The IMPROVE-IT study (Špinar J 2014) is the first study powered for atherosclerotic cardiovascular disease (ASCVD) outcomes to show a benefit of a non-statin agent (ezetimibe) when added to a statin in patients post-acute coronary syndrome (ACS) (Cannon CP 2015). The primary endpoint of cardiovascular death/ myocardial infarction (MI)/ unstable angina (UA)/ coronary revascularization beyond 30 days/stroke was significantly lower in the ezetimibe/simvastatin arm compared with the simvastatin arm over the duration of follow-up (32.7% vs. 34.7%, hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.89-0.99; p = 0.016). These results offer important hope to patients who have unacceptable side effects from statin

therapy and to those who may not achieve adequate LDL-C reduction with statins (Jarcho JA 2015). Moreover, this study results reinforce the LDL-C hypothesis and suggest that an LDL-C closer to 50 mg/dl is even better (Špinar J 2014). Also, the large meta-analysis confirmed that 1 mmol/L reduction in LDL-C corresponded to a relative risk reduction of 19%, irrespective of baseline LDL-C concentration or drug class used (Berberich AJ 2020). The investigators now report that adding ezetimibe to statin reduces not only first cardiovascular events, but also additional and total cardiovascular events during the entire study period (relative risk reductions of 6%, 11%, and 8%, respectively) correlating with persistent lower LDL-C levels throughout the study period (Murphy SA 2016). In other words, approximately 11 total cardiovascular events (MI, stroke and revascularizations) can be prevented for every 100 patients treated for 10 years with ezetimibe and statin, which is essentially double the number of first cardiovascular events prevented.

Furthermore, a study was conducted on the benefits of ezetimibe addition therapy when compared to high doses of statins. In the RACING study (Kim BK 2022), patients with ASCVD at 26 clinical centres in South Korea were randomly assigned (1:1) to receive either moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg). As a result, among patients with ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the 3-year composite outcomes with a higher proportion of patients with LDL-C concentrations of less than 70 mg/dL and lower intolerance-related drug discontinuation or dose reduction (Kim BK 2022). Moreover, a pooled analysis of 17 double-blind trials of patients who were already on a statin showed that the largest percent reductions in LDL-C were seen with adding ezetimibe (Ambegaonkar BM 2014).

Based on these research results, the 2019 dyslipidemia management guidelines from the European Society of Cardiology set an LDL-C target for very high-risk people of less than 55 mg/dL (as well as at least a 50% cut from baseline), a class I recommendation (Mach F 2020). Accordingly, the Korean Society of Lipid and Atherosclerosis has also updated the treatment guidelines. However, the 2021 EAS practical guidance says that the new LDL-C goals for high and very-high risk group patients with dyslipidema are more demanding; in real-world practice, only 1/3 patients reach the LDL-C target (Averna M 2021). Therefore, this study aims to confirm the effectiveness of ezetimibe add-on therapy on LDL-C levels compared to atorvastatin monotherapy, especially in very high-risk patients. We intend to lay the foundation for a standard treatment for these patients through ezetimibe add on lipid-lowering therapy.

3.0 OBJECTIVES AND ENDPOINTS

Table 3–1 presents the objectives and corresponding endpoints of the study.

Table 3–1 Study objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the effectiveness of early add-on of ezetimibe with atorvastatin in very high-risk patients.	• Percentage change in LDL-C from baseline to week 6
Secondary	
• To evaluate the clinical effectiveness of early add-on of ezetimibe with atorvastatin in very high-risk patients.	• Proportion of patients achieving LDL-C goal of <55 mg/dL after 6 weeks and 12 weeks of treatment • Proportion of patients achieving LDL-C goal of <70 mg/dL after 6 weeks and 12 weeks of treatment • Percentage change in LDL-C from baseline to week 12 • Percentage change in HDL-C, non-HDL-C, triglycerides, and total cholesterol from baseline to week 6 and week 12
• To evaluate the safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.	• Treatment-emergent adverse events (TEAEs) at 6 weeks and 12 weeks • Dropout rate due to TEAEs at 6 weeks and 12 weeks

Abbreviations: LDL-C=Low-density lipoprotein cholesterol; HDL-C= High-density lipoprotein cholesterol

4.0 STUDY DESIGN

4.1 Overall Design

This is Phase 4, multicenter, randomized, open-label, active-controlled study. The study has been designed to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

In Visit 1, screening is conducted for patients in the very high-risk group. LDL-C needs to be above 70 mg/dL in patients (a) who failed to achieve their target LDL-C goals with mild to moderate intensity statin; (b) who are statin-naive or have not been on a stable statin regimen for at least 4 weeks prior to enrollment. However, by tracking the registration status of patients, (b) patients should be enrolled not to exceed 40% of each group. All laboratory tests are performed in the local laboratory and the Visit 1 results may be substituted if available within 2 weeks prior to the screening visit. The study participation is determined through the inclusion/exclusion criteria based on the test results conducted for Visit 1. In the case of the lipid parameter, Visit 1 results are used as the baseline. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

In Visit 2, randomization is performed on patients who meet the inclusion criteria and do not meet any of the exclusion criteria and will be distributed 1:1 between test group (arm Eze/Ato) and control group (arm Ato). The results of laboratory tests at the Visit 2 are used as baseline except lipid parameters. Visit 1 and Visit 2 may be conducted on the same date.

In Visit 2 and Visit 3, the appropriate investigational medical product (IMP) is given to each group. In principle, IMPs are administered orally once a day from the day of distribution.

For participants whose LDL-C value has reached the target (LDL-C < 55 mg/dL) according to the lipid indicator test at Visit 3, they will continue treatment with the same dose for 6 weeks. If the LDL-C level has not reached target, the dose of atorvastatin should be increased to ezetimibe/atorvastatin 10/80 mg or atorvastatin 80 mg according to the group assigned. In principle, a morning visit is recommended so that the laboratory test results can be checked and the IMP can be prescribed and taken on the same day. However, if the test results are not confirmed on the same day and a participant has enough IMP to take until the next visit, IMP compliance is checked, and the same dose of IMP (ezetimibe/atorvastatin 10/40mg or atorvastatin 40mg) is continued. An additional visit is made within 1 week to return the remaing IMP and receive new IMP. If the test results are not confirmed on the same day and a particpant does not have remaining IMP, the investigator prescribes the same dose of IMP (ezetimibe/atorvastatin 10/40mg or atorvastatin 40mg) that the participant was taking previously, and an additional visit is made within 1 week to receive new IMP. Visit 4 is the end of study visit, and tests for effectiveness and safety are conducted.

4.2 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Patients who are ≥ 30 years old.
2. Patients with very high-risk*
   *: clinical or unequivocal on imaging ASCVD. ASCVD includes previous ACS (MI or UA), stable angina, coronary revascularization (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), and other arterial revascularization procedures), stroke and transient ischaemic attack (TIA), and peripheral arterial disease (Mach F 2020).
3. Patients (a) who failed to achieve LDL-C lower than 70 mg/dL with low and/or moderate intensity[$] statin mono therapy for ≥ 4 weeks or (b) who are statin-naïve or have not been on a stable (unchanged) statin regimen for at least 4 weeks prior to enrollment.
   [$]: rosuvastatin < 20 mg, atorvastatin < 40 mg, and all dose of pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin (Stone NJ 2014).
4. Patients with LDL-C levels ≥ 70 mg/dL
5. Patients who are willing to maintain TLC throughout the study.
6. Patients who are willing to provide written informed consent prior to study enrollment.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patients with hypersensitivity to ezetimibe, atorvastatin or any of its inactive ingredients.
2. Patients with active liver disease or unexplained persistent elevations of hepatic transaminase levels. (aspartate transaminase (AST) or alanine transaminase (ALT) > 3 x upper limit of normal (ULN)).
3. Patients who have predisposing conditions with muscle disease (i.e., rhabdomyolysis or myopathy) or neuromuscular disease.

4. Patients with myasthenia gravis.
5. If female, patient is a pregnant woman or a women intending to become pregnant within a year.
6. Patients who are taking glecaprevir and pibrentasvir.
7. Patients with hereditary problems of galactose intolerance, lapp lactase deficiency, or of glucose-galactose malabsorption.
8. Patients with disease known to influence serum lipids or lipoproteins excluding dyslipidemia.
9. Patients with a history of cancer within 5 years.
10. Patients whose life expectancy is less than 6 months due to their medical conditions.
11. Patients with any condition or situation that might pose a risk to the participant or interfere with participation in the study.
12. Patients who have received any investigational medicine within 12 weeks of written informed consent or are going to receive during the clinical trial period.
13. Patients who are judged to be difficult to conduct clinical trials according to the judgment of the investigator

5.3 Lifestyle Considerations

Participants should be educated on TLC to be conducted during the entire clinical trial period. TLC includes diet, weight loss, and exercise therapy and is performed according to the standard guide of each site.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to a study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from institutional review boards (IRBs)/ independent ethics committees (IECs). Minimal information includes demography, screen failure details, eligibility criteria, and any medical history/current medical conditions.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be given a new participant number. Re-

screening is decided at the discretion of the investigator, and is performed after consulting with the sponsor.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Enrollment and randomization can be paused, at the Sponsor's discretion, in the event of restrictions related to the coronavirus disease 2019 (COVID-19) pandemic or a similar national emergency.

6.0 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

Details of the treatments administered in this study are presented in Table 6–1 and Table 6–2.

Table 6–1 Study Interventions Administered

Intervention Label	Ezetimibe/Atorvastatin	Atorvastatin
Intervention Name	Atozet	Lipitor
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	10/40 mg 10/80 mg	40 mg 80 mg
Dosage Level(s)	QD	QD
Route of Administration	Oral	Oral
Use	Experimental	Active comparator
IMP and NIMP/AMP.	IMP	IMP
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and Labeling **Do not include a sample of the label text or details of pack design in the protocol.**	Study intervention will be provided in bag. Each bag will be labeled as required per country requirement.	Study intervention will be provided in bag. Each bag will be labeled as required per country requirement.

Abbreviations: QD = once a day; IMP = investigational medical product

Table 6–2 Study Arms

Arm Title	Eze/Ato	Ato
Arm Type	Experimental	Active comparator
Arm Description	Participants will receive ezetimibe/atorvastatin 10/40 mg QD from Visit 2 (Day 1) to Visit 3 (Week 6). If the LDL-C target is reached (LDL-C < 55 mg/dL) at Visit 3, maintain the dose to Visit 4 (Week 12). If the LDL-C target level is not reached at Visit 3, dose is increased to ezetimibe/atorvastatin 10/80 mg QD from Visit 3 to Visit 4.	Participants will receive atorvastatin 40 mg QD from Visit 2 (Day 1) to Visit 3 (Week 6). If the LDL-C target is reached (LDL-C < 55 mg/dL) at Visit 3, maintain the dose to Visit 4 (Week 12). If the LDL-C target is not reached on at Visit 3, dose is increased to atorvastatin 80 mg QD from Visit 3 to Visit 4.

Associated Intervention Labels	Ezetimibe/Atorvastatin	Atorvastatin

Abbreviations: QD = once a day

6.2 Preparation, Handling, Storage, and Accountability

The investigator or authorized study site staff must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized study site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff.

The investigator, site, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study intervention using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

6.3 Measures to Minimize Bias: Randomization

All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each study site.

Study intervention will be dispensed at the study visits as summarized in the Section 1.3.

Returned study intervention should not be redispensed to the participants.

If the IWRS system is unavailable, contact the medical monitor in charge of the site to solve the problem.

6.3.1 Stratified block randomization

The randomization code will be set so that the test group and control group can be assigned in a 1:1 ratio by the stratified block randomization method for each institution and using statin administration history as a stratification factor.

Inclusion criterion No. 3 is the stratification factor, and the classification is as follows:

(a) patients who failed to achieve their target LDL-C goals with low and/or moderate intensity statin mono therapy for ≥ 4 weeks
(b) patients who are statin-naïve or have not been on a stable (unchanged) statin regimen for at least 4 weeks prior to enrollment

However, in the case of (b) patients, less than 40% of each group should be recruited.

6.4 Study Intervention Compliance

The prescribed dosage and regimen of administration may not be changed. Any departures from the intended regimen must be recorded in the electronic case report form (eCRF).

Participants exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of study intervention during any evaluation period (visit to visit).

When participants self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the study site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study interventions dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 Continued Access to Study Intervention after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study.

6.6 Treatment of Overdose

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately (see Section 8.4.7).
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/serious adverse event (SAE) and laboratory abnormalities until end of study.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7 Concomitant Therapy

The Investigator must instruct the participant to notify the study site about any new medications he/she takes after signing the study informed consent. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRFs.

Any therapy that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Concomitant therapy name
- Reason for use
- Period including start and end dates

In particular, in the case of medication, the following items are also collected:

- Route of administration
- Dosage information including dose and frequency

Prior medication up to 1 month prior to enrollment is also collected.

The following drugs are not allowed to be administered during the clinical trial period. However, partial permission is possible at the discretion of the investigator.

1. Lipid modulating agents other than IMP.
    - statin, fibric acid derivatives, ezetimibe, bile acid sequestrants, PCSK9 inhibitor, nicotinic acid (niacin)
    - alipogene tiparvovec, bempedoic acid, dextrothyroxine, inclisiran, lomitapide, magnesium pyridoxal 5-phosphate glutamate, meglutol, mipomersen, omega-3-triglycerides incl. other esters and acids, policosanol, probucol, tiadenol
2. Other drugs or foods that may affect blood lipids.
    - systemic steroids, lipolytic enzyme inhibitors (e.g., orlistat), hormone replacement therapy, thyroid therapy (e.g., levothyroxine, benzylthiouracil), fish oil, fiber-based laxatives, cholestine, phytosterol margarines, grapefruit.
3. Drugs with known drug interactions with IMP according to label.
    - cyclosporine, HIV protease inhibitors, hepatitis C protease inhibitors, gemfibrozil, fusidic acid.
4. Drugs or foods described in the label precautions.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.10.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for lipid profile. See the SoA in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The following criteria should be considered for discontinuation:

- Protocol deviation
- Lost to follow-up
- AST or ALT level > 3 × ULN for 2 consecutive times
- CK > 10 × ULN for 2 consecutive times
- Pregnancy
- Termination of the study by the investigator or Sponsor
- Difficult to continue the study according to the judgment of the investigator
- Adverse event
- Withdrew informed consent

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study intervention and the Sponsor or designee, must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the investigator must obtain documented approval from the Sponsor or designee, to allow the participant to continue in the study.

Participants who discontinue study intervention will not be replaced.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance, positive COVID-19 test or suspected Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or authorized study site staff must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

8.1 Baseline characteristics

8.1.1 Demography

Demographics will be evaluated at screening visit and include age, sex, smoking history, alcohol history.

8.1.2 General medical history

Medical history including disease name, severity, period will be presented by Medical dictionary for regulatory activities (MedDRA) terminology. At the time of randomization, past/present disease is determined according to whether it is ongoing or not.

8.1.3 Medical history related to dyslipidemia

Medical history related to dyslipidemia includes risk classification factors (ACS (MI or UA), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease), statin administration history, family history, dyslipidemia diagnosis date.

8.2 Effectiveness Assessments

8.2.1 Lipid parameter laboratory test

Lipid laboratory tests for efficacy evaluation include LDL-C, HDL-C, triglycerides, and total cholesterol.

8.3 Safety Assessments

8.3.1 Physical Examinations

A physical examination will include, at a minimum, assessments of height and weight. Height is measured at screening only and body weight is measured at each visit.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Heart rate and blood pressure will be assessed.

Heart rate and blood pressure measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs will be measured in a relax position after 5 minutes rest. Three readings of heart rate and blood pressure will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

8.3.3 12-Lead Electrocardiograms (ECG)

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.3.4 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. However, abnormal lab result will not be followed up after study completion.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor or designee notified.

If laboratory values from non-protocol-specified laboratory tests performed at the site's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy Testing

Women of childbearing potential (WOCBP) should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

Additional pregnancy testing should be performed at each visit during the treatment period and as required locally.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3. Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first administration of the study treatment during the treatment period.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator who is a qualified physician, will assess events that meet the definition of an AE or SAE with respect to seriousness, severity and causality. The investigator and authorized study site staffs are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 10.3). For any guidance regarding AE/SAE reporting, the Investigator should contact the medical monitor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

From the time of screening to the last visit, all AEs, SAEs, and other reportable safety events must be recorded and reported by the investigator to the Sponsor or designee within the time frames indicated in Table 8–1.

Additionally, any SAE brought to the attention of the investigator at any time outside the period specified in the previous paragraph must be reported immediately.

Table 8–1 Reporting Time Periods and Time Frames for Adverse Events, Serious Adverse Events, and other reportable safety events.

Type of Event	Reporting Time Period: Treatment Allocation Through End of Study	Time Frame to Report Event and Follow-up Information to Sponsor or designee
Adverse Event (AE)	Report all	Per study manual
Serious Adverse Event (SAE)	Report all	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report all	Within 24 hours of learning of event

All AE/SAEs will be collected from the study participation until the last visit. However, if events are collected up to a period of 14 days after the intake of study treatment, it is recorded as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the investigator's awareness of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.3.

AEs that are reported after the AE reporting time period of study should be forwarded to Sponsor or designee and reported as spontaneous cases.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable events, including pregnancy complications/outcomes and exposure during breastfeeding will be followed. Further information on follow-up procedures is provided in Section 10.3. Also, the

investigator will make every attempt to follow all non-serious AEs that occur in eligible participants for outcome.

Investigators remain responsible for following up on final event outcomes and events that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or withdraw from the study.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the corresponding regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or designee will review and then file it along with the package insert and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 1 month after the estimated date of delivery (EDD) (see Section 10.4).

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant pregnancy and should follow the procedures outlined in Section 10.3.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly including that in an ectopic pregnancy, aborted fetus, stillbirth, or fetal death) the investigator will report according to the SAE reporting procedures described in Section 10.3.

The female participant will be followed to determine the outcome of the pregnancy (e.g., until delivery of baby or for longevity). The investigator will collect follow-up information on the female participant and the neonate and the information will be forwarded to the Sponsor or designee.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor or designee as described in Section 10.3. While the investigator is not obligated to actively seek this information in former female study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6 Adverse Events of Special Interest

Not applicable

8.4.7 Special Situations

The following special situations are considered important safety information and can be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

• Overdose

Note: In this study, an overdose is defined as the patient has taken, accidentally or intentionally, a dose exceeding the dose as stated in the local label.

• Lack of therapeutic effect

• Off-label use, medication error, misuse, abuse, or occupational exposure

• Suspected transmission via a medicinal product of an infectious agent

These special situations are not considered as AEs, but do require to be reported to Sponsor or designee on the same timeline as the AE.If special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in eCRF.

9.0 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The primary endpoint of the study is the percentage change in LDL-C from baseline to 6 weeks. The primary hypothesis is that the addition of ezetimibe to atorvastatin would result in a significantly greater reduction in percentage change in LDL-C compared with atorvastatin monotherapy.

9.2 Analysis Sets

The safety analysis set (SAS) includes all randomized patients who received at least one dose of study treatment. Patients in the SAS will be included in the actual treatment group, regardless of their randomized treatment.

The full analysis set (FAS) comprises all randomized patients who had a baseline assessment of LDL-C and received at least one dose of study treatment. Patients in the FAS will be included in their randomized treatment group, regardless of their actual treatment. The FAS is the primary analysis set for efficacy analyses.

The per-protocol set (PPS) is a subset of the FAS who completed the 6-week follow-up observation with no major protocol deviations. The efficacy analysis based on the PPS will be considered supportive.

9.3 Statistical Analyses

9.3.1 General Considerations

All analyses will be performed by a designated CRO using SAS 9.4 or above.

Descriptive statistics will include n, mean, standard deviation (SD), median, minimum, and maximum for continuous variables and the number and percentage of patients for categorical variables. If necessary, more detailed information will be provided.

For continuous efficacy variables, the statistical comparisons between treatment groups are performed using an analysis of covariance (ANCOVA) with treatment group as a factor and the corresponding baseline and history of statin administration as the covariate. For categorical efficacy variables, the statistical significance of the differences between treatment groups is tested using Chi-square test or Fisher's exact test. All the statistical tests use a two-sided test at the significance level of 0.05.

Unless otherwise specified, missing for all efficacy parameters will be imputed by last observation carried forward (LOCF) method. For patients with no post-baseline value, the baseline values are carried forward.

9.3.2 Primary Endpoint

The primary endpoint analysis will be performed on the FAS and PPS, and the primary analysis set is the FAS. The primary endpoint is defined as 100 x (LDL-C value at 6 weeks – LDL-C value at baseline) / LDL-C value at baseline.

The statistical significance of the difference in the percentage change between treatment groups will be analyzed by fitting ANCOVA model with treatment group as a factor and the baseline LDL-C and history of statin administration as the covariate. Estimates of least squares (LS) mean and standard error (SE) for within-treatment effects and treatment differences along with corresponding two-sided 95% CI and p-value will be provided. If the upper limit of the 95% two-sided CI for the corresponding treatment difference (ezetimibe/atorvastatin 10/40 mg - atorvastatin 40 mg) is less than 0, ezetimibe/atorvastatin 10/40 mg is considered superior to atorvastatin 40 mg.

In addition, descriptive statistics will be presented for LDL-C at each visit and for percentage change from baseline.

9.3.3 Secondary Endpoints

All secondary endpoint analyses will be performed on the FAS and PPS.

The number and percentage of patients achieving LDL-C goal of < 55 mg/dL and LDL-C goal of < 70 mg/dL at 6 weeks and 12 weeks will be presented by treatment group and tested using Chi-square test or Fisher's exact test as appropriate. The difference in the percentage will be presented with its corresponding 95% CI and p-value.

For continuous secondary variables, the percentage change from baseline at time point of interest will be analyzed by fitting ANCOVA model with treatment group as a factor and its corresponding baseline and history of statin administration as a covariate. Estimates of LS mean and SE for within-treatment effects and treatment differences along with corresponding two-sided 95% CI and p-value will be provided. In addition, descriptive statistics will be presented for outcome of interest at each visit and for percentage change from baseline.

9.3.4 Subgroup Analysis

If possible, subgroup analysis will be performed on the primary endpoint and all secondary endpoins at 6 and/or 12 weeks to assess the homogeneity of the treatment effect across various subgroups including history of statin administration, age, sex and status of a dose up-titration.

9.3.5 Safety Analysis

All safety analyses will be performed on the SAS.

The number and percentage of patients experiencing TEAEs, treatment-emergent serious adverse events (TESAE)s, Treatment-related adverse events (TRAEs) and TEAEs leading to the premature discontinuation of the study at 6 weeks and 12 weeks will be presented by treatment group and tested using Chi-square test or Fisher's exact test as appropriate. The difference in the percentages will be presented with its corresponding 95% CI and p-value.

The numbers and percentages of patients experiencing TEAEs will be summarized by system organ class (SOC) and preferred term (PT) according to the MedDRA dictionary for each treatment group.

Individual TESAEs and TEAEs leading to the premature discontinuation of the study will be listed with details including reported term, SOC, PT, start and stop date, severity, seriousness with criteria, causality, action taken and outcome.

For continuous other variables such as weight and vital signs parameters, descriptive statistics will be presented for outcome of interest at each visit and for change from baseline by treatment group.

Individual clinically significant changes in 12-lead ECG will be listed.

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

The statistical hypothesis of this study is as follows.

$$H_0: \mu_t - \mu_c = 0 \text{ vs. } H_1: \mu_t - \mu_c \neq 0$$

μ_t = Percentage change in LDL-C from baseline to 6 weeks in ezetimibe/atorvastatin 10/40 mg

μ_c = Percentage change in LDL-C from baseline to 6 weeks in atorvastatin 40 mg

Azar et al. reported that the between-treatment difference in percentage change in LDL-C at 8 weeks was -10% in favor of ezetimibe/atorvastatin 10/40 mg compared to atorvastatin 40 mg (-20% vs -10%; p-value=0.01) (Azar RR 2010). This is the only study that has assessed the efficacy of ezetimibe/atorvastatin 10/40 mg versus atorvastatin 40 mg among very high-risk patients with stable CAD or CAD equivalent (coronary stenosis >50%, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, diabetes

mellitus, stroke, peripheral vascular disease) who were taking the potency of the background statins ≤ 20 mg/day of atorvastatin prior to the randomization. Although the evaluation time point for the LDL-C lowering effect in Azar et al. study is at 8 weeks, it is noted that a reduction in LDL-C is usually achieved with all statins as well as ezetimibe as early as 2 weeks, with a maximum response occurring by 4 weeks and maintaining thereafter during continued therapy (ACH-Ezetimibe Product Monograph 2019; Shankar PR 2019). Given that, this study sets -10% as the expected difference in percentage change in LDL-C from baseline to 6 weeks between the treatment groups.

The pooled standard deviation of 19.0% was obtained from the p-value of 0.01 and a total of 50 patients per treatment group reported in the study of Azar et al.; The t-value that corresponds with a p-value of 0.01 and 50 + 50 – 2 = 98 degrees of freedom is t=2.627, considering that the degrees of freedom are given $N_1 + N_2 - 2$, where N_1 and N_2 are the number of study patients per each treatment group. As the t-value is the ratio of the difference in means to the standard error of the difference in means, the standard error is therefore obtained by dividing 10 (treatment difference in percentage change in LDL-C) by 2.627, which gives 3.8066. In turn, the standard deviation obtained from standard error is 19% (3.8066 / SQRT (1/50 + 1/50)).

Based on this, the number of patients in each treatment group calculated by the formula below is about 57 under the assumption of two-sided significance level $\alpha = 0.05$, power $1-\beta = 0.80$ with a randomization ratio $\lambda = 1$. Considering the dropout rate of 10%, 63 patients for each group and thus, a total of 126 patients will be randomized in this study.

$$n = \frac{(\gamma + 1)\left(Z_\alpha + Z_\beta\right)^2 \sigma^2}{\gamma(\mu_t - \mu_c)^2} = \frac{(1+1)(1.96 + 0.842)^2(19)^2}{(-10)^2} = 56.69$$

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH good clinical practice (GCP) guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, product information, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or designee. The study will not start at any study site at which the investigator has not signed the protocol.

10.1.2 Adequate Resources

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

If the investigator/site retains the services of any individual or party to perform study-related duties and functions, the investigator/site should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and authorized study site staffs will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

10.1.5 Informed Consent Process

The investigator or authorized study site staff will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF during their participation in the study.

A copy of the ICF must be provided to the participant or their legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 7 days from the previous ICF signature date.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in a separate document.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Study Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.
- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Study Monitoring Plan.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations (CROs)).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

The investigator/site should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in source data acknowledgment or monitoring guidelines or eCRF completion guidelines.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first study site open is considered the first act of recruitment and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For study site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell count with differential:
	Red blood cell count	Neutrophils
	Hemoglobin	Lymphocytes
	Hematocrit	Monocytes
		Eosinophils
		Basophils
Clinical Chemistry[a]	Blood urea nitrogen (BUN)	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Creatinine	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)
	Glucose	Alkaline phosphatase (ALP)
	Gamma glutamyl transferase (GGT)	Creatine kinase (CK)
	Potassium	Chloride
	Sodium	Total and direct bilirubin
	Calcium	Total protein
	Albumin	Phosphate
	Lactate Dehydrogenase (LDH)	C-reactive protein
	Uric acid	HbA1c [b]
Lipid parameter	LDL-C	Triglycerides
	HDL-C	Total cholesterol
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
Other screening tests	Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of non-childbearing potential only).	
	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c].	

Laboratory Assessments	Parameters

<<NOTES:

[a] All events of ALT or AST ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] The test is performed in participants with confirmed history of diabetes at V1 and V4. However, there will not be a separate testing to confirm diabetes in patients as part of this study. If participants already have diabetes in their current medical history, they will be classified as participants with confirmed diabetes.

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report. The results of each test must be entered into the (e)CRF.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with that product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention/treatment, whether or not considered related to the study intervention/treatment by the investigator. • AEs are defined as events occurring from screening to the last visit. • TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of the study treatment during the treatment period.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition. • New condition detected or diagnosed after screening visit even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions listed below are met. (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death • For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form (CRF).
b. Is life-threatening • The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma

(e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The severity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL

refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study intervention will be considered "related." Events assessed as having no reasonable possibility of being related to study intervention will be considered "unrelated."
- The investigator will also consult the Investigator's Brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the investigator's awareness of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection System
• The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the investigator's awareness of the event. • If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available. • After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data. • If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to the Sponsor or designee. • Contacts for SAE reporting can be found in study manual, investigator study file binder, or equivalent.

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form
• Email transmission of the SAE form should be done in case there are technical issues with the electronic data collection system and SAE cannot be reported within 24 hours of awareness per the ICH guidelines via electronic data capture. The SAE form* should be emailed to the Sponsor or designee mailbox detailed in the form. SAE form*: AE form includes SAE criteria and if investigator checks one of SAE criteria, it is considered as SAE form. • Facsimile transmission may be utilized as an alternative mode of submission, if necessary. • Notification of SAE information via telephone does not replace the need for the investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the investigator's awareness of the event. • Contacts for SAE reporting Email: PPD

10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral.

• Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study intervention.

10.4.3 Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up is required by 1 month after the EDD. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, fetal death, or

congenital anomalies, ectopic pregnancy), the investigator will report according to the SAE reporting procedures described in Section 10.3.

- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor or designee as described in Section 10.3. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

10.4.4 Reporting Pregnancy Information

Email transmission of the paper Pregnancy Report Form is the preferred method to transmit safety event information to Organon or IQVIA with facsimile as a back-up method, if necessary.

Safety events should be reported to:

Email: PPD

Fax: PPD

10.5 Appendix 5: Abbreviations

Abbreviation	Definition
ACS	Acute coronary syndrome
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft surgery
CFR	Code of federal regulations
CI	Confidence interval
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CVD	Cardiovascular disease
eCRF	Electronic case report form
EDD	Estimated date of delivery
FAS	Full analysis set
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee

Abbreviation	Definition
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PPS	Per-protocol set
PT	Preferred term
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischaemic attack
TLC	Therapeutic lifestyle change
TRAE	Treatment-related adverse event
UA	Unstable angina
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

10.6 Appendix 6: Target Enroll Clarification

According to current protocol (OG-KORATO-001_V4_21Mar2023), it describes that a total of 126 patients will be randomized in this study. The target number of enrollment in protocol was calculated considering statistical assumptions and a 10% dropout rate as per protocol.

However, during the course of the study, the actual dropout rates, stratification (b) ratios and so on for each group may differ from the assumptions stated in protocol, so additional subject enrollment within a range that does not exceed 10% of the target number of enrollment may be carried out to ensure that the results based on the study objective are derived with sufficient statistical power.

Table of Contents	Related Contents
1.0 PROTOCOL SUMMARY	1.1 Synopsis Number of Participants: The number of patients in each treatment group is about 57 under the assumption of two-sided significance level $\alpha = 0.05$, power $1-\beta = 0.80$ with a randomization ratio $\lambda = 1$. Considering the dropout rate of 10%, 63 patients for each group and thus, a total of 126 patients will be randomized in this study
9.5 Sample Size Determination	(…) Based on this, the number of patients in each treatment group calculated by the formula below is about 57 under the assumption of two-sided significance level $\alpha = 0.05$, power $1-\beta = 0.80$ with a randomization ratio $\lambda = 1$. Considering the dropout rate of 10%, 63 patients for each group and thus, a total of 126 patients will be randomized in this study. $n = \frac{(\gamma+1)(Z_\alpha + Z_\beta)^2\sigma^2}{\gamma(\mu_t-\mu_c)^2} = \frac{(1+1)(1.96+0.842)^2(19)^2}{(-10)^2} = 56.69$
6.3.1 Stratified block randomization	The randomization code will be set so that the test group and control group can be assigned in a 1:1 ratio by the stratified block randomization method for each institution and using statin administration history as a stratification factor. Inclusion criterion No. 3 is the stratification factor, and the classification is as follows:

	(a) patients who failed to achieve their target LDL-C goals with low and/or moderate intensity statin mono therapy for ≥ 4 weeks (b) patients who are statin-naïve or have not been on a stable (unchanged) statin regimen for at least 4 weeks prior to enrollment **However, in the case of (b) patients, less than 40% of each group should be recruited.**

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Signature of Investigator

PROTOCOL TITLE: A phase 4, multicenter, randomized, open-label, active-controlled study to evaluate the effectiveness and safety of early add-on of ezetimibe with atorvastatin in very high-risk patients.

PROTOCOL NO: OG-KORATO-001

VERSION: 4.1 dated 27-Jun-2024

This protocol is a confidential communication of Organon. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Organon or IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____