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A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With a 40-Week, Active-Controlled, Open-Label Extension to Evaluate the Efficacy and Safety of K-877 in Adult Patients With Fasting Triglyceride Levels ≥500 mg/dL and <2000 mg/dL and Mild or Moderate Renal Impairment

Clinical Study Protocol

Drug Name:	K-877
Study Number:	K-877-303
U.S. IND Number:	109388
EudraCT Number:	2016-001518-39
Protocol Version Date:	13 Sep 2016
Version Number:	1.0
Name of Sponsor:	**Kowa Research Institute, Inc.**
Address:	430 Davis Drive, Suite 200 Morrisville, NC 27560 United States of America

[redacted]

INVESTIGATOR'S STATEMENT

I, the Investigator, understand that all information concerning the product supplied to me by Kowa Research Institute, Inc. (KRI) and [redacted] in connection with this study and not previously published is confidential information. This information includes the Investigator's Brochure, protocol, case report forms, assay methods, technical methodology, and basic scientific data.

I understand that any changes to the protocol must be approved in writing by KRI, [redacted] and the Institutional Review Board/Ethics Committee (IRB/EC) before implementation, except where necessary to eliminate apparent immediate hazards to the patients.

I confirm that I will report all adverse events (AEs) following the regulations indicated in the protocol.

I confirm that I will conduct this study in conformance with the principles of the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA), Food and Drug Administration (FDA) Good Clinical Practice (GCP), regulations (Code of Federal Regulations [CFR] Title 21 Parts 11, 50, 54, 56, and 312), International Council for Harmonisation (ICH) Guideline for GCP (E6/R1), local laws, and the laws and regulations of the country where the study is to be conducted.

I confirm that I am informed of the need for record retention and that no data can be destroyed.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this version of the protocol dated 13 September 2016.

Investigator's Signature: _____ **Date:** _____
mm/dd/yyyy

Printed Name: _____

SIGNATURE PAGE

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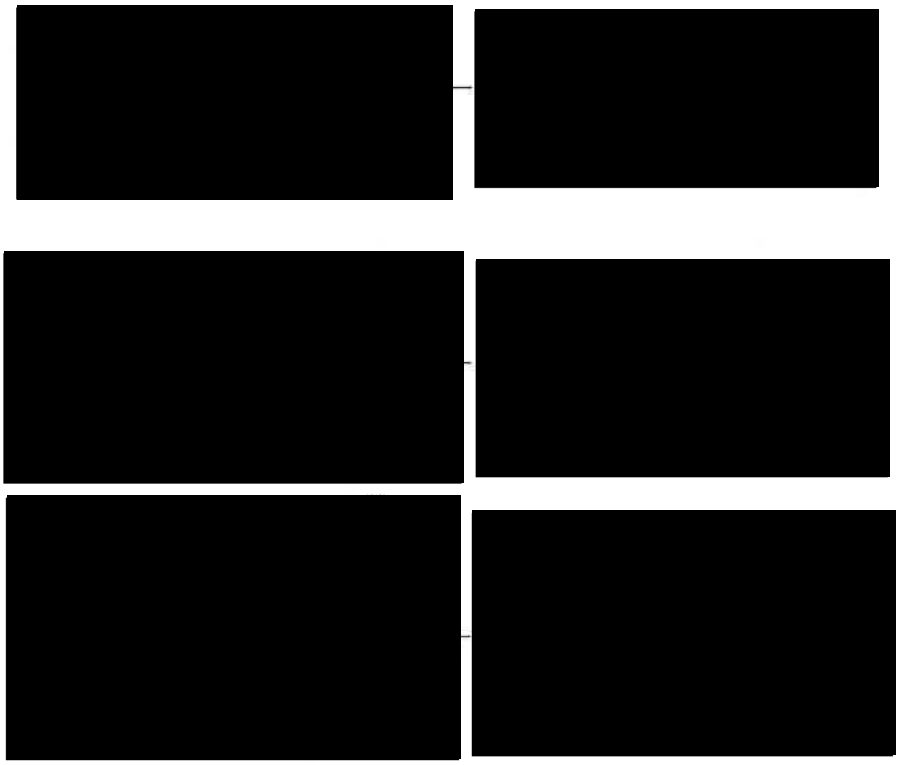


PROTOCOL SYNOPSIS

Name of Sponsor Company: Kowa Research Institute, Inc.		**Drug Under Study:** K-877
Title of Protocol: A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With a 40-Week, Active-Controlled, Open-Label Extension to Evaluate the Efficacy and Safety of K-877 in Adult Patients With Fasting Triglyceride Levels ≥500 mg/dL and <2000 mg/dL and Mild or Moderate Renal Impairment		
Protocol Number: K-877-303	**Phase:** 3	**Indication:** Dyslipidemia
Study Design: Study K-877-303 is a Phase 3, multi-center, randomized study to confirm the efficacy and safety of K-877 0.2 mg twice daily compared to matching placebo (in the double-blind 12-week Efficacy Period) and an active comparator, fenofibrate (in the open-label 40-week Extension Period), in patients with fasting triglyceride (TG) levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2). Eligible patients will enter a 4- to 6-week lifestyle stabilization period (4-week stabilization for patients not requiring washout and 6-week washout and stabilization for patients on lipid-altering therapy other than statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors). The stabilization period will be followed by a 2-week TG qualifying period (Visits 2 [Week -2] and 3 [Week -1]), and patient eligibility will be assessed based on the mean TG value from these 2 visits. If the patient's mean TG level during the TG qualifying period is ≥450 mg/dL (5.09 mmol/L) and <500 mg/dL (5.65 mmol/L), an additional TG measurement can be taken 1 week later at Visit 3.1. The mean of all 3 TG measurements will be used to determine eligibility for the study. After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind Efficacy Period. At Visit 4 (Day 1), patients will be randomly assigned in a 2:1 ratio to K-877 0.2 mg twice daily or identical matching placebo tablets twice daily. During the 12-week Efficacy Period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) for efficacy and safety evaluations. Patients who successfully complete the 12-week Efficacy Period are eligible to continue in a 40-week, open-label, active-controlled Extension Period after completing the Visit 7 (Week 12) procedures. Patients randomized to receive K-877 0.2 mg twice daily in the 12-week Efficacy Period will continue to receive K-877 0.2 mg twice daily in the 40-week Extension Period. Patients randomized to receive placebo matching K-877 0.2 mg twice daily in the 12-week Efficacy Period will initiate fenofibrate dosing at 48 mg once daily at Visit 7 (Week 12). Starting from Visit 8 (Week 16), Investigators can adjust fenofibrate dosing (to 145 mg once daily) at their discretion according to the local standard of care. From Visit 7 (Week 12), patients not on statins, ezetimibe, or PCSK9 inhibitors may initiate therapy, and patients receiving statins, ezetimibe, or PCSK9 inhibitors may alter their dose, as indicated by guidelines or local standard of care. After Visit 8 (Week 16), patients are to return to the site every 12 weeks until the last visit (Visit 11 [Week 52]).		
Primary Objective: The primary objective of the study is to demonstrate the efficacy of K-877 0.2 mg twice daily compared to placebo from baseline to Week 12 in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment.		

Secondary Objectives:

The secondary objectives of the study are the following:

- To evaluate the efficacy of K-877 0.2 mg twice daily from baseline to Week 52 in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment;
- To evaluate the efficacy of K-877 0.2 mg twice daily from baseline to Week 12 and Week 52 in altering lipid parameters in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment;
- To evaluate the safety and tolerability of K-877 0.2 mg twice daily in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment; and
- To determine the plasma concentrations of K-877 for the purpose of use in population pharmacokinetic (PK) analysis and PK/pharmacodynamic (PD) analysis.

Exploratory Objective:

[redacted]

Patient Population:

The study population will consist of male and female patients ≥18 years of age with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) after washout from lipid-altering therapy other than statins, ezetimibe, or PCSK9 inhibitors and with mild or moderate renal impairment. Stable therapy with statins, ezetimibe, or PCSK9 inhibitors will be allowed. The 40-week, active-controlled Extension Period population will consist of patients completing the 12-week placebo-controlled Efficacy Period. Patients in the 40-week, active-controlled Extension Period will be allowed to continue in the study even if the background lipid-altering therapy with statins, ezetimibe, or PCSK9 inhibitors requires adjustment.

Number of Patients:	**Number of Centers:**
Approximately 420 patients (280 patients receiving K-877; 140 patients receiving placebo/fenofibrate)	Approximately 160 sites globally
Dose Levels: 12-week Efficacy Period • K-877: 0.2 mg twice daily • Placebo: twice daily 40-week Extension Period • K-877: 0.2 mg twice daily • Fenofibrate: 48 mg once daily or 145 mg once daily	**Route of Administration:** Oral

Duration of Treatment:

This study consists of a 12-week, double-blind, placebo-controlled Efficacy Period, followed by a 40-week open-label, active-controlled Extension Period, for a total of 52 weeks on study drug.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint is the percent change in fasting TG from baseline to Week 12. Baseline for TG will be defined as the mean of Visit 4 (Day 1) and the preceding TG qualifying visit (either Visit 3 [Week -1] or Visit 3.1, if required) measurements.

The secondary efficacy endpoints for the 12-week Efficacy Period include the following:

- Percent change from baseline to Week 12 in remnant cholesterol (calculated as total cholesterol [TC] – low-density lipoprotein C [LDL-C] – high-density lipoprotein C [HDL-C]), HDL-C, apolipoprotein (Apo) A1, and non-HDL-C;
  - Low-density lipoprotein cholesterol will be determined by preparative ultracentrifugation;
- Percent change from baseline to Week 12 in TC, LDL-C, free fatty acids (FFAs), Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, and Apo E;
- Change from baseline to Week 12 in fibroblast growth factor 21 (FGF21) and high-sensitivity C-reactive protein (hsCRP), and percent change from baseline to Week 12 in ion mobility analysis and lipoprotein fraction (nuclear magnetic resonance [NMR]); and
- Percent change from baseline to Week 12 in the lipid and lipoprotein ratios of TG:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, LDL-C:Apo B, Apo B:Apo A1, and Apo C3:Apo C2.

The secondary efficacy endpoints for the 40-week Extension Period include the following:

- Percent change from baseline to Week 52 in fasting TG;
- Percent change from baseline to Week 52 in remnant cholesterol (calculated as TC − LDL-C − HDL-C), HDL-C, Apo A1, and non-HDL-C;
  - Low-density lipoprotein cholesterol will be determined by preparative ultracentrifugation;
- Percent change from baseline to Week 52 in TC, LDL-C, FFAs, Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, and Apo E;
- Change from baseline to Week 52 in FGF21 and hsCRP, and percent change from baseline to Week 52 in ion mobility analysis and lipoprotein fraction (NMR); and
- Percent change from baseline to Week 52 in the lipid and lipoprotein ratios of TG:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, LDL-C:Apo B, Apo B:Apo A1, and Apo C3:Apo C2.

Baseline for TG, TC, HDL-C, non-HDL-C, LDL-C, and remnant cholesterol will be defined as the mean of Visit 4 (Day 1) and the preceding TG qualifying visit (either Visit 3 [Week -1] or Visit 3.1, if required) measurements. Baseline for all other efficacy and safety variables will be defined as Visit 4 (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug will be used.

[redacted]

Safety:

Safety assessments include adverse events (AEs), clinical laboratory measurements (chemistry, hematology, coagulation profile, [redacted] and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (heart rate, respiratory rate, and blood pressure), and physical examinations.

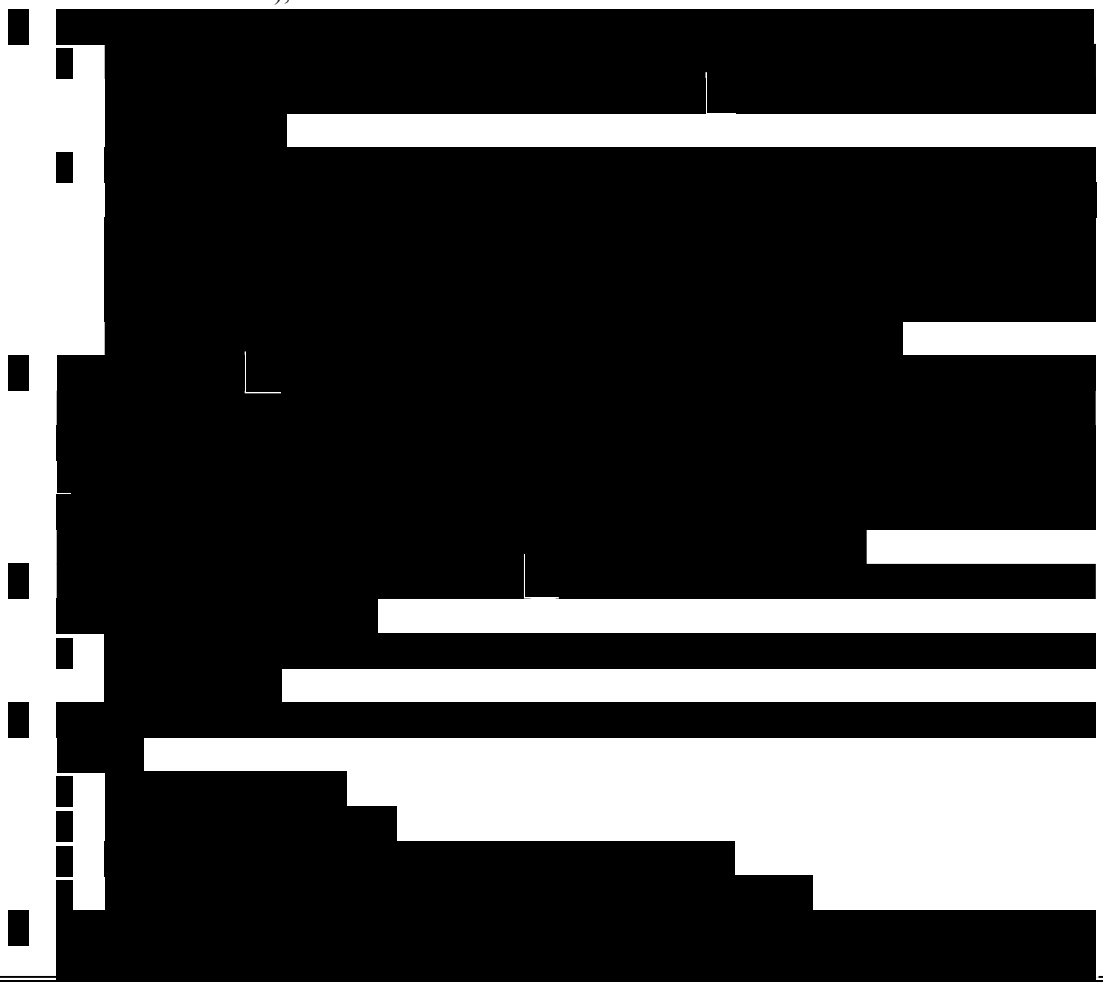
Pharmacokinetics/Pharmacodynamics:

Pharmacokinetic concentrations collected during the 12-week Efficacy Period will be used for population PK analysis and PK/PD analysis.

Criteria for Inclusion:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Able to understand and willing to comply with all study requirements and procedures throughout the duration of the study and give written informed consent;
2. Aged ≥18 years;
3. Patients receiving statin therapy must meet one of the following criteria[1]:
   - Aged ≥21 years with clinical atherosclerotic cardiovascular disease (ASCVD) (history of acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary revascularization, stroke, transient ischemic attack [TIA] presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization), on a high-intensity statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns);
   - Aged ≥21 years with a history of LDL-C ≥190 mg/dL, which is not due to secondary modifiable causes, on a high-intensity statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns);
   - Aged 40 to 75 years, inclusive, without clinical ASCVD but with diabetes and a history of LDL-C of 70 to 189 mg/dL, inclusive, on a moderate- or high-intensity statin; or
   - Aged 40 to 75 years, inclusive, without clinical ASCVD or diabetes, with a history of LDL-C of 70 to 189 mg/dL, inclusive, with estimated 10-year risk for ASCVD of ≥7.5% by the Pooled Cohort Equation on a moderate- or high-intensity statin;
4. Patients not currently on statins, must not meet the criteria for statin therapy listed above (see inclusion criterion 3);



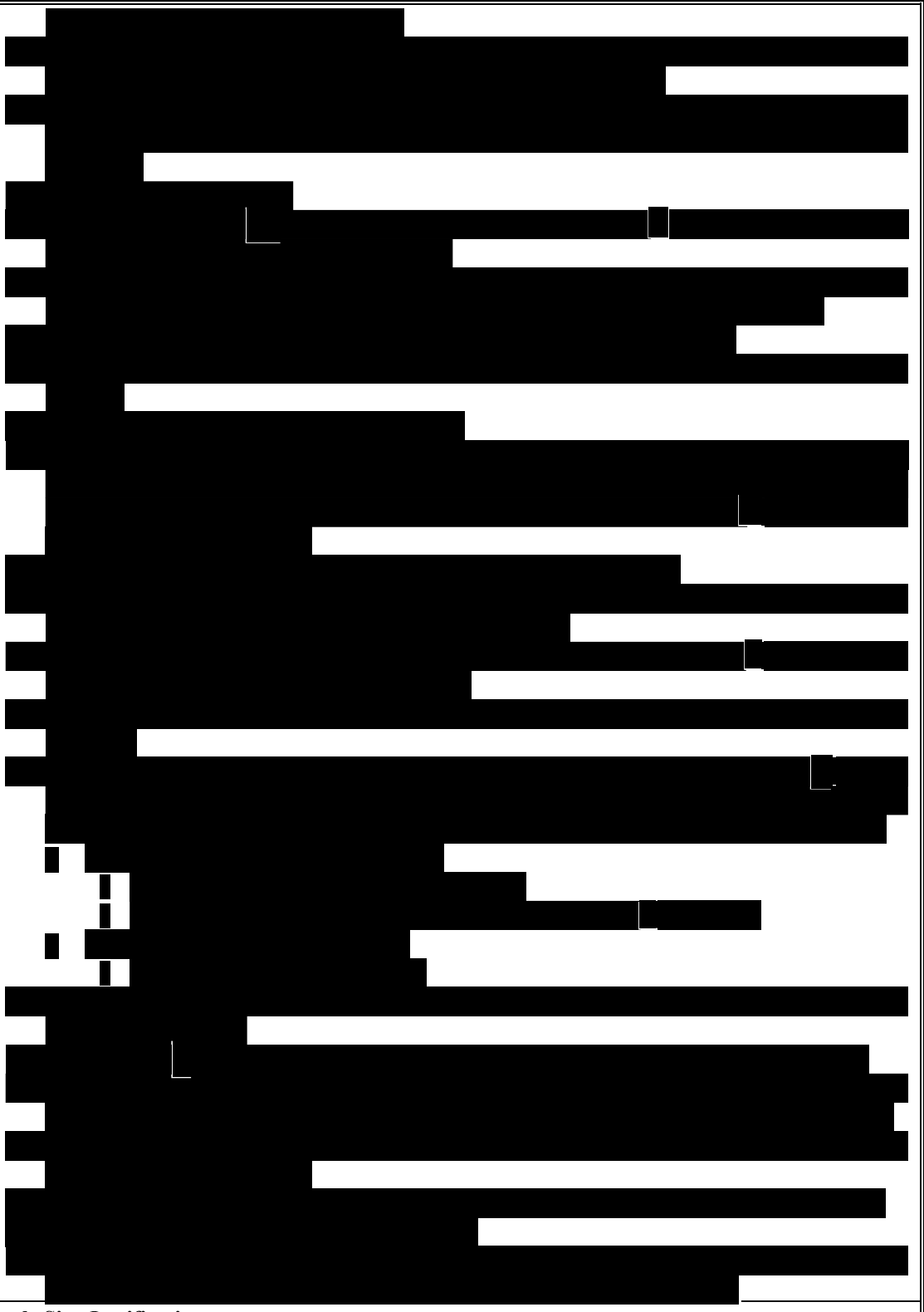
[redacted]

Criteria for Exclusion:

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Patients who will require lipid-altering treatments other than study drugs (K-877 or fenofibrate), statins, ezetimibe, or PCSK9 inhibitors during the course of the study. These include bile acid sequestrants, non-study fibrates, niacin (>100 mg/day), omega-3 fatty acids (>1000 mg/day), or any supplements used to alter lipid metabolism including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols;
2. Body mass index (BMI) >45 kg/m^2 at Visit 1 (Week -8 or Week -6);
3. Patients with type 1 diabetes mellitus;
4. Patients with newly diagnosed (within 3 months prior to Visit 2 [Week -2]) or poorly controlled type 2 diabetes mellitus (T2DM), defined as hemoglobin A_{1c} >9.5% at Visit 1 (Week -8 or Week -6);

[redacted]



Sample Size Justification:
Approximately 420 patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment will be randomized in a 2:1 ratio into one of the following treatment groups: K-877 0.2 mg twice daily or identical matching placebo twice daily.

[redacted]

Statistical Analysis:

Efficacy:

In order to control the family-wise Type I error at a 0.05 level, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary endpoint will be tested first, followed by secondary endpoints, tested in the following hierarchical manner: percent change from baseline to Week 12 in a fixed sequence of (1) remnant cholesterol (calculated as TC − LDL-C − HDL-C), (2) HDL-C, (3) Apo A1, and (4) non-HDL-C. Each test is planned to be performed at a 0.05 significance level. Inferential conclusions about these efficacy endpoints will require statistical significance of the previous one.

For other efficacy endpoints, nominal p-values and 95% confidence intervals (CIs) will be presented, but should not be considered as confirmatory.

The primary efficacy analysis will be based on Hodges-Lehmann estimator with pattern-mixture model imputation based on the Full Analysis Set (FAS). The pattern-mixture model will be used as the primary imputation method as part of the primary analysis for the percent change in fasting TGs from baseline to Week 12. This imputation model will include factors such as patient demographics, disease status, and baseline TG, as well as adherence to therapy. The imputation model will impute missing Week 12 TG values as follows:

- For patients who do not adhere to therapy and who do not have a Week 12 measurement, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have a Week 12 measurement; and
- If there are no patients in the same treatment arm who do not adhere to therapy and have a Week 12 measurement, missing Week 12 TG values will be imputed as follows:
    - For the K-877 arm, the treatment effect is considered washed out and baseline TG values will be used to impute the Week 12 TG values; and
    - For the placebo arm, missing Week 12 TG values will be imputed assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data from the placebo arm.

After the multiple imputation step, each imputed dataset will be analyzed by the nonparametric Hodges-Lehmann method and the Hodges-Lehmann estimator and standard error will be combined to produce treatment difference estimate and 95% CI and p-value.

[redacted]

The primary efficacy analysis will be repeated on the Per-Protocol Set.

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile) at baseline, each scheduled visit, and change and percent change in fasting TG from baseline to each scheduled visit will be provided.

Secondary efficacy endpoints included in the hierarchical step-down testing procedure include percent change from baseline to Week 12 in a fixed sequence of (1) remnant cholesterol, (2) HDL-C, (3) Apo A1, and (4) non-HDL-C.

The secondary and exploratory efficacy endpoints during the 12-week Efficacy Period will be analyzed using an ANCOVA model with the same imputation method used for the primary analysis. The ANCOVA model will include country, current statin therapy use (not on statin therapy versus currently receiving statin therapy), and treatment as factors; baseline value as a covariate. If the normality assumption is not met, the Hodges-Lehmann estimator with the same imputation method used for the primary analysis will be used.

The secondary efficacy endpoint of percent change in fasting TG from baseline to Week 52 will be summarized descriptively. [redacted] Other efficacy endpoints during the 40-week Extension Period will be summarized descriptively. No hypothesis testing will be performed.

[redacted]

Safety:

The safety endpoint data will be summarized for the Safety Analysis Set for the 12-week Efficacy Period, 40-week Extension Period, and overall.

The AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the AEs and serious AEs (SAEs) will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of AEs will be summarized by body system and treatment group. The incidence of treatment-emergent AEs will also be summarized by system organ class and preferred term.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest, such as liver function tests and pancreatitis events, will be summarized.

Vital signs and 12-lead ECGs will also be summarized by visit and by treatment group, along with the changes from baseline.

Pharmacokinetics:

Population PK and PK/PD data will be analyzed and reported separately. [redacted]

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[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
[redacted]	[redacted]
C_{max}	Maximum plasma pharmacokinetic concentration
CRA	Clinical Research Associate
CSR	Clinical Study Report
CVD	Cardiovascular disease
CYP	Cytochrome P450
EC	Ethics Committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFA	Free fatty acid
FGF21	Fibroblast growth factor 21
[redacted]	[redacted]
GCP	Good Clinical Practice
HbA_{1c}	Hemoglobin A_{1c}
HDL-C	High-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
HOMA-β	Homeostatic model assessment for beta-cell function
HOMA-IR	Homeostatic model assessment for insulin resistance
hsCRP	High-sensitivity C-reactive protein
HTG	Hypertriglyceridemia
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational New Drug

INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
KRI	Kowa Research Institute, Inc.
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MMRM	Mixed effect model repeat measurement
[redacted]	[redacted]
NCEP	National Cholesterol Education Program
NMR	Nuclear magnetic resonance
OATP	Organic anion-transporting polypeptide
PAC	Pancreatitis Adjudication Committee
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
PPAR	Peroxisome proliferator-activated receptor
QUICKI	Quantitative insulin sensitivity check index
SAE	Serious adverse event
SHTG	Severe hypertriglyceridemia
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
[redacted]	[redacted]
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TIA	Transient ischemic attack
TLC	Therapeutic Lifestyle Changes
T_{max}	Time to maximum plasma concentration
[redacted]	[redacted]
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
WOCBP	Women of childbearing potential

1.0 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

1.1 BACKGROUND INFORMATION

K-877 is a potent and selective peroxisome proliferator-activated receptor (PPAR) modulator, which is several thousand times more selective for the PPARα receptor than the PPARγ or PPARδ receptor. [redacted]

[redacted]

1.2 RATIONALE

A variety of primary disorders of lipoprotein metabolism have been described which may lead to elevated levels of the atherogenic lipoproteins (VLDL, remnant particles, LDL, etc.) or reduced levels of the anti-atherogenic high-density lipoprotein, any or all of which can confer increased risk of coronary artery disease. Of greater concern, elevated levels of TG, in particular TG levels ≥500 mg/dL (5.65 mmol/L), confer an increased risk of acute pancreatitis.[2,3] Acute pancreatitis caused by hypertriglyceridemia (HTG) is associated with increased severity and rates of complications compared to pancreatitis with causes other than HTG.[4,5]

Fibrates improve TG and HDL-C by activating PPARα,[6] and are labeled in the United States for the treatment of severe HTG (SHTG). In the United States, fenofibrate, fenofibric acid, and gemfibrozil are available. Fibrates available in Europe are bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil. In Japan, bezafibrate, clinofibrate, clofibrate, and fenofibrate are available.

The United States Adult Treatment Panel III National Cholesterol Education Program (NCEP) guidelines[7] recommend reduction of TG through lifestyle, diet, and pharmacologic methods as the first priority of therapy when serum TG are ≥500 mg/dL. Treatment with omega-3 fatty acids, such as those found in fish oils, has been shown to effectively decrease TG levels up to 30%; however, for individuals with SHTG (serum TG ≥500 mg/dL), increasing omega-3 fatty acid intake does not adequately manage TG levels.[8]

The European Society for Cardiology and European Atherosclerosis Society consensus guidelines note that patients can develop pancreatitis with TG concentrations between 5 and 10 mmol/L (440 and 880 mg/dL).[9] These guidelines also recommend initiating fibrates to prevent acute pancreatitis.

Most fibrates are contraindicated or require careful administration in patients with renal dysfunction. Furthermore, coadministration of these drugs with statins is contraindicated in patients with severe renal dysfunction. Thus, there are restrictions in the use of existing PPARα agonists.[10,11,12,13,14,15,16,17]

K-877 is a selective PPARα agonist [redacted]

[redacted]

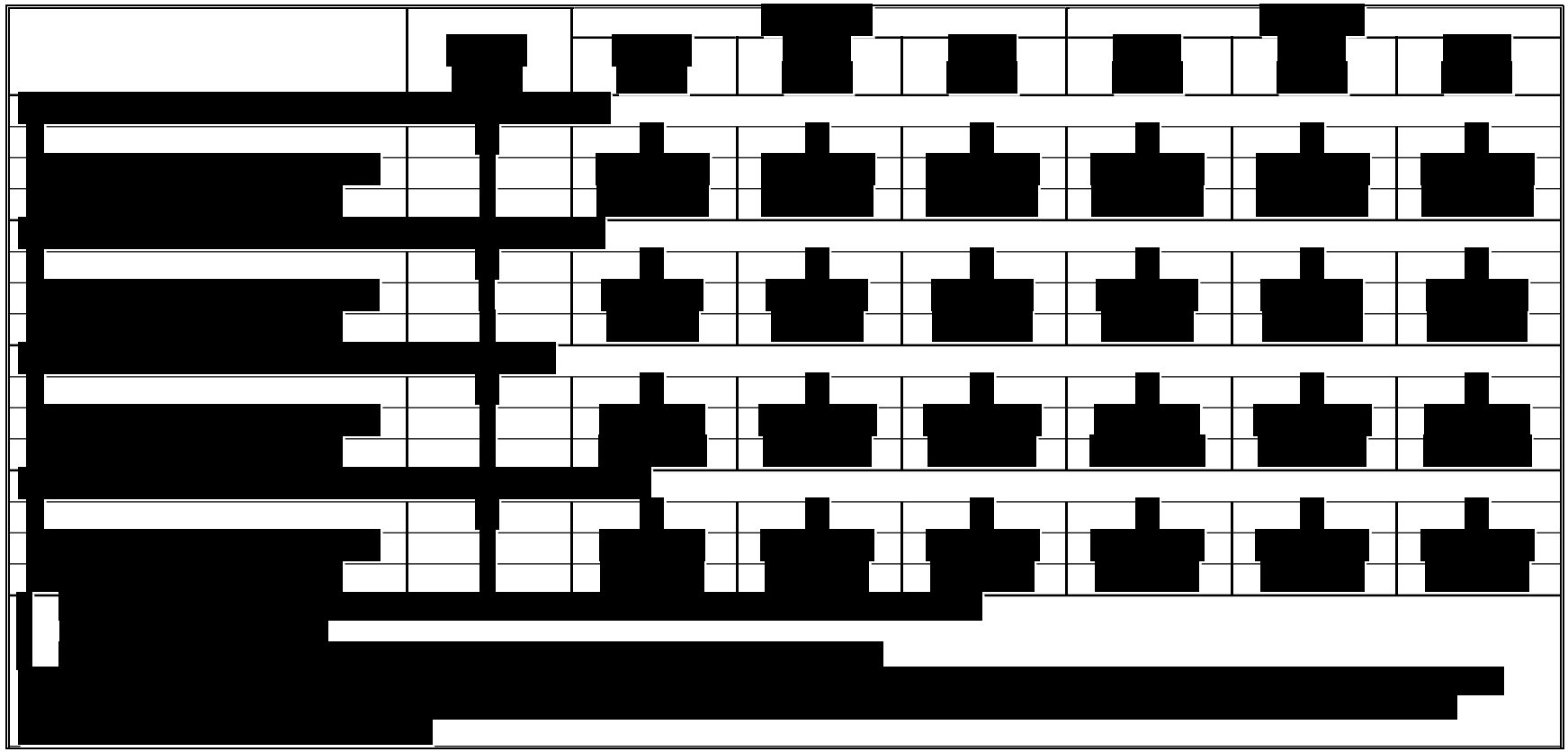
Therefore, K-877 is expected to exhibit not only a potent lipid metabolism-improving effect but also to serve as a drug with a broad therapeutic range with fewer restrictions in patients with renal dysfunction or with concomitant drugs than existing PPARα agonists.

Fenofibrate (48 mg once daily) was chosen as the active comparator for the 40-week Extension Period of this study based on current guidelines for the management of SHTG. As per the United States product insert for fenofibrate, the initial dosage will be 48 mg once daily. A higher dose, 145 mg, is also available for patients who will tolerate this dose. To facilitate the management of fenofibrate, the 40-week Extension Period will be conducted with open-label study drug.

Data from study K-877-12 in Japanese patients with renal impairment found no meaningful differences in K-877 pharmacokinetics (PK), even in patients with severe renal impairment, suggesting adjustment of dosing for renal impairment will not be necessary with K-877 to ensure patient safety.

The present study is a Phase 3 multi-center, placebo-controlled, randomized, double-blind, 12-week study with a 40-week, active-controlled, open-label extension designed to evaluate the efficacy and safety of K-877 0.2 mg twice daily in patients with fasting TG levels ≥500 mg/dL and <2000 mg/dL and mild or moderate renal impairment. The results of this study will provide a better understanding of the efficacy and safety of K-877 0.2 mg twice daily in patients with SHTG.

[redacted]



2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to demonstrate the efficacy of K-877 0.2 mg twice daily compared to placebo from baseline to Week 12 in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are the following:

- To evaluate the efficacy of K-877 0.2 mg twice daily from baseline to Week 52 in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment;
- To evaluate the efficacy of K-877 0.2 mg twice daily from baseline to Week 12 and Week 52 in altering lipid parameters in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment;
- To evaluate the safety and tolerability of K-877 0.2 mg twice daily in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment;
- To determine the plasma concentrations of K-877 for the purpose of use in population PK analysis and PK/pharmacodynamic (PD) analysis.

2.3 EXPLORATORY OBJECTIVE

[redacted]

2.4 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the percent change in fasting TG from baseline to Week 12. Baseline for TG will be defined as the mean of Visit 4 (Day 1) and the preceding TG qualifying visit (either Visit 3 [Week -1] or Visit 3.1, if required) measurements.

2.5 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints for the 12-week Efficacy Period include the following:

- Percent change from baseline to Week 12 in remnant cholesterol (calculated as total cholesterol [TC] − LDL-C − HDL-C), HDL-C, Apo A1, and non-HDL-C;
    - Low-density lipoprotein cholesterol will be determined by preparative ultracentrifugation;
- Percent change from baseline to Week 12 in TC, LDL-C, free fatty acids (FFAs), Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, and Apo E;
- Change from baseline to Week 12 in FGF21 and high-sensitivity C-reactive protein (hsCRP), and percent change from baseline to Week 12 in ion mobility analysis and lipoprotein fraction (nuclear magnetic resonance [NMR]); and
- Percent change from baseline to Week 12 in the lipid and lipoprotein ratios of TG:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, LDL-C:Apo B, Apo B:Apo A1, and Apo C3:Apo C2.

The secondary efficacy endpoints for the 40-week Extension Period include the following:

- Percent change from baseline to Week 52 in fasting TG;
- Percent change from baseline to Week 52 in remnant cholesterol (calculated as TC − LDL-C − HDL-C), HDL-C, Apo A1, and non-HDL-C;
    - Low-density lipoprotein cholesterol will be determined by preparative ultracentrifugation;
- Percent change from baseline to Week 52 in TC, LDL-C, FFAs, Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, and Apo E;
- Change from baseline to Week 52 in FGF21 and hsCRP, and percent change from baseline to Week 52 in ion mobility analysis and lipoprotein fraction (NMR); and
- Percent change from baseline to Week 52 in the lipid and lipoprotein ratios of TG:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, LDL-C:Apo B, Apo B:Apo A1, and Apo C3:Apo C2.

Baseline for TG, TC, HDL-C, non-HDL-C, LDL-C, and remnant cholesterol will be defined as the mean of Visit 4 (Day 1) and the preceding TG qualifying visit (either Visit 3 [Week -1] or Visit 3.1, if required) measurements. Baseline for all other efficacy and safety variables will be defined as Visit 4 (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug will be used.

[redacted]

2.6 EXPLORATORY EFFICACY ENDPOINTS

[redacted]

2.7 SAFETY ENDPOINTS

Safety assessments include adverse events (AEs), clinical laboratory measurements (chemistry, hematology, coagulation profile, [redacted] and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (heart rate, respiratory rate, and blood pressure), and physical examinations.

2.8 PHARMACOKINETIC/PHARMACODYNAMIC ENDPOINTS

Pharmacokinetic concentrations collected during the 12-week Efficacy Period will be used for population PK analysis and PK/PD analysis.

3.0 STUDY DESCRIPTION

3.1 STUDY DESIGN

This is a Phase 3, multi-center, randomized study to confirm the efficacy and safety of K-877 0.2 mg twice daily compared to matching placebo (in the double-blind 12-week Efficacy Period) and an active comparator, fenofibrate (in the open-label 40-week Extension Period), in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2).

Eligible patients will enter a 4- to 6-week lifestyle stabilization period (4-week stabilization for patients not requiring washout and 6-week washout and stabilization for patients on lipid-altering therapy other than statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors). The stabilization period will be followed by a 2-week TG qualifying period (Visits 2 [Week -2] and 3 [Week -1]), and patient eligibility will be assessed based on the mean TG value from these 2 visits. If the patient's mean TG level during the TG qualifying period is ≥450 mg/dL (5.09 mmol/L) and <500 mg/dL (5.65 mmol/L), an additional TG measurement can be taken 1 week later at Visit 3.1. The mean of all 3 TG measurements will be used to determine eligibility for the study. After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind Efficacy Period. At Visit 4 (Day 1), patients will be randomly assigned in a 2:1 ratio to K-877 0.2 mg twice daily or identical matching placebo tablets twice daily. During the 12-week Efficacy Period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who successfully complete the 12-week Efficacy Period are eligible to continue in a 40-week, open-label, active-controlled Extension Period after completing the Visit 7 (Week 12) procedures. Patients randomized to receive K-877 0.2 mg twice daily in the 12-week Efficacy Period will continue to receive K-877 0.2 mg twice daily in the 40-week Extension Period. Patients randomized to receive placebo matching K-877 0.2 mg twice daily in the 12-week Efficacy Period will initiate fenofibrate dosing at 48 mg once daily at Visit 7 (Week 12). Starting from Visit 8 (Week 16), Investigators can adjust fenofibrate dosing (to 145 mg once daily) at their discretion according to the local standard of care.

From Visit 7 (Week 12), patients not on statins, ezetimibe, or PCSK9 inhibitors may initiate therapy, and patients receiving statins, ezetimibe, or PCSK9 inhibitors may alter their dose, as indicated by guidelines or local standard of care.

After Visit 8 (Week 16), patients are to return to the site every 12 weeks until the last visit (Visit 11 [Week 52]).

Table 2 presents the clinical evaluation schedule performed during the study.

Table 2: Clinical Evaluation Schedule

	STUDY PERIOD										
	Screening Period			Treatment Period							
ASSESSMENTS PERFORMED	Lifestyle Stabilization/ Washout Period	Triglyceride Qualifying Period [1]		12-Week Efficacy Period				40-Week Extension Period [2]			
Time	Week -8 or -6	Week -2 ±3 days	Week -1 ±3 days	Day 1	Week 4 ±3 days	Week 8 ±3 days	Week 12 ±3 days	Week 16 ±3 days	Week 28 ±7 days	Week 40 ±7 days	Week 52 ±7 days or ET
Visit Number	1 [3]	2	3 [1]	4	5	6	7	8	9	10	11
Informed consent	X										
Medical, surgical, and family history, and demographics	X										
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X	X	X							
Vital signs (heart rate, respiratory rate, and blood pressure)	X	X	X	X	X	X	X	X	X	X	X
Height [4], weight, and waist circumference	X			X			X				X
Register screening number with IRT	X										
Urine drug and blood alcohol screen [5]	X										
[redacted]	[redacted]										
Amylase and lipase	X			X							
HbA_{1c}	X			X			X		X	X	X
Insulin, glycated albumin, HOMA-IR, HOMA-β, and QUICKI				X			X		X	X	X
Serum pregnancy test for WOCBP	X										
Urine pregnancy test for WOCBP				X			X		X		X
Chemistry, hematology, coagulation, and urinalysis	X			X	X		X	X	X	X	X
Plasma Population PK sampling [8]	[redacted]										
PK/PD sampling [9]											
TG, TC, HDL-C, non-HDL-C, LDL-C, and remnant cholesterol [10]	X	X	X	X	X	X	X	X	X	X	X

**footnotes on following page*

Table 2: Clinical Evaluation Schedule (Continued)

	STUDY PERIOD										
	Screening Period			Treatment Period							
ASSESSMENTS PERFORMED	Lifestyle Stabilization/ Washout Period	Triglyceride Qualifying Period [1]		12-Week Efficacy Period				40-Week Extension Period [2]			
Time	Week -8 or -6	Week -2 ±3 days	Week -1 ±3 days	Day 1	Week 4 ±3 days	Week 8 ±3 days	Week 12 ±3 days	Week 16 ±3 days	Week 28 ±7 days	Week 40 ±7 days	Week 52 ±7 days or ET
Visit Number	1 [3]	2	3 [1]	4	5	6	7	8	9	10	11
Apo A1, Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, and Apo E				X	X		X		X		X
FFAs				X			X		X		X
Ion mobility analysis and lipoprotein fraction (NMR)				X			X				X
[redacted]											
[redacted]											
Withdraw lipid-altering medication(s) other than statins, ezetimibe, or PCSK9 inhibitors, if applicable	X										
12-lead electrocardiogram	X			X			X				X
Physical examination	X			X			X				X
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X
TLC counseling [13]	X	X	X	X	X	X	X	X	X	X	X
Randomization				X							
Dispense study drug (efficacy period)				X	X	X					
Dispense study drug (extension period)							X	X	X	X	
Collect study drug and record accountability					X	X	X	X	X	X	X

1. Triglyceride levels are based on the mean of the Visit 2 (Week -2) and Visit 3 (Week -1) values. In cases in which a patient's mean TG level from Visit 2 (Week -2) and Visit 3 (Week -1) falls outside the required range for entry into the study but is ≥450 mg/dL (5.09 mmol/L) and <500 mg/dL (5.65 mmol/L), an additional TG measurement can be collected 1 week (±3 days) later (Visit 3.1). If Visit 3.1 is required, the TG qualifying period will be extended, and Visit 4 will occur 1 week (±3 days) after Visit 3.1. If a third sample is collected, entry into the 12-week Efficacy Period is based on the mean of the values from Visit 2 (Week -2), Visit 3 (Week -1), and Visit 3.1.
2. Starting from Visit 8 (Week 16), Investigators can adjust fenofibrate dosing (to 145 mg once daily) at their discretion according to the local standard of care.
3. Visit 1 for patients who require a washout is at Week -8. Visit 1 for patients who do not require a washout is at Week -6.
4. Height is measured at Visit 1 (Week -8 or Week -6) only.
[redacted]

**footnotes continued on following page*

Table 2: Clinical Evaluation Schedule (Continued)

[redacted]

g.

10. All lipid laboratory blood specimens must be obtained under fasting conditions (i.e., after the patient has fasted for at least 10 hours).

[redacted]

13. TLC counseling can be provided by the Investigator or designee (see Section 8.5.1).

AE = adverse event; Apo = apolipoprotein; ET = Early Termination; FFA = free fatty acid; [redacted] HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HOMA-β = homeostasis model assessment for beta-cell function; HOMA-IR = homeostasis model assessment for insulin resistance; IRT = Interactive Response Technology; LDL-C = low-density lipoprotein cholesterol; NMR = nuclear magnetic resonance; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic; PK = pharmacokinetic; QUICKI = quantitative insulin sensitivity check index; [redacted] TC = total cholesterol; TG = triglycerides; TLC = therapeutic lifestyle changes; T_{max} = time to maximum plasma concentration; [redacted] WOCBP = women of childbearing potential.

4.0 PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 INCLUSION CRITERIA

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Able to understand and willing to comply with all study requirements and procedures throughout the duration of the study and give written informed consent;

2. Aged ≥18 years;

3. Patients receiving statin therapy must meet one of the following criteria[1] (see Appendix B for statin eligibility and monitoring):
   - Aged ≥21 years with clinical atherosclerotic cardiovascular disease (ASCVD) (history of acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary revascularization, stroke, transient ischemic attack [TIA] presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization), on a high-intensity statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns [see Appendix B]);
   - Aged ≥21 years with a history of LDL-C ≥190 mg/dL, which is not due to secondary modifiable causes, on a high-intensity statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns [see Appendix B]);
   - Aged 40 to 75 years, inclusive, without clinical ASCVD but with diabetes and a history of LDL-C of 70 to 189 mg/dL, inclusive, on a moderate- or high-intensity statin; or
   - Aged 40 to 75 years, inclusive, without clinical ASCVD or diabetes, with a history of LDL-C of 70 to 189 mg/dL, inclusive, with estimated 10-year risk for ASCVD of ≥7.5% by the Pooled Cohort Equation (see Appendix C) on a moderate- or high-intensity statin;

4. Patients not currently on statins, must not meet the criteria for statin therapy listed above (see inclusion criterion 3);

[redacted]

[redacted]

[redacted]

4.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Patients who will require lipid-altering treatments other than study drugs (K-877 or fenofibrate), statins, ezetimibe, or PCSK9 inhibitors during the course of the study. These include bile acid sequestrants, non-study fibrates, niacin (>100 mg/day), omega-3 fatty acids (>1000 mg/day), or any supplements used to alter lipid metabolism including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols;

2. Body mass index (BMI) >45 kg/m^2 at Visit 1 (Week -8 or Week -6);

3. Patients with type 1 diabetes mellitus;

4. Patients with newly diagnosed (within 3 months prior to Visit 2 [Week -2]) or poorly controlled type 2 diabetes mellitus (T2DM), defined as hemoglobin A_{1c} (HbA_{1c}) >9.5% at Visit 1 (Week -8 or Week -6);

[redacted]

[redacted]

[redacted]

4.3 STUDY DRUG DISCONTINUATION CRITERIA

It will be necessary to make a distinction between patients who prematurely discontinue study drug treatment and those who withdraw from the study for any reason.

If the patient discontinues study drug, the reason should be captured and could include the following:

1. The patient requests discontinuation of the study drug;
2. The patient begins to take any medication(s) that is contraindicated by the protocol;
3. The patient develops an AE that, in the opinion of the Investigator, would compromise the patient's safety to continue the study drug;
4. The patient meets any of the criteria specified in Section 4.6;
5. A female patient becomes pregnant during the study;
6. In the Investigator's judgment, it is in the patient's best interests; or
7. The patient is unblinded during the 12-week Efficacy Period.

During the 12-week Efficacy Period, patients who discontinue study drug prematurely will remain in the study until Visit 7 (Week 12). However, patients who discontinue study drug during the 40-week Extension Period will be required to withdraw from the study and requested to complete the full panel of assessments scheduled for the Early Termination (ET) Visit (see Section 4.4). If a patient who has discontinued study drug fails to attend any follow-up appointments, reasonable efforts (telephone calls to family members or friends, e-mail contacts, etc.) will be made in order to encourage the patient to complete the study visits.

Although a patient is not obligated to give his/her reason for discontinuing study drug, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. The reason for discontinuation of study drug must be documented in the electronic case report form (eCRF). The Clinical Study Report (CSR) will include the reason(s) for discontinuation of study drug.

Patients will not be allowed to restart the study drug in the event of discontinuation; however, study drug may be restarted in cases of study drug interruption due to temporary use of prohibited medication(s).

4.4 WITHDRAWAL CRITERIA

The patient has the right to withdraw from the study at any time. Nevertheless, in this study, every attempt will be made to prevent missing data and to obtain complete follow-up of all patients during the 12-week Efficacy Period. Investigators will be trained to minimize full withdrawals from the 12-week Efficacy Period wherever possible.

Patients who discontinue study drug during the first 12 weeks are not required to withdraw from the study. These patients will be encouraged to remain in the study and asked to conduct the remaining study visits as outlined in the protocol through Visit 7 (Week 12). At a minimum, measurements of lipid parameters at key time points, particularly Visit 7 (Week 12), should be taken for all study patients, regardless of adherence to therapy or study protocol. If a patient fails to actively maintain contact with the Investigator, reasonable efforts (telephone calls to family members or friends, e-mail contacts, etc.) will be made in order to encourage the patient to complete the study visits.

If the patient withdraws from the study, the reason should be captured and could include the following:

1. The patient withdraws consent at any time or requests discontinuation of the study drug during the 40-week Extension Period;

2. The patient begins to take any medication(s) during the 40-week Extension Period that is prohibited by the protocol;

3. The patient develops an AE that, in the opinion of the Investigator, would compromise the patient's safety by continuing in the study;

4. The patient meets any of the criteria specified in Section 4.6 during the 40-week Extension Period;

5. A female patient becomes pregnant during the study;

6. The patient fails to comply with protocol requirements or study-related procedures if, in the opinion of the Investigator or the Sponsor, the non-compliance will significantly compromise data interpretation or safety;

7. In the Investigator's judgment, it is in the patient's best interests;

8. Violation of the protocol inclusion and exclusion criteria is discovered, if, in the opinion of the Investigator or the Sponsor, the violation will significantly compromise data interpretation or safety; or

9. The Sponsor or the regulatory authority terminates the study.

Patients who choose to withdraw consent will be asked to document withdrawal of consent in writing.

Although a patient is not obligated to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. The reason for withdrawal from the study must be documented in the eCRF. The CSR will include the reason(s) withdrawal from the study.

If a patient withdraws prematurely from the study, study staff will make every effort to complete the full panel of assessments scheduled for the ET Visit.

If a patient withdraws from the study due to an AE, the patient will be asked to return to the site for, at a minimum, the evaluations scheduled for the ET Visit. If the AE has still not resolved, additional follow-up will be performed, as appropriate, and documented in the patient's medical records. As a minimum requirement, ongoing AEs are to be followed for 30 days after the patient's last dose of study drug. If patients are lost to follow-up, attempts to contact them must be made and documented in the study records. Withdrawn patients will not be replaced.

4.5 RE-SCREENING OF SCREEN FAILURES

Patients who are screen failures for a modifiable condition (such as elevated HbA_{1c} or uncontrolled hypertension), other than failing the TG criteria, can be re-screened once and enrolled in the study at a future date if they are then deemed eligible for study participation based on protocol entry criteria after having medications adjusted and stabilized. Before each patient is re-screened, the Investigator should discuss the case with the Medical Monitor.

4.6 STUDY DRUG DISCONTINUATION FOR PERSISTENT ABNORMAL CLINICAL LABORATORY VALUES

A patient will discontinue treatment with study drug if persistent elevations in ALT, AST, CK, or TG, or a persistent decrease in eGFR, occur according to the following criteria:

1. ALT or AST >8 × ULN, confirmed on repeat;

2. ALT or AST >3 × ULN and bilirubin >2 × ULN or International Normalized Ratio (INR) >1.5, confirmed on repeat;

3. ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) confirmed on repeat;

4. ALT or AST >5 × ULN which persists for 2 weeks;

5. Unexplained CK >5 × ULN confirmed on repeat. For patients with CK ≥10 × ULN, Investigators should immediately interrupt study drug while awaiting re-evaluation;

6. Fasting TG levels >2000 mg/dL (22.60 mmol/L) with signs or symptoms of pancreatitis at any time during the study. For repeated or persistent elevations of TG >2000 mg/dL (22.60 mmol/L) that are not accompanied by signs or symptoms of pancreatitis, Investigators may discontinue study drug at their discretion; or

7. eGFR <30 mL/min/1.73 m^2 occurring at or after Visit 7 (Week 12), confirmed on repeat for patients who are receiving fenofibrate 48 mg. For patients on fenofibrate 145 mg, Investigators may decrease the fenofibrate dose and reassess the patient.

If at any time during the study a patient develops elevations in ALT or AST >3 × ULN, CK >5 × ULN, TG >2000 mg/dL (>22.60 mmol/L), or a decrease in eGFR <30 mL/min/1.73 m^2 at Visit 7 (Week 12) or any subsequent visit, the study site will receive an alert from the central laboratory.

For further details regarding study drug discontinuation for persistent abnormal clinical laboratory tests, see Section 5.2.2.

4.7 SURVEILLANCE FOR POSSIBLE PANCREATITIS

Investigators should be vigilant for potential cases of pancreatitis. If a patient experiences abdominal pain or unexplained gastrointestinal symptoms (e.g., nausea, vomiting, or diarrhea), they should return to the site for an unscheduled visit as soon as possible. A history including symptoms, concomitant medication and dietary and alcohol intake, a physical examination, and laboratory evaluation of TG, amylase and lipase, as well as any other evaluations deemed necessary by the Investigator should be performed and documented on the appropriate eCRF. Patients who are diagnosed with pancreatitis; who have elevations of amylase or lipase, with or without symptoms; or who have severe abdominal pain, or sustained (>7 days), unexplained abdominal pain, even without elevations of amylase or lipase should have their cases submitted for adjudication of pancreatitis.

5.0 PROCEDURES FOR EFFICACY, SAFETY, AND PHARMACOKINETIC EVALUATIONS

5.1 EFFICACY EVALUATIONS

Blood samples for the determination of laboratory analytes for efficacy assessment will be collected as specified in Table 2. All visits with laboratory sampling are fasting visits and blood specimens must be obtained under fasting conditions (i.e., after the patient has fasted [nothing by mouth except water] for at least 10 hours).

The following parameters will be measured or derived to assess efficacy in this study:

- Lipid parameters including HDL-C, LDL-C, TC, TG, non-HDL-C, free fatty acids, remnant cholesterol (calculated as TC – LDL-C – HDL-C), Apo A1, Apo A2, Apo B, Apo B48, Apo B100, Apo C2, Apo C3, Apo E, TG:HDL-C ratio, TC:HDL-C ratio, non-HDL-C:HDL-C ratio, LDL-C:Apo B ratio, Apo B:Apo A1 ratio, Apo C3:Apo C2 ratio, ion mobility analysis, and lipoprotein fraction (NMR); and
- Biomarkers and exploratory parameters including FGF21, hsCRP, [redacted]

5.2 SAFETY EVALUATIONS

5.2.1 Adverse Events

The Investigator will determine at each study visit whether any AEs have occurred since the signing of informed consent. The patients will be questioned in a general way and no specific symptoms will be suggested. Section 9.0 presents further information with regard to AEs.

5.2.2 Clinical Laboratory Tests

Blood and urine samples for the determination of laboratory analytes will be collected as specified in Table 2. [redacted] All standard blood and urine tests will be performed by [redacted] All visits with laboratory sampling are fasting visits and blood specimens must be obtained under fasting conditions (i.e., after the patient has fasted [nothing by mouth except water] for at least 10 hours).

The following parameters will be measured or derived at the time points indicated in Table 2:

- Serum chemistry – sodium, chloride, potassium, bicarbonate, calcium, inorganic phosphorus, blood urea nitrogen, creatinine, eGFR, uric acid, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase, total and direct bilirubin, albumin, total protein, lipase, amylase, CK, lactate dehydrogenase, glucose, insulin, HbA_{1c}, glycated albumin, homeostatic model assessment for insulin resistance (HOMA-IR), homeostatic model assessment for beta-cell function (HOMA-β), quantitative insulin sensitivity check index (QUICKI), homocysteine, and alcohol;
- Hematology – hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count and differential;
- Coagulation – fibrinogen, activated partial thromboplastin time, INR, and prothrombin time;
- [redacted]
- Urinalysis – bilirubin, blood, glucose, ketones, leukocyte esterase, microscopy (as needed based on dipstick results), nitrite, pH, protein, specific gravity, urobilinogen, urine albumin, urine creatinine, urine albumin:creatinine ratio, and [redacted] and
- [redacted]

See Appendix A for a complete list of clinical laboratory analytes to be measured.

The Investigator or a delegated physician will evaluate all laboratory test results for their clinical significance and review, sign, and date all laboratory reports.

For WOCBP, serum pregnancy tests will be analyzed by [redacted] at Visit 1 (Week -8 or Week -6). [redacted] will provide urine pregnancy test kits to the investigative sites so that sites may conduct urine pregnancy tests at Visit 4 (Day 1), Visit 7 (Week 12), Visit 9 (Week 28), and Visit 11 (Week 52) or the ET Visit.

5.2.2.1 *Liver Function Test Elevations*

With any of the following liver function test elevations, patients should undergo repeat laboratory measurements as soon as possible, preferably within 72 hours (unless otherwise specified), and no later than 1 week. Local laboratory measurements may be used to facilitate follow-up:

- ALT or AST >8 × ULN;
- ALT or AST >3 × ULN and bilirubin >2 × ULN or INR >1.5 × ULN;
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%); and
- ALT or AST >5 × ULN, regardless of symptoms should be followed up within 1 week.

Repeat evaluation should include AST, ALT, prothrombin time/INR, total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, creatinine, CK, and complete viral hepatitis screen. The patient should be questioned regarding symptoms, as well as potential causative factors. This information, including results and normal ranges of any laboratory parameters collected at a local laboratory, should be collected on the appropriate eCRF. Hepatobiliary ultrasonography and/or consultation with a hepatologist should be considered if clinically indicated.

Abnormal laboratory parameters should be followed at least weekly (more frequently as clinically indicated) until they have returned to baseline or have stabilized.

5.2.2.2 *Creatine Kinase Elevations*

In the event of a CK elevation >5 × ULN, the patient should return to the site within 1 week for evaluation.

For a CK elevation >10 × ULN, study drug should be interrupted immediately while awaiting evaluation.

Evaluation should include the patient being questioned about symptoms (e.g., muscle or tendinous pain, cramping, or weakness) and potential causes for the CK elevation (e.g., medications, exercise, or trauma). The following laboratory measurements should be obtained: CK, CK-MB, CK-MM, troponin, creatinine, myoglobin (serum and urine), transaminases, total bilirubin, and urinalysis including urine sediment. A physical examination should be performed, documenting findings such as muscle tenderness, weakness, or rash. An ECG should be collected as well. This information should be collected on the appropriate eCRF. For abnormalities to be reported as AEs, see Appendix D for a list of muscle AE definitions.

Abnormalities should be followed until they have returned to baseline, or the Investigator considers them clinically stable.

5.2.2.3 *Triglyceride Elevations*

For alerts due to fasting TG levels >2000 mg/dL (22.60 mmol/L), the patient should return to the site within 1 week for clinical and laboratory assessments. Patients should be assessed for potential signs or symptoms of pancreatitis (including measurements of serum amylase and lipase), and a repeat assessment of fasting TG will be obtained. For patients with asymptomatic elevations of TG, compliance with study drug and lifestyle recommendations should be assessed and reinforced. Patients should be closely followed for the emergence of signs and symptoms of pancreatitis until TG levels are <2000 mg/dL (22.60 mmol/L). If 2 consecutive alerts for a patient are sent due to elevated TG levels >2000 mg/dL (22.60 mmol/L), the Investigator may contact the Medical Monitor to discuss study drug discontinuation and further monitoring.

To maintain the integrity of the blind, TG values from post-randomization blood samples obtained prior to Visit 7 (Week 12), run by the central laboratory, will not be communicated to the sites (see Section 6.6).

5.2.2.4 *Estimated Glomerular Filtration Rate Decrease*

For eGFR <30 mL/min/1.73 m^2, the patient should return to the site within 1 week for repeat laboratory assessment. Patients who are receiving fenofibrate 145 mg can have their dose decreased prior to the repeat assessment. Abnormal laboratory parameters should be followed at least weekly (more frequently as clinically indicated) until they have returned to baseline or have stabilized.

5.2.3 Electrocardiogram and Vital Signs

Twelve-lead ECGs will be performed at Visit 1 (Week -8 or Week -6), Visit 4 (Day 1), Visit 7 (Week 12), and Visit 11 (Week 52) or the ET Visit. Site personnel will make every attempt to perform a patient's ECG using the same equipment at each visit.

Vital signs (heart rate, respiratory rate, and blood pressure) will be assessed at all study visits. All blood pressure measurements will be obtained after a 5-minute rest in the sitting or supine position with a standard mercury sphygmomanometer or an automated oscillometric blood pressure monitor. Heart rate measurements will be made by counting events (heartbeats) for a period of 30 seconds and multiplying this value by 2 to obtain the rate per minute. Whenever possible, the same person will do all of the assessments for a given patient throughout the study.

5.2.4 Physical Examination

A physical examination will be performed at Visit 1 (Week -8 or Week -6), Visit 4 (Day 1), Visit 7 (Week 12), and Visit 11 (Week 52) or the ET Visit. The physical examination will consist of an examination of the following body systems: general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological; mental status; and extremities.

5.2.5 Demographics and Medical History

Demographics and brief, relevant medical/social and surgical history, as well as alcohol consumption, cigarette smoking, hypertension, diabetes history, and family history of heart disease will be taken at Visit 1 (Week -8 or Week -6) and recorded in the eCRF.

5.2.6 Body Weight, Height, Body Mass Index, and Waist Circumference

Body weight, height, and waist circumference will be measured at Visit 1 (Week -8 or Week -6). Body weight and height will be used to calculate the BMI. Body weight and waist circumference will also be measured at Visit 4 (Day 1), Visit 7 (Week 12), and Visit 11 (Week 52) or the ET Visit. Waist circumference will be measured with a tape measure. Starting at the top of the hip bone then bringing the tape measure all the way around, level with the navel. The tape measure should be snug around the waist, but without compressing the skin, and parallel with the floor. Patients should not hold their breath while measuring waist circumference.

5.3 PHARMACOKINETIC EVALUATIONS

[redacted]

[redacted]

5.4 DATA MONITORING COMMITTEE

A data monitoring committee is not planned for this study.

5.5 PANCREATITIS ADJUDICATION COMMITTEE

An external expert Pancreatitis Adjudication Committee (PAC) will blindly adjudicate all suspected pancreatitis events reported by Investigators. A PAC Charter will describe the operations of the PAC and definitions to be utilized for adjudication.

6.0 CONDUCT OF THE STUDY

6.1 STUDY BLINDING AND RANDOMIZATION

This is a multi-center, placebo-controlled, randomized, double-blind, 12-week study with a 40-week, active-controlled, open-label extension. Patients will be randomly assigned in a 2:1 ratio to treatment with either K-877 0.2 mg twice daily or a matching placebo twice daily. An Interactive Response Technology (IRT) system will be used to perform the randomization. At Visit 7 (Week 12), patients will enter into the open-label, 40-week Extension Period. Patients who were randomized to receive K-877 0.2 mg twice daily during the 12-week Efficacy Period will continue to receive K-877 0.2 mg twice daily. Patients randomized to receive placebo matching K-877 0.2 mg twice daily in the 12-week Efficacy Period will initiate fenofibrate dosing at 48 mg once daily at Visit 7 (Week 12). Starting from Visit 8 (Week 16), Investigators can adjust fenofibrate dosing (to 145 mg once daily) at their discretion according to the local standard of care.

The Investigator or designee must contact the IRT system to register each patient. Patient numbers will consist of an 8-digit number and will be assigned based on the pre-printed value on the selected central laboratory requisition binder. Patient numbers will be composed of a 5-digit site identification (ID) plus a 3-digit patient ID, assigned sequentially starting at 001 for the first patient at each site.

The patient number will be used to identify the patient throughout the study and will be entered on all documentation.

A patient number will not be assigned to more than 1 patient. If a patient is not eligible to receive treatment, or should a patient discontinue from the study, the patient number cannot be reassigned to another patient.

At Visit 4 (Day 1), qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will receive the randomly assigned treatment. The Investigator or designee must contact the IRT system to randomize each patient. Randomization will be stratified by country and current statin therapy use (not on statin therapy versus currently receiving statin therapy).

Investigators will be blinded to key results from lipid parameters, such as TG and LDL-C, obtained prior to Visit 7 (Week 12), in order to maintain the blind of the treatment assignments. Investigators are encouraged not to check lipid panels locally, especially during the 12-week Efficacy Period to avoid becoming unblinded. Beginning at Week 12, Investigators will receive unblinded lipid data. Investigators will receive an alert for TG levels >2000 mg/dL (22.60 mmol/L) at any time during the study. To ensure study blinding can be maintained, Investigators may receive a sham alert for TG elevation during the 12-week Efficacy Period (see Section 6.6).

6.2 PATIENT INFORMED CONSENT

Written consent will be obtained from the patient prior to any study-specific procedure or investigation.

Information about the study will be given to the patient both verbally and in writing. The written patient information will explain the objectives of the study, its potential risks, and benefits and the impact of early withdrawal on the scientific validity of the study. The patient must have adequate time to read the information and to ask the Investigator any questions. The Investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient should not enter the study.

Participating patients will be asked to sign and date an ICF, the original copy of which will be kept by the Investigator. A copy of the signed ICF will be given to the patient. A record will be made in the source document that the patient voluntarily agreed to participate in the study.

6.3 STUDY VISITS

The procedures and assessments to be performed at each visit are indicated in Table 2. All visits with laboratory sampling are fasting visits and blood specimens must be obtained under fasting conditions (i.e., after the patient has fasted [nothing by mouth except water] for at least 10 hours).

A detailed list of procedures to be conducted at each study visit is also described below.

Visit 1: Screening/Lifestyle Stabilization/Washout Period (Week -8 or Week -6)

Screening procedures that will be performed at Visit 1 (Week -8 or Week -6) include:

- Obtain written informed consent;
- Evaluate inclusion and exclusion criteria;
- Obtain medical history (including information on prior and concomitant medications), surgical history, family history, and demographic information;
- Assess vital signs, height, weight, and waist circumference;
- Perform physical examination;
- Perform 12-lead ECG;
- Obtain fasting blood sample for the following assessments:
    - Serum chemistry (see Appendix A for a complete list of analytes);
    - Hematology (see Appendix A for a complete list of analytes);
    - Coagulation (see Appendix A for a complete list of analytes);

[redacted]

- Lipid parameters (see Appendix A for a complete list of analytes);

[redacted]

- Serum pregnancy test for WOCBP;

- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes);

[redacted]

- Instruct the patient to discontinue all lipid-altering medications other than statins, ezetimibe, or PCSK9 inhibitors, if applicable;
- Provide Therapeutic Lifestyle Changes (TLC) counseling (see Section 8.5.1);
- Contact the IRT system to register the patient's screening number;
- Assess and record AEs; and
- Schedule Visit 2 (4 weeks or 6 weeks ±3 days from Visit 1).

Visit 2: Triglyceride Qualifying Period (Week -2)

Procedures that will be performed at Visit 2 (Week -2) include:

- Evaluate inclusion and exclusion criteria;
- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for lipid parameters (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Assess and record AEs; and
- Schedule Visit 3 (1 week ±3 days from Visit 2).

Visit 3: Triglyceride Qualifying Period (Week -1)

Procedures that will be performed at Visit 3 (Week -1) include:

- Evaluate inclusion and exclusion criteria;
- Record concomitant medication(s);

- Assess vital signs;
- Obtain fasting blood sample for lipid parameters (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Assess and record AEs; and
- Schedule Visit 4 or Visit 3.1, if applicable (1 week ±3 days from Visit 3).

Visit 3.1: Optional Triglyceride Qualifying Period (1 Week ±3 Days From Visit 3)

Patients with a mean TG level ≥450 mg/dL (5.09 mmol/L) and <500 mg/dL (5.65 mmol/L) from Visit 2 (Week -2) and Visit 3 (Week -1) may have a third TG measurement collected 1 week later at Visit 3.1. Visit 4 (Day 1) will be scheduled for 1 week (±3 days) after Visit 3.1. The following procedures will be performed at Visit 3.1:

- Evaluate inclusion and exclusion criteria;
- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for lipid parameters (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Assess and record AEs; and
- Schedule Visit 4 (1 week ±3 days from Visit 3.1).

Visit 4: Randomization (Day 1)

Procedures that will be performed at Visit 4 (Day 1) include:

- Evaluate inclusion and exclusion criteria;
- Record concomitant medication(s);
- Assess vital signs, weight, and waist circumference;
- Perform 12-lead ECG;
- Perform physical examination;
- Obtain fasting blood sample for the following assessments:
    - Serum chemistry (see Appendix A for a complete list of analytes);
    - Hematology (see Appendix A for a complete list of analytes);
    - Coagulation (see Appendix A for a complete list of analytes);
    - Lipid parameters (see Appendix A for a complete list of analytes);
    - [redacted]

- [redacted]
- [redacted]
- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes) and urine pregnancy test (WOCBP only);
- Provide TLC counseling (see Section 8.5.1);
- Contact the IRT system to randomize the patient if all inclusion and exclusion criteria are met and the laboratory results and physical examination findings are acceptable;
- Dispense study drug via the IRT system and provide instructions for proper use;
- Assess and record AEs; and
- Schedule Visit 5 (4 weeks ±3 days from Visit 4).

Visit 5: Efficacy Period (Week 4)

Procedures that will be performed at Visit 5 (Week 4) include:

- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes);
  - Lipid parameters (see Appendix A for a complete list of analytes); and
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 6 (8 weeks ±3 days from Visit 4).

Visit 6: Efficacy Period (Week 8)

Procedures that will be performed at Visit 6 (Week 8) include:

- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for lipid parameters (see Appendix A for a complete list of analytes);
- [redacted]
- [redacted]
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 7 (12 weeks ±3 days from Visit 4).

Visit 7: Efficacy Period (Week 12)

Procedures that will be performed at Visit 7 (Week 12) include:

- Record concomitant medication(s);
- Assess vital signs, weight, and waist circumference;
- Perform 12-lead ECG;
- Perform physical examination;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes);

- Lipid parameters (see Appendix A for a complete list of analytes);
- [redacted]

- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes) and urine pregnancy test (WOCBP only);
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 8 (16 weeks ±3 days from Visit 4).

Visit 8: Extension Period (Week 16)

Procedures that will be performed at Visit 8 (Week 16) include:

- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes); and
  - Lipid parameters (see Appendix A for a complete list of analytes);
- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 9 (28 weeks ±7 days from Visit 4).

Visit 9: Extension Period (Week 28)

Procedures that will be performed at Visit 9 (Week 28) include:

- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes); and
  - Lipid parameters (see Appendix A for a complete list of analytes);
- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes) and urine pregnancy test (WOCBP only);
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 10 (40 weeks ±7 days from Visit 4).

Visit 10: Extension Period (Week 40)

Procedures that will be performed at Visit 10 (Week 40) include:

- Record concomitant medication(s);
- Assess vital signs;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes); and
  - Lipid parameters (see Appendix A for a complete list of analytes);
- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes);
- Provide TLC counseling (see Section 8.5.1);
- Dispense study drug via the IRT system and provide instructions for proper use;
- Collect study drug and assess study drug accountability;
- Assess and record AEs; and
- Schedule Visit 11 (52 weeks ±7 days from Visit 4).

Visit 11: Extension Period (Week 52) or Early Termination Visit

Procedures that will be performed at Visit 11 (Week 52) include:

- Record concomitant medication(s);
- Assess vital signs, weight, and waist circumference;
- Perform 12-lead ECG;
- Perform physical examination;
- Obtain fasting blood sample for the following assessments:
  - Serum chemistry (see Appendix A for a complete list of analytes);
  - Hematology (see Appendix A for a complete list of analytes);
  - Coagulation (see Appendix A for a complete list of analytes);
  - Lipid parameters (see Appendix A for a complete list of analytes);
  - [redacted]
- Obtain urine sample for urinalysis (see Appendix A for a complete list of analytes) and urine pregnancy test (WOCBP only);
- Provide TLC counseling (see Section 8.5.1);
- Collect study drug and assess study drug accountability; and
- Assess and record AEs.

6.4 COMPLIANCE WITH THE PROTOCOL

The Investigator must agree to implement the study protocol as written and adhere to the guidelines given in the "Investigator's Statement," which will be signed by the Investigator prior to the start of the study. The study will be performed in accordance with Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local laws, and other applicable guidance documents. Sites in the United States will also comply with the Health Insurance Portability and Accountability Act (HIPAA) and Food and Drug Administration (FDA) GCP regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312).

Protocol noncompliance must be reported to [redacted] and Kowa Research Institute, Inc. (KRI). Each deviation and the reason for its occurrence must be documented. Kowa Research Institute, Inc. retains the right to require the withdrawal of any patient who violates the protocol.

6.5 TERMINATION OF THE STUDY

6.5.1 Site Termination

If it becomes apparent that patient enrollment is unsatisfactory with respect to quality or quantity, or data recording is inaccurate or incomplete on a chronic basis, KRI has the right to terminate the study at an investigational site and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the Institutional Review Board (IRB)/Ethics Committee (EC), and regulatory authorities, if required. In the event of any serious or non-serious AE(s) having occurred at a site, all documentation relating to the event(s) must be obtained.

6.5.2 Study Termination

If, in the opinion of KRI, the clinical observations in the study suggest that it may be unwise to continue, the study may be terminated. In addition, KRI may terminate the study at any time.

6.6 LABORATORY ALERT RELATED TO HIGH TRIGLYCERIDES

Sites will receive an alert for any reported TG level >2000 mg/dL (22.60 mmol/L) during the study. In order to maintain the study blind during the placebo-controlled 12-week Efficacy Period, sites may receive a sham alert. A sham alert is an alert which will be sent to a site for randomly selected patients who do not actually meet the alert criteria for TG levels >2000 mg/dL (22.60 mmol/L). These alerts will be programmed to occur in patients assigned to K-877, at the expected (low) frequency that they would occur in the placebo population, and will be indistinguishable from "true" alerts. Investigators are expected to respond to every alert (see Section 5.2.2.3).

7.0 INVESTIGATIONAL DRUG

7.1 DESCRIPTION OF STUDY DRUGS

Kowa Research Institute, Inc. will supply sufficient K-877 0.2 mg film-coated tablets and matching placebo to allow for completion of the study. The lot numbers of the study drug will be recorded in the final study report.

All K-877 and matching placebo tablets are [redacted] To ensure study blinding can be maintained, each tablet is indistinguishable by size, markings, or weight. Each K-877 tablet contains 0.2 mg of K-877; each K-877 and placebo tablet also contains the following excipients: [redacted]

Fenofibrate is supplied as a white to off-white bi-convex oblong tablet containing 48 mg or 145 mg fenofibrate, as well as the following excipients: anhydrous lactose, croscarmellose sodium, hypromellose, magnesium stearate, purified water, simethicone emulsion, sodium lauryl sulfate, polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, and xanthan gum. The 48 mg fenofibrate tablet additionally contains D&C Yellow No. 10 aluminum lake, FD&C Yellow No. 6/sunset yellow FCF aluminum lake, and FD&C Blue No. 2/indigo carmine aluminum lake.

7.2 DRUG PACKAGING

Drug packaging will be completed by an independent clinical packager, [redacted]

K-877 and matching placebo will be packaged in clear polyvinyl chloride/aluminum foil blisters within a child-resistant sleeve. Fenofibrate will be packaged in high-density polyethylene bottles with a child-resistant screw-top cap. Patients will have approximately a 1-month supply of study drug in each blister card or bottle. Study drug will be labeled in accordance with Section 7.3. Patients will receive an adequate supply of study drug at each visit to ensure proper dosing can occur until the next scheduled study visit.

7.3 DRUG LABELING

Study drugs will be labeled according to country/state/province specific requirements. For example, the label will include the following information:

- Name and address of Sponsor (i.e., KRI);
- A study reference code (e.g., protocol number) allowing ID of the investigational site and Investigator;
- Blank space for patient ID;

- Blank space for site/Investigator ID;
- Route of administration, quantity of dosage units, and pharmacological form as appropriate;
- A code number that will allow appropriate blinded assignment of the correct clinical trial material kit via the randomization code;
- Lot number (as required);
- Directions for use;
- The statement "Caution - New Drug - Limited by Federal (United States) Law to Investigational Use";
- The statement "Keep out of reach of children";
- The storage conditions; and
- Expiration date (as required).

7.4 DRUG STORAGE

K-877 0.2 mg tablets, fenofibrate 48 mg and 145 mg tablets, and matching placebo tablets for K-877 will be stored at controlled room temperatures of 20°C to 25°C (68°F to 77°F) in a secured area with access limited to the Investigator and the site staff. The permitted excursion temperature range is 15°C to 30°C (59°F to 86°F).

7.5 DISPENSING AND ADMINISTRATION OF TREATMENT

Study drugs will be dispensed to eligible patients beginning at Visit 4 (Day 1) after randomization via the IRT system and at Visit 5 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 28), and Visit 10 (Week 40). From Visit 4 (Day 1) to Visit 6 (Week 8), an approximately 1-month supply of blinded study drug will be dispensed to patients at each visit. Each patient will receive 1 blister card of K-877 0.2 mg or matching placebo. At Visit 7 (Week 12), an approximately 1-month supply of open-label study drug will be dispensed. Each patient will receive 1 blister card of K-877 0.2 mg or 1 bottle of fenofibrate 48 mg. From Visit 8 (Week 16) to Visit 10 (Week 40), an approximately 3-month supply of open-label study drug will be dispensed at each visit. Each patient will receive 3 blister cards of K-877 0.2 mg or 3 bottles of fenofibrate 48 mg or 145 mg.

Starting at Visit 8 (Week 16), patients who receive fenofibrate 48 mg may have their dose titrated to fenofibrate 145 mg and may subsequently have their dose down-titrated to fenofibrate 48 mg, at the discretion of the Investigator according to the local standard of care.

7.5.1 Drug Administration

Patients will receive an oral dose of K-877 0.2 mg or matching placebo twice daily starting at Visit 4 (Day 1) until Visit 7 (Week 12). Starting at Visit 7 (Week 12), patients will receive an oral dose of K-877 0.2 mg twice daily or fenofibrate 48 mg or 145 mg once daily. Patients may take study drug in a fed or fasted state (before or after meals); however, patients should be instructed that fed/fasted state and dosing time should remain consistent for all doses throughout the study. Study drug will be dispensed at Visit 4 (Day 1) through Visit 10 (Week 40). Patients will be instructed by the site to follow dosing instructions on the drug packaging and to return the remaining study drug at the next visit.

7.6 COMPLIANCE WITH PRESCRIBED STUDY DRUG DOSING REGIMEN

Study drug or placebo will be dispensed in excess of the amount required between study visits. Patients will be instructed to return all unused study drug at the next visit. The patient will be asked whether there have been any problems with taking the medication, and the Investigator will record any significant departure from the dosing instructions (e.g., misuse or overdose) as a protocol deviation. A record of the number of tablets dispensed, taken, and returned for each patient must be documented on the Drug Accountability Log and eCRF. Compliance will be assessed from information recorded in the eCRF, including study drug count and the start and end date of therapy. Patients will be considered compliant if they have taken between 80% and 120% of the intended regimen.

During the treatment period, if compliance is not between 80% and 120%, inclusive, the patient will be counseled about the importance of compliance with the regimen. See Section 7.5.1 for study drug administration.

7.7 DRUG ACCOUNTABILITY

Sites will be instructed to maintain drug accountability and retain all used, partially used, and unused study drug materials until the end of the study.

7.8 PROCEDURE FOR UNBLINDING

As needed, the randomization code may be broken by the Investigator to manage an urgent medical event. If possible, the Medical Monitor will be contacted to discuss the case and ET assessments will be completed before the code is broken.

For each patient, the treatment group can be unblinded using the IRT system and the site's Emergency Unblinding IRT Code, provided with the site's study start-up materials. Using the Emergency Unblinding IRT Code, the Investigator or designee will be able to unblind a patient by following the instructions on the [redacted] When the unblinding is completed, the study's Medical Monitor, the Clinical Trial Manager, and designated KRI personnel will be notified that the unblinding has taken place.

If it becomes necessary to unblind treatment information during the study, the reason for unblinding must be documented in the eCRF. The Investigator must contact the Medical Monitor within one business day and explain the reason for the premature unblinding (e.g., unblinding due to a serious AE [SAE]). Patients whose treatment assignment is unblinded during the 12-week Efficacy Period are no longer eligible to receive treatment, but should complete the 12-week Efficacy Period and ET assessments.

8.0 CONCOMITANT MEDICATION

All concomitant medications, both prescribed and over-the-counter, as well as dietary supplements, must be recorded in the eCRF. This includes drugs used on a chronic and as-needed basis.

8.1 GENERAL CONSIDERATIONS

Patients shall be advised not to start any new medication, either prescribed or over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use.

[redacted]

8.3 PROHIBITED MEDICATION

The following medications and products (prescription and over-the-counter) must not be taken by the patient during the course of the study, except as noted:

- Insulin or insulin analogues, except for basal insulin therapy with a single insulin that has been stable for ≥4 weeks prior to Visit 1 (Week -8 or Week -6);
- All systemic corticosteroids, except for local, topical, inhaled, or nasal corticosteroids;
- Prescription or over-the-counter agents taken for the purpose of weight reduction;
- Any non-study lipid-lowering treatments except for statins, ezetimibe, and PCSK9 inhibitors including bile acid sequestrants, fibrates, niacin (>100 mg/day), omega-3 fatty acids (>1000 mg/day), or any supplements used to alter lipid metabolism including but not limited to red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols;
- During the 12-week Efficacy Period, dietary fiber supplements cannot be increased or started; or
- Cyclosporine, rifampin, or other strong inhibitors of OATP1B1 or OATP1B3.

8.4 PERMITTED MEDICATION

The following frequently prescribed medications are permitted by the protocol, if the patient has been on a stable dose for ≥4 weeks prior to Visit 1 (Week -8 or Week -6) unless otherwise noted, and doses should remain stable throughout the duration of the study:

- Basal insulin therapy with a single insulin;
- Oral contraceptives and hormone replacement therapy;
- Statins, ezetimibe, or PCSK9 inhibitors that have been at a stable dose for ≥6 weeks prior to Visit 1 (Week -8 or Week -6);
    - After Week 16, patients not on statins, ezetimibe, or PCSK9 inhibitors may initiate therapy, and patients receiving statins, ezetimibe, or PCSK9 inhibitors may alter their dose; and
    - Simvastatin 80 mg or Vytorin (ezetimibe/simvastatin) 10/80 mg are permitted if tolerated for ≥6 weeks prior to Visit 1 (Week -8 or Week -6). However, simvastatin 80 mg or Vytorin 10/80 mg cannot be started at any point during the study;
- Dietary fiber supplements that are taken as part of the TLC diet during the lifestyle stabilization period may be used at a stable dose for the duration of the study. Dietary fiber supplements cannot be increased or started during the 12-week Efficacy Period;
- Chronic prescription pharmacotherapy for metabolic or CVD management or risk factor modification;
    - During the 40-week Extension Period, patients not on chronic prescription pharmacotherapy for metabolic or CVD management (other than statins, ezetimibe, or PCSK9 inhibitors) or risk factor modification may initiate therapy, and patients receiving therapy may alter their dose, as indicated by guidelines or local standard of care;
- Tamoxifen, estrogens, or progestins that have been at a stable dose for ≥4 weeks prior to the first TG qualifying visit (Visit 2 [Week -2]);
- Thyroid replacement therapy that has been at a stable dose for ≥4 weeks prior to the first TG qualifying visit (Visit 2 [Week -2]); and
- Local, topical, inhaled, or nasal corticosteroids.

Note: Other than the prohibited medications (see Section 8.3), medications needed for chronic conditions and AEs are permitted.

8.5 PATIENT RESTRICTIONS

8.5.1 Therapeutic Lifestyle Changes

The Investigator or designee will provide TLC instructions based on the NCEP recommendations (see Appendix E) with implementation beginning at Visit 1 (Week -8 or Week -6). From Visit 4 (Day 1), the Investigator or designee will instruct patients to stably maintain these lifestyle changes. Goals and recommendations on diet,[18] weight loss, physical activity, and abstaining from alcohol will be reviewed at all study visits.

9.0 ADVERSE EVENTS

9.1 ADVERSE EVENT DEFINITION

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the patient's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that patient.

Clinically meaningful (for a given patient) changes in physical examination findings and abnormal objective test findings (e.g., clinical laboratory tests, ECGs) will also be recorded as AEs. The criteria for determining whether an abnormal objective test finding will be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms, and/or;

2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or;

3. Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or;

4. Test result leads to any of the outcomes included in the definition of an SAE.

Merely repeating a test, in the absence of any of the above conditions, does not meet condition number 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

A treatment-emergent AE (TEAE) is defined as an AE that begins after the start of study drug or an event that begins before the start of the study drug and worsens in intensity after starting treatment with the study drug.

9.2 ADVERSE DRUG REACTIONS

All noxious and unintended responses to a medicinal product related to any dose will be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and the AE is at least a reasonable possibility (see Section 9.3).

9.3 REPORTING ADVERSE EVENTS

At each evaluation, the Investigator will determine whether any AEs have occurred. The patient will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the eCRF and in the

patient's medical record. If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms.

Adverse event assessment and reporting begins with the signing of informed consent, and occurs at every scheduled study visit through Visit 11 (Week 52), unless an unresolved AE is still being followed (see Section 9.4).

The severity (intensity) of AEs will be classified as follows:

- Mild: An AE that is easily tolerated by the patient, causes minimal discomfort, and does not interfere with everyday activities;
- Moderate: An AE that causes enough discomfort to interfere with normal everyday activities and may require intervention; and
- Severe: An AE that prevents normal everyday activities;
    - Note: Treatment or intervention will usually be required.

The Investigator will make a judgment regarding whether or not the AE was related to the study drug. The following factors should be considered:

- The temporal sequence from study drug administration-
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drugs-
    - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
    - The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

- Definite: An AE which is consistent with the suspected type of reaction known for the drug, in line with the reasonable temporal order after treatment, and is alleviated or disappears upon discontinuation of the study drug;
- Probable: An AE which is consistent with the suspected type of reaction known for the drug, in line with the reasonable temporal order after treatment, alleviates or disappears upon discontinuation of the study drug, but could also be caused by the clinical conditions of the study patient or other factors;
- Possible: An AE which is consistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order after treatment, and could also be caused by the clinical conditions of the study patient or other factors;
- Improbable: An AE which is inconsistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order after treatment, and could also be caused by the clinical conditions of the study patient or other factors; and
- Not related: An AE which is inconsistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order from administration of the study drug, or that can be easily explained by other factors, such as underlying diseases, complication, concomitant drugs, and concurrent treatment.

If the causality assessment for an individual event is “Definite,” “Probable,” or “Possible,” the event will be considered a suspected adverse drug reaction.

The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to the study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or laboratory abnormality **MUST** be recorded in the eCRF.

The Investigator will record the action taken to treat the AE, if any, the action taken with study treatment, and the outcome for each AE in the eCRF according to the following:

Action taken to treat the AE

- None,
- Treatment required,
- Hospitalization,
- Patient withdrawn, or
- Other (specify).

Action taken with study treatment

- Dose not changed,
- Dose reduced,
- Drug interrupted,
- Drug withdrawn,
- Not applicable, or
- Unknown.

Outcome

- Resolved: The event has recovered;
  - Note: An SAE/AE stop date should be provided.
- Resolved with sequelae: The study patient has recovered as much as may be expected but is left with sequelae of the event that are not expected to recover further;
  - Note: If the sequelae are severe enough to represent a significant disability or incapacity then the event should be reported as an SAE.
- Resolving: Can be used in cases where study patient is known to be clearly recovering from the event at the end of a study, although the event is not yet resolved, and the Investigator and Medical Monitor agree that further follow-up is not necessary;
- Death: The study patient died as a result of the AE;
  - Note: Death is considered an outcome of an AE rather than an AE in its own right, and the cause of death should be recorded as the AE. There may be rare circumstances where the cause of death is unknown and the death may have to be recorded as the event (e.g., "sudden cardiac death"). Adverse events resulting in death are SAEs.
- Not resolved: The patient has an AE that has not improved or recuperated at the time of the report; or
  - Note: The decision not to continue follow-up should be discussed between the Investigator and Medical Monitor and recorded in the source documents.
- Unknown: The outcome of the event is genuinely unknown in spite of efforts to contact the patient.

9.4 FOLLOW-UP OF ADVERSE EVENTS

If any AEs are present when a patient completes the study, or if a patient is withdrawn from the study, the patient will be re-evaluated. At the Investigator's discretion, clinically minor AEs can be re-evaluated via telephone and documented. If the AE is still not resolved, additional follow-up will be performed as appropriate. Every effort will be made by the Investigator or delegate to contact the patient until the AE is resolved or stabilized, or until the Medical Monitor and Investigator agree that further follow-up is not necessary. The follow-up of AEs will be documented in the patient's study records.

10.0 SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

10.1 LIFE-THREATENING ADVERSE EVENT

The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.

10.2 HOSPITALIZATION OR PROLONGATION OF EXISTING HOSPITALIZATION

Hospitalization is defined as the patient being hospitalized overnight, or the patient's hospital stay being prolonged for at least an additional overnight stay. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before the signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations. Twenty-three hour hospitalizations for observation should be discussed with the Medical Monitor to determine whether they are appropriate for SAE reporting.

10.3 PREGNANCY

If a patient becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator will report the pregnancy to [redacted] within 24 hours of being notified (see Section 10.6.1 for contact information). [redacted] will then forward the Exposure In Utero form to the Investigator for completion.

A patient who becomes pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed.

The patient will be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator will notify [redacted]. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will follow the procedures for reporting an SAE (see Section 10.6).

10.4 PATIENT WITHDRAWAL

If a patient experiences an AE that leads to discontinuation of study drug treatment and/or withdrawal from the study, the eCRF will identify the AE as the reason for study drug discontinuation or withdrawal.

10.5 SERIOUS UNEXPECTED SUSPECTED ADVERSE REACTIONS

According to FDA CFR 312.32(a), FDA Guidance "Safety Reporting Requirements for Investigational New Drugs (INDs) and Bioavailability/Bioequivalence (BA/BE) Studies" finalized December 2012, European Directives 2001/20/EC and CT-3 Guideline, suspected adverse reaction means any AE for which there is a reasonable possibility that the medicinal product caused the AE. The phrase "reasonable possibility" means there is evidence to suggest a causal relationship between the AE and the medicinal product (see Section 9.3).

The following are examples of types of evidence that would suggest a causal relationship between the drug and the AE:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); or
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

A suspected adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information in Section 6 of the K-877 Investigator's Brochure or is not listed at the specificity or severity that has been described in the K-877 Investigator's Brochure or the approved package insert of fenofibrate. Study sites will be provided with the current version of the fenofibrate package insert.

The Sponsor will report suspected unexpected serious adverse reactions (SUSARs) to Investigators, Competent Authorities, and IRB/ECs in an expedited manner according to national requirements. Fatal and life-threatening SUSARs will be reported within 7 calendar days of Day 0, where Day 0 is defined as the day on which the information containing the minimum reporting criteria is received by the Sponsor. All other SUSARs will be reported within 15 calendar days of Day 0. All cases will be unblinded for reporting purposes, as required.

10.6 REPORTING SERIOUS ADVERSE EVENTS, URGENT SAFETY ISSUES, AND SERIOUS BREACHES

10.6.1 Serious Adverse Events

10.6.1.1 *Initial Reports*

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30 day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] or call [redacted] and fax the completed paper SAE form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours.

Safety Contact Information: [redacted]

10.6.1.2 *Follow-Up Reports*

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs. Written confirmation that these serious, unexpected, and related AEs have been submitted to the IRB/EC must be forwarded to KRI and kept in the Investigator files.

10.6.2 Urgent Safety Issues and Serious Breaches of Clinical Trial Regulation

If [redacted] or any Investigator become aware of an actual or potential urgent safety issue or a serious breach of clinical trial regulations, the Medical Monitor and the Sponsor must be immediately contacted so that agreement can be made on appropriate urgent safety measures. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of study patients participating in a clinical trial, or
- A serious risk to human health or potentially a serious risk to human health.

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, intercurrent illness (including pandemic infections), concomitant medications, concurrent medical conditions, or any other issues related to the safe conduct of the study or that pose a risk to study patients.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, [redacted] may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has been resolved.

11.0 STATISTICAL METHODS AND DATA ANALYSIS

11.1 SAMPLE SIZE JUSTIFICATION

Approximately 420 patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and mild or moderate renal impairment will be randomized in a 2:1 ratio into one of the following treatment groups: K-877 0.2 mg twice daily or identical matching placebo twice daily.

11.2 ANALYSIS POPULATIONS

The study population will consist of male and female patients ≥18 years of age with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) after washout from background lipid-altering therapy other than statins, ezetimibe, or PCSK9 inhibitors and with mild or moderate renal impairment. The active-controlled study population will consist of patients who complete the 12-week portion of the efficacy study and who continue the study.

11.2.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized patients who take at least 1 dose of double-blind study drug and have a baseline TG measurement. The FAS Population is the primary analysis population. All efficacy analyses will be performed on the FAS Population.

11.2.2 Per-Protocol Set

The Per-Protocol Set will include all FAS patients for the 12-week Efficacy Period who complete the 12-week, placebo-controlled Efficacy Period without any major protocol deviations and have valid baseline and Week 12 fasting serum TG measurements. Major protocol deviations will be pre-specified prior to unblinding the study. The Per-Protocol

Set will be used to assess robustness of the primary analysis results during the 12-week Efficacy Period.

11.2.3 Safety Analysis Set

The Safety Analysis Set will include all randomized patients who receive at least 1 dose of randomized study drug. All safety analyses will be conducted on the Safety Analysis Set.

11.2.4 Pharmacokinetic Analysis Set

The PK Analysis Set will include all patients from the Safety Analysis Set who have at least 1 PK sample.

11.3 DEMOGRAPHIC/BASELINE INFORMATION

Summary statistics will be provided by treatment group for demographics (e.g., age, gender, race, and ethnicity).

Baseline for TG, TC, HDL-C, non-HDL-C, LDL-C, and remnant cholesterol will be defined as the mean of Visit 4 (Day 1) and the preceding TG qualifying visit (either Visit 3 [Week -1] or Visit 3.1, if required) measurements. Baseline for all other efficacy and safety variables will be defined as Visit 4 (Day 1). If the measurement at this visit is missing, the last measurement prior to the first dose of randomized study drug will be used.

[redacted]

11.4 STUDY DRUG EXPOSURE, COMPLIANCE, AND CONCOMITANT THERAPIES

Days of exposure to randomized study drug and study drug for the 12-week Efficacy Period and the 40-week Extension Period will be summarized with descriptive statistics by treatment for the Safety Analysis Set. Exposure in days is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1.

Patient compliance with the study drug will be summarized by treatment group in each period.

Prior/concomitant medications will be coded with Anatomical Therapeutic Chemical (ATC) class and preferred term (defined by the most recent version of the World Health Organization Drug Dictionary) and summarized by ATC class and preferred term for each treatment group for the Safety Analysis Set.

11.5 ANALYSIS OF EFFICACY

11.5.1 Hypothesis Testing Procedure

In order to control the family-wise Type I error at a 0.05 level, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary endpoint will be tested first, followed by secondary endpoints, tested in the following hierarchical manner: percent change from baseline to Week 12 in a fixed sequence of (1) remnant cholesterol (calculated as TC − LDL-C − HDL-C), (2) HDL-C, (3) Apo A1, and (4) non-HDL-C. Each test is planned to be performed at a 0.05 significance level. Inferential conclusions about these efficacy endpoints will require statistical significance of the previous one.

For other efficacy endpoints, nominal p-values and 95% confidence intervals (CIs) will be presented, but should not be considered as confirmatory.

11.5.2 Analysis of Primary Efficacy Parameters

The primary efficacy analysis will be based on Hodges-Lehmann estimator with pattern-mixture model imputation based on the FAS. The pattern-mixture model will be used as the primary imputation method as part of the primary analysis for the percent change in fasting TGs from baseline to Week 12. This imputation model will include factors such as patient demographics, disease status, and baseline TG, as well as adherence to therapy. The imputation model will impute missing Week 12 TG values as follows:

- For patients who do not adhere to therapy and who do not have a Week 12 measurement, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have a Week 12 measurement; and

- If there are no patients in the same treatment arm who do not adhere to therapy and have a Week 12 measurement, missing Week 12 TG values will be imputed as follows:

    - For the K-877 arm, the treatment effect is considered washed out and baseline TG values will be used to impute the Week 12 TG values; and

    - For the placebo arm, missing Week 12 TG values will be imputed assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data from the placebo arm.

After the multiple imputation step, each imputed dataset will be analyzed by the nonparametric Hodges-Lehmann method and the Hodges-Lehmann estimator and standard error will be combined to produce treatment difference estimate and 95% CI and p-value.

[redacted]

The primary efficacy analysis will be repeated on the Per-Protocol Set.

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile) at baseline, each scheduled visit, and change and percent change in fasting TG from baseline to each scheduled visit will be provided.

11.5.3 Analysis of Secondary and Exploratory Efficacy Parameters

Secondary efficacy endpoints included in the hierarchical step-down testing procedure include percent change from baseline to Week 12 in a fixed sequence of (1) remnant cholesterol, (2) HDL-C, (3) Apo A1, and (4) non-HDL-C.

The secondary and exploratory efficacy endpoints during the 12-week Efficacy Period will be analyzed using an ANCOVA model with the same imputation method used for the primary analysis. The ANCOVA model will include country, current statin therapy use (not on statin therapy versus currently receiving statin therapy), and treatment as factors; baseline value as a covariate. If the normality assumption is not met, the Hodges-Lehmann estimator with the same imputation method used for the primary analysis will be used.

The secondary efficacy endpoint of percent change in fasting TG from baseline to Week 52 will be summarized descriptively. [redacted] Other efficacy endpoints during the 40-week Extension Period will be summarized descriptively. No hypothesis testing will be performed.

[redacted]

11.6 ANALYSIS OF SAFETY DATA

The safety endpoint data will be summarized for the Safety Analysis Set for the 12-week Efficacy Period, 40-week Extension Period, and overall.

The AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the AEs and SAEs will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of AEs will be summarized by body system and treatment group. The incidence of TEAEs will also be summarized by system organ class and preferred term.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from the baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest, such as liver function tests and pancreatitis events, will be summarized.

Vital signs and 12-lead ECGs will also be summarized by visit and by treatment group, along with the changes from baseline.

11.7 ANALYSIS OF PHARMACOKINETIC DATA

Population PK and PK/PD data will be analyzed and reported separately. [redacted]

11.8 INTERIM ANALYSIS

No interim analysis is planned for this study.

12.0 STUDY MANAGEMENT AND DATA COLLECTION

12.1 ETHICAL CONDUCT OF THE TRIAL

This study will be conducted according to the protocol; FDA GCP, as described in 21 CFR Parts 11, 50, 54, 56, and 312 and HIPAA (in the United States) or Directive 2001/20/EC; the World Medical Association Declaration of Helsinki; ICH GCP (E6/R1), and the laws and regulations of the country where the study is to be conducted. Each Investigator will also conduct the study according to applicable local or regional regulatory requirements.

12.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The IRB/EC must be constituted according to the applicable state, federal, and local requirements of each participating location, and those of the ICH GCP guidance and, in the United States, FDA GCP regulations.

It is the responsibility of each investigational site to submit the protocol, Investigator's Brochure, patient informed consent, patient recruitment materials (if applicable), and other required documentation to the IRB/EC for review and approval. Copies of the written approvals must be provided to [redacted] The documentation should clearly mention the approval/favorable opinion of the protocol, the patient ICF, and patient recruitment materials (if applicable). The respective version dates are to be included. The written approvals and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRB/EC and provided to [redacted] prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB/EC has direct participation in the study, written notification regarding his or her abstinence from voting must also be obtained.

Sites must adhere to all requirements stipulated by the IRB/EC. This includes notification to the IRB/EC regarding protocol amendments; updates to the patient informed consent and recruitment materials intended for viewing by patients; IND safety reports; serious and unexpected AEs; updates regarding the ongoing review of the study at intervals specified by the IRB/EC; and final study reports or summaries.

It is the responsibility of each investigational site to submit information to the appropriate IRB/EC for annual review and annual re-approval.

12.3 PATIENT INFORMED CONSENT

Prior to the implementation of study procedures, patients and persons conducting the consent discussion will be required to sign and date the IRB/EC-approved ICF, and each patient will be given a copy. In addition, this information will be recorded in the patient's medical record (i.e., source document).

The written consent document will embody the elements of informed consent as described in HIPAA, World Medical Association Declaration of Helsinki, FDA 21 CFR

Part 50.25, ICH GCP, and in accordance with any local regulations. The Investigator is responsible for the preparation, content, and IRB/EC approval of the ICF. The ICF must be approved by the site-designated IRB/EC and be acceptable to KRI and [redacted]

The ICF must be written in a language fully comprehensible to the prospective patient. The Investigator or designee will give the patient adequate opportunity to read it before it is signed and dated. Information provided will be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB/EC. Patients must be given ample opportunity to inquire about study details.

12.4 AMENDMENTS TO THE PROTOCOL

An amendment must be agreed to in writing by KRI and [redacted] submitted as an IND application amendment in the United States, and submitted to and approved by the respective IRB/EC for each investigational site, and an applicable regulatory authority before it is implemented. Written approval of a protocol amendment is not required prior to implementation for changes to the protocol that eliminate immediate hazard to the patient; however, approval must be obtained as soon as possible thereafter. Approved amendments must also be signed by the Investigator.

12.5 STUDY INITIATION

The Investigator must not enroll any patients prior to the completion of a formal meeting conducted by a representative of [redacted] or KRI. This meeting will include a detailed review of the study protocol and eCRFs. Study drug will not be supplied to an Investigator until all the necessary pre-study requirements have been completed and essential signed documents are received by [redacted] and KRI.

12.6 STUDY MONITORING

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH/FDA GCPs, other applicable regional or local regulatory requirements, HIPAA, and the current Declaration of Helsinki. Valid data are to be entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, [redacted] and KRI in the maintenance of accurate, complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol with the Investigator. In addition, the monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of KRI and [redacted] to monitor the study as frequently as [redacted] or KRI deems is necessary to determine that data recording and protocol adherence are acceptable. The eCRFs and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant Standard Operating Procedures (SOPs), ICH GCP guidance, and FDA GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as

medical history and secondary diagnoses. The Investigator and staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be summarized in a report, which will be filed in the Trial Master File. In addition, performance of monitoring visits will be acknowledged at the investigational site by the monitor's signature and date on the study-specific monitoring log.

12.7 CASE REPORT FORM

All patient data generated during the study will be recorded on the eCRF. Data will be reviewed by the KRI or [redacted] Clinical Research Associate (CRA) during monitoring visits. The CRA will verify the accuracy of data recorded on the eCRF using source documents.

The Investigator will ensure that all data are entered promptly, legibly, and completely, in accordance with specific instructions accompanying the eCRFs, which will be designed for this study and supplied by [redacted] for each patient. The Investigator will also ensure that all applicable entries agree with the source data.

[redacted] will only consider the eCRFs to be complete after they are reviewed and signed by the Investigator, indicating his/her assurance of the accuracy of all recorded data. It is expected that the Investigator and staff will cooperate with the monitoring team and provide missing data in a timely manner.

12.8 VERIFICATION PROCEDURES

In fulfillment of their obligations to KRI and to verify compliance with this protocol, ICH GCP guidance, FDA GCP regulations (in the United States), local regulations, and regulations in the countries in which the study is conducted, the Investigator will permit [redacted] the IRB/EC, the monitor, the auditors, and regulatory authorities to have direct access to the patient's medical records.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical record. The patient's medical record will be considered the source document and must include the following information: medical history/concomitant disease, patient ID number, confirmation of informed consent and the date of study enrollment, visit dates, administration of study drugs, AEs (start and stop dates), and all concomitant medications (start and stop dates). This information may not be recorded directly into the eCRF.

The Investigator will maintain a Patient ID Code List to enable unambiguous ID of the patients (patient names and corresponding patient numbers).

12.9 RETENTION OF RECORDS

All documentation pertaining to the study will be retained by KRI in accordance with regulatory requirements and the ICH GCP guidance document.

[redacted] will provide each Investigator with a study file, which will be used to file the Investigator's Brochure; protocol; drug accountability records; correspondence with the IRB/EC, KRI, and [redacted] and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the ID of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and KRI or its designees.

The Investigator will retain records required to be maintained under federal regulations for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, these documents will be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by KRI. In addition, the Investigator must make provision for the patient's medical records to be kept for the same period of time.

Patients' medical records and other original data will be archived in accordance with applicable regulations and requirements established by the investigational sites.

12.10 INSURANCE AND INDEMNITY

Kowa Research Institute, Inc.'s obligations regarding insurance and indemnification are described in other documents or agreements.

12.11 AUDIT

It is the responsibility of [redacted] and KRI to perform audits (if applicable), as part of implementing quality assurance. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, ICH/FDA GCPs, HIPAA, and other applicable regulatory requirements. The auditor and regulatory authorities will require direct access to the patients' medical records.

13.0 USE OF INFORMATION

13.1 GENERAL ASPECTS

All information concerning [redacted] and KRI, such as patent applications, formula, manufacturing processes, basic scientific data or formulation information supplied by KRI and not previously published, are considered confidential and will remain the sole property of KRI. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of KRI, except for official representatives, such as regulatory authorities.

It is understood by the Investigator that the information developed in this clinical study, in connection with the development of K-877 will be used by KRI and, therefore, may be disclosed by KRI as required to other clinical Investigators, other pharmaceutical companies, and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to KRI complete test results and all data compiled in this study.

13.2 PATIENT CONFIDENTIALITY AND DATA PROTECTION

Kowa Research Institute, Inc. and its designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, all data will be linked to the eCRF via a unique ID number. The data will be blinded correspondingly in all data analyses.

However, in compliance with the guidelines and regulations of the United States FDA concerning the acceptance of clinical studies in support of IND applications and the ICH GCP (whether performed in the United States or elsewhere), and in fulfillment of its obligations to KRI to verify compliance with this protocol, KRI's designee requires that the Investigator permit its monitor, representatives from the FDA, KRI's designated auditors, IRBs/ECs, and other governmental regulatory authorities to review the patient's primary medical records (source data or documents) including, but not limited to laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports related to deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the patient before the patient is entered into the study.

13.3 FINAL REPORT AND PUBLICATION POLICY

All information regarding this study will be kept strictly confidential. All data derived from the study will be the property of KRI. The Investigator must undertake not to submit any part of the data from this study for publication without prior consent of KRI. Kowa Research Institute, Inc. may disclose data derived from the study to other Investigators and drug regulatory authorities.

After completion of the study, and as agreed by the Investigator and KRI, the Investigator may send a draft manuscript to KRI to be reviewed in order to reach an agreement regarding publication. The Investigator must receive written approval from KRI before the final version of the manuscript is submitted for publication.

At the conclusion of the study, after the data are analyzed, KRI or its designee will prepare a final CSR.

14.0 REFERENCES

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12 Package insert for Clofibrate Capsules, revised in July 2009 (6th edition).

13 Ciprofibrate 100 mg tablets, Summary of Product Characteristics at eMedicines Compendium.

14 Lopid 300 mg capsules and 600 mg tablets, Summary of Product Characteristics at eMedicines Compendium.

15 Package insert for Tricor® tablets, revised in September 2011.

16 Package insert for Trilipix® capsule, revised in September 2012.

17 Package insert for Lopid® tablets, revised in September 2010.

18 US Department of Health and Human Services; National Institutes of Health; and National Heart, Lung and Blood Institute. Your Guide to Lowering Your Cholesterol With Therapeutic Lifestyle Changes. NIH Publication. December 2005; No. 06-5235.

15.0 APPENDICES

APPENDIX A: CLINICAL LABORATORY PARAMETERS

Chemistry

Sodium
Chloride
Potassium
Bicarbonate
Calcium
Inorganic phosphorus
Blood urea nitrogen
Creatinine
Estimated glomerular filtration rate
Uric acid

Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline phosphatase
Gamma-glutamyl transpeptidase (GGT)
Total bilirubin
Direct bilirubin
Albumin
Total protein

Lipase (Visits 1 and 4 only)
Amylase (Visits 1 and 4 only)

Creatine kinase (CK)
Lactate dehydrogenase

Glucose
Insulin (Visits 4, 7, 9, 10, and 11 only)
Glycosylated hemoglobin (HbA_{1c}) (Visits 1, 4, 7, 9, 10, and 11 only)
Glycated albumin (Visits 4, 7, 9, 10, and 11 only)
Homeostasis model assessment for insulin resistance (Visits 4, 7, 9, 10, and 11 only)
Homeostasis model assessment for beta-cell function (Visits 4, 7, 9, 10, and 11 only)
Quantitative insulin sensitivity check index (Visits 4, 7, 9, 10, and 11 only)
Homocysteine

[redacted]

Hematology

Hematocrit
Hemoglobin
Platelets
Red blood cell count

White blood cell count and differential [1]
Mean corpuscular hemoglobin
Mean corpuscular volume
Mean corpuscular hemoglobin concentration

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Fibrinogen
Activated partial thromboplastin time
International Normalized Ratio (INR)
Prothrombin time

[redacted]

Urinalysis

Bilirubin
Blood
Glucose
Ketones
Leukocyte esterase
Microscopy [1]
Nitrite
pH
Protein
Specific gravity
Urobilinogen
Urine albumin [2]
Urine creatinine [2]

1. Microscopy is performed only as needed based on positive dipstick test results.
2. Urine albumin:creatinine ratio will be derived based on laboratory values obtained at that particular visit.

[redacted]

[redacted]

Pregnancy Test

Serum (× 1; Visit 1) and urine (× 4; Visits 4, 7, 9, and 11) pregnancy tests will be administered to all female patients of childbearing potential.

Lipid Parameters

The following laboratory tests will be performed to assess efficacy in this study:

High-density lipoprotein cholesterol (HDL-C)
Low-density lipoprotein cholesterol (LDL-C)
Total cholesterol (TC)
Triglycerides (TG)
Non-HDL-C
Free fatty acids (Visits 4, 7, 9, and 11 only)
Lipoprotein fraction (via nuclear magnetic resonance) (Visits 4, 7, and 11 only)
Ion mobility analysis (Visits 4, 7, and 11 only)
Apolipoprotein (Apo) A1 (Visits 4, 5, 7, 9, and 11 only)
Apo A2 (Visits 4, 5, 7, 9, and 11 only)
Apo B (Visits 4, 5, 7, 9, and 11 only)
Apo B48 (Visits 4, 5, 7, 9, and 11 only)
Apo B100 (Visits 4, 5, 7, 9, and 11 only)
Apo C2 (Visits 4, 5, 7, 9, and 11 only)
Apo C3 (Visits 4, 5, 7, 9, and 11 only)
Apo E (Visits 4, 5, 7, 9, and 11 only)

The following values will be derived based on laboratory values obtained at that particular visit:

Remnant cholesterol (calculated as TC – LDL-C – HDL-C)
TG:HDL-C ratio
TC:HDL-C ratio
Non-HDL-C:HDL-C ratio
LDL-C:Apo B ratio
Apo B:Apo A1 ratio
Apo C3:Apo C2 ratio

Biomarkers and Exploratory Parameters

The following laboratory tests will be performed to assess efficacy in this study:

Fibroblast growth factor 21 (Visits 4, 7, and 11 only)
High-sensitivity C-reactive protein (Visits 4, 7, and 11 only)

[redacted]

APPENDIX B: ASSESSING STATIN ELIGIBILITY CRITERIA AND MONITORING STATIN USE DURING THE STUDY

Table B1: Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults - Statin Treatment

Recommendations	NHLBI Grade	ACC/AHA COR	ACC/AHA LOE
Secondary Prevention			
1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD*,* unless contraindicated.	A (Strong)	I	A
2. Individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated.	A (Strong)	I	A
3. In individuals with *clinical ASCVD** >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug-drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	E (Expert Opinion)	IIa	B
Primary Prevention in Individuals ≥21 Years of Age with LDL-C ≥190 mg/dL			
1. Individuals with LDL-C ≥190 mg/dL or TG ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia.	B (Moderate)	I‡	B
2. Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): • Use high-intensity statin therapy unless contraindicated; and • For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.	B (Moderate)	I§	B
3. For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.	E (Expert Opinion)	IIa	B
4. For individuals ≥21 years of age with an untreated primary LDL-C of ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions, and consider patient preferences.	E (Expert Opinion)	IIb	C
Primary Prevention in Individuals With Diabetes and LDL-C 70-189 mg/dL			
1. Moderate-intensity statin therapy should be initiated or continued for adults 40-75 years of age with diabetes.	A (Strong)	I	A
2. High-intensity statin therapy is reasonable for adults 40-75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVDǁ risk unless contraindicated.	E (Expert Opinion)	IIa	B
Footnotes are located at the end of the table on a later page.			

Table B1: Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults - Statin Treatment (Continued)

Recommendations	NHLBI Grade	ACC/AHA COR	ACC/AHA LOE
Primary Prevention in Individuals With Diabetes and LDL-C 70-189 mg/dL			
3. In adults with diabetes, who are <40 years of age or >75 years of age, or with LDL <70 mg/dL it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects and drug-drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.	E (Expert Opinion)	IIa	C
Primary Prevention in Individuals Without Diabetes and LDL-C 70-189 mg/dL			
1. The Pooled Cohort Equations should be used to estimate 10-year ASCVD‖ risk for individuals with LDL-C 70-189 mg/dL without *clinical ASCVD** to guide initiation of statin therapy for the primary prevention of ASCVD.	E (Expert Opinion)	I	B
2. Adults 40-75 year of age with LDL-C 70-189 mg/dL, without *clinical ASCVD** or diabetes and with an estimated 10-year ASCVD‖ risk of ≥7.5% should be treated with moderate- to high-intensity statin therapy.	A (Strong)	I	A
3. It is reasonable to offer treatment with a moderate-intensity statin to adults 40-75 years of age, with LDL-C 70-189 mg/dL, without *clinical ASCVD** or diabetes, and with an estimated 10-year ASCVD‖ risk of 5 to <7.5%.	C (Weak)	IIa	B
4. Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70-189 mg/dL without *clinical ASCVD** or diabetes, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug-drug interactions, as well as patient preferences for treatment.	E (Expert Opinion)	IIa	C
5. In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions and consider patient preferences.	E (Expert Opinion)	IIb	C

Footnotes are located at the end of the table on the following page.

Table B1: Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults - Statin Treatment (Continued)

Recommendations	NHLBI Grade	ACC/AHA COR	ACC/AHA LOE
*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin. †Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information. ‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. A TG level ≥500 mg/dL was an exclusion criterion for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy. §No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL, and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses have shown that each 39-mg/dL reduction in LDL-C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL-C levels. Therefore, individuals with primary LDL-C ≥190 mg/dL should be treated with stain therapy. ‖Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations. ¶These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity; ABI <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future. ABI = ankle-brachial index; ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; COR = Class of Recommendation; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LOE = Level of Evidence; MI = myocardial infarction; NA = not applicable; NHLBI = National Heart, Lung, and Blood Institute; RCT = randomized controlled trials; TG = triglyceride; TIA = transient ischemic attack. Source: American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults; Table 4 (2013)			

Table B2: High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by approximately <30%
Atorvastatin (40†)-80 mg	**Atorvastatin 10** ***(20)*** **mg**	*Simvastatin 10 mg*
Rosuvastatin 20 ***(40)*** **mg**	**Rosuvastatin** ***(5)*** **10 mg**	**Pravastatin 10-20 mg**
	Simvastatin 20-40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 ***(80)*** **mg**	*Fluvastatin 20-40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

Boldface type indicates specific statins and doses that were evaluated in RCTs included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3. All of these RCTs demonstrated a reduction in major cardiovascular events.
Italic type indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.
*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the Incremental Decrease through Aggressive Lipid Lowering study.
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.
BID = twice daily; FDA = Food and Drug Administration; LDL-C = low-density lipoprotein cholesterol; CQ = critical question; RCT = randomized controlled trials.
Source: American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults; Table 5 (2013)

Table B3: Characteristics Predisposing Individuals to Statin Adverse Effects

Recommendations	NHLBI Grade	ACC/AHA COR	ACC/AHA LOE
Safety			
1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include but are not limited to: • Multiple or serious comorbidities, including impaired renal or hepatic function; • History of previous statin intolerance or muscle disorders; • Unexplained ALT elevations ≥3 times ULN; • Patient characteristics or concomitant use of drugs affecting statin metabolism; • Age >75 years; and • Additional characteristics that could modify the decision to use higher statin intensities might include but are not limited to: o History of hemorrhagic stroke, and o Asian ancestry.	A (Strong)	I	B

*Based on the presence of clinical ASCVD, diabetes, LDL-C ≥190 mg/dL, or level of estimated 10-year ASCVD risk.
ACC = American College of Cardiology; AHA = American Heart Association; ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; COR = Class of Recommendation; NHLBI = National Heart, Lung, and Blood Institute; LDL-C = low-density lipoprotein cholesterol; LOE = Level of Evidence; ULN = upper limit of normal.
Source: American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults; Table 8 (2013)

Statin Intolerance

Statin intolerance occurs when a patient is unable to continue statin therapy due to a negative side effect or because creatine kinase (elevations >10 × upper limit of normal [ULN]) and/or hepatic transaminases (alanine aminotransferase and aspartate aminotransferase; elevations >3 × ULN) are sufficiently abnormal to cause concern for muscle and liver function, respectively. Intolerance can be partial (statin-specific and/or specific doses) or complete (all statins at any dose).

Myalgia is the most common presentation of statin intolerance, which can occur in up to 15% of treated patients. Other common presentations of statin intolerance include myopathy and rhabdomyolysis (see Appendix D for muscle event definitions). Table B4 contains a complete list of potential adverse effects due to statin therapy.

Table B4: Potential Adverse Effects of Statins

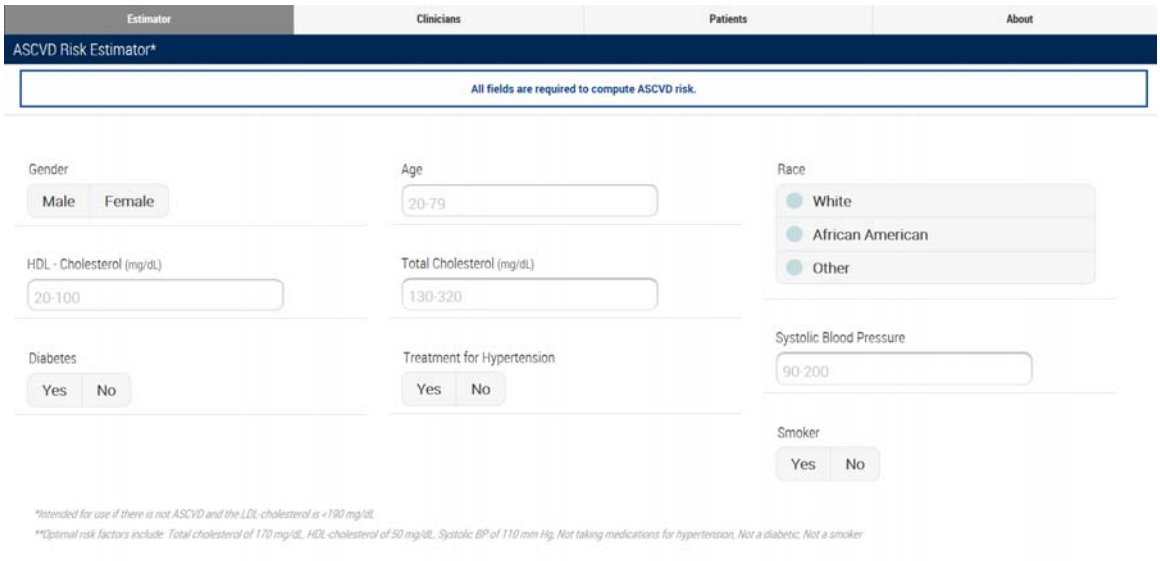
Adverse Effects for Which There is Good Supportive Evidence	Adverse Effects for Which There is Little or No Supportive Evidence
Myopathy (muscle aches/cramps, myositis, rhabdomyolysis)	Cancer
Increase in liver function enzymes	Intracerebral hemorrhage (bleeding stroke)
New-onset diabetes mellitus	Cognitive decline (Alzheimer disease)
	Lung disease
	Erectile dysfunction
	Fatigue, headaches, or dizziness
	Psychiatric illness
	Cataracts
	Rheumatoid arthritis
	Gastrointestinal upset, abdominal cramping
	Permanent liver or kidney damage
Source: Cardiology Patient Page. Statin Intolerance. Circulation. 2015;131(13)e389-391; Table 2	

Statin intolerance will be managed by reducing the dose of statin to the maximum tolerated statin intensity per Table B1 and in accordance with the study design (see Section 8.4).

APPENDIX C: POOLED COHORT EQUATION

The Pooled Cohort Equation for estimating atherosclerotic cardiovascular disease (ASCVD) risk in qualified patients will be entered using the ASVCD risk estimator and recorded in the electronic data capture system (see Figure C1).

Figure C1: ASCVD Risk Estimator



Source: American College of Cardiology Atherosclerotic Cardiovascular Disease Risk Estimator: http://tools.acc.org/ASCVD-Risk-Estimator/#page_calc

APPENDIX D: MUSCLE ADVERSE EVENT DEFINITIONS

Spectrum of Muscle Adverse Events	
• Myalgia	Unexplained muscle discomfort often described as "flu-like" symptoms with normal creatine kinase (CK) level. The spectrum of myalgia complaints includes: Muscle aches, Muscle soreness, Muscle stiffness, Muscle tenderness, and Muscle cramps with or shortly after exercise (not nocturnal cramping).
• Myopathy	Muscle weakness (not attributed to pain and not necessarily associated with elevated CK).
• Myositis	Muscle inflammation.
• Myonecrosis	Muscle enzyme elevations or hyperCKemia. o **Mild =** >3-fold upper limit of normal. o **Moderate =** ≥10-fold upper limit of normal. o **Severe =** ≥50-fold upper limit of normal.
• Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine ≥0.5 mg/dL (clinical rhabdomyolysis).	

Source: Adapted from the National Lipid Association Task Force on Statin Safety – 2014 Update

APPENDIX E: THERAPEUTIC LIFESTYLE CHANGES (TLC)

Table E1: Summary of Lifestyle Management

Lifestyle	Recommended Management [1,2]
Diet	Maintenance of the diet outlined in Table E2
Physical activity	Encourage 30 minutes of moderate exercise on most, if not all, days
Smoking	Support cessation from using tobacco products or e-cigarettes
Alcohol consumption	Support abstinence from use of alcohol
Weight management	Provide support to patients to maintain or attain a healthy weight

1. At each study visit, patients will be counseled on the importance of maintaining the lifestyle management guidelines (see Section 8.5.1).
2. From Visit 4 (Day 1), the Investigator or designee will instruct patients to stably maintain these lifestyle changes.

Source: National Institutes of Health, National Heart, Lung, and Blood Institute (2002)[7]

Table E2: Summary of the TLC Diet for High Cholesterol

TLC Diet for High Cholesterol	
Total fat	25% - 35% total calories [1]
Saturated fat	<7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates	50% - 60% total calories
Protein	~15% total calories
Cholesterol	<200 mg/dL
Plant sterols	2 g
Soluble fiber such as psyllium	10 g - 25 g

1. For subjects with triglycerides >1000 mg/dL, it is recommended that <15% of total calories come from total fat.

Source: National Heart, Lung, and Blood Institute (2005)[18]