NCT03071692

KOWA

RESEARCH INSTITUTE, INC.

CLINICAL STUDY PROTOCOL

K-877 (PEMAFIBRATE)

PROTOCOL K-877-302

PROMINENT

PEMAFIBRATE TO REDUCE CARDIOVASCULAR OUTCOMES BY REDUCING TRIGLYCERIDES IN PATIENTS WITH DIABETES

Development phase:	Phase 3
Study design:	Multicenter, multinational, randomized, double-blind, placebo-controlled event-driven efficacy and safety study
IND number:	109,388
EudraCT number:	2016-003818-26
Sponsor:	Kowa Research Institute, Inc. 430 Davis Dr. Suite 200 Morrisville, NC 27560, USA
Medical monitor:	[redacted]
Coordinating Center:	Center for Cardiovascular Disease Prevention Brigham and Women's Hospital 900 Commonwealth Avenue 3rd Floor, Research Office Boston, MA 02215
Co-Principal Investigators, Center for Cardiovascular Disease Prevention:	[redacted]
Version Number:	1
Date:	16-November-2016

Confidentiality Statement

This confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

INVESTIGATOR'S AGREEMENT

I, the Investigator, understand that all information concerning the product supplied to me in connection with this study and not previously published is confidential information.

I understand that any changes to the protocol must be approved in writing by the Sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Committee (REC) 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); 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(ies) in which the study is 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 the protocol.

_____

Printed Name of Investigator

_____

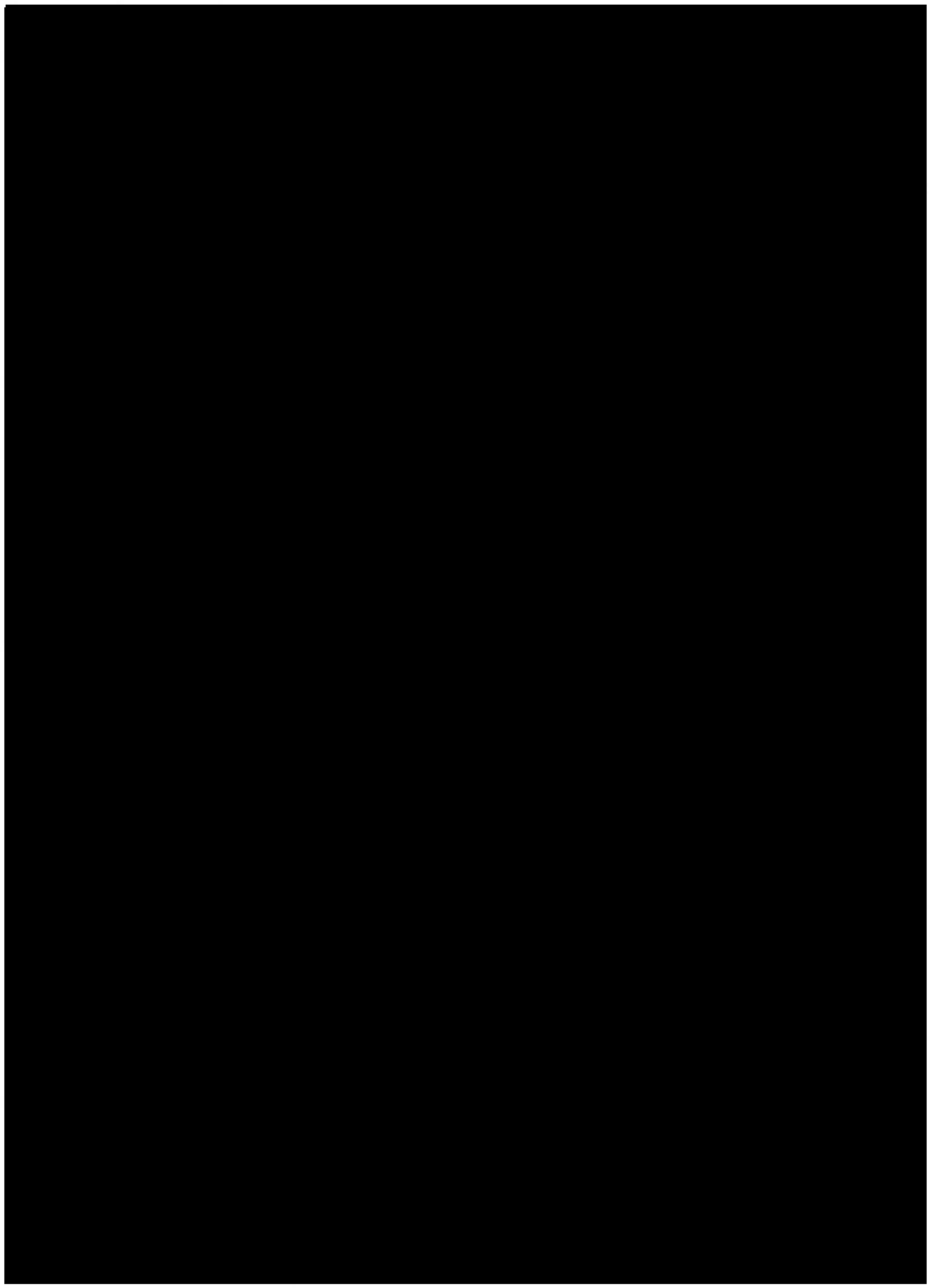
Signature of Investigator

_____

Date

PROTOCOL SIGNATURE PAGE

Approved By:



1. SYNOPSIS

Name of Sponsor/Company:
Kowa Research Institute, Inc.

Name of Investigational Product:
K-877 (pemafibrate) 0.2mg tablet and matching placebo tablet

Name of Active Ingredient:
K-877 (pemafibrate)

Title of Study:
Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes (PROMINENT)

Study center(s): This study will be conducted at approximately **750** investigational centers in 20-25 countries (exact locations to be decided)

Coordinating Center:
Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital
900 Commonwealth Avenue
3rd Floor, Research Office
Boston, MA 02215
[redacted]

Investigators: A Principal Investigator list by site will be provided upon request.

Studied period (years):	**Phase of development:**
Estimated date first participant enrolled: Q2/2017 Estimated date last participant completed: Q2/2022	Phase 3

Objectives:

Primary Objective:

The primary scientific aim of the PROMINENT study is to assess whether treatment with the selective peroxisome proliferator activated receptor modulator alpha (SPPARM-α), pemafibrate, will prevent myocardial infarction (MI), ischemic stroke, unstable angina requiring unplanned revascularization, and cardiovascular (CV) death in adults with type 2 diabetes (T2D) who have elevated triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) levels and are at high risk for future CV events. Participants will be on moderate- to high-intensity statin therapy (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day) or meet low density lipoprotein cholesterol (LDL-C) criteria (by chart review) within 12 months prior to enrollment.

Specifically, the **primary objective** of the study is to determine whether pemafibrate

administered at a dose of 0.2 mg twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of:

- nonfatal MI;
- nonfatal ischemic stroke;
- hospitalization for unstable angina requiring unplanned coronary revascularization; or
- CV death.

At the time of the Screening/Enrollment Visit (Visit 1), participants must be either:

1. Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate-to high-intensity statin (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day[a], or pitavastatin 4 mg/day), or
2. Have evidence of LDL-C ≤ 70 mg/dL (1.81 mmol/L) by local laboratory determination within the previous 12 months[b], or
3. Statin intolerant[c] and have evidence of LDL-C ≤ 100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months.

[a] Participants enrolled on simvastatin > 40 mg/day must have been taking and tolerating that dose for at least 12 months.

[b] If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor

[c] Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (e.g., 1-3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.

Methodology:

The PROMINENT study is a randomized, double-blind, placebo-controlled, international study evaluating the ability of pemafibrate to prevent CV events among 10,000 male and female adults with T2D and moderate hypertriglyceridemia with low HDL-C, and on background moderate- to high-intensity statin therapy (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day) unless meeting LDL-C criteria with or without statin intolerance. Fasting TG levels must be ≥ 200 mg/dL (2.26 mmol/L) and < 500 mg/dL (5.65 mmol/L) and HDL-C must be ≤ 40 mg/dL (1.03 mmol/L). Two-thirds of the enrolled study population will have prior evidence of systemic atherosclerosis (secondary prevention cohort) while one-third will not (primary prevention cohort, age ≥ 50 years [male] or ≥ 55 years [female]). PROMINENT will be conducted in 20-25 countries to ensure generalizability and allow for the enrollment and

follow-up period to complete in 5 years.

The primary endpoint will be the first occurrence of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or CV death. The study is event-driven such that after 1,092 events have been confirmed, with a minimum of 200 events accrued in women, and assuming a conservative 1% annual loss to follow-up, there will be 90% power to detect clinically meaningful relative reductions in the primary endpoint of at least 18% in the pemafibrate group. In addition to spontaneous adverse event (AE) reporting, systematic surveillance for liver disease and muscle AEs will occur.

This study will include the following: a Pre-Screening Visit (Visit 0), a Screening/Enrollment Visit (Visit 1), a 21-day (maximum 35 day) Placebo Run-In Period, a Randomization Visit (Visit 2), a Treatment Period consisting of approximately 30 visits (post-randomization Visits 3 through 33, as applicable), a Common Study End Date (CSED) Visit, and a Post-Study Safety Call.

During the Pre-Screening Visit (Visit 0; Week -6), participants will provide informed consent to participate in the study and follow-up. After consent, the site will be asked to submit medical records for a qualifying cardiovascular disease (CVD) event if applicable and entry criteria including: documentation of diabetes; documentation of statin intolerance, if applicable; and prior TG, HDL-C, and LDL-C levels, if available, within the last 12 months. Screening lab values may be used if prior local laboratory documentation is unavailable. At the Screening/Enrollment Visit (Visit 1; Week -3), participants will be queried regarding their medical histories (including clinical and lifestyle CV risk factors and alcohol use) and concomitant medication use, and will be screened against the inclusion/exclusion criteria. A physical examination comprising a general review of body systems will be performed. Additionally, fasting blood samples will be collected from all participants for eligibility assessment, including a serum pregnancy test in women of child-bearing potential (WOCP). Where local regulations permit, study participants may be asked to arrive fasting at the Pre-Screening Visit (Visit 0) such that activities of the Screening/Enrollment Visit (Visit 1) can be performed concurrently with the Pre-Screening Visit. For expediency, participants meeting all applicable inclusion and exclusion criteria at the end of the Screening/Enrollment Visit (Visit 1), other than screening TG, HDL-C, and other exclusionary lab testing, can be enrolled into the Placebo Run-In Period while awaiting results of qualifying laboratory testing. Placebo tablets will be dispensed to participants at Visit 1 along with administration instructions for the Placebo Run-In Period, which is designed to select compliant individuals for long-term follow-up and adherence. The placebo dosing card will contain sufficient placebo tablets for a maximum duration of 35 days.

On a one-time basis, at the optional Retesting Visit (Visit 1.1), participants may undergo retesting for borderline lipid values, specifically TG 175-199 mg/dL (1.98-2.25 mmol/L) or 500-650 mg/dL (5.65-7.34 mmol/L) and/or HDL-C 41-45 mg/dL (1.06-1.16 mmol/L).

Rescreening of participants for failure to meet other eligibility criteria (eg, hemoglobin A1c [HbA1c] >9.5%, severe hypertension, or medical instability of concurrent clinical condition) may occur once only. Prior to Randomization, serious adverse events (SAEs) and primary endpoints will be recorded and adjudicated, respectively. Thereafter, all AEs and endpoints

will be assessed.

Participants who continue to be eligible, are compliant with medication during the Placebo Run-In Period, and have completed submission of relevant medical records will return for the Randomization Visit (Visit 2; Week 0) to be randomly allocated in a 1:1 ratio to receive either pemafibrate at a dose of 0.2 mg twice daily or a matching placebo tablet to be taken twice daily. A non-fasting sample for lipid testing will be collected, and the participant will complete a quality of life questionnaire. Importantly, in addition to other eligibility criteria, randomized participants must have the following:

- Medical record documentation of diabetes longer than 12 weeks duration
- Medical record documentation of a qualifying CV event (if secondary prevention cohort)
- TG levels ≥ 200 mg/dL (2.26 mmol/L) and < 500 mg/dL (5.65 mmol/L)
- HDL-C ≤ 40 mg/dL (1.03 mmol/L)
- LDL-C ≤ 70 mg/dL (1.81 mmol/L) if not on qualifying statin regimen or ≤ 100 mg/dL (2.59 mmol/L) if documented statin intolerant

At 2-weeks post randomization (Visit 3), sites will perform a well-being telephone visit to provide general support and to reinforce dosing instructions. Adverse events and endpoints will also be collected. If a participant reports or is reported to have an efficacy endpoint, then additional data about the nature and date of the event, and the treatment and care provided during and after the event will be collected by the investigator.

Throughout the treatment period, beginning with Month 2 (Visit 4), telephone visits will alternate with in-person visits occurring approximately every 2 months after Month 10. During each telephone call and in-person visit, concomitant medication use will be reviewed, and the participant will be queried for AEs and efficacy events. During the in-person visits, in addition, physical examinations will be performed and vital signs will be measured, change in risk factors will be documented, and study drug compliance will be determined by tablet count.

At the Months 4 and 12 visits, at annual visits thereafter (ie, Months 24, 36, 48, and 60, as applicable) and at the CSED Visit, fasting blood samples and urine samples will be collected for safety and efficacy assessments. After Month 12, blood samples will also be collected for safety assessment (chemistry panel only) at each intervening in-person visit (eg, Months 16, 20, 28, 32, etc.) throughout the study. Frequency of these additional blood safety measurements may be reduced to once annually after DSMB review of blood safety data. In addition, WOCP will undergo serum pregnancy testing. At the Month 6 visit an on-treatment, non-fasting sample will be collected. Participants will complete a quality of life questionnaire annually, at the first in-person visit after a study endpoint occurs, and at the CSED Visit.

Lipid parameters will be measured in *all participants*, including testing for TG, HDL-C, LDL-C (direct and calculated), very low-density lipoprotein cholesterol (VLDL-C) and non-HDL-C (both calculated), total cholesterol (TC), apolipoprotein B (ApoB), ApoE, directly measured remnant cholesterol, ApoA1, ApoC3, LDL-C by beta-quantification (preparative

ultracentrifugation [PUC]), lipoprotein particles (nuclear magnetic resonance size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured small dense LDL-C (sdLDL-C) and low-density lipoprotein associated triglycerides (LDL-TG). Inflammatory and glycemic parameters will be measured in all participants and include high-sensitivity C-reactive protein (hsCRP), fasting glucose, hemoglobin A1c (HbA1c), and fibroblast growth factor-21 (FGF-21). A subcohort of participants in the United States (US) and Canada will have additional blood testing for ApoA5, ApoB48, angiopoietin-like 3 (ANGPTL3), ANGPTL4, PSCK9 mass, cytokeratin-18 (CK-18), and type IV collagen.

At Screening/Enrollment, Randomization, and Month 4 Visits, a blood sample will be collected for archiving in countries and sites approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Committee (REC) and regulatory authorities, as applicable.

Throughout the course of the study, several steps will be taken to minimize changes in LDL-C lowering therapies including frequent monitoring of ApoB with guided institution of additional lipid lowering therapy for evidence of persistent ApoB elevation when evident.

The CSED Visit will be scheduled within a 60-day window after the study termination is announced, irrespective of the date that the participants were randomized. At the CSED Visit, participants will undergo physical examinations, risk factors will be documented, and study drug compliance will be determined by unused tablet count. Additionally, WOCP will undergo a serum pregnancy test. Finally, fasting blood and urine samples will be collected from all participants for safety and efficacy assessments. A Post Study Safety Call will follow 30 days later to collect post study efficacy events and SAEs.

Participants will be followed for an average period of approximately 4 years after randomization; estimated study duration is 5 years. The study will be completed when the required number of adjudicated and confirmed primary endpoints have accrued. The aim is to collect a complete set of data from all participants from the time of randomization to the end of the study. Participants should be encouraged to continue taking their assigned study medication during the entire treatment period, with as little change of background medication as possible, even if they experience an AE or event which constitutes a study endpoint. Participants who discontinue their medication for any reason and are not able to recommence therapy should still continue to be followed for the collection of data and samples.

PROMINENT will be conducted to fulfill all international standards of Good Clinical Practice (GCP) to ensure that a positive finding will lead to changes in the care of at-risk participants globally and to a labeling indication for CV event reduction for pemafibrate by worldwide regulatory authorities.

Number of Participants (planned):

Approximately 10,000 participants will be randomized in a 1:1 ratio to receive either pemafibrate or matching placebo.

Diagnosis and Inclusion Criteria:

Participants must meet all of the following criteria for enrollment into the study:

1. Fasting TG ≥ 200 mg/dL (2.26 mmol/L) and < 500 mg/dL (5.65 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)

2. HDL-C ≤ 40 mg/dL (1.03 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)

3. Type 2 diabetes of longer than 12 weeks duration documented in medical records, for example: local laboratory evidence through medical record review of elevated HbA1c (≥ 6.5% [48 mmol/mol]), elevated plasma glucose (fasting ≥ 126 mg/dL [7.0 mmol/L], 2-hour ≥ 200 mg/dL [11.1 mmol/L] during oral glucose tolerance testing, or random value ≥ 200 mg/dL with classic symptoms, or currently taking medication for treatment of diabetes; AND either

    a) Age ≥ 50 years if male or ≥ 55 years if female (primary prevention cohort); OR

    b) Age ≥ 18 years and established systemic atherosclerosis (secondary prevention cohort), defined as any 1 of the following:

        i. Prior MI or ischemic (non-hemorrhagic) stroke

        ii. Coronary angiographic lesion of ≥ 60% stenosis in a major epicardial vessel or ≥ 50% left main stenosis

        iii. Asymptomatic carotid disease with ≥ 70% carotid artery stenosis

        iv. Symptomatic carotid disease with ≥ 50% carotid artery stenosis

        v. Symptomatic lower extremity peripheral artery disease (PAD) (ie, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index ≤ 0.9 or other diagnostic testing [eg, toe-brachial index, angiogram, or other imaging study])

        vi. Prior arterial revascularization procedure (including coronary, carotid, or peripheral angioplasty/stenting, bypass, or atherectomy/endarterectomy)

4. In addition, by Visit 1 (Screening/Enrollment Visit), participants must be either:

    a) Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate- to high-intensity statin (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day*, or pitavastatin 4 mg/day); or

    b) Have evidence of LDL-C ≤ 70 mg/dL (1.81 mmol/L) by local laboratory

determination within the previous 12 months[#], or

c) Statin intolerant[+] and have evidence of LDL-C ≤ 100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months.

[*] Participants enrolled on simvastatin > 40 mg/day must have been taking and tolerating that dose for at least 12 months.

[#] If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a PCSK9 inhibitor

[+] Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (e.g., 1-3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.

5. Ability to understand and comply with study procedures and give written informed consent.

Exclusion Criteria:

Presence of exclusionary criteria will be assessed at the Screening/Enrollment Visit (Visit 1), which is then followed by a 21-day Placebo Run-In Period preceding randomization into the study. Participants are excluded from participation if any of the following criteria apply:

1. Current or planned use of fibrates or agents with potent peroxisome proliferator activated receptor (PPAR)-α agonist activity (eg, saroglitazar) within 6 weeks (42 days) of Visit 1 (Screening/Enrollment Visit). Note: PPAR-γ agonists (eg, glizatones such as pioglitazone and rosiglitazone) are allowed

2. Known sensitivity to PPAR-α agonists or tablet excipients

3. Initiation of, or change in, current TG-lowering therapy within 12 weeks of Visit 1 (if applicable). Note: TG-lowering therapy is defined as niacin > 100 mg/day or dietary supplements or prescription omega-3 fatty acids > 1 g/day

4. Type 1 diabetes mellitus

5. Uncontrolled diabetes mellitus as defined by a HbA1c > 9.5% [80 mmol/mol] at Visit 1 (Screening/Enrollment Visit)

6. Untreated or inadequately treated hypothyroidism [thyroid stimulating hormone (TSH) > 2.0 X the upper limit of normal (ULN) or free thyroxine (T4) ≤ ULN] or hyperthyroidism; controlled thyroid disease (permitted) requires normal TSH and

stable therapy for at least 4 weeks

7. Recent CVD event (eg, MI or stroke) within 8 weeks of Visit 2 (Randomization Visit)
8. Recent or planned vascular intervention within 8 weeks of Visit 2 (Randomization Visit)
9. New York Heart Association Class IV heart failure (HF)
10. Known homozygous familial hypercholesterolemia (heterozygous is permitted) or familial hypoalphalipoproteinemia
11. Documented previous occurrence of myositis/myopathy
12. Unexplained creatine kinase (CK) > 5 X ULN
13. Liver disease defined as cirrhosis or Child-Pugh class B and C, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 X ULN
14. Biliary obstruction or hyperbilirubinemia (ie, total bilirubin > 2 X ULN, except with a documented diagnosis of Gilbert's disease)
15. Chronic renal insufficiency, defined by an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or kidney transplant, regardless of renal function
16. Unexplained anemia (hematocrit ≤ 30%)
17. Uncontrolled hypertension (seated systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg) at Visit 2 (Randomization Visit).
18. History of chronic active hepatitis B or hepatitis C, or known infection with human immunodeficiency virus (HIV); participants with documented hepatitis C resolution after treatment are permitted
19. Active malignancy, except non-melanoma skin cancer or carcinoma in situ of the cervix, within the last 2 years.
20. Prior organ transplant or any condition likely to lead to organ transplantation in the next 5 years
21. Current or anticipated chronic use of cyclosporine, rifampicin, or other inhibitors of organic anion transporting polypeptides (OATP)1B1, or OATP1B3
22. History of alcoholism or unwillingness to limit alcohol intake to < 15 alcoholic beverages (or units) per week or < 5 alcoholic beverages (or units) during a single occasion for men and < 8 alcoholic beverages (or units) per week or < 4 alcoholic beverages (or units) during a single occasion for women during the study period. Note:

One alcoholic beverage (unit) is defined as 12 oz. (350 mL) of beer, 5 oz. (150 mL) of wine, or 1.5 oz. (45 mL) of liquor

23. History of hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption

24. Women who are pregnant, lactating, planning to be pregnant or lactating during the study period, or WOCP who are not using an acceptable method of contraception

    WOCP are adult females who are sexually active with a non-sterilized male partner *unless* she meets 1 of the following criteria as documented by the investigator:

    - history of hysterectomy or tubal ligation prior to signing the informed consent form (ICF); or

    - menopause, defined as either a) age > 50 years old and ≥ 1 year since last menstrual period or documented follicle-stimulating hormone (FSH) level in the post-menopausal range or b) for women ≤ 50 years old, ≥ 2 years since her last menstrual period without an alternative medical cause, and documented FSH level in the post-menopausal range

    To be eligible, WOCP must have a negative pregnancy test at Visit 1 (Screening/Enrollment Visit) and agree to use an adequate method of contraception during the study and for 1 additional menstrual cycle following the final study visit. Adequate methods of contraception for WOCP include: oral, implanted or injectable contraceptive hormones; mechanical products (eg, intrauterine device [IUD]); or barrier methods (eg, diaphragm, condoms, cervical cap) with spermicide. Local regulatory authorities or IRB/IEC/REC may impose additional restrictions on acceptable contraceptive methods which must be applied by relevant sites and be documented in the investigator study documents. The participant's understanding of the contraceptive requirements must be documented by the investigator.

25. A medical condition, other than vascular disease, with life expectancy < 3 years, which might prevent the participant from completing the study

26. Any factors likely to limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within the next 2 years, and/or history of noncompliance with medication or scheduled appointments, and

27. Participation in another clinical study at the time of informed consent, or has received an investigational drug within 90 days before signing the informed consent for this study.

Participants with uncontrolled diabetes, uncontrolled hypertension, uncontrolled thyroid disease, recent CVD event or revascularization procedure, or other medical instability due to an intervening medical condition may be re-evaluated for re-screening at the investigator's discretion once remedies have been instituted and the participant is stable for at least 4 weeks (28 days) at the time of the repeat Pre-Screening Visit (Visit 0). Re-screening may occur on a

one-time basis only and should occur after a discussion with the [redacted] Medical Monitor.
Investigational product, dosage and mode of administration: Test Product: K-877 (pemafibrate) 0.2 mg Dose: 1 tablet twice daily Mode of Administration: Oral
Duration of treatment: The total expected treatment duration is up to 5 years, with an expected average follow-up period of approximately 4 years.
Reference product, dosage and mode of administration: Reference Product: Matching placebo tablet (placebo) Dose: 1 tablet twice daily Mode of Administration: Oral
Criteria for evaluation: **Efficacy:** <u>Primary Efficacy Endpoint:</u> The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the clinical composite endpoint of: • Nonfatal MI • Nonfatal ischemic stroke • Hospitalization for unstable angina requiring unplanned coronary revascularization • Cardiovascular death <u>Secondary Clinical Efficacy Endpoints:</u> The group A (clinical) endpoints are time to first occurrence of: 1. Any component of the 3-component composite endpoint of non-fatal MI, non-fatal stroke, or cardiovascular death

2. Any component of the primary endpoint or hospitalization for HF

3. Any component of the primary endpoint or all-cause mortality

4. Any component of the primary endpoint, any coronary revascularization, or hospitalization for HF

5. Any new or worsening PAD, defined as incidence of lower extremity revascularization, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index ≤ 0.9 or other diagnostic testing (eg, toe-brachial index, angiogram, or other imaging study)

The group B (lipid) endpoints are:

- The change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for the following lipid biomarkers: TC, TG, HDL-C, non-HDL-C (calculated), VLDL-C (calculated), ApoA1, ApoC3, and ApoE; and

- The change from Randomization Visit (Visit 2) to Month 6 Visit (Visit 6) for non-fasting remnant cholesterol

  * VLDL-C will be calculated as TC minus HDL-C minus LDL-C, where LDL-C is measured by a direct homogenous method.

Tertiary Efficacy Endpoints:

Tertiary endpoints include microvascular endpoints (ie, diabetic retinopathy and diabetic nephropathy as defined below) as well as exploratory mechanistic studies evaluating differences in average achieved levels and change from baseline between pemafibrate and placebo arms in:

- **Core lipid parameters (total cohort):** TG, HDL-C, calculated and directly measured LDL-C, calculated VLDL-C and non-HDL-C, TC, ApoB, ApoE, and directly measured remnant cholesterol

- **Advanced lipid parameters (total cohort):** ApoA1, ApoC3, LDL-C by beta-quantification (PUC), lipoprotein particles (nuclear magnetic resonance [NMR] size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured sdLDL-C and LDL-TG

- **Inflammatory and glycemic parameters (total cohort):** hsCRP, fasting glucose, HbA1c, and FGF-21

- **Expanded exploratory lipid and non-lipid parameters (US/Canada subcohort):** ApoA5, ApoB48, ANGPTL3, ANGPTL4, PCSK9 mass, CK-18, and type IV collagen

Microvascular endpoints will also be examined. These will include *diabetic retinopathy,*

defined as use of retinal laser treatment, anti-vascular endothelial growth factor therapy, or vitrectomy due to development of and/or deterioration in diabetic retinopathy and blindness; and *diabetic nephropathy*, defined as an increase in microalbumin/creatinine ratio to > 30 mg/g among those without microalbuminuria at baseline, or categorical change from baseline albuminuria (normo-, micro-, or macroalbuminuria), doubling of creatinine from baseline, creatinine level > 6.0 mg/dL, eGFR < 15 mL/min/1.73 m^2, or initiation of renal replacement therapy (dialysis or transplant) among all participants.

Safety:

Safety will be evaluated through a comprehensive assessment of the extent of exposure to study drug, the occurrence of AEs, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs (blood pressure, heart rate, height, body weight, waist circumference, body mass index [BMI]), and physical examinations comprising of a general review of body systems.

Statistical methods:

Sample Size Justification:

Sample size and power have been estimated using an event-driven approach where all participants are followed until a sufficient number of events have accrued. All estimates are based on a 2-sided log-rank test comparing the time to occurrence between the 2 treatment groups at the 0.05 significance level, incorporating interim analyses. These estimates use the approach of Lachin and Foulkes under the assumption of a uniform hazard and allow for a 1% annual attrition rate due to drop-outs.

In order to achieve 90% power to detect the anticipated 18% reduction in the rate of the primary endpoint in the pemafibrate arm compared to placebo, at least 1,092 participants who meet a component of the primary endpoint are required, with a minimum of 200 events accrued in women. Given the study sample size of 10,000 participants, an expected enrollment period of 30 months, and an anticipated annual event rate of 3.5 to 4.5 per 100 person-years in the placebo group, the expected study duration is 5 years (with a 3.75-year average follow-up with approximately uniform enrollment).

Primary Analyses:

The primary analysis of the study will use a likelihood ratio test based on a proportional hazards model stratified sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline (defined as those who are taking no statin at baseline or are statin intolerant compared to all others) to test the null hypothesis of no association between assignment to pemafibrate and the rate of the primary endpoint. The Intent-To-Treat (ITT) population will serve as the primary analysis population and will include all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment. Statistical significance will be based on a 2-sided test with level 0.05. The estimated relative hazard in the pemafibrate group compared to the placebo group with an

accompanying 95% confidence interval (CI) will quantify the treatment effect. If this relative hazard is less than 1, then 100*(1-estimated relative hazard) will be defined as the percent reduction in hazard associated with pemafibrate treatment. Rates of occurrence of the primary endpoint will be defined as the total number of participants who have this event in a treatment group per 100 person-years of follow-up, counting all time from randomization until the event, death, end of trial, or withdrawal of consent, whichever comes first. Estimates of the probability of the primary endpoint by time after randomization within treatment groups will be based on the method of Kaplan and Meier. We will also use the proportional hazards model to control for baseline factors that might influence the rate of the primary endpoint (eg, age, race, sex, baseline comorbidities, and concomitant medications), as control for these variables may yield more efficient estimates of relative treatment effects. If Kaplan-Meier plots of event-free survival by study time, or related plots of log (-log) (survival), indicate violations of the proportional hazards assumption, or a formal test of trend in the scaled Schoenfeld residuals indicates such a violation, then weighted log-rank tests will be used according to strategies described by Pecková and Fleming. However, even in the presence of an apparent violation of the proportional hazards assumption, the primary analysis described above gives a valid (although perhaps not optimal) test of the main study hypothesis and will remain the primary analytic strategy, with these weighted log-rank tests serving as sensitivity analyses.

Secondary Analyses:

Secondary clinical endpoint analyses will follow the same outline as the primary analysis for time to event data. Secondary lipid efficacy endpoints will use analysis of covariance with adjustment for baseline measurements and imputation of missing values.

Safety Analyses:

The safety population includes all participants who received at least 1 dose of study treatment. Participants will be analyzed according to their randomized treatment group, unless a participant inadvertently receives the incorrect drug during the entire study, in which case, the participant will be grouped according to the treatment actually received. Safety analyses will include comparisons of post-randomization laboratory values by treatment group and rates of SAEs and AEs by treatment group, both overall and within system organ class (SOC).

Planned Interim Analyses:

To preserve alpha and to minimize the likelihood of an inflated effect estimate associated with early stopping, preplanned efficacy analyses will occur only upon accrual of approximately 50% and 75% of the planned study primary endpoints. The design of the study, including evaluation of the implications of interim monitoring on study power, considered that stopping boundaries will be based on the Haybittle-Peto method. Inefficacy will be assessed at 30%, 50%, and 75% of endpoints, based upon the Linear 10% Inefficacy Boundary approach described by Freidlin, Korn, and Gray.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANGPTL	Angiopoietin-like
Apo	Apolipoprotein
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BMI	Body Mass Index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBC	Complete blood count
CCS	Canadian Cardiovascular Society
CCVDP	Center for Cardiovascular Disease Prevention
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-18	Cytokeratin-18
C_{max}	Maximum plasma concentration
CrCl	Creatinine clearance
CRO	Contract Research Organization
CSED	Common Study End Date
CSR	Clinical Study Report
CT	Computed tomography

Abbreviation	Explanation
cTn	Cardiac troponin
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Executive Committee
EC_{50}	Effective concentration in 50% of participants
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life–5 Dimensions 5 Level Questionnaire
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FGF-21	Fibroblast growth factor -21
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
HTG	Hypertriglyceridemia
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation	Explanation
IDL	Intermediate-density lipoprotein
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KOL	Key Opinion Leader
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDL-TG	Low-density lipoprotein associated triglycerides
LPL	Lipoprotein lipase
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
NMR	Nuclear magnetic resonance
NTCP	Na+ taurocholate cotransporting polypeptides
OATP	Organic anion transporting polypeptides
OC	Operations Committee
OCT	Organic cation transporter
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Pulmonary embolism
PK	Pharmacokinetic(s)
PP	Per Protocol

Abbreviation	Explanation
PPAR	Peroxisome proliferator activated receptor
PROMINENT	Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes
PUC	Preparative ultracentrifugation
RBC	Red blood cell
REC	Research Ethics Committee
RLP	Remnant lipoprotein
RRR	Relative risk reduction
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SC	Steering Committee
sdLDL-C	Small dense low-density lipoprotein cholesterol
SLC	Several solute carrier
SOC	System organ class
SPPARM-α	Selective peroxisome proliferator activated receptor modulator alpha
TC	Total cholesterol
T2D	Type 2 diabetes
T4	Thyroxine
TG	Triglyceride(s)
TQT	Thorough QT/QTc
TRL	Triglyceride-rich lipoprotein
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
URL	Upper reference limit
US	United States
VLDL-C	Very low-density lipoprotein cholesterol
WHO DD	World Health Organization Drug Dictionary
WOCP	Women of childbearing potential

4. INTRODUCTION

4.1. Evolving Role of Hypertriglyceridemia in Cardiovascular Disease Prevention

Treatment of dyslipidemia for cardiovascular disease (CVD) prevention has traditionally focused on mitigating the atherogenic potential of elevated low-density lipoprotein cholesterol (LDL-C), which today is the chief lipid target in clinical practice. While statins are the mainstay of therapy for lowering LDL-C in the majority of patients, many individuals retain a high CVD risk despite achieving LDL-C goals.[1, 2] Specifically, the 5-year incidence of major vascular events among patients with established coronary disease remains above 20% while on aggressive statin therapy.[3]

In efforts to ameliorate this residual CVD risk, the last decade in lipid research has been dominated by investigations into the potential added vascular benefits of raising high-density lipoprotein cholesterol (HDL-C). However, despite seemingly concordant in vitro and in vivo experimental data, consistent evidentiary support for the pharmacologic strategy of raising plasma HDL-C levels is currently lacking. Indeed, results from several recent interventional trials with a cholesteryl ester transfer protein inhibitor or with nicotinic acid to increase HDL-C levels have failed to show a reduction in cardiovascular (CV) events.[4-7] Yet, importantly, low HDL-C remains a potent *marker* of increased vascular risk after statin therapy[8] and improving HDL functionality may ultimately prove to be a promising therapeutic strategy.

As described below, the recognition that hypertriglyceridemia (HTG) commonly accompanies low HDL-C, a plausible pathobiology, associative prospective epidemiologic data, showing consistent benefits in subgroup analyses of completed triglyceride (TG) reduction trials, and more recent Mendelian randomization and other genetic studies supporting a causal link have all fueled renewed interest in HTG as a secondary lipid target, especially in the context of type 2 diabetes (T2D).[9] Yet, no clinical trial has examined the effect of TG reduction on hard CVD outcomes among patients most likely to benefit, that is, those with established dyslipidemia (elevated TG and low HDL-C). This knowledge gap is especially disconcerting, given that mean TG levels have risen in the United States (US), as elsewhere, along with the growing global pandemic of obesity and T2D.[10-12]

4.2. Triglyceride Elevation, Remnant Cholesterol, and ApoC3 in Atherogenesis: Targets for PPAR-α Modulation

In humans, cholesterol accumulation, *not TG accumulation,* is the classic pathological feature in atherosclerotic lesions. Indeed, TGs per se are not traditionally implicated in the atherogenic process; rather TG-rich lipoprotein (TRL) metabolism and subsequent release of downstream atherogenic mediators is the probable pathogenic link. Two alternative mechanisms have been described to explain why hypertriglyceridemia is pro-atherogenic: the remnant infiltration hypothesis and the lipolytic toxin hypothesis (Figure 1).[13, 14]

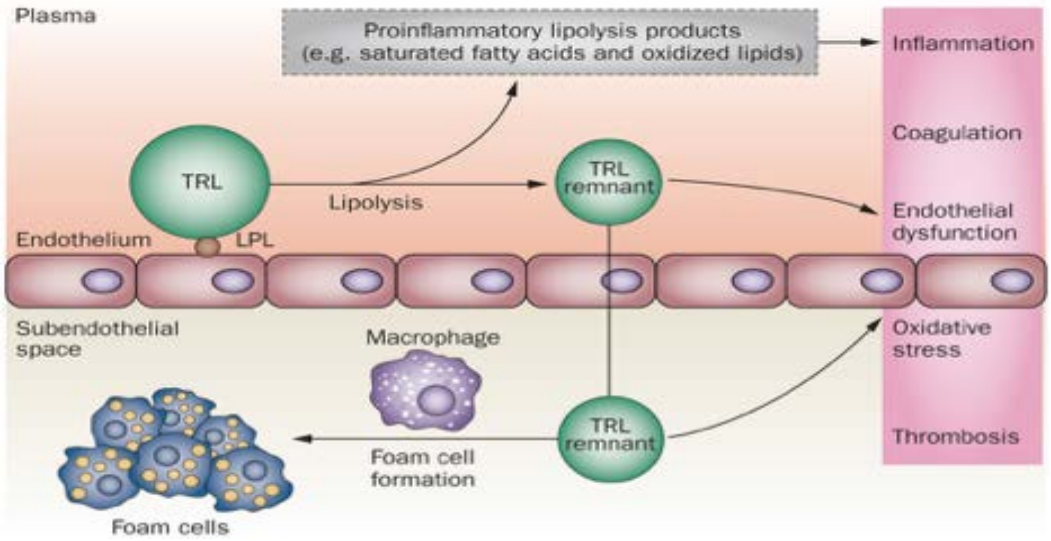
Remnant Infiltration Hypothesis

Triglyceride-rich lipoproteins in plasma consist of chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), and intermediate-density lipoproteins (IDL). Conversion of TRLs to remnant lipoproteins (RLPs) by arterial lipoprotein lipase (LPL) yields TG-depleted but cholesterol-rich particles, which due to their size, contain up to 20 times more cholesterol than LDL-C and can cross the endothelial barrier. Importantly, unlike native LDL, RLPs may undergo direct uptake by resident macrophages in the subendothelial space in an unregulated fashion via scavenger receptors, leading to foam-cell formation and ensuing atherosclerosis.[15] Thus, high plasma concentrations of TG-rich particles result in accelerated lipid deposition in the arterial intima.

Lipolytic Toxin Hypothesis

Perhaps the major toxicity of TRLs is not from intact particles, but from their lipolysis along the arterial wall. Byproducts of TRL lipolysis act at the arterial wall to unfavorably alter endothelial cell biology. Lipolysis of TRLs, especially VLDL, releases oxidized fatty acids, which have a number of adverse effects, including promotion of inflammation, macrophage cytotoxicity, expression of adhesion molecules, and enhanced coagulation.[16-19]

Figure 1: Hypotheses to Explain Why Hypertriglyceridemia is Pro-Atherogenic



Source: Reproduced from Watts GF, et al. *Nature Rev Card*. 2013;10:648-661.

In this framework, it is important to note that hypertriglyceridemia results not only from overproduction of VLDL, but delayed clearance. The key enzyme involved in the VLDL-IDL-LDL delipidation cascade is LPL. Among inhibitors of LPL, apolipoprotein (Apo)C3, a resident surface protein on ApoA- and ApoB-containing lipoproteins, has emerged as a key modulator of lipid metabolism via a number of recently elucidated pathways, which specifically alter plasma TRLs. These include increase in their hepatic production through promotion of VLDL assembly and secretion,[20] impaired intravascular processing by direct noncompetitive inhibition of LPL (and hepatic lipase),[21, 22] and delayed removal by interference with ApoB100[23] or ApoE[24] binding to hepatic receptors.

The great promise of peroxisome proliferator activated receptor (PPAR)-α agonists, particularly in high-risk patients with overt hypertriglyceridemia, lies with the potential of these agents to remedy each of these lipid abnormalities. PPAR-α agonism increases acyl-coenzyme A synthase and fatty acid transporter protein, with the end result being decreased availability of fatty acids for TG synthesis and hepatic VLDL-ApoB secretion.[25] In vitro, these agents can induce the expression of genes encoding LPL,[26] ApoA1,[27] ApoA3,[28] and ABCAI,[29] a transporter that controls ApoA1-mediated cholesterol efflux from macrophages. Reduction in the expression of ApoC3 is perhaps the most consistent effect of PPAR-α agonists,[30] with a 36% reduction in plasma ApoC3 levels observed among patients with metabolic syndrome treated with fenofibrate over a 5-week period.[31]

4.3. Epidemiologic and Mendelian Randomization Data Support a Causal Link

Several meta-analyses, aggregating data from over 29 observational studies conducted through the mid-2000s, showed that elevated TG levels are associated with increased risk of coronary heart disease.[32, 33]

The major difficulty in assessing CV risk attributable to HTG in observational studies has been the association of high TG with other CVD risk factors such as obesity, dysglycemia, and low HDL-C. Thus, residual confounding factors cannot be excluded on the basis of these studies. Mendelian randomization studies utilize a different approach to assess causality. In these studies, the effect of common genetic variants on TG level and CV risk are evaluated. If the effect of a variant on CVD risk is similar in direction and magnitude to that which would be predicted based on the variant's effects on TG concentrations, the Mendelian randomization study supports a causal role for TG in the development of CVD.

With regard to hypertriglyceridemia, several Mendelian randomization studies support a causal role for TG (Table 1). In a case-control study of 20,842 patients with coronary heart disease and 35,206 controls, the -1131T>C (rs662799) variant in *APOA5* was associated with a 16% (95% confidence interval [CI]: 12.9-18.7%) increase in TG, and an increase in the odds ratio (OR) of coronary heart disease (OR 1.18, 95% CI: 1.11-1.26), which was consistent with predicted hazard ratio [HR] of 1.10 (95% CI: 1.08-1.12) predicted based on the change in TG.[34] In another study, investigators identified the -1131T>C variant, as well as 2 other variants in APOA5, that led to an average increase of 68% in non-fasting TG.[35] These variants were then associated with a near doubling in the risk of myocardial infarction (MI) (OR 1.94, 95% CI: 1.40-2.85), which was not statistically different than the expected effect based on the variants' effects on TG concentrations.

Table 1: Mendelian Randomization Studies of Genetic Variants, Associations with TG Elevation, and CVD Events

Publication	Difference in TG	Total Sample (n)	Total Events (n)	Hazard Ratio (95% CI)
Jorgensen, Eur Heart J 2013[35]	2-fold increase	60,113	5705	1.9 (1.4-2.7)

Publication	Difference in TG	Total Sample (n)	Total Events (n)	Hazard Ratio (95% CI)
Thomsen, Clin Chem 2014[36]	1 mmol/L (88.5 mg/dL) increase	10,208	4005	2.0 (1.2-3.3)
TG and HDL WG, NEJM 2014[37]	38.5% increase	110,970	34,002	1.7 (1.3-2.1)
Jorgensen, NEJM 2014[38]	4.0 vs 1.0 mmol/L (350 vs 90 mg/dL)	75,725	7557	2.3 (1.9-2.9)

Variants that lead to reductions in TG may also be causally linked to lower CVD risk, and 2 studies have demonstrated this. These studies assessed the effects of rare variants in ApoC3 on TG concentrations, and found evidence that decreased TG is causally related to CVD risk.[37, 38] In a study of 75,725 Danish men and women, carriers of at least 1 copy of 4 different variants in ApoC3 had TG concentrations that were 44% lower than non-carriers. Carriers of any of the variants were at 41% lower risk of CVD (HR 0.59, 95% CI: 0.41-0.86), which was similar to the predicted risk reduction of 0.77 (0.73-0.81) based on the observed TG reduction.[38] In a sequencing study of more than 18,000 genes in 3734 individuals, investigators identified the same variants in ApoC3 and also found they were associated with a 39% lower TG concentration. Compared to more than 110,000 non-carriers, they found that the 498 carriers of any of the rare ApoC3 mutations were at 40% lower risk for CVD (OR: 0.60, 95% CI: 0.47-0.95).[37]

4.4. Fibrates, Triglyceride Reduction, and Cardiovascular Events: Evidence from Prior Randomized Clinical Studies

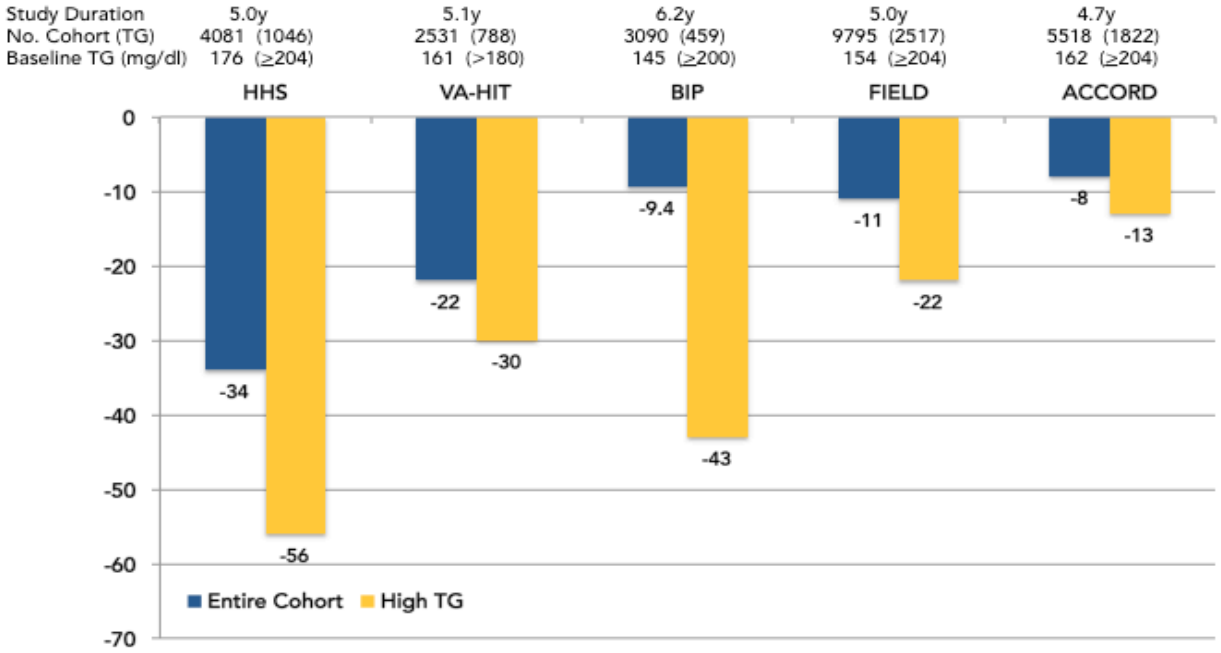
Fibrates, 1 class of compounds with PPAR-α agonist activity, have demonstrated efficacy in lowering TG and raising HDL-C concentrations. In addition to their lipid-modifying properties, PPAR-α agonists exhibit anti-inflammatory activity, may increase plaque stability, and modulate atherothrombosis subsequent to plaque rupture, which may also confer vascular benefit.[39] A 2010 meta-analyses[40] of randomized clinical study data from 18 studies including over 45,000 participants, showed that fibrate therapy produced a modest 10% relative risk reduction (RRR) [RR 0.90; 95% CI: 0.82-1.00; p = 0.048] for major CV events and a 13% RRR (RR 0.87; 95% CI: 0.81-0.93; p < 0.001) for coronary events. However, none of the randomized studies included in the meta-analysis utilized high TGs as an entry criterion. Importantly, the authors note a significant relationship between higher baseline TG level (p = 0.03) and the observed benefit in risk reduction for coronary events, whereas there was no apparent difference in benefit according to baseline HDL-C (p = 0.47).

The efficacy of fibrates in subpopulations marked by hypertriglyceridemia at study entry in the 5 large fibrate trials (HHS, VA-HIT, BIP, FIELD, and ACCORD-Lipid) was formally assessed in 2 subsequent meta-analyses,[41, 42] both yielding similar results. The greatest benefit was seen among patients with elevated TGs relative to the entire cohort in each study (Figure 2). Furthermore, the pooled relative risk reduction associated with fibrate therapy was 25% (95% CI: 14%-45%) for subgroups with elevated TGs compared to 16% (95% CI: 9%-13%) for low HDL-C. When combining lipid parameters, the subpopulation with the greatest benefit was that

marked by both elevated TG and low HDL-C (relative risk reduction [RRR] 29%; 18%-38%). Despite these promising findings, to date, no randomized clinical study has been conducted with enrollment based on hypertriglyceridemia.

A direct test of the TG hypothesis of atherogenesis with pemafibrate in the PROMINENT study is well timed. This newer generation selective PPAR-α modulator (SPPARM-α) has greater potency and PPAR-α selectivity, and hence, greater TG-lowering efficacy and an improved safety and tolerability profile compared to fenofibrate.

Figure 2: Relative Risk Reduction Compared with Placebo



Source: Adapted from Bruckert E, et al. *J Cardiovasc Pharmacol.* 2011;57:267-272.

4.5. Current Guidelines for the Classification and Treatment of Hypertriglyceridemia

Although prospective cohort and case-control studies have identified high plasma TG levels as an independent risk factor for CVD,[32, 33] and post hoc analyses of interventional studies have characterized subgroups most likely to benefit (with most studies using a cut-off point of ~200 mg/dL (2.26 mmol/L), mild-to-moderate hypertriglyceridemia is often viewed as simply a marker of CV risk that does not mandate treatment in most current guidelines. Table 2 summarizes the major international guidelines for classification of hypertriglyceridemia as they have evolved over the past 15 years. In the US, mild-to-moderate hypertriglyceridemia is diagnosed at a level of 200 mg/dL (2.26 mmol/L) whereas current European guidelines use a lower threshold of 175 mg/dL (1.98 mmol/L).

Table 2: Guideline-Specified Categories of Hypertriglyceridemia

International Guideline	Categories	TG Concentration		Fasting Status
		(mg/dL)	(mmol/L)	
2002 NCEP-ATP III[43]	Normal Borderline High Very High	< 150 150-199 200-499 ≥ 500	< 1.7 1.7-2.3 2.3-5.6 ≥ 5.6	Fasting
2011 ESC/EAS[44, 45]	Normal Hypertriglyceridemia Severe	< 150 150-884 ≥ 885	< 1.7 1.7-9.9 ≥ 10	Fasting
2012 Endocrine Society[46]	Normal Mild Moderate Severe Very Severe	< 150 150-199 200-999 1000-1999 ≥ 2000	< 1.7 1.7-2.3 2.3-11.2 11.2-22.4 ≥ 22.4	Fasting
2013 Japanese Expert Guidelines[47-49]	Desirable Elevated Very High Extremely High	< 150 150-400 400-2000 > 2000	< 1.7 1.7-4.5 4.5-22.5 > 22.5	Fasting
2014 EAS Consensus Panel[50]	Normal Mild-Moderate Severe	< 175 175-885 > 885	< 2.0 2.0-10.0 > 10.0	Not Specified

4.6. Prevention of CVD Among Diabetic Patients: Targeting of PPAR-α Agonism in the Right Patient Population

It is well known that T2D is a complex metabolic disorder characterized by elevated blood glucose and a marked increase in CVD risk. Progressive insulin resistance, the core metabolic defect in T2D, is strongly associated with disordered lipid metabolism, which manifests as HTG and low levels of HDL-C. The prevalence of hypertriglyceridemia in this patient population is quite high. A recent analysis[51] conducted in an adult US population (National Health and Examination Surveys 2003-2006; NHANES) estimates that 70.6%, 72.1%, and 74.9% of diabetic patients are at intermediate risk (Framingham CVD Risk Score 10%-20%), high risk (FRS > 20%), or with diagnosed CVD, respectively, fail to achieve optimal TG levels of < 150 mg/dL (1.70 mmol/L).

Contemporary data also demonstrate that despite advances in CV care, diabetes remains associated with a 2-fold increase in CVD risk[52, 53], and this risk increase compared to nondiabetic patients is greatest among diabetic women.[53] Unfortunately, results of large randomized studies evaluating a strategy of intensive glucose control for CVD prevention (ACCORD, ADVANCE, and VADT) have failed to show consistent and substantive reductions in macrovascular events.

Thus, reducing the rate of diabetes-related complications requires more than just adequate glycemic control, and to ameliorate residual macrovascular risk, lipid management may require more than statins alone.

Table 3 summarizes the placebo event rates in major contemporary CVD prevention studies conducted in diabetic populations. None of these studies have shown treatment-related reductions in the prespecified primary CV endpoints, which varied across studies. The placebo rate of major adverse cardiovascular events (MACE) and MACE+ (inclusive of unstable angina requiring unplanned coronary revascularization) with endpoint definitions most closely aligned to those planned for use in the current study are indicated in the table when available from the primary publications. These data demonstrate the high event rates and residual CV risk in this patient population for whom PPAR-α agonism may have the greatest benefit.

Table 3: Placebo Event Rate and Risk Reduction in Major Cardiovascular Disease Prevention Trials in Patients with Diabetes With/Without Baseline CVD and With/Without Baseline Elevated TG

Trial	Year of Publication	Characteristics	CER (%)	Average F/U	Est. Annualized MACE Rate (% per year)	Est. Annualized MACE+ Rate (% per year)	RRR (%)	MACE Definition
PROACTIVE[54] (pioglitazone)	2005	DM with CVD 43% baseline statin	13.6%	2.8 years	4.9% per year	NR	NR	MI, stroke, all cause death
ADVANCE[55] (intensive glycemic control)	2008	DM with CVD/Micro or 1+ RF; 32% prior CVD 28% baseline statin	10.6%	5.0 years	2.1% per year	NR	NR	MI, stroke, CVD death
VADT[56] (intensive glycemic control)	2009	DM; 40% prior CVD % baseline statin NR	29.4%	5.6 years	5.2% per year	NR	NR	MI, stroke, CVD death, CHF, surgical intervention for CVD, inoperable CAD, amputation
SAVOR-TIMI[50, 57] (saxagliptin)	2013	DM with CVD or age +1 RF; 79% prior CVD 78% baseline statin	7.2%	2.1 years	3.4% per year	5.9%*	NR	MI, stroke, CVD death
FIELD[58], DM (All Patients)	2007	DM no baseline statin, 22% prior CVD	13.9%	5.0 years	2.8% per year	already included	10.1 %	MI, stroke, CVD death, coronary/carotid revascularization
DM+TG ≥ 200 mg/dL (2.26 mmol/L)	2005	DM no baseline statin + baseline TG ≥ 200	17.2%	5.0 years	3.4% per year	already included	22.1 %	"

Trial	Year of Publication	Characteristics	CER (%)	Average F/U	Est. Annualized MACE Rate (% per year)	Est. Annualized MACE+ Rate (% per year)	RRR (%)	MACE Definition
DM+CVD	2005	DM no baseline statin + baseline CVD	25.1%	5.0 years	5.0% per year	already included	+1.0 %	"
ACCORD-Lipid[59], DM All Patients	2010	DM + Simva 36.5% prior CVD	11.3%	4.7 years	2.4% per year	5.6%*	6.6%	MI, stroke, CVD death
DM+TG ≥ 200 mg/dL (2.26 mmol/L)	2010	DM + Simva + baseline TG ≥ 200 mg/dL	12.8%	4.7 years	2.7% per year	NR	13.3 %	"
DM+CVD	2010	DM + Simva + baseline CVD	18.1%	4.7 years	3.9% per year	NR	10.5 %	"

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CAD: coronary artery disease; CER: cumulative event rate; Estimated Annualized Event Rate = CER/Average Duration of F/U; CHF: congestive heart failure; CVD: cardiovascular disease; DM: diabetes mellitus; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; F/U: follow-up (mean or median); MACE: major adverse cardiovascular events; MACE+: MACE + unstable angina requiring unplanned coronary revascularization; MI: myocardial infarction; NR: not reported; PROACTIVE: Prospective Pioglitazone Clinic Trial In Macrovascular Events; RRR: relative risk reduction; SAVOR-TIMI 53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; Simva: simvastatin; VADT: Veterans Affairs Diabetes Trial.

* Includes hospitalization for CHF and any coronary revascularization

Note: Fibrate trials are shown below the line.

4.7. Drug Profile from Nonclinical and Clinical Studies

4.7.1. Nonclinical Studies

Pemafibrate, a SPPARM-α, is approximately 2,500 times more potent than fenofibric acid, in terms of the concentration producing 50% effectiveness (ie, effective concentration in 50% of participants [EC_{50}]) of the PPAR-α-activating effect. Pemafibrate is approximately 5,000 times more potent for PPAR-α than PPAR-γ and 11,000 times more potent for PPAR-α than for PPAR-δ. It is also more effective than fenofibrate in decreasing TG, increasing HDL-C, and ameliorating atherosclerosis in disease-model animals.

Pemafibrate is metabolized by oxidation and glucuronidation. Cytochrome P450 (CYP)2C8, CYP2C9, CYP3A4, and CYP3A7 are involved in oxidation, and UGT1A1, UGT1A3, and UGT1A8 are involved in glucuronidation. Pemafibrate is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), as well as for several solute carrier (SLC) transporter proteins (organic cation transporter [OCT] 2, Na+ taurocholate cotransporting polypeptide [NTCP], and organic anion transporting polypeptides [OATP] OATP1A2, OATP1B1, and OATP1B3). Pemafibrate has minimal inhibitory effects on major drug-metabolizing enzymes and transporters.

The liver appears to be the primary target organ of pemafibrate toxicity in nonclinical studies. In 2-year carcinogenicity studies in mice and rats, increased incidences of hepatocellular adenomas/carcinomas, pancreatic acinar cell adenomas/carcinomas, testicular Leydig cell adenomas, and thyroid follicular cell adenomas were observed. Additional data from studies in rats and monkeys to assess the mode of action of these tumors suggests that the carcinogenicity profile of pemafibrate in rodents is consistent with the generally accepted greater sensitivity of rodents to effects elicited by PPAR-α activation, relative to nonhuman primates and, by extension, humans. Pemafibrate was not genotoxic in bacterial reverse mutation, chromosomal aberration, or micronucleus tests.

No teratogenic effects have been observed in rats or rabbits. Decreases in the number of corpora lutea and live embryos were observed at 50 mg/kg/day in a fertility and early embryonic development study in rats, but there were no effects on pre- or post-implantation loss. Deaths and poor nursing occurred in dams, and delayed physical development of subsequent generations was observed at ≥ 3 mg/kg/day in a prenatal and postnatal development study in rats.

4.7.2. Clinical Studies

The clinical pharmacology of pemafibrate has been studied in 18 Phase 1 studies. Doses of 0.05-1.6 mg administered as a single daily dose or divided twice per day, were assessed in multiple-dose studies, for up to 7 days. Increases in maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) were dose-dependent. The oral bioavailability of pemafibrate was approximately 62%. Pemafibrate is extensively metabolized and exists in plasma predominantly as 1 of 2 metabolites (K-23605 and K-23467) or as pemafibrate. Pemafibrate is excreted mostly as metabolites, predominantly through the feces (73% of dosed radioactivity), with some excretion through the urine (15% of dosed radioactivity).

Clinically important drug interactions were observed with cyclosporine and rifampicin. Based on these findings, inhibitors of OATP1B1 or OATP1B3 should not be used with K-877. Other drug interaction studies demonstrated clarithromycin and clopidogrel increased the blood level of pemafibrate by approximately 2-fold and fluconazole increased K-877 levels by approximately 1.7-fold, while no meaningful effect was seen on the pharmacokinetics (PK) of digoxin. Drug interaction studies were also conducted with multiple statins (pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, and fluvastatin) with no interactions observed. Refer to Sections 7.2, 7.3, and 8.2 for information on the use/restrictions of these drugs in this study.

In patients with hepatic dysfunction dosed with pemafibrate, C_{max} and AUC were increased approximately 2- and 4-fold for Child-Pugh A and B cirrhosis patients, respectively. A minor increase of 20% was observed in both C_{max} and AUC among patients with hepatic steatosis.

In patients with renal dysfunction, ranging from mild impairment (creatinine clearance [CrCl]: 50 to < 80 mL/min) to end-stage renal disease (ESRD; treated with hemodialysis), the increases in AUC ranged from approximately 15%-63%, and the increases in C_{max} ranged from approximately 9%-64%. There was no apparent correlation between degree of renal dysfunction and effect on maximum or total exposure, and the largest changes for both AUC and C_{max} were observed in patients with mild renal dysfunction.

A thorough QT/QTc (TQT) study was conducted, which demonstrated that neither clinical (0.4 mg) nor supratherapeutic (1.6 mg) single doses of pemafibrate caused prolongation of the corrected QT (QTc) interval.

The efficacy and safety of pemafibrate was evaluated in 6 clinical studies of up to 12 weeks duration at daily doses ranging from 0.05-0.4 mg taken once daily or divided twice daily in participants with dyslipidemia and: (1) HTG; (2) HTG with low HDL-C; (3) HTG with elevated non-HDL-C. Pemafibrate was used as monotherapy and in combination with statins in both diabetic and non-diabetic participants. Major efficacy and safety findings are summarized below.[60]

Efficacy

Treatment with pemafibrate produced statistically significant and clinically relevant reductions in fasting plasma TGs, and also reduced postprandial HTG. Other effects on lipids and lipoproteins, included reductions in non-HDL-C, total cholesterol (TC), VLDL-C, remnant-like lipoprotein particle cholesterol (RLP-C), ApoB, ApoB48, ApoC2, ApoC3, and increases in ApoA1, ApoA2, and HDL-C were also observed.

Increases in LDL-C were observed in some studies; however, the absence of corresponding increases in ApoB suggests that this change is not associated with an increase in LDL particles.

Safety

The adverse events (AEs) in the pemafibrate group tended to occur at rates similar to those in the placebo or active comparator (fenofibrate at 100 or 200 mg/day) groups. No AE pattern indicative of organ system toxicity or pathophysiology was observed. The occurrence of AEs related to transaminase elevation (eg, liver function test abnormal, alanine aminotransferase

[ALT] increased, or aspartate aminotransferase [AST] increased) in the pemafibrate group occurred at frequencies higher than those in the placebo group, but lower than those in the fenofibrate group. In general, transaminase and γ-glutamyl transpeptidase (GGT) levels decreased from baseline and increases in AST or ALT ≥ 5 × upper limit of normal (ULN) were infrequent. Mean creatinine levels increased with pemafibrate, but at a lower magnitude and incidence than those with fenofibrate; these increases were not clinically significant, and very few AEs were reported. Statistically significant decreases in mean fibrinogen levels were noted in multiple studies; however, these changes did not occur in the setting of AEs, so the clinical relevance of this decrease is unknown.

4.8. Benefit-Risk Assessment

The overall drug profile outlined in Section 4.7 is favorable for human studies at chronic doses up to 0.4 mg/day. The maximum dose administered in a single-dose study was 1.6 mg and the maximum dose for 1-week of treatment was 1.6 mg/day; both regimens were well tolerated. In patients with dyslipidemia, a maximum dose of 0.4 mg/day was well tolerated for up to 52 weeks.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when pemafibrate is administered. Other risks to the patients are the risks inherent to any clinical study with an unapproved drug such as unexpected adverse clinical or laboratory events.

Because of the mechanism of action, 2 important potential risks are identified. Since other fibrates have been shown to increase the risk for cholelithiasis, pemafibrate could also increase the risk of cholelithiasis. Other fibrates have been shown to increase the risk for rhabdomyolysis when co-administered with statins. Rhabdomyolysis has not been reported with the use of pemafibrate, and no difference has been observed in the incidence of musculoskeletal-related AEs between patients with and without co-administered statins. Although rare, the risk of rhabdomyolysis cannot be excluded when pemafibrate is co-administered with statins, especially in patients with severe renal impairment, as there is limited experience to date with the combined use of pemafibrate and statins in such patients. In this study, patients with severe renal impairment will be excluded from participation.

Other potential risks include elevated transaminases (ALT, AST), decreases in red blood cell (RBC) count and hemoglobin, and musculoskeletal and connective tissue disorders (eg, myopathy, myalgia, and increased creatine kinase [CK]).

Because of significant increases in plasma concentrations of pemafibrate in patients with severe hepatic disorders, patients with liver disease will be excluded from the study. Concomitant use of cyclosporine, rifampicin, or other OATP inhibitors will be prohibited in the study (Section 8.2), as co-administration of pemafibrate with cyclosporine and single doses of rifampicin have resulted in increases in pemafibrate exposure due to inhibition of OATP1B1 or OATP1B3 by these drugs.

Although initiation of bile acid sequestrants is discouraged while on study drug, should combined therapy with bile acid sequestrants be deemed necessary, pemafibrate should be taken

2 hours before or 4-6 hours after the intake of bile acid sequestrants (Section 8.2.2), as the absorption of pemafibrate may otherwise be reduced.

All participants in this study will be treated with a statin and/or another LDL-C-lowering drug or will be statin intolerant with LDL-C ≤ 100 mg/dL in accordance with the best standard-of-care and in compliance with local guidelines and recommendations. In addition to standard-of-care treatment, half of the participants in this study may derive a direct benefit from being treated with pemafibrate, which has already demonstrated favorable lipid profile changes at the doses tested, although it has yet to be determined whether this lipid improvement confers clinical benefit (ie, reduction in atherosclerotic CV events). All participants taking part in the study may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by assessing participants for AEs and laboratory test results.

Pemafibrate may be able to address the significant unmet medical need of preventing CV events in high-risk patients with T2D. Given the favorable safety profile, the careful monitoring during the study visits, including phone visits, ongoing safety monitoring by the Sponsor and Data Safety Monitoring Board (DSMB), and the absence of any other agent that has demonstrated a reduction in CV events with TG lowering in the population to be tested, the Sponsor feels the risks to the study participants are minimized and justified, compared with the potential benefits that the successful clinical development of pemafibrate could provide for patients.

5. TRIAL OBJECTIVES AND ENDPOINTS

Abundant laboratory, clinical, and genetic evidence implicates HTG in the development of atherosclerotic vascular disease. Furthermore, epidemiologic and currently available clinical study data demonstrate that among patients with dyslipidemia, *the combination* of elevated TG and low HDL-C identifies individuals at greatest CV risk. These data have generated the hypothesis that reducing TG levels in the appropriate patient population can prevent vascular events. To date, however, no randomized clinical study has directly addressed whether TG reduction can lower vascular event rates in patients with hypertriglyceridemia and low HDL-C.

5.1. Primary Objective

The primary scientific aim of the PROMINENT study is to assess whether treatment with the SPPARM-α, K-877 (pemafibrate), will prevent MI, ischemic stroke, unstable angina requiring unplanned revascularization, and CV death in participants with T2D who have elevated TGs and HDL-C levels and are at high risk for future CV events. Participants will be on moderate- to high-intensity statin therapy (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day) or meet LDL-C criteria (by chart review) within 12 months prior to enrollment.

Specifically, the primary objective of the study is to determine whether pemafibrate administered at a dose of 0.2 mg twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of:

- nonfatal MI
- nonfatal ischemic stroke
- hospitalization for unstable angina requiring unplanned coronary revascularization, or
- CV death

At the time of the Screening/Enrollment Visit (Visit 1), participants must be either:

1. Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate-to high intensity statin (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day[a], or pitavastatin 4 mg/day), or
2. Have evidence of LDL-C ≤ 70 mg/dL (1.81 mmol/L) by local laboratory determination within the previous 12 months[b], or
3. Statin intolerant[c] and have evidence of LDL-C ≤ 100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months.

[a] Participants enrolled on simvastatin > 40 mg/day must have been taking and tolerating that dose for at least 12 months.

[b] If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

[c] Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (e.g., 1-3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.

5.1.1. Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the clinical composite endpoint of:

- Nonfatal MI
- Nonfatal ischemic stroke
- Hospitalization for unstable angina requiring unplanned coronary revascularization
- Cardiovascular death

5.2. Secondary Objective

The secondary scientific aim of this study is to investigate 1) the efficacy (time to first occurrence) of a number of secondary CV and diabetes-related vascular and nonvascular endpoints in the study population, and 2) the efficacy (as measured by the percent change from baseline) for a number of lipid measures.

5.2.1. Group A: Clinical Endpoints

The group A (clinical) endpoints are time to first occurrence of:

1. Any component of the 3-component composite endpoint of non-fatal MI, non-fatal stroke, or cardiovascular death
2. Any component of the primary endpoint or hospitalization for heart failure (HF)
3. Any component of the primary endpoint or all-cause mortality
4. Any component of the primary endpoint, any coronary revascularization, or hospitalization for HF

5. Any new or worsening peripheral artery disease (PAD), defined as incidence of lower extremity revascularization, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index ≤ 0.9 or other diagnostic testing (eg, toe-brachial index, angiogram, or other imaging study)

5.2.2. Group B: Lipid Endpoints

The group B (lipid) endpoints are time to first occurrence of:

- The change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for the following lipid biomarkers: TC, TG, HDL-C, non-HDL-C (calculated), VLDL-C (calculated), ApoA1, ApoC3, and ApoE; and

- The change from Randomization Visit (Visit 2) to Month 6 Visit (Visit 6) for non-fasting remnant cholesterol

* Very low-density lipoprotein cholesterol (VLDL-C) is calculated as TC minus HDL-C minus LDL-C, where LCL-C is measured by a direct homogenous method.

5.3. Tertiary Objective

The tertiary aim of this study is to investigate the effect of pemafibrate on various lipid factors, inflammatory biomarkers, and other circulating biomarkers.

5.3.1. Tertiary Endpoints

Tertiary endpoints include microvascular endpoints (ie, diabetic retinopathy and diabetic nephropathy as defined below) as well as exploratory mechanistic studies evaluating differences in average achieved levels and change from baseline between pemafibrate and placebo arms in:

- **Core lipid parameters (total cohort):** TG, HDL-C, calculated and directly measured LDL-C, calculated VLDL-C and non-HDL-C, TC, ApoB, ApoE, and directly measured remnant cholesterol

- **Advanced lipid parameters (total cohort):** ApoA1, ApoC3, LDL-C by beta-quantification (preparative ultracentrifugation [PUC]), lipoprotein particles (nuclear magnetic resonance [NMR] size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured small dense low-density lipoprotein cholesterol (sdLDL-C) and low-density lipoprotein associated TG (LDL-TG)

- **Inflammatory and glycemic parameters (total cohort):** High-sensitivity C-reactive protein (hsCRP), fasting glucose, hemoglobin A1c (HbA1c), and fibroblast growth factor-21 (FGF-21)

- **Expanded exploratory lipid and non-lipid parameters (US/Canada subcohort):** ApoA5, ApoB48, angiopoietin-like 3 (ANGPTL3), ANGPTL4, PCSK9 mass, cytokeratin-18 (CK-18), and type IV collagen

Microvascular endpoints will also be examined. These will include *diabetic retinopathy,* defined as use of retinal laser treatment, anti-vascular endothelial growth factor therapy, or vitrectomy due to development of and/or deterioration in diabetic retinopathy and blindness; and *diabetic nephropathy*, defined as an increase in microalbumin/creatinine ratio to > 30 mg/g among those without microalbuminuria at baseline, or categorical change from baseline albuminuria (normo-, micro-, or macroalbuminuria), doubling of creatinine from baseline, creatinine level > 6.0 mg/dL, estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2, or initiation of renal replacement therapy (dialysis or transplant) among all participants.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Hypertriglyceridemia is associated with increased CV risk, appears to play a causal role in atherothrombosis, and can be effectively reduced with the novel SPPARM-α pemafibrate. Importantly, more than 70% of high-risk patients with diabetes have TG levels above values considered "optimal" by international prevention guidelines. To date, however, no definitive study data have established that lowering TGs by treatment with any available agent can reduce CV event rates.

The Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes (PROMINENT) study is a randomized, double-blind, placebo-controlled, international study evaluating the ability of pemafibrate to prevent CV events among 10,000 male and female adults with T2D and moderate hypertriglyceridemia with low HDL-C, and on background moderate- to high-intensity statin therapy (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day) unless meeting LDL-C criteria with or without statin intolerance. Fasting TG levels must be ≥ 200 mg/dL (2.26 mmol/L) but < 500 mg/dL (5.65 mmol/L) and HDL-C must be ≤ 40 mg/dL (1.03 mmol/L). Two-thirds of the enrolled study population will have prior evidence of systemic atherosclerosis (secondary prevention cohort) while one-third will not (primary prevention cohort, age ≥ 50 years [male] or ≥ 55 years [female]). PROMINENT will be conducted in 20-25 countries to ensure generalizability and allow for the enrollment and follow-up period to complete in 5 years.

The primary endpoint will be the first occurrence of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or CV death. The study is event-driven such that after 1,092 events have been confirmed, with a minimum of 200 events accrued in women, and assuming a conservative 1% annual loss to follow-up, there will be 90% power to detect clinically meaningful relative reductions in the primary endpoint of at least 18% in the pemafibrate group. In addition to spontaneous adverse event (AE) reporting, systematic surveillance for liver disease and muscle AEs will occur.

This study will include the following: a Pre-Screening Visit (Visit 0), a Screening/Enrollment Visit (Visit 1), a 21-day (maximum 35 day) Placebo Run-In Period, a Randomization Visit (Visit 2), a Treatment Period consisting of approximately 30 visits (post-randomization Visits 3 through 33, as applicable), a Common Study End Date (CSED) Visit, and a Post-Study Safety Call.

During the Pre-Screening Visit (Visit 0; Week -6), participants will provide informed consent to participate in the study and follow-up. After consent, the site will be asked to submit medical records for a qualifying CVD event if applicable and entry criteria including: documentation of diabetes; documentation of statin intolerance, if applicable; and prior TG, HDL-C, and LDL-C levels, if available, within the last 12 months. Screening lab values may be used if prior local laboratory documentation is unavailable. At the Screening/Enrollment Visit (Visit 1; Week -3), participants will be queried regarding their medical histories (including clinical and lifestyle CV risk factors and alcohol use) and concomitant medication use, and will be screened against the inclusion/exclusion criteria. A physical examination comprising a general review of body

systems will be performed. Additionally, fasting blood samples will be collected from all participants for eligibility assessment, including a serum pregnancy test in women of child-bearing potential (WOCP). Where local regulations permit, study participants may be asked to arrive fasting at the Pre-Screening Visit (Visit 0) such that activities of the Screening/Enrollment Visit (Visit 1) can be performed concurrently with the Pre-Screening Visit. For expediency, participants meeting all applicable inclusion and exclusion criteria at the end of the Screening/Enrollment Visit (Visit 1), other than screening TG, HDL-C, and other exclusionary lab testing, can be enrolled into the Placebo Run-In Period while awaiting results of qualifying laboratory testing. Placebo tablets will be dispensed to participants at Visit 1 along with administration instructions for the Placebo Run-In Period, which is designed to select compliant individuals for long-term follow-up and adherence. The placebo dosing card will contain sufficient placebo tablets for a maximum duration of 35 days.

On a one-time basis, at the optional Retesting Visit (Visit 1.1), participants may undergo retesting for borderline lipid values, specifically TG 175-199 mg/dL (1.98-2.25 mmol/L) or 500-650 mg/dL (5.65-7.34 mmol/L) and/or HDL-C 41-45 mg/dL (HDL-C 1.06-1.16 mmol/L).

Rescreening of participants for failure to meet other eligibility criteria (eg, HbA1c > 9.5%, severe hypertension, or medical instability of concurrent clinical condition) may occur once only. Prior to Randomization, serious adverse events (SAEs) and primary endpoints will be recorded and adjudicated, respectively. Thereafter, all AEs and endpoints will be assessed.

Participants who continue to be eligible, are compliant with medication during the Placebo Run-In Period, and have completed submission of relevant medical records will return for the Randomization Visit (Visit 2; Week 0) to be randomly allocated in a 1:1 ratio to receive either pemafibrate at a dose of 0.2 mg twice daily or a matching placebo tablet to be taken twice daily. A non-fasting sample for lipid testing will be collected, and the participant will complete a quality of life questionnaire. Importantly, in addition to other eligibility criteria, randomized participants must have the following:

- Medical record documentation of diabetes longer than 12 weeks duration
- Medical record documentation of a qualifying CV event (if secondary prevention cohort)
- TG levels ≥ 200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.65 mmol/L)
- HDL-C ≤ 40 mg/dL (1.03 mmol/L)
- LDL-C ≤ 70 mg/dL (1.81 mmol/L) if not on qualifying statin regimen or ≤ 100 mg/dL (2.59 mmol/L) if documented statin intolerant

At 2-weeks post randomization (Visit 3), sites will perform a well-being telephone visit to provide general support and to reinforce dosing instructions. Adverse events and endpoints will also be collected. If a participant reports or is reported to have an efficacy endpoint, then additional data about the nature and date of the event, and the treatment and care provided during and after the event will be collected by the investigator.

Throughout the treatment period, beginning with Month 2 (Visit 4), telephone visits will alternate with in-person visits occurring approximately every 2 months after Month 10. During each telephone call and in-person visit, concomitant medication use will be reviewed, and the participant will be queried for AEs and efficacy events. During the in-person visits, in addition, physical examinations will be performed and vital signs will be measured, change in risk factors will be documented, and study drug compliance will be determined by tablet count.

At the Months 4 and 12 visits, at annual visits thereafter (ie, Months 24, 36, 48, and 60, as applicable) and at the CSED Visit, fasting blood samples and urine sample will be collected for safety and efficacy assessments. After Month 12, blood samples will also be collected for safety assessment (chemistry panel only) at each intervening in-person visit (eg, Months 16, 20, 28, 32, etc.) throughout the study. Frequency of these additional blood safety measurements may be reduced to once annually after DSMB review of blood safety data. In addition, WOCP will undergo serum pregnancy testing. At the Month 6 visit an on-treatment, non-fasting sample will be collected. Participants will complete a quality of life questionnaire annually and at the first in-person visit after a study endpoint occurs.

Lipid parameters, as outlined in Section 11.3, will be measured in all participants.

At Screening/Enrollment, Randomization, and Month 4 Visits, a blood sample will be collected for archiving in countries and sites approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Committee (REC) and regulatory authorities, as applicable.

Throughout the course of the study, several steps will be taken to minimize changes in LDL-lowering therapies including frequent monitoring of ApoB with guided institution of additional lipid lowering therapy for evidence of persistent ApoB elevation when evident. Details of managing LDL-lipid lowering therapy during the study are outlined in Section 8.2.2.

The CSED Visit will be scheduled within a 60-day window after the study termination is announced, irrespective of the date that the participants were randomized. At the CSED Visit, participants will undergo physical examinations, risk factors will be documented, and study drug compliance will be determined by unused tablet count. Additionally, WOCP will undergo a serum pregnancy test. Finally, fasting blood and urine samples will be collected from all participants for safety and efficacy assessments (per Appendix A in Section 21.1). A Post Study Safety Call will follow 30 days later to collect any post study efficacy events and SAEs. The end of study is defined as the last in-person visit of the last participant.

Participants will be followed for an average period of approximately 4 years after randomization (estimated study duration: 5 years). The study will be completed when the required number of adjudicated and confirmed primary endpoints have accrued. The aim is to collect a complete set of data from all participants from the time of randomization to the end of the study. Participants should be encouraged to continue taking their assigned study medication during the entire treatment period, with as little change to background medication as possible, even if they experience an adverse event or event which constitutes a study endpoint. Participants who discontinue their medication for any reason and are not able to recommence therapy should still continue to be followed for the collection of data and samples.

PROMINENT will be conducted to fulfill all international standards of Good Clinical Practice (GCP) to ensure that a positive finding will lead to changes in the care of at-risk participants globally and to a labeling indication for CV event reduction for pemafibrate by worldwide regulatory authorities.

A by-visit description of the study procedures is presented in Section 10, and efficacy and safety assessments are described in Section 11 and Section 12, respectively. The study plan is shown in Table 4.

Table 4: Study Design and Schedule of Assessments

		Placebo Run-In Period[a]			Treatment Period										
	Pre-screen	Screening/ Enrollment	Retest	Random-ization											
Visit	**0**	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**V8(M10), V10 (M14), V12 (M18), V14 (M22), V16 (M26), V18 (M30), V20 (M34), V22 (M38), V24 (M42), V26 (M46), V28 (M50), V30 (M54), V32 (M58), V34 (M62)**	**V11 (M16), V13 (M20), V17 (M28), V19 (M32), V23 (M40), V25 (M44), V29 (M52), V31 (M56)**	**V15 (M24), V21 (M36), V27 (M48), V33 (M60)**	**CSED Visit[b]**	**Post-Study Safety Call[c]**
Week (W) or Month (M)	**-6W**	**-3W**		**0**	**2W**	**M2**	**M4**	**M6**	**M8**	**M12**					
Study Visit Window	**Within 6W prior to V2**	**Up to 6W from V0**	**Up to 2W from V1**	**3W to 5W from V1**	**±3D**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**Within 60D[b]**	**Within 30D[c]**
In-Person Visit	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**		**X [c]**	**X [c]**	**X**	
Telephone Visit[d]					**X[e]**	**X**					**X**				**X**
Assessment															
Informed consent	X														
Demographic Data and Medical History[f]	X	X		X											
Medical records submission[h]	X	X		X											
Inclusion/exclusion	X	X	X	X											
Cardiovascular risk factors and alcohol use		X		X			X	X	X	X		X	X	X	
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L Questionnaire[g]				X[g]						X[g]		X[g]	X[g]	X[g]	

		Placebo Run-In Period[a]			Treatment Period										
	Pre-screen	Screening/ Enrollment	Retest	Random-ization											
Visit	**0**	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**V8(M10), V10 (M14), V12 (M18), V14 (M22), V16 (M26), V18 (M30), V20 (M34), V22 (M38), V24 (M42), V26 (M46), V28 (M50), V30 (M54), V32 (M58), V34 (M62)**	**V11 (M16), V13 (M20), V17 (M28), V19 (M32), V23 (M40), V25 (M44), V29 (M52), V31 (M56)**	**V15 (M24), V21 (M36), V27 (M48), V33 (M60)**	**CSED Visit[b]**	**Post-Study Safety Call[c]**
Week (W) or Month (M)	**-6W**	**-3W**		**0**	**2W**	**M2**	**M4**	**M6**	**M8**	**M12**					
Study Visit Window	**Within 6W prior to V2**	**Up to 6W from V0**	**Up to 2W from V1**	**3W to 5W from V1**	**±3D**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**Within 60D[b]**	**Within 30D[c]**
In-Person Visit	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**		**X [c]**	**X [c]**	**X**	
Telephone Visit[d]					**X[e]**	**X**					**X**				**X**
Assessment															
Physical exam/ Vital signs[h]		X		X			X	X	X	X		X	X	X	
Dispense study drug[i]		X[i]		X[i]			X		X	X		X	X		
Compliance check				X			X	X	X	X		X	X	X	
Blood sample for archival[j]		X		X			X								
Non-fasting blood sample[k]				X				X							
Fasting blood sample[k]		X	X				X			X		X[l]	X[l]	X	
Urine sample				X			X			X			X[l]	X	
Pregnancy test in WOCP[m]		X		X			X	X		X			X	X	

		Placebo Run-In Period[a]			Treatment Period										
	Pre-screen	Screening/ Enrollment	Retest	Random-ization											
Visit	**0**	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**V8(M10), V10 (M14), V12 (M18), V14 (M22), V16 (M26), V18 (M30), V20 (M34), V22 (M38), V24 (M42), V26 (M46), V28 (M50), V30 (M54), V32 (M58), V34 (M62)**	**V11 (M16), V13 (M20), V17 (M28), V19 (M32), V23 (M40), V25 (M44), V29 (M52), V31 (M56)**	**V15 (M24), V21 (M36), V27 (M48), V33 (M60)**	**CSED Visit[b]**	**Post-Study Safety Call[c]**
Week (W) or Month (M)	**-6W**	**-3W**		**0**	**2W**	**M2**	**M4**	**M6**	**M8**	**M12**					
Study Visit Window	**Within 6W prior to V2**	**Up to 6W from V0**	**Up to 2W from V1**	**3W to 5W from V1**	**±3D**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**±2W**	**Within 60D[b]**	**Within 30D[c]**
In-Person Visit	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**		**X [c]**	**X [c]**	**X**	
Telephone Visit[d]					**X[e]**	**X**					**X**				**X**
Assessment															
Adverse events[n]		X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy events[o]		X		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: Apo= apolipoprotein; AE= adverse event; ALP= alkaline phosphatase; ALT= alanine aminotransferase; ANGPTL= angiopoietin-like; AST= aspartate aminotransferase; BMI= body mass index; BUN= blood urea nitrogen; CBC= complete blood count; CK= creatine kinase; CK-18= cytokeratin-18; CSED= Common Study End Date; CV= cardiovascular; CVD= cardiovascular disease; D=day; EQ-5D-5L= European Quality of Life–5 Dimensions 5 Level Questionnaire; eGFR= estimated glomerular filtration rate; FGF-21= fibroblast growth factor – 21; GGT= gamma glutamyl transpeptidase; HbA1c= Hemoglobin A1c; HF= heart failure; hsCRP= high-sensitivity C-reactive protein; HCG= human chorionic gonadotropin; HDL-C= high-density lipoprotein cholesterol; IEC= Institutional Ethics Committee; IRB= Institutional Review Board; LDH= lactate dehydrogenase; LDL-C= low-density lipoprotein cholesterol; M=month; NMR= nuclear magnetic resonance; PAD: peripheral artery disease; PUC: preparative ultracentrifugation; REC= Research Ethics Committee; SAE= serious adverse event; sdLDL-C= small dense low-density lipoprotein cholesterol; TG=triglyceride(s); TSH= thyroid stimulating hormone; T4= thyroxine; W=week; WOCP: Women of child-bearing potential

[a] A 21-day Placebo Run-In Period (maximum 35 days) begins at the Screening/Enrollment Visit (Visit 1).

[b] The CSED Visit will be scheduled within a 60-day window after study termination is announced, irrespective of the date that the participants were randomized. Participants will continue study medications through the CSED Visit unless the study is stopped for evidence of increased hazard.

[c] The Post-Study Safety call will occur approximately 30 days after the CSED Visit, during which final AEs and post study efficacy events will be collected.

[d] Telephone visits will alternate with in-person visits occurring approximately every 2 months; after Month 10; the Month 6 visit is an in-person visit for non-fasting blood collection.

[e] Visit 3 will be a well-being telephone call conducted at Week 2 (±3 days) after the Randomization Visit to provide participant support and reinforce dosing. During this telephone call, SAEs and efficacy endpoints (see footnote o) will be recorded.

[f] May occur up to Randomization Visit. Medical history/medical record submission includes: qualifying at least 1 TG level is ≥ 150 mg/dL (1.69 mmol/L), and at least 1 HDL-C level is ≤ 45 mg/dL (1.16 mmol/L); qualifying type 2 diabetes diagnosis; qualifying CVD event; evidence of LDL-C ≤ 100 mg/dL (2.59 mmol/L) within 12 months if documented statin intolerant, or LDL-C ≤ 70 mg/dL (1.81 mmol/L) within 12 months if not on qualifying moderate- to high-intensity statin (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day); and documentation of statin intolerance (if applicable). See Section 10.1 for details on required evidence and acceptable documentation.

[g] Self-administered Quality of Life questionnaire will be completed at the Randomization Visit, annually, at the first in-person visit after a study endpoint occurs, and at the CSED Visit.

[h] The physical examination comprised a brief routine examination of body systems (eg, general appearance, head and neck, chest and lungs, etc.). Vital signs include blood pressure and heart rate, height (Visit 1 and CSED Visit only), body weight, and waist circumference; the BMI will be calculated. Height will only be measured at Visit 1 and the CSED Visit. Vital signs should be collected after the participant has been resting for 5 minutes in a seated position.

[i] At Visit 1 (Screening/Enrollment Visit), only placebo tablets will be dispensed to all enrolled participants for the Placebo Run-In Period (maximum 35 days), along with administration instructions for the Placebo Run-In Period. At the other indicated visits, randomized participants will receive either pemafibrate or placebo according to their treatment assignment.

[j] Fasting (Visit 1 and Visit 5) and non-fasting (Visit 2) blood samples for archival will be collected from consenting participants at sites in countries where allowed by local regulations and where approved by the IRB/IEC/REC and regulatory authorities, as applicable; samples will be stored in a biobank at the Brigham and Women's Hospital for future biomarker studies (all consenting participants) and genetic testing (only participants who consent additionally to genetic testing).

[k] Blood samples will be collected for safety and efficacy assessments (See Appendix A in Section 21.1 for details):

- Safety laboratory tests: biochemistry panel (including electrolytes [K, Na, Cl], AST, ALT, GGT, ALP, total bilirubin, direct bilirubin, CK, total protein, LDH, uric acid, creatinine, calculated eGFR, BUN) and hematology (CBC with differential), TSH, and free T4.
- Core and advanced lipid parameters (total cohort): TG, HDL-C, LDL-C (direct and calculated), calculated VLDL-C and non-HDL-C, TC, ApoB, ApoA1, ApoC3, ApoE, directly measured remnant cholesterol; LDL-C by beta quantification (PUC), lipoprotein particles (NMR size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured sdLDL-C and LDL-TG;
- Inflammatory and glycemic parameters (total cohort): fasting glucose, HbA1c, hsCRP, and FGF-21.
- Expanded exploratory lipid and non-lipid parameters (US/Canada subcohort): ApoA5, ApoB48, ANGPTL3, ANGPTL4, PCSK9 mass, CK-18, and type IV collagen.

[l] After the first year (Month 12), fasting blood and urine samples will be collected for safety laboratory assessment and for lipid profiles and albumin/creatinine assessments at annual in-person visits (ie, Month 24/Visit 15; Month 36/Visit 21; Month 48/Visit 27, and Month 60/V33 as applicable). Fasting or non-fasting blood samples for safety assessment (chemistry panel only) will be collected at each in-person visit after Month 12. Frequency of these additional blood safety measurements may be reduced to once annually after DSMB review of blood safety data. Urine samples need not be fasting but are collected at time points when participants are fasting for other laboratory assessments.

[m] Pregnancy testing will be performed by serum testing (beta-HCG) at all specified time points. Testing need not be fasting but specimens are collected at time points when participants are fasting for other laboratory assessments.

[n] SAEs will be collected up to and including the Randomization Visit, with serious and non-serious AEs collected thereafter.

[o] Primary and secondary efficacy events include: MI, ischemic stroke, coronary revascularization, CV death, total mortality, hospitalization for HF, non-ischemic stroke, diabetic retinopathy, diabetic nephropathy, and PAD (see Section 11.1 and Section 11.2 for definitions of efficacy events).

6.2. Number of Participants

Approximately 10,000 participants will be randomized at approximately 750 investigational centers in 20-25 countries. Approximately 20% of participants will be women.

6.3. Treatment Assignment

All participants who successfully complete the 21-day Placebo Run-In Period with ≥75% adherence to placebo tablets will be eligible for randomization to pemafibrate or placebo at the Randomization Visit (Visit 2). Participants who meet all inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to study drug by the responsible site investigator using an interactive computer system. The randomization process will involve stratification by sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline, defined as those who are taking no statin at baseline or are statin intolerant compared to all others. There will be recruitment caps such that no more than one-third of the study population will consist of participants without prior CVD (primary prevention cohort).

6.4. Study Drug Dose Adjustment Criteria

Not applicable.

6.5. Study Withdrawal

6.5.1. Overall Study Termination

The closeout phase of the study will be initiated when approximately 1,092 adjudicated and confirmed primary endpoints have accrued with a minimum of 200 events in women, or in accordance with DSMB recommendations, should there be evidence of futility or excess harm to participants. In addition, if in the opinion of the Sponsor, the clinical observations in the study suggest it may be unwise to continue, the study may be terminated. In addition, the Sponsor may terminate the study at any time.

6.5.2. Study Termination at Investigational Sites

If it becomes apparent that participant enrollment at a specific investigational site is unsatisfactory with respect to quality or quantity, or data recording is repeatedly inaccurate or incomplete, the Sponsor has the right to terminate the study and remove all study materials from that investigational site. A written statement will be provided to the investigator, the IRB/IEC/REC, 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.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

Study participants will be adult men and women with T2D and who are at high risk (primary prevention cohort; one-third of randomized participants) or very high risk (secondary prevention cohort; two-thirds of randomized participants) of incurring a major CVD event based on study inclusion criteria.

7.1. Participant Inclusion Criteria

Participants must meet all of the following criteria for enrollment into the study:

1. Fasting TG ≥ 200 mg/dL (2.26 mmol/L) and < 500 mg/dL (5.65 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)

2. HDL-C ≤ 40 mg/dL (1.03 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)

3. Type 2 diabetes of longer than 12 weeks duration documented in medical records, for example: local laboratory evidence through medical record review of elevated HbA1c (≥ 6.5% [48 mmol/mol]), elevated plasma glucose (fasting ≥ 126 mg/dL [7.0 mmol/L], 2-hour ≥ 200 mg/dL [11.1 mmol/L] during oral glucose tolerance testing, or random value ≥ 200 mg/dL with classic symptoms, or currently taking medication for treatment of diabetes; AND either

    a) Age ≥ 50 years if male or ≥ 55 years if female (primary prevention cohort), OR

    b) Age ≥ 18 years and established systemic atherosclerosis (secondary prevention cohort), defined as any 1 of the following:

        i. Prior MI or ischemic (non-hemorrhagic) stroke

        ii. Coronary angiographic lesion of ≥ 60% stenosis in a major epicardial vessel or ≥ 50% left main stenosis

        iii. Asymptomatic carotid disease with ≥ 70% carotid artery stenosis

        iv. Symptomatic carotid disease with ≥ 50% carotid artery stenosis

        v. Symptomatic lower extremity PAD (ie, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index ≤ 0.9 or other diagnostic testing [toe-brachial index, angiogram, or other imaging study])

        vi. Prior arterial revascularization procedure (including coronary, carotid, or peripheral angioplasty/stenting, bypass, or atherectomy/endarterectomy)

4. In addition, by Visit 1 (Screening/Enrollment Visit), participants must be either:

a) Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate- to high-intensity statin (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day*, or pitavastatin 4 mg/day); or
b) Have evidence of LDL-C ≤ 70 mg/dL (1.81 mmol/L) by local laboratory determination within the previous 12 months[#], or
c) Statin intolerant[+] and have evidence of LDL-C ≤ 100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months.

[*] Participants enrolled on simvastatin > 40 mg/day must have been taking and tolerating that dose for at least 12 months.

[#] If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a PCSK9 inhibitor.

[+] Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (eg, 1-3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.

5. Ability to understand and comply with study procedures and give written informed consent.

7.2. Participant Exclusion Criteria

Presence of exclusionary criteria will be assessed at the Screening/Enrollment Visit (Visit 1), which is then followed by a 21-day Placebo Run-In Period preceding randomization into the study. Participants are excluded from participation if any of the following criteria apply:

1. Current or planned use of fibrates or agents with PPAR-α agonist activity (eg, saroglitazar) within 6 weeks (42 days) of Visit 1 (Screening/Enrollment Visit). Note: PPAR-γ agonists (eg, glizatones such as pioglitazone and rosiglitazone) are allowed

2. Known sensitivity to PPAR-α agonists or tablet excipients

3. Initiation of, or change in, current TG-lowering therapy within 12 weeks of Visit 1 (if applicable). Note: TG-lowering therapy is defined as niacin > 100 mg/day or dietary supplements or prescription omega-3 fatty acids > 1 g/day

4. Type 1 diabetes mellitus

5. Uncontrolled diabetes mellitus as defined by a HbA1c > 9.5% [80 mmol/mol] at Visit 1 (Screening/Enrollment Visit)

6. Untreated or inadequately treated hypothyroidism [thyroid stimulating hormone (TSH) > 2.0 X the ULN or Free T4 ≤ ULN] or hyperthyroidism; controlled thyroid disease (permitted) requires normal TSH and stable therapy for at least 4 weeks

7. Recent CVD event (eg, MI or stroke) within 8 weeks of Visit 2 (Randomization Visit)

8. Recent or planned vascular intervention within 8 weeks of Visit 2 (Randomization Visit)

9. New York Heart Association Class IV HF

10. Known homozygous familial hypercholesterolemia (heterozygous is permitted) or familial hypoalphalipoproteinemia

11. Documented previous occurrence of myositis/myopathy

12. Unexplained CK > 5 X ULN

13. Liver disease defined as cirrhosis or Child-Pugh class B and C, or ALT or AST > 3 X ULN

14. Biliary obstruction or hyperbilirubinemia (ie, total bilirubin > 2 X ULN, except with a documented diagnosis of Gilbert's disease)

15. Chronic renal insufficiency, defined by an eGFR < 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or kidney transplant, regardless of renal function

16. Unexplained anemia (hematocrit ≤ 30%)

17. Uncontrolled hypertension (seated systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg) at Visit 2 (Randomization Visit)

18. History of chronic active hepatitis B or hepatitis C, or known infection with human immunodeficiency virus (HIV); participants with documented hepatitis C resolution after treatment are permitted

19. Active malignancy, except non-melanoma skin cancer or carcinoma in situ of the cervix, within the last 2 years

20. Prior organ transplant or any condition likely to lead to organ transplantation in the next 5 years

21. Current or anticipated chronic use of cyclosporine, rifampicin, or other inhibitors of organic anion transporting polypeptides (OATP)1B1, or OATP1B3

22. History of alcoholism or unwillingness to limit alcohol intake to < 15 alcoholic beverages (or units) per week or < 5 alcoholic beverages (or units) during a single occasion for men and < 8 alcoholic beverages (or units) per week or < 4 alcoholic beverages (or units) during a single occasion for women during the study period. Note: One alcoholic beverage (unit) is defined as 12 oz. (350 mL) of beer, 5 oz. (150 mL) of wine, or 1.5 oz. (45 mL) of liquor

23. History of hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption

24. Women who are pregnant, lactating, planning to be pregnant or lactating during the study period, or WOCP who are not using an acceptable method of contraception

    WOCP are adult females who are sexually active with a non-sterilized male partner *unless* she meets 1 of the following criteria as documented by the investigator:

    - history of hysterectomy or tubal ligation prior to signing the informed consent form (ICF); or

    - menopause, defined as either a) age > 50 years old and ≥ 1 year since last menstrual period or documented follicle-stimulating hormone (FSH) level in the post-menopausal range or b) for women ≤ 50 years old, ≥ 2 years since her last menstrual period without an alternative medical cause, and documented FSH level in the post-menopausal range

    To be eligible, WOCP must have a negative pregnancy test at Visit 1 (Screening/Enrollment Visit) and agree to use an adequate method of contraception during the study and for 1 additional menstrual cycle following the final study visit. Adequate methods of contraception for WOCP include: oral, implanted or injectable contraceptive hormones; mechanical products (eg, intrauterine device [IUD]); or barrier methods (eg, diaphragm, condoms, cervical cap) with spermicide. Local regulatory authorities or IRB/IEC/REC may impose additional restrictions on acceptable contraceptive methods which must be applied by relevant sites and be documented in the investigator study documents. The participant's understanding of the contraceptive requirements must be documented by the investigator.

25. A medical condition, other than vascular disease, with life expectancy < 3 years, which might prevent the participant from completing the study

26. Any factors likely to limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within the next 2 years, and/or history of noncompliance with medication or scheduled appointments, and

27. Participation in another clinical study at the time of informed consent, or has received an investigational drug within 90 days before signing the informed consent for this study.

Participants with uncontrolled diabetes, uncontrolled hypertension, uncontrolled thyroid disease, recent CVD event or revascularization procedure, or other medical instability due to an intervening medical condition may be re-evaluated for re-screening at the investigator's discretion once remedies have been instituted and the participant is stable for least 4 weeks (28 days) at the time of the repeat Pre-Screening Visit (Visit 0). Re-screening may occur on a one-time basis only and should occur after a discussion with the [redacted] Medical Monitor.

7.3. Study Drug Discontinuation

It will be necessary to make a distinction between participants who prematurely discontinue study drug treatment and those who withdraw from the study. All study drug discontinuations should be considered temporary interruptions because participants are allowed to restart medication at any time if the condition leading to study drug interruption has resolved, eg, a woman who becomes pregnant while in the study can resume study drug when she is no longer pregnant or breastfeeding.

Participants who discontinue study drug are not required to withdraw from the study and should continue all in-person visits and telephone contacts to monitor for AEs and the occurrence of potential endpoint events until the CSED Visit. At a minimum, vital signs should be obtained at in-person visits, but blood draws are at the investigator's discretion until the participant resumes study drug.

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

1. The participant meets any of the criteria specified in Section 7.3.1
2. The participant begins to take any medication(s) that is contraindicated by the protocol
3. The participant develops an AE that, in the opinion of the investigator, would compromise the participant's safety to continue the study drug
4. The participant becomes pregnant
5. The participant withdraws consent
6. The participant requests discontinuation of the study drug for any reason, or
7. In the investigator's judgment, it is in the participant's best interest

Although a participant 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 participant'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.

7.3.1. Study Drug Discontinuation Criteria for Persistent Abnormal Clinical Laboratory Values

If at any time during the study a participant develops elevations in ALT or AST > 3 X ULN, or CK >5 X ULN, the study site will receive an alert from the central laboratory.

Study drug should be discontinued immediately and permanently when any of the following criteria are met:

- ALT or AST > 8 X ULN

- ALT or AST > 3 X ULN with bilirubin > 2 X ULN
- ALT or AST > 3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Rhabdomyolysis regardless of CK value

Study drug should be discontinued temporarily and requires repeating laboratory testing when any of the following criteria are met:

- ALT or AST > 3 X ULN
- CK > 10 X ULN

Participants should undergo repeat laboratory measurements as soon as possible, within 72 hours (unless otherwise specified). Repeat laboratory measurements will include those tests outlined in Section 12.1.2.2.1 and Section 12.1.2.2.2. Local laboratory measurements may be used to facilitate follow-up.

If the repeat ALT or AST is > 3 X ULN with INR > 1.5, study drug should be discontinued permanently. If the INR is <1.5 but the ALT or AST is > 5 X ULN and persists beyond 2 weeks, study drug should be discontinued permanently. If the ALT or AST values recover without meeting the discontinuation criteria, study drug can be resumed at the investigator's discretion.

For CK > 10 X ULN, if the repeat CK elevation remains > 5 X ULN and is not explained by exercise or trauma, study drug should be discontinued permanently. If the CK elevation remains > 5 X ULN and is explained by exercise or trauma, the patient may continue therapy and be followed until they have returned to baseline, or the investigator considers them clinically stable. If exercise- or trauma-related elevation does not resolve, the study drug should be discontinued permanently. If the CK values recover without meeting the discontinuation criteria, study drug can be resumed at the investigator's discretion.

Study drug can be continued, but requires repeating laboratory testing when the following criterion is met:

- CK > 5 X ULN but < 10 X ULN

Participants should undergo repeat laboratory measurements as soon as possible, within 72 hours (unless otherwise specified). Repeat laboratory measurements will include those tests outlined in Section 12.1.2.2.2. Local laboratory measurements may be used to facilitate follow-up.

If the CK elevation remains > 5 X ULN and is not explained by exercise or trauma, study drug should be discontinued permanently. If the CK elevation remains > 5 X ULN and is explained by exercise or trauma, the patient may continue therapy and be followed at least weekly until CK values fall below 5 X ULN, at which time the study drug may be resumed by the investigator. If exercise- or trauma-related elevation does not resolve, the study drug should be discontinued permanently.

7.4. Follow-up after Early Study Drug Discontinuation or Withdrawal

The participant has the right to withdraw from the study at any time. Nevertheless, in this study, investigators will be trained to minimize full withdrawals from study wherever possible. Every attempt will be made to prevent missing data and to obtain complete follow up of all participants at the end of the study. Participants who interrupt or discontinue study drug will be encouraged to remain in the study and asked to conduct the remaining study visits as outlined in the protocol to the end of the study if possible, or at a minimum to maintain contact with the investigator and site to allow for the assessment of the occurrence of primary endpoint events.

Participants who choose to withdraw consent will be asked to document their withdrawal of consent in writing and acknowledge that they have been offered options for limited participation. For participants who withdraw consent, assessment of the participant's health status at the end of the study will be performed in compliance with local privacy laws, regulations, and practices and may include a phone call to the participant or next-of-kin to ascertain vital status and occurrence of primary endpoint events.

Although a participant 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 participant'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.

Withdrawn participants will not be replaced.

7.4.1. Lost-to-Follow-up

As adherence to the protocol, ascertainment of primary study endpoints, vital status, and minimization of participants who are lost-to-follow-up are paramount, participant contact information will be collected centrally as specified in the written informed consent for participation in the study. Text messaging, newsletters, and a web-based study participant portal may be employed for purposes of retention, compliance, and to minimize participants being lost-to-follow-up. Local IRB/IEC/REC regulations will apply.

For participants who are lost-to-follow-up (ie, those participants whose life or death status is unclear because they fail to appear for study visits without stated intention to withdraw or fail to contact the site), the investigator must show due diligence in the steps taken to contact participants. Steps taken may include telephone calls to the participant or next-of-kin, e-mail, or registered letters. For participants who are lost-to-follow-up, the site will be required to complete the Missed Visit eCRF at regularly scheduled study visits and to document, in a separate eCRF designed for this purpose, the attempts made to contact the participant. If contact is reinitiated, it is possible for the participant to return for clinic visits with resumption of study activities based upon their original randomization date.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Study Drug

Pemafibrate 0.2 mg tablets and matching placebo will be provided as investigational medicinal products (Table 5).

Table 5: Investigational Product

Product Name:	Pemafibrate	Placebo
Dosage Form:	Tablet	Tablet
Unit Dose	0.2 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	7.1 mm round, white film-coated tablets	7.1 mm round, white film-coated tablets
Sponsor	Kowa Research Institute	Kowa Research Institute
Packager	Catalent CTS, LLC	Catalent CTS, LLC

8.2. Concomitant Medications

Any medications administered during the study period must be documented in the Concomitant Medication eCRF. Participants may not take part in any other investigational drug study while participating in this study and must not have taken any other investigational drug within 90 days prior to Pre-screening Visit (Visit 0).

Fibrates or agents with PPAR-α agonist activity during the study are contraindicated (see Section 8.2.1).

Initiation of the following non-study medications is strongly discouraged during the study, with the exception of compelling medical need for:

- Niacin (>100 mg/day)
- Dietary supplements or prescription omega-3 fatty acids (>1 g/day)
- Bile acid sequestrants

- Although initiation of bile acid sequestrants is discouraged while on study drug, should combined therapy with bile acid sequestrants be deemed necessary, pemafibrate should be taken 2 hours before or 4-6 hours after the intake of bile acid sequestrants (Section 8.2.2), as the absorption of pemafibrate may otherwise be reduced. For participants entering the study already on sequestrants, this same interval of dose administration with pemafibrate should be initiated.

With the exception of fibrates or other agents with PPAR-α agonist activity (eg, saroglitazar), use of the above-listed medications is permitted during the study if the participant has been receiving these medications at stable dosing for at least 12 weeks prior to Visit 1 (Screening/Enrollment Visit).

Caution is recommended when coadministering medications that are strong CYP3A4 or strong CYP2C8 inhibitors, as there are limited data available. In a Phase 1 study in healthy volunteers, strong CYP3A4 inhibition increased peak and total exposure of K-877 by approximately 2-fold. Coadministration of K-877 with a moderate CYP2C9 and CYP3A4 inhibitor increased peak and total exposure by <2-fold. In a Phase 1 study in healthy volunteers, strong CYP2C8 inhibition increased peak and total exposure of K-877 by approximately 2-fold. In vitro, CYP3A4, CYP2C9, and CYP2C8 contribute similarly to the metabolism of K-877.

Information on supplemental intake of omega-3 fatty acids and niacin will be collected at each visit.

8.2.1. Contraindicated Medications

The following medications are contraindicated in participants taking study medications:

- Fibrates or other agents with PPAR-α agonist activity (eg, saroglitazar)

If the participant is considered to need such treatment then the investigator should discuss this with the Medical Monitor. If the treatment is considered unavoidable, the participant should discontinue study medication before initiating treatment with fibrates or other PPAR-α agonists, but continue to attend follow-up visits.

- Cyclosporine, rifampicin, or other inhibitors of OATP1B1 or OATP1B3

When these medications are used temporarily, the study drugs should be interrupted until the completion of the intercurrent treatment.

8.2.2. Statins and Other LDL-Lowering Therapies

An elevation in LDL-C without increase in number of LDL-C particles has been observed during pemafibrate administration. In Phase 2 studies, this increase in LDL concentration is associated with a favorable shift in LDL particle size distribution: an *increase* in large and medium LDL subclasses, a *decrease* in smaller LDL subclasses, and importantly, with an overall *decrease* in non-HDL-C and *decrease* in Apo B (decreased particle number). Nonetheless, off-protocol LDL-C measurement and changes in statin dosing or addition of other LDL-C lowering therapies may lead to an imbalance in the use of these agents between the 2 treatment arms. Thus, several steps

will be taken to minimize changes in LDL-lowering therapies during the course of the study (Figure 3) and to ensure standardization across clinical sites. These steps will identically be implemented for all study participants, regardless of allocation to active therapy or to placebo.

1. The baseline statin regimen must be 1 of 3 agents at moderate- to high-intensity (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day) dosing **unless** there is local laboratory evidence within the past 12 months of LDL-C ≤ 100 mg/dL (2.59 mmol/L) for participants who are proven statin intolerant or LDL-C ≤ 70 mg/dL (1.81 mmol/L) for participants who are untreated or on another lipid-lowering regimen that may include a maximally tolerated dose of a statin with or without ezetimibe and/or PCSK9 inhibitors.

2. ApoB will be monitored frequently during the first year and annually thereafter.

3. Although investigators will remain blinded to the ApoB value, whenever a value ≥ 90 mg/dL AND either ≥ 20% increase from the prior value or ≥ 40% increase from the baseline value occurs, investigators will be alerted and instructed to confirm study drug or other lipid lowering therapy compliance, retest ApoB at the next in-person visit, and if ApoB elevation is still present institute 1 of 3 possible therapy optimizations in the recommended order listed below:

    a. Add ezetimibe 10 mg/day (if participant is not already receiving)

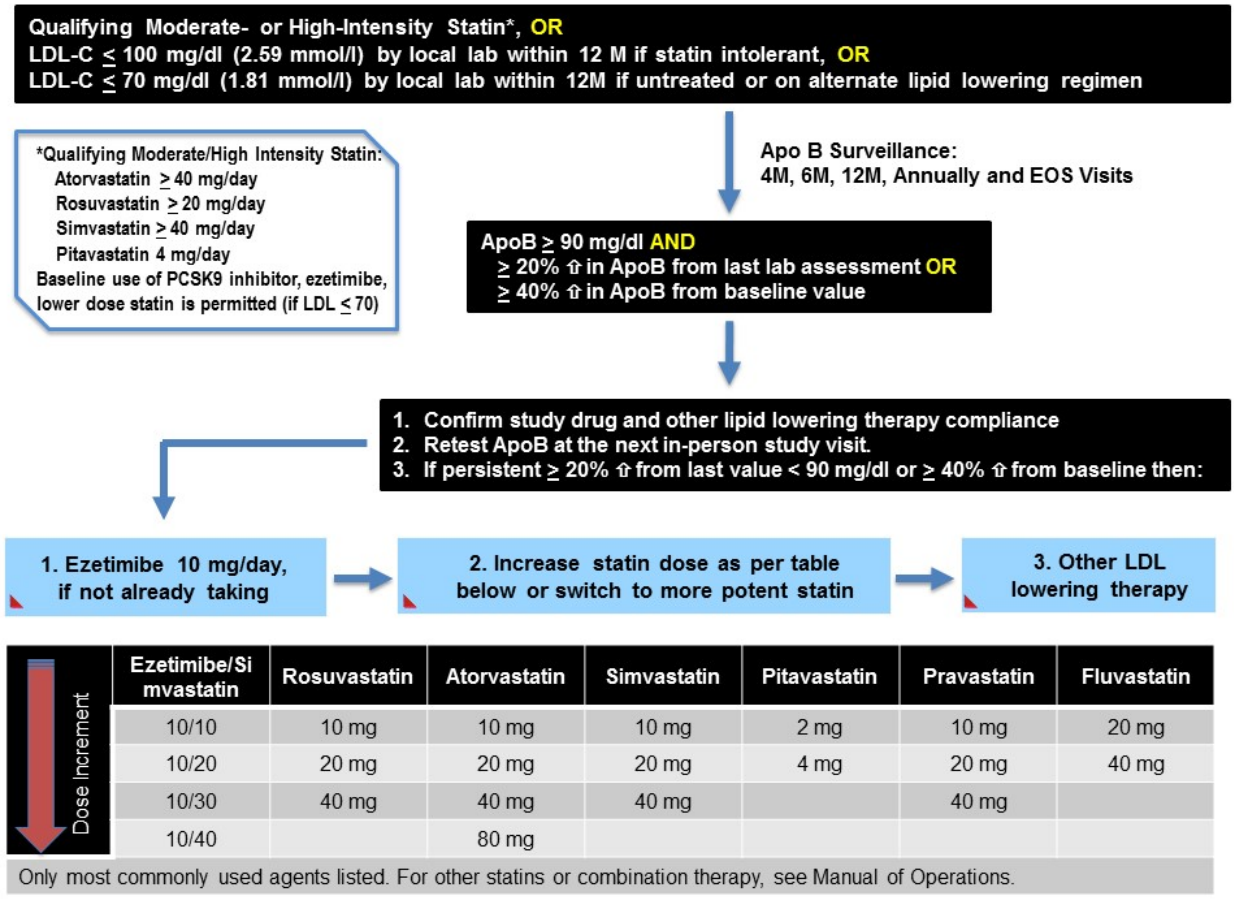
    b. Increase statin dose by increments listed in Figure 3 until the maximum permissible dosing is reached, or switch to a more potent statin

    c. Add other LDL-lowering therapy

4. Change in lipid-lowering therapies that occur without the trigger described in step 3 above will be strongly discouraged.

5. In addition, intensive education on these issues and reinforcement of the protocol will be a core feature of investigator meetings and webinars conducted throughout the study.

Figure 3: Approaches to Minimize Changes in Statins and Other LDL-Lowering Therapies During the Study



Ezetimibe/Simvastatin	Rosuvastatin	Atorvastatin	Simvastatin	Pitavastatin	Pravastatin	Fluvastatin
10/10	10 mg	10 mg	10 mg	2 mg	10 mg	20 mg
10/20	20 mg	20 mg	20 mg	4 mg	20 mg	40 mg
10/30	40 mg	40 mg	40 mg		40 mg	
10/40		80 mg				

Only most commonly used agents listed. For other statins or combination therapy, see Manual of Operations.

Thus, these steps, including requirement for baseline moderate- to high-intensity lipid lowering therapy, implementation of LDL-C entry thresholds for those not on a qualifying moderate- to high-intensity therapy (atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day), central monitoring of Apo B, study-wide standardization of changes to lipid-lowering therapy, and intensive investigator education will be utilized to address potential concerns and minimize changes in lipid therapy that would deviate from the protocol. All changes to lipid-lowering therapies will be documented in the electronic data capture (EDC) system, along with the justification for the change (Section 18.1).

8.2.3. Rescue Therapy for Persistently Elevated TG During the Study

In the event that TG levels rise during follow-up to ≥ 800 mg/dL (9.03 mmol/L), investigators will be alerted. Investigators will ensure compliance with study drug and other prescribed lipid lowering therapy prior to repeat lab testing at the next in-person visit. If TG elevation of ≥ 800 mg/dL (9.03 mmol/L) persists, investigators will be advised to reinforce diet and exercise and consider add on therapy with niacin or prescription omega-3 fatty acids (per local lipid guidelines).

8.2.4. Other Study Restrictions

Dietary Supplements

Participants will be discouraged from initiation of dietary supplements containing niacin or omega-3 fatty acids (eg, flaxseed, fish, krill, or algal oils) during the study. Specifically, initiation of dietary supplements containing more than 1 g/day of omega-3 fatty acids will be prohibited. Dietary supplements must be recorded in the EDC system.

Alcohol Consumption

Beginning at the Screening/Enrollment Visit (Visit 1) and each visit thereafter, all participants will be instructed to refrain from excessive alcohol consumption. Self-reported alcohol consumption will be reviewed throughout the study. Excessive alcohol consumption is defined as:

- For men, an average of ≥ 15 alcoholic beverages (or units) per week or > 5 alcoholic beverages (or units) during a single occasion
- For women, ≥ 8 alcoholic beverages (or units) per week or > 4 alcoholic beverages (or units) during a single occasion.

One alcoholic beverage (unit) is defined as 12 oz. (350 mL) of beer, 5 oz. (150 mL) of wine, or 1.5 oz. (45 mL) of liquor.

8.3. Treatment Compliance

At each in-person visit, participants will be reminded by the sites of the importance of adhering to their treatment regimen for the entire duration of the study. Any interruptions of therapy should be as brief as possible and only for clinically-indicated reasons, such as AEs. Study medication can be re-started at any time in participants willing to resume treatment. Discontinuations will be discouraged and should be based on compelling clinical reasons.

For every participant, an assessment of compliance with study drug must be obtained at each scheduled in-person visit. Compliance is defined as ≥ 75% for the Placebo Run-In Period and ≥ 80% during the treatment period.

Study medication will be dispensed in amounts exceeding the amount required until the next scheduled study visit. Participants will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated by tablet count of unused tablets and will be documented in the eCRF. If compliance falls below 80% during the post-randomization period, the investigator or designee will assess potential factors leading to the lack of compliance and counsel the participant. At the end of the study, the final study drug compliance will be calculated by unused tablet count.

8.4. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. Neither the investigator, site staff, Sponsor, [redacted] Center for

Cardiovascular Disease Prevention (CCVDP), nor the individual participants will be aware of which treatment a given participant receives. The treatment codes will be held by [redacted] and the IVRS/IWRS service provider.

All participants who successfully complete the Placebo Run-In Period with ≥75% compliance will be eligible for randomization to pemafibrate or placebo. The responsible investigator will use an interactive computer system (Interactive Voice Response System [IVRS] or Interactive Web Response System [IWRS]) for randomization. The randomization process will involve stratification by sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline, defined as those who are taking no statin at baseline or are statin intolerant compared to all others at the Screening/Enrollment Visit. One-third of the study population will comprise participants without prior CVD and will constitute the primary prevention cohort.

Blinding of Laboratory Results

All lipid profiles will be blinded (values not provided) to participants, investigators, and other supporting staff at research sites, blinded personnel of the Study Sponsor, and blinded staff at the coordinating center, with the exception of the laboratory personnel and unblinded safety monitoring personnel.

Emergency Unblinding

In an emergency, when knowledge of the participant's treatment assignment is essential for the clinical management and welfare of the participant, the investigator may request the participant's treatment assignment for unblinding. Prior to unblinding, the investigator should assess the relationship of the AE to the administration of the study drug. If the blind is broken for any reason, the investigator must record on the appropriate eCRF the date and reason for breaking the blind. There is no antidote for the investigational drug, so unblinding is not expected to have an impact on the medical evaluation and intervention needed.

The process for breaking the blind will be handled through the IVRS/IWRS. If possible, attempts should be made to discuss with the Medical Monitor prior to unblinding. The blind may be broken only for the participant in question. Any site that breaks the blind under inappropriate circumstances may be asked to discontinue their participation in the study. Study drug must be discontinued but the unblinded participant must be retained in passive follow-up.

Both the Sponsor and [redacted] must be notified immediately if a participant and/or investigator is unblinded during the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Following a 21-day Placebo Run-In Period (maximum 35 days) designed to select compliant individuals for long-term follow-up and adherence, eligible participants will be randomized to receive either pemafibrate 0.2 mg twice daily or an identical matching placebo. The assigned investigational product is to be administered twice daily on an outpatient basis beginning the day after the Randomization visit (Visit 2) until the end of the study.

The Sponsor will supply sufficient pemafibrate 0.2 mg film-coated tablets and matching placebo to allow the participants to complete the study. The lot numbers of the study drug will be recorded in the final CSR.

All pemafibrate and matching placebo tablets are 7.1 mm round, white film-coated tablets. To ensure that study blinding can be maintained, each tablet is indistinguishable by size, markings, and weight. Each pemafibrate tablet contains 0.2 mg of pemafibrate, and each pemafibrate and matching placebo tablet contains the following excipients: lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hypromellose, hydroxypropyl cellulose, triethyl citrate, light anhydrous silicic acid (also known as colloidal anhydrous silica or colloidal silicon dioxide), titanium oxide (also known as titanium dioxide), and carnauba wax.

9.2. Study Drug Packaging and Labeling

Study drug packaging will be completed by an independent clinical packager, Catalent CTS, LLC (Catalent). The packager will be supplied with both the pemafibrate 0.2 mg tablets and the matching placebo tablets for packaging into child-resistant blister packs.

Study drug will be packaged in clear polyvinyl chloride/aluminum foil blister cards and kept inside a cardboard sleeve. Participants will have an approximately 1-month supply of study drug in each blister card, and will receive an adequate supply of study drug at each visit to ensure proper dosing until the next scheduled visit.

Study drug will be labeled to maintain double blind study design during the treatment period according to country-/state-/province-specific requirements for each location, as applicable. For example, the label may include, but not be limited to the following information:

- Name and address of the Sponsor and packager
- Study reference code (eg, protocol number) allowing identification of the investigational site and investigator
- Blank space to write participant’s initials
- Blank space for site/investigator number

- Route of administration, quantity of dosage units, and pharmacological form, as appropriate
- Unique code number that will allow appropriate blinded assignment of the correct clinical trial material kit via the randomization code
- Lot number (as applicable)
- Directions for use
- The statement: "Caution - New Drug - Limited by Federal (US) Law to Investigational Use"
- The statement "Keep out of reach of children"
- Storage conditions
- Expiration date (as applicable)

Study drug labeling and packaging for the Placebo Run-In Period will be identical to the study drug labeling and packaging for the double blind treatment phase.

9.3. Study Drug Storage

At the investigative sites, study drugs must be stored at room temperature, 68°F to 77°F (20°C to 25°C). Temporary excursions between 59°F (15°C) and 86°F (30°C) are permitted. Study drugs must be stored in the original package in a pharmacy or locked in a secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug.

9.4. Study Drug Preparation

Not applicable, as the study drug formulation will be tablets and will be provided to the investigational centers to dispense directly to the participants.

9.5. Study Drug Administration

Participants will self-administer their assigned study drug daily over the course of the study treatment period. Participants will take an oral dose of pemafibrate 0.2 mg or matching placebo tablet twice daily starting the day after completion of Visit 2. Participants may take the study drug in either a fed or fasted state (before or after meals); however, participants should be instructed by the sites to try and remain consistent with the time of dosing for all doses throughout the study. Participants will be instructed by the site to follow dosing instructions on the drug packaging, and to return all remaining unused study drug and packages at the next visit.

Participants 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 (eg, misuse or overdose) as a protocol deviation. For each participant, the number of tablets dispensed, taken, and returned will be recorded on the site's Drug Accountability Log and recorded in the eCRF. Participant compliance will be assessed from information recorded in the eCRF, including study

drug count and the start and end date of therapy. Participants will be considered compliant if they have taken ≥ 75% and ≥ 80% of the intended regimen during Placebo Run-In and Treatment Periods, respectively.

During the active treatment period, if compliance is < 80%, the participant will be counseled by the site on the importance of compliance with the study drug administration.

9.6. Study Drug Accountability

The study drug will be shipped to the study site. The investigator must inventory and acknowledge receipt of all shipments. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. The investigator will agree not to distribute study drug to any participant, except those participants participating in the study.

9.7. Study Drug Handling and Disposal

All study drug supplies will be returned to the shipper or the local depot and processed for destruction by the packager.

10. STUDY PROCEDURES

10.1. Pre-Screening Visit (Visit 0)

At the Pre-Screening Visit (Visit 0), the following procedures will be performed:

- Discuss study details, study procedures, and potential benefits and risks with the participant and thereafter obtain written informed consent
- Record participant demographics and medical history
- Review and submit medical records for the following (see Section 7.1):
    - Qualifying at least 1 TG level is ≥ 150 mg/dL (1.69 mmol/L) within 12 months
    - Qualifying at least 1 HDL-C level is ≤ 45 mg/dL (1.16 mmol/L) within 12 months
    - Qualifying type 2 diabetes by either diagnosis, laboratory parameters, or anti-diabetic medicines
    - Qualifying CVD event (secondary prevention cohort); submitted any time prior to the Randomization Visit (Visit 2)
    - LDL-C ≤ 70 mg/dL (1.81 mmol/L) if not on qualifying moderate- to high-intensity statin [atorvastatin ≥ 40 mg/day, rosuvastatin ≥ 20 mg/day, simvastatin ≥ 40 mg/day, or pitavastatin 4 mg/day] regimen) or ≤ 100 mg/dL (2.59 mmol/L) if documented statin intolerant within 12 months
    - Statin intolerance (if applicable)
- Schedule the Screening/Enrollment Visit (Visit 1) up to 3 weeks from Visit 0 (may be extended up to 6 weeks, if needed) or same day if the participant arrives fasting
- Instruct the participant to fast for ≥ 8 hours immediately prior to the next visit (ie, nothing by mouth, except water and essential medications)

Participants may proceed to the Screening/Enrollment Visit (Visit 1) and enter the Placebo Run-In Period without submission of qualifying events, qualifying lipids, and statin intolerance (when applicable), but **may not be randomized without complete submission of these records**.

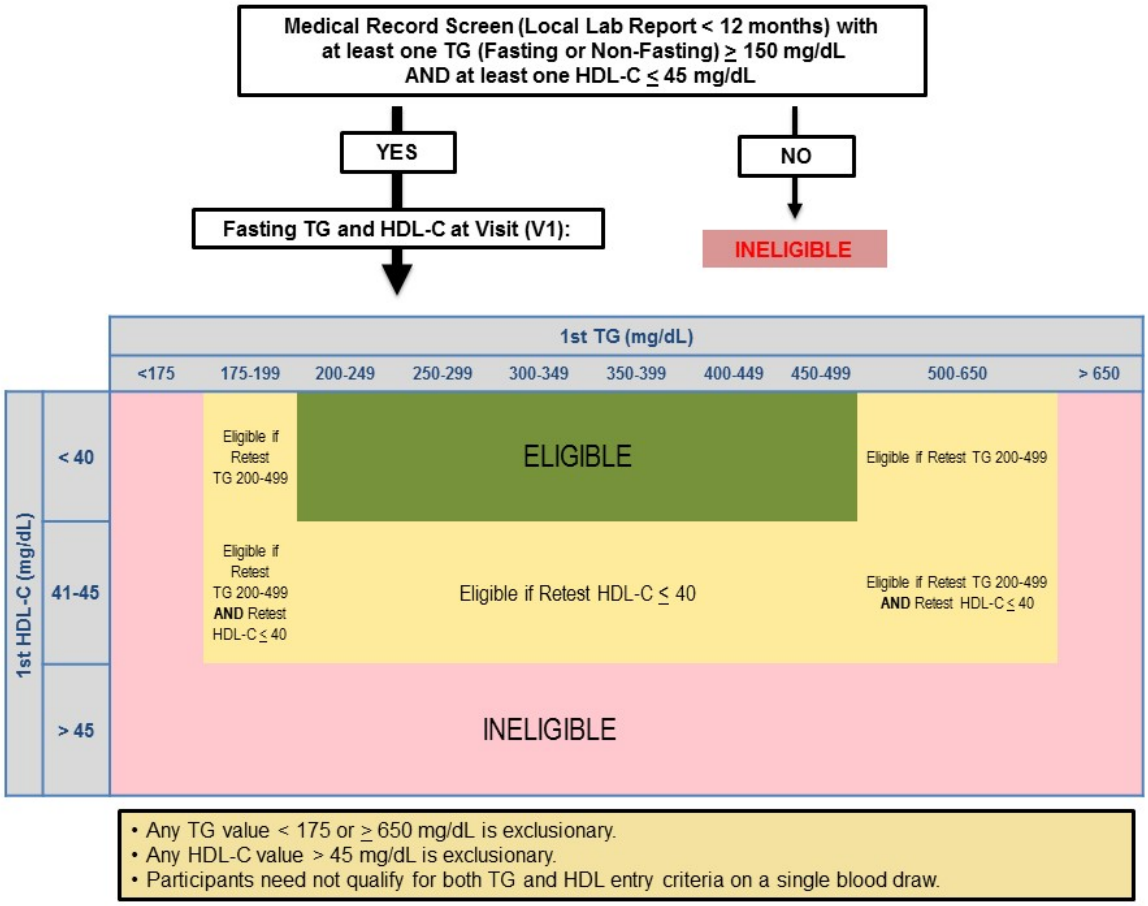
Ascertainment of Qualifying TG and HDL-C

Study sites are encouraged to determine qualifying TG and HDL-C in PROMINENT by obtaining pre-screening evidence of fasting or non-fasting TG and HDL-C that are documented by the investigator through local laboratory values within the previous 12 months (Figure 4). If at least 1 pre-screening TG level is ≥ 150 mg/dL (1.69 mmol/L), and at least 1 pre-screening HDL-C level is ≤ 45 mg/dL (1.16 mmol/L), then the participant may proceed to the

Screening/Enrollment Visit (Visit 1) at which time fasting TG and HDL-C levels and eligibility labs will be obtained and the Placebo Run-In Period will begin.

Thus, the screening approach that will be adopted in PROMINENT (Figure 4) begins with pre-screening evidence of fasting or non-fasting TG levels that are documented by the investigator through local laboratory values within the previous 12 months. If at least 1 pre-screening TG level is ≥ 150 mg/dL (1.69 mmol/L), and at least 1 HDL-C level is ≤ 45 mg/dL (1.16 mmol/L), then fasting levels obtained at the Screening/Enrollment Visit (Visit 1) using standardized methodology (5 minutes in the seated position, < 1 minute tourniquet time) will determine eligibility. For expediency, participants meeting all applicable inclusion and exclusion criteria at the end of the Pre-screening Visit, other than pre-screening (chart documented) TG, HDL-C, and other exclusionary lab testing, may proceed with the Screening/Enrollment Visit (Visit 1) and have qualifying laboratory testing performed at Visit 1 and enroll in the Placebo Run-In Period. If results of qualifying laboratory testing meet all applicable inclusion and exclusion criteria, the participants will proceed with the Randomization Visit (Visit 2) or the Retesting Visit (Visit 1.1), if applicable.

Figure 4: Screening Approach - Ascertainment of Qualifying TG and HDL-C



10.2. Screening/Enrollment Visit (Visit 1)

A 21-day (maximum 35 day) Placebo Run-In Period will begin at Visit 1. The purpose of this Placebo Run-In Period is to ensure that participants are compliant with study medications, and are able to adhere to study procedures.

The Screening/Enrollment Visit (Visit 1) should occur within 3 weeks of the Pre-Screening Visit (Visit 0), but may be extended up to within 6 weeks of Visit 0, if needed. At this visit, clinical eligibility and exclusion criteria will be confirmed, including relevant medical history and concomitant medication use. The following procedures will be performed at the Screening/Enrollment Visit (Visit 1):

- Complete submission of medical records, if not completed at Visit 0
- Review inclusion and exclusion criteria
- Document CV risk factors and alcohol use
- Review concomitant medication use
- Perform a physical examination (eg, general appearance, head and neck, chest and lungs, etc.)
- Collect vital signs (blood pressure, heart rate, height, body weight, waist circumference, and body mass index [BMI] [to be calculated])
- Instruct participants on study drug administration
- Dispense placebo tablets for the Placebo Run-In Period
- Confirm that the participant has fasted per instructions provided during the previous visit
- Collect ***fasting*** blood samples for safety, eligibility, and baseline efficacy assessment (per Appendix A in Section 21.1): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)
- Collect a ***fasting*** blood sample for archiving (in countries and at sites where it is approved by the IRB/IEC/REC) and other regulatory authorities, as applicable
- Collect urine sample (for creatinine and microalbumin)
- Collect serum for pregnancy testing (WOCP only)
- Query participant and record any reported or observed SAEs

- Query participant and record any CV efficacy events (see Section 11.1 and Section 11.2 for definitions of efficacy events)

- The Randomization Visit (Visit 2) should be scheduled for 21 days after the Screening/Enrollment Visit, but may be extended to 35 days if necessary

- Participants should be instructed by the site to be non-fasting for Visit 2 lab tests

Note: All participants leave the Screening/Enrollment Visit with the placebo blister card and will start taking tablets for the Placebo Run-In Period. Results of entry TG level, HDL-C, and all other exclusionary laboratory testing may require up to 4 business days to return. If any eligibility laboratory results return outside the eligibility range (Figure 4), the participant will be notified that they are no longer eligible to participate. Retesting for TG and HDL-C (Section 10.3), if necessary, will also occur during the Placebo Run-In Period.

10.2.1. Re-screening (if applicable)

Participants with uncontrolled diabetes, uncontrolled hypertension, uncontrolled thyroid disease, recent CVD event or revascularization procedure, or other medical instability due to an intervening medical condition prior to randomization, may be re-evaluated for re-screening at the investigator's discretion once remedies have been instituted and the participant is stable for at least 4 weeks (28 days) at the time of the repeat Pre-Screening Visit (Visit 0). Re-screening for medical instability may occur on a one-time basis only and should occur after a discussion with the [redacted] Medical Monitor. Re-screening of participants for non-medical instability issues after 4 weeks may occur on a one-time basis after discussion with the [redacted] Medical Monitor.

10.3. Retesting Visit (Visit 1.1) (if applicable)

Retesting for qualifying TG and HDL-C levels will be permissible per the guidelines described as shown Figure 4.

Retesting in cases of borderline levels of fasting TG will be permissible **on a one-time basis** if the initial value measured at Visit 1 is in the range of 175-199 (1.98-2.25 mmol/L) or 500-650 mg/dL (5.65-7.34 mmol/L). The fasting retest value must be ≥ 200 mg/dL and < 500 mg/dL for the participant to be eligible for participation in the study. Retesting for borderline levels of HDL-C will also be permissible **on a one-time basis** if the initial value measured at Visit 1 is in the range of 41-45 mg/dL (1.06-1.16 mmol/L). The fasting retest value must be ≤ 40 mg/dL.

Participants do not need to qualify for both TG and HDL-C entry criteria on a single blood draw.

This visit will solely include collection of a fasting lipid sample for screening lipid levels (TG and HDL-C).

10.4. Randomization Procedures and the Randomization Visit (Visit 2)

All participants who successfully complete the Placebo Run-In Period with ≥ 75% adherence to placebo tablets will be eligible for randomization to pemafibrate or placebo. The Randomization

Visit (Visit 2) will involve collection of key medical, social, and anthropometric information from the participant, as well as a brief physical examination and collection of blood samples for the non-fasting lipid panel.

The following procedures will be performed at the Randomization Visit (Visit 2):

- Review inclusion and exclusion criteria and confirm eligibility
- Document complete medical history
- Document CV risk factors and alcohol use
- Review concomitant medication use
- Administer the EQ-5D-5L quality of life questionnaire
- Perform a physical examination (eg, general appearance, head and neck, chest and lungs, etc.)
- Collect vital signs (blood pressure, heart rate, body weight, waist circumference, and BMI [to be calculated])
- Perform a compliance check through unused Placebo Run-In tablet count
- Randomize participants and dispense study drug
- Collect a ***non-fasting*** blood sample for safety and efficacy assessments (see Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)
- Collect a ***non-fasting*** blood sample for archiving (in countries and at sites where it is approved by the IRB/IEC/REC) and other regulatory authorities, as applicable
- Collect urine samples (for creatinine and microalbumin)
- Collect blood for serum pregnancy testing (WOCP only)
- Query participant and record any reported or observed SAEs
- Query participant and record any CV efficacy events (see Section 11.1 and Section 11.2 for definitions of efficacy events)

Randomization

The site investigator will use an interactive computer system for randomization. The randomization process will involve stratification by sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline, defined as those who are taking no statin at baseline or are statin intolerant compared to all others at the Screening/Enrollment Visit.

No more than one-third of the study population will comprise participants without prior CVD (primary prevention cohort). The DSMB and Executive Committee (EC) will monitor participant profiles and may increase or restrict enrollment of certain subgroups to control this proportion.

10.5. Treatment Period Telephone Visits: Week 2 and at 4-Month Intervals

In order to improve retention, provide support, and reinforce study medication dosing, a brief telephone call (Visit 3) will be conducted 2 weeks (± 3 days) after the Randomization Visit. Subsequent telephone visits will be conducted at 4-month intervals beginning 1 month after randomization (Month 2) and continuing to the end of the study. Thus, Visits 3, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34 will be conducted by telephone. All telephone visits after Visit 3 will have a 2 week window (ie, ± 2 weeks on either side of the scheduled visit).

During each telephone call, the following information will be gathered:

- Review concomitant medication use
- Query participant and record any reported AEs
- Query participant and record any CV efficacy events (see Section 11.1 and Section 11.2 for definitions of efficacy events)
- Instruct participants to bring all study supplies with them to the next in-person visit
- Instruct participants to fast for ≥ 8 hours immediately prior to the next in-person visit (ie, nothing by mouth, except water and essential medications)

10.6. Treatment Period In-Person Visits: 4-Month Intervals Starting at Month 4

In-person visits will continue to occur every 4 months starting at Month 4 after randomization (with the addition of a Month 6 visit) and will continue until the conclusion of the study. Thus, Visits 5, 6, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 33 will take place in person and will have a 2-week window (ie, can take place ±2 weeks on either side of the scheduled visit). Each in-person visit will involve the following procedures:

- Document CV risk factors and alcohol use
- Review concomitant medications
- Perform a physical examination (eg, general appearance, head and neck, chest and lungs, etc.)
- Collect vital signs (blood pressure, heart rate, body weight, waist circumference, and BMI [to be calculated])
- Collect unused study drug and determine study drug compliance by unused tablet count

- Dispense study drug
- Query participant and record any reported or observed AEs
- Query participant and record any CV efficacy events (see Section 11.1 and Section 11.2 for definitions of efficacy events)
- Instruct participants to bring all study supplies with them to the next in-person visit
- Instruct participants to fast for ≥ 8 hours immediately prior to the next in-person visit (ie, nothing by mouth, except water and essential medications)

At the **Month 4 Visit (Fasting)**, in addition to the in-person visit procedures listed above:

- Confirm that the participant has fasted
- Collect ***fasting*** blood samples for safety and efficacy assessments (see Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)
- Collect a ***fasting*** blood sample for archiving (in countries and at sites where it is approved by the IRB/IEC/REC) and other regulatory authorities, as applicable
- Collect urine samples (for creatinine and microalbumin)
- Perform serum pregnancy testing (WOCP only)

At the **Month 6 Visit (Non-fasting)**, in addition to the in-person visit procedures listed above:

- Collect a ***non-fasting*** blood sample for safety and efficacy assessments (See Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)
- Perform serum pregnancy testing (WOCP only)

At the **Month 12 Visit (Fasting)**, in addition to the in-person visit procedures listed above:

- Administer the EQ-5D-5L quality of life questionnaire
- Collect ***fasting*** blood samples for safety and efficacy assessments (see Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)

At **subsequent Annual Visits (Fasting)**, in addition to the in-person visit procedures listed above:

- Confirm that the participant has fasted

- Collect ***fasting*** blood samples for safety and efficacy assessments (see Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)

- Collect urine samples (for creatinine and microalbumin)

- Perform serum pregnancy testing (WOCP only)

At subsequent in-person visits after Month 12, beginning at Month 16 Visit (Fasting or Non-fasting), in addition to the in-person visit procedures listed above:

- Collect fasting or non-fasting blood samples for safety assessment (chemistry panel only)

10.7. Common Study End Date (CSED) Visit

Study close out will begin after 1,092 adjudicated and confirmed primary endpoint events have accrued, with a minimum of 200 events in women. The estimated total study duration will be approximately 5 years. The CSED Visit will be scheduled within a 60-day window after the study termination is announced, irrespective of the date that the participant was randomized.

The CSED Visit is required for all participants. During scheduling of this visit, participants will be instructed to fast for ≥ 8 hours immediately prior to this visit (ie, nothing by mouth, except water and essential medications).

In the rare case that the CSED Visit cannot occur within the 60-day timeframe following the study termination, attempts to contact the participant must be recorded on a special contact form, until/unless appropriate information is obtained. The following procedures will be performed at the CSED Visit:

- Document CV risk factors and alcohol use

- Review concomitant medication use

- Administer the EQ-5D-5L quality of life questionnaire

- Perform a physical examination (eg, general appearance, head and neck, chest and lungs, etc.)

- Collect vital signs (blood pressure, heart rate, body weight, height, waist circumference, and BMI [to be calculated])

- Collect unused study drug and determine study drug compliance by unused tablet count

- Query participant and record any reported or observed AEs

- Query participant and record any CV efficacy events (see Section 11.1 and Section 11.2 for definitions of efficacy events)

- Collect ***fasting*** blood samples for safety and efficacy assessments (see Appendix A in Section 21.1 for details): chemistry, hematology, thyroid studies, lipids, and other tertiary exploratory parameters (Section 11.3)

- Collect urine samples (for creatinine and microalbumin)

- Collect serum for pregnancy testing (WOCP only)

The CSED Visit will be followed 30 days later by a Post-Study Safety telephone call to collect any final AEs unless the participant had interrupted or discontinued study drug greater than 30 days before the CSED Visit.

11. ASSESSMENT OF EFFICACY

11.1. Monitoring for the Occurrence of Cardiovascular Events

Monitoring for the occurrence of CV events will occur through querying the participant at each study visit. Documentation in the form of medical records will be collected and used in endpoint adjudication. Formal definitions for the individual components of the primary endpoint, all-cause mortality, and hospitalization for HF are provided below:

Endpoint Definitions and Documentation

Clinical endpoints defined as primary or secondary efficacy parameters will be assessed beginning with the day of randomization. Although excluded from the efficacy assessments, clinical endpoint events occurring between the Screening/Enrollment Visit (ie, the time of informed consent) and randomization will also be identified. All potential clinical endpoint events are collected for all randomized participants through study completion/CSED Visit whether or not the participant is currently receiving study drug. A complete description of the endpoints, data to be collected, and methodology for adjudication of both primary and secondary endpoints will be detailed in a Clinical Endpoint Committee (CEC) Charter. Primary endpoint definitions are included below.

It is important to note, that the study medication will not be interrupted for reported or confirmed primary or secondary endpoints.

Definition of Myocardial Infarction

Acute MI: The definition of MI used in PROMINENT is consistent with the Third Universal Definition of MI.[61] The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any 1 of the following meets the diagnosis for MI:

Spontaneous MI: Detection of a rise and/or fall in cardiac biomarker values (preferably cardiac troponin [cTn]), with at least 1 value above the 99th percentile of the upper reference limit (URL) and with at least 1 of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the electrocardiogram (ECG)*
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

*Note: While the Universal Criteria for MI includes criteria for silent MI, for the purposes of this study, reports of silent MI will not be adjudicated as an MI, and will not be included in the study composite primary endpoint.

Cardiac death MI: Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Percutaneous Coronary Intervention (PCI)-related MI is arbitrarily defined by elevation of cTn values (> 5 X 99th percentile URL) in participants with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either: 1) symptoms suggestive of myocardial ischemia; or 2) new ischemic ECG changes; or 3) angiographic findings consistent with a procedural complication; or 4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Stent thrombosis associated with MI, when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL.

Coronary artery bypass grafting (CABG)-related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 X 99th percentile URL) in participants with normal baseline cTn values (≤ 99th percentile URL). In addition, either: 1) new pathological Q waves or new LBBB; or 2) angiographic documented new graft or new native coronary artery occlusion; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Universal Clinical Classification of MI: Each MI identified will be classified into 1 of the following clinical categories:

- Type 1: Spontaneous MI

  Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in 1 or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The participant may have underlying severe coronary artery disease (CAD), but on occasion non-obstructive or no CAD.

- Type 2: MI secondary to an ischemic imbalance

  In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand (eg, coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, or hypertension with or without LVH).

- Type 3: MI resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases, cardiac biomarkers were not collected.

- Type 4a: MI related to percutaneous coronary intervention (PCI)

  Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values > 5 X 99th percentile URL in participants with normal baseline values (< 99th percentile URL) or a rise of cTn values ≥ 20% if the baseline values are elevated and are stable or falling. In addition, either: 1) symptoms suggestive of myocardial ischemia; or 2) new ischemic ECG changes or new LBBB; or 3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization; or 4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

- Type 4b: MI related to stent thrombosis

  Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least 1 value above the 99th percentile URL.

- Type 4c: MI related to stent restenosis

  MI associated with stent restenosis, as detected by coronary angiography or at autopsy, occurring > 48 hours after PCI, without evidence of stent thrombosis, but with symptoms suggestive of myocardial ischemia, and with elevation of cTn values to > 99th percentile of the URL. This classification also requires: 1) Does not meet the criteria for any other classification of MI; 2) presence of a ≥ 50% stenosis at the site of the previous successful stent PCI or a complex lesion and no other significant obstructive CAD of greater severity following (a) initially successful stent deployment or (b) dilation of a coronary artery stenosis with balloon angioplasty to < 50% stenosis.

- Type 5: MI related to CABG.

  Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values > 10 X 99th percentile URL in participants with normal baseline cTn values (< 99th percentile URL). In addition, either: 1) new pathological Q waves or new LBBB, or 2) angiographic documented new graft or new native coronary artery occlusion, or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

ECG Manifestation of Acute Myocardial Ischemia (in the Absence of LVH and LBBB):

- ST Elevation - New ST elevation at the J-point in 2 contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men < 40 years, or ≥ 0.15 mV in women.

- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in 2 contiguous leads; and/or T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R waves or R/S ratio >1.

Criteria for Prior Myocardial Infarction

Any 1 of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior MI

ECG Changes Associated with Prior MI

- Any Q wave in leads V2–V3 ≥ 0.02 sec or QS complex in leads V2 and Vr
- Q wave ≥ 0.03 sec and ≥ 0.1 mV deep or QS complex in Leads 1, II, aVL, aVF or V4–V6 in any 2 leads of a contiguous lead grouping (1, aVL; V1–V6; II, III, aVF)
- R wave ≥ 0.04 sec in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in absence of conduction defect

Definition of Nonfatal Ischemic Stroke

The definition of stroke used here is drawn from the definitions proposed by Hicks et al. and Sacco et al.[62, 63] Stroke is defined as the acute onset of focal neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

A stroke is the acute onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow with no apparent nonvascular cause (eg, tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. To the extent possible, all strokes will be classified as ischemic, hemorrhagic, or unknown. While all types of strokes will be adjudicated by the CEC, only ischemic strokes will be included in the primary endpoint.

For the diagnosis of stroke, the following criteria should be fulfilled:

1. Rapid onset of a focal neurological deficit not related to any other known non-cerebrovascular process with at least 1 of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis

- Numbness or sensory loss affecting 1 side of the body
- Dysphasia/aphasia
- Hemianopia
- Amaurosis fugax
- Other new neurological sign/symptom(s) consistent with stroke
- If the timing of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.

AND

2. Duration of a focal/global neurological deficit that is EITHER:

- ≥ 24 hours,

  OR

- < 24 hours if:
  - Resolution of symptoms is due to least 1 of the following interventions:
    1. Pharmacologic: intravenous or intra-arterial thrombolysis
    2. Non-pharmacologic: (ie, neuro-interventional procedure such as intracranial angioplasty)

       OR

- Available brain imaging clearly documents a new hemorrhage or infarct

  OR

- The neurological deficit results in death

Ideally, at least 1 of the following should be present to confirm the diagnosis of stroke:

1. Neurology or neurosurgery specialist
2. Brain imaging procedure (at least 1 of the following): computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, or cerebral vessel angiography
3. Lumbar puncture (ie, spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must have either:

1. Persisted for more than 1 week; or

2. Persisted for more than 24 hours and were accompanied by an appropriate new MRI or CT scan finding

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Hemorrhage in the brain is documented by neuroimaging or autopsy or lumbar puncture. Note that subdural hematomas are intracranial hemorrhagic events and not strokes.

Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Definition of Hospitalization for Unstable Angina Requiring Unplanned Revascularization

Hospitalization for unstable angina requiring unplanned revascularization is defined as an unscheduled hospitalization for the management of unstable angina, occurring within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in a 24-hour stay (or a change in calendar date if the hospital admission or discharge times are not available). Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity are required.

For the diagnosis of hospitalization for unstable angina requiring unplanned revascularization, the following criteria are required:

- Worsening ischemic discomfort (rest angina, or severe angina (Canadian Cardiovascular Society (CCS) classification severity ≥ Class III) new in onset (<2 months) or increasing angina intensity, duration, and/or frequency, with an increase in severity of at least 1 CCS class to at least CCS III)

- Unscheduled hospitalization

- No elevation in cardiac biomarkers

- An attempt (even if unsuccessful) at percutaneous or surgical coronary revascularization during the index hospitalization, or after a transfer to another institution that then performs those procedures, provided that there is no interceding home discharge

Definitions of Cardiovascular, Non-Cardiovascular, and Undetermined Cases of Death

The classifications for death are drawn from Hicks et al.[62] Death is classified into 1 of 3 categories: CV, non-CV, or undetermined cause of death. The intent is to identify 1 of these categories as the underlying cause of death. The key priority is differentiating between CV and non-CV causes of death. Death attribution can be difficult, particularly for sudden death, even when witnessed. Sudden deaths are usually attributed to sudden cardiac death (CV death) or death due to an undetermined cause. The underlying cause of death (the attributable cause of death) and the most proximate event associated with death may overlap substantially. Generally, the attributable cause of death is preferred.

Cardiovascular death can be due to: acute MI; sudden cardiac death; HF; stroke; a CV procedure; CV hemorrhage; or other CV cause.

Cardiovascular death due to acute MI: Death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, PAD within 30 days after an acute MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable (attributable) mechanisms of CV death during this time period, but for simplicity, if the CV death occurs within 30 days of an acute MI, it will be considered a death due to MI.

Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (PCI or CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (ie, chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered a death due to a CV procedure.

Cardiovascular death due to sudden cardiac death: Death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic recording, witnessed on a monitor, or unwitnessed but found on ICD review)
- Death after unsuccessful resuscitation from cardiac arrest (eg, ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)

- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology

- Unwitnessed death in a participant seen alive and clinically stable ≤ 24 hours before being found dead without any evidence supporting a specific non-CV cause of death (information about the participant's clinical status preceding death should be provided if available)

- Unless additional information suggests an alternate specific cause of death (eg, Death due to Other Cardiovascular Causes), if a participant is seen alive ≤ 24 hours before being found dead, sudden cardiac death should be recorded. For participants who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (eg, a participant found dead in bed, but who had not been seen by family members for > 24 hours)

Cardiovascular death due to HF: Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. Note: Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

Death due to stroke: Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Note: acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Cardiovascular death due to CV procedure: Death caused by the immediate complication(s) of a CV procedure.

Cardiovascular death due to CV hemorrhage: Death related to hemorrhage, such as a non-stroke intracranial hemorrhage (eg, subdural hematoma), non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage resulting in cardiac tamponade.

Cardiovascular death due to other CV causes: Cardiovascular death not included in the above categories with specific, known cause (eg, pulmonary embolism [PE], PAD).

Definition of Non-CV Death: When death is due to a non-CV cause, a CV cause of death is excluded.

- Pulmonary (excludes malignancy)

- Renal

- Gastrointestinal (disease of the esophagus, stomach, or intestines [excludes malignancy])

- Hepatobiliary (disease of the liver, gall bladder, or biliary ducts [excludes malignancy])

- Pancreatic (disease of the pancreas [excludes malignancy])

- Infection (including sepsis)
- Inflammatory/immune (death attributable to an inflammatory or immune-mediated disease or process, including SIRS, immunological, and autoimmune disease and disorders. Includes anaphylaxis from environmental allergies)
- Hemorrhage (bleeding that is not considered CV hemorrhage or stroke
- Non-CV procedure or surgery (death caused by the immediate complications of a non-CV procedure or surgery)
- Trauma (death attributable to trauma, including homicide)
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (includes anaphylaxis)
- Neurological (excludes malignancy, as well as death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke, or CV hemorrhage of central nervous system)
- Malignancy (leukemia, lymphoma, or other malignancy)
- Other (death attributable to a cause other than those listed in this classification; specify organ system)

Undetermined cause of death: Causality may be difficult to determine if information available from the time of death is minimal or non-existent. It may be difficult to determine causality if 2 lethal conditions may contribute to death equally. In this circumstance, 1 condition should be chosen, taking into consideration the population being studied in PROMINENT.

Definition of Hospitalization for HF

Hospitalization for HF is a secondary endpoint of the study and is defined as an event where the participant is admitted to the hospital with a primary diagnosis of HF where the length of stay is at least 24 h (or extends over a calendar date if the hospital admission and discharge times are unavailable), where the participant exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF.

Definition of Peripheral Artery Disease

Peripheral artery disease (lower extremity) is also a secondary endpoint of the study and is defined as the occurrence of lower extremity peripheral vascular intervention or new or worsening PAD defined as the new occurrence of 1) revascularization; 2) intermittent claudication, 3) rest pain, 4) lower extremity ischemic ulceration, or 5) major amputation with

ankle-brachial index ≤ 0.9 or other diagnostic testing (eg, toe-brachial index, angiogram, or other imaging study).

11.2. Monitoring for the Occurrence of Diabetes-Related Events and Parameters

New or progressive diabetic retinopathy is confirmed when medical records document use of retinal laser treatment, antivascular endothelial growth factor therapy, or vitrectomy due to development of and/or deterioration of diabetic retinopathy. Initial reports of diabetic retinopathy will be collected by querying the participant at each study visit.

New and or progressive diabetic nephropathy is confirmed by laboratory evidence of an increase in microalbumin/creatinine ratio to ≥ 30 mg/g among those without microalbuminuria at baseline, and categorical change from baseline albuminuria (normo-, micro-, or macroalbuminuria), doubling of creatinine from baseline, creatinine level > 6.0 mg/dL, eGFR <15 mL/min/1.73 m^2, or initiation of renal replacement therapy (dialysis or transplant), among all participants. Laboratory data obtained during safety laboratory collections will be used for laboratory values and participants will be queried at each study visit for initiation of renal replacement therapy.

11.3. Monitoring of Tertiary Efficacy Endpoints (Biomarkers)

Tertiary exploratory markers include core lipid parameters, advanced lipid parameters, inflammatory and glycemic parameters, and expanded lipid and non-lipid parameters as noted below:

- **Core lipid parameters (total cohort):** TG, HDL-C, calculated and directly measured LDL-C, calculated VLDL-C and non-HDL-C, TC, ApoB, ApoE, and directly measured remnant cholesterol

- **Advanced lipid parameters (total cohort):** ApoA1, ApoC3, LDL-C by beta-quantification (PUC), lipoprotein particles (nuclear magnetic resonance [NMR] size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured sdLDL-C and LDL-TG

- **Inflammatory and glycemic parameters (total cohort):** hsCRP, fasting glucose, HbA1c, and FGF-21

- **Expanded exploratory lipid and non-lipid parameters (US/Canada subcohort):** ApoA5, ApoB48, ANGPTL3, ANGPTL4, PCSK9 mass, CK-18, and type IV collagen

Lipid markers critical to the central hypotheses (including core lipid parameters and advanced lipid parameters) are measured frequently throughout the course of the study and most often measured in the fasting state unless otherwise specified below. Likewise, inflammatory and glycemic exploratory biomarkers are measured frequently throughout the study in the entire study population.

Expanded tertiary exploratory biomarkers (listed above) will be measured in a subcohort of participants (all randomized participants in the US and Canada) at the Screening/Enrollment Visit (for randomized participants only) at Month 4 and Month 12.

Appendix A (Section 21.1) provides a schedule of biomarker testing in the study.

Fasting Lipid Profile

A **fasting** lipid profile is obtained at the Screening/Enrollment Visit (Visit 1), Month 4 (Visit 5), Month 12 (Visit 9), annually thereafter and at the CSED Visit.

Non-Fasting Lipid Profile

A **non-fasting** lipid profile will be measured at the Randomization and Month 6 Visits.

11.4. Future Genetic Testing

Genetic material (buffy coat or extracted DNA) will be stored for future genetic testing from consenting participants. This sample is further contingent upon local regulations, which may prohibit genetic samples from being collected or shipped outside the country.

Results of genetic testing will not be reported to the participant, relatives, or attending physician and will not be recorded in the participant's medical records. The participant may withdraw consent for genetic testing at any time up to analysis, even after the sample has been obtained. In the event of withdrawal of consent, the biorepository will be notified to pull and destroy the sample.

For all samples collected for genetic testing, precautions are to be taken to maintain confidentiality by de-identifying the sample with the participant and preventing the genetic data from being linked to the identity of the participant.

11.5. Archival of Blood Samples

A **fasting** blood sample will be obtained for archiving at Visit 1 (Screening/Enrollment Visit), a **non-fasting** sample at Visit 2 (Randomization), and a **fasting** sample at Visit 5 (4 months). Total blood draw volumes for these archived specimens will be 22 mL at Visit 1, and 16 mL at each of Visit 2 and Visit 5 visits. The blood samples will be collected only at sites in countries where allowed by local regulations and where approved by the IRB/IEC/REC and relevant regulatory authorities. These blood samples may be used for exploratory purposes.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Vital Signs and Physical Examination

Vital signs will be measured and physical examinations performed at the Screening/Enrollment and Randomization Visits, at all in-person visits conducted during the treatment period, and at the CSED Visit as indicated in the schedule of assessments (Table 4). Vital signs measurements will consist of the following: blood pressure, heart rate, height (Visit 1 and CSED Visit), body weight, and waist circumference; the BMI will be calculated based on baseline height and the most recent recorded weight. Vital signs should be collected after the participant has been resting for 5 minutes in a seated position. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. Physical examinations will be comprised of a general review of body systems.

12.1.2. Laboratory Assessments

The central laboratory will provide all collection materials and instruction for sample collection, packaging, and shipment.

Where indicated in the schedule of assessments (Table 4) and the Appendix, samples for clinical laboratory procedures will be obtained after fasting for at least 8 hours, when possible and appropriate. For purposes of this study, fasting is defined as nothing to take in by mouth except water and any essential medications (ie, prescribed concomitant medications that may be taken with water only). Prescribed concomitant medications that must be taken with food or after meals should not be taken until after blood sampling.

At Randomization Visit (Visit 2), any participants that have lipid laboratory values outside the exclusionary limits (following retesting) specified in the protocol exclusion criteria (Section 7.2) may not participate further in the study. After randomization, the investigator will be blinded to lipid laboratory test values and only notified if the values exceed clinical alert levels. In this case, clinically appropriate follow-up procedures will occur at the discretion of the investigator.

A detailed summary of laboratory testing is provided in the Appendix.

12.1.2.1. Safety Laboratory Tests

The safety laboratory tests include:

1. Chemistry panel including electrolytes (K, Na, Cl), AST, ALT, GGT, ALP, total bilirubin, direct bilirubin, calculated eGFR, BUN, CK, total protein, LDH, uric acid, and creatinine

2. Hematology with complete blood count (CBC), including RBC count, hemoglobin, hematocrit, white blood cell count, white cell differential, and platelet count

3. Thyroid studies, including TSH and free T4

4. Urinalysis, including creatinine, albumin, and chemistry panel

Safety laboratory testing with the exception of urinalysis will occur at the Screening/Enrollment Visit, Randomization Visit, Months 4, 6 and 12 Visits, at annual visits thereafter, and at the CSED Visit. Additionally, at each 4-month interval (during in-person visits) after year 1, a chemistry panel will be collected for safety testing. A urinalysis will performed at the Randomization Visit, Months 4, and annually thereafter.

Summary statistics of safety laboratory testing will be reviewed by the DSMB in important subgroups such as participants requiring CYP3A and CYP2C8 inhibitors. Should these data demonstrate no adverse safety signal, the frequency of safety blood laboratory testing after year 1 will be reduced to once annually, ie, the chemistry panel testing at intervening in-person visits will be discontinued.

12.1.2.2. Reporting of Critical Laboratory Values

Critical laboratory values are values that may warrant medical intervention to avoid possible harm to the participants. Critical laboratory values for the study are defined in the below subsections. The research site will be notified expeditiously (eg, fax, phone, etc.) by the central laboratory in the event of a critical laboratory value (high or low).

12.1.2.2.1. Liver Function Test Elevations

Refer to Section 7.3.1 for details on study drug discontinuation procedures related to elevated liver function results.

Repeat evaluation should include AST, ALT, prothrombin time/INR, total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, creatinine, CK, and complete viral hepatitis screen. The participant 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.

12.1.2.2.2. Creatine Kinase Elevations

Refer to Section 7.3.1 for details on study drug discontinuation procedures related to elevated CK results.

The participant should be questioned about symptoms (eg, muscle or tendinous pain, cramping, or weakness) and potential causes for the CK elevation (eg, 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.

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

12.1.3. Pregnancy Screen

Serum pregnancy testing will occur at the Screening/Enrollment Visit (Visit 1), Randomization (Visit 2), Month 4 (Visit 5), Month 6 (Visit 6), Month 12 (Visit 9), and at subsequent in-person visits including the CSED for all WOCP.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Events

An AE is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

Any medical condition that is present at the time the participant is consented but does not deteriorate should not be reported as an AE. However, if it deteriorates or worsens significantly at any time during the study, it should be recorded as an AE.

12.2.1.2. Serious Adverse Events

An adverse event is categorized as serious if it:

- results in death
- is life-threatening
- requires inpatient hospitalization OR prolongs an existing hospitalization
- is associated with a persistent or significant disability or incapacity or with a congenital anomaly or birth defect, or
- is a medically significant event, as determined by the Principal Investigator, even if it does not meet any of the other criteria for seriousness

Death is considered an outcome of an adverse event, and as such, the cause of death should be recorded as the adverse event. 'Death' should not be reported as an event term unless the cause of death is unknown at the time of reporting. If 'death' is reported as an event, the investigator should update the event term to the cause of death when this information becomes available.

Life threatening: An adverse event is considered 'life-threatening' if, in the view of either the investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Hospitalization or prolongation of hospitalization: Kowa considers 'hospitalization' as admission to a hospital for any inpatient care, or an emergency room stay with a duration of 24 hours or longer. The definition of hospitalization does not include:

- an emergency room visit for less than 24 hours or admission to an outpatient facility
- a hospitalization that was elective or pre-planned for a pre-existing condition and not related to worsening of an underlying condition
- a hospitalization for social reasons and not related to a change in the participant's general condition

Medically significant/important medical event: An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above (ie, death, life-threatening, hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity or congenital anomaly).

12.2.2. Adverse Event Severity

The intensity of the AE will be rated by the investigator as mild, moderate, or severe using the following criteria:

Mild: an event that is transient and easily tolerated by the participant, requires minimal or no treatment, and does not interfere with the participant's daily activities.

Moderate: an event that causes the participant discomfort and may cause some interference in the participant's usual activities.

Severe: an event that causes considerable interference with the participant's usual activities, may require drug therapy or other treatment.

12.2.3. Relationship to Study Drug

An investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

The following guidance should be used by investigators when assessing relationship:

Related:

- Occurs within a reasonable temporal sequence to administration of study drug
- Cannot be explained by concurrent disease or other drugs or chemicals

- Improves or disappears on stopping or reducing study drug (de-challenge)
- Reappears on repeated exposure to study drug (re-challenge)
- Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the participant's physical condition
- Unlikely to be attributed to concurrent disease or other drugs or a clinically reasonable response on withdrawal (de-challenge)

Unrelated:

- Occurs with a temporal relationship to administration of study drug which makes a causal relationship improbable
- Other drugs, chemicals or underlying disease provide plausible explanations of causality
- Is known to be associated with the participant's clinical condition, or with other medication taken by the participant

12.2.4. Action Taken Due to AE

The following are actions taken to treat the AE and actions taken on study treatment as a result of the AE, and must be recorded in the event of an AE:

Action taken to treat the AE

- None
- Treatment required
- Hospitalization
- Participant withdrawn
- Other (specify)

Action taken with study treatment

- Drug interrupted
- Drug withdrawn
- Not applicable, or
- Unknown

12.2.5. Adverse Event Outcomes

The following are AE outcomes, and must be recorded in the event of an AE:

- Resolved: The event has recovered
    - Note: An SAE/AE stop date should be provided
- Resolved with sequelae: The study participant 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 participant 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 participant 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 (eg, "sudden cardiac death"). Adverse events resulting in death are SAEs
- Not resolved: The participant 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 participant.

12.2.6. Adverse Event Collection Period

The SAE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent) and will continue until the Post-Study safety call, 30 days after the CSED Visit. Adverse events occurring prior to and inclusive of the randomization visit and following the CSED Visit will comprise SAEs only; otherwise, all AEs will be recorded.

12.2.7. Adverse Events of Special Interest

Adverse events of particular interest as they pertain to pemafibrate will include muscle-related AEs and liver disease. Adverse event forms will be used to collect additional relevant clinical information at each study visit at which AEs will be assessed. Instructions for entry of these events will be provided in the eCRF Completion Guidelines.

12.2.8. Pregnancy

If a participant becomes pregnant during the study, she must discontinue the study drug, but the investigator must follow up the pregnancy until the pregnancy outcome is available. Her obstetrician should be made aware of her study participation. The investigator should request information about the pregnancy outcome, including any possible fetal abnormalities and congenital defects. If a congenital abnormality or abortion (spontaneous) is reported, then it should be reported as an SAE.

Specific instructions for entry of these events will be provided in the eCRF Completion Guidelines.

12.3. Recording Adverse Events

12.3.1. Detection and Initial Report of Adverse Events

All participants will be monitored at the local study sites on a regular basis during the course of study involvement. Routine in-person and telephone follow-up visits offer the opportunity for PROMINENT study sites to ascertain any untoward medical events that might meet the criteria of an adverse event. Both in-person and telephone visits ask whether the participant has experienced any adverse events. All AEs are reported by completing an Adverse Event/Endpoint Form in the eCRF. A record of the type of AE, onset date, seriousness, severity (mild, moderate, or severe), and causality will be entered by the study site.

12.3.2. Trial Endpoints and Adverse Events

Primary endpoints are routinely assessed during in-person and telephone follow-up visits. Many of these clinical events will meet the criteria for serious adverse events. Endpoints will be reported by completing an Adverse Event/Endpoint Form in the eCRF.

12.3.3. Reporting Adverse Events

12.3.3.1. Investigator Responsibilities

Within 24 hours of receiving initial or additional information on SAEs, pregnancies, and special situations (ie, overdose, medication errors, off-label use, abuse, and suspected transmission of an infectious agent), the investigator should complete the relevant eCRF pages in the EDC system. Specific instructions for entry of these events will be provided in the eCRF Completion Guidelines.

The following minimum information must be reported:

- AE that meets the definition for serious
- Participant identification/randomization number
- Investigator/site number
- Study drug (pemafibrate vs. placebo)

In addition, the following information must be provided to the Sponsor with the initial report: 1) the date the investigator (or other site personnel) became aware of the event; and 2) the causality assessment.

Supporting source documents must be thoroughly blinded to protect the confidentiality of participants participating in the study before such documents are provided to the Sponsor or designated staff. Participant identifiers that should be redacted include but are not limited to participants' names, relatives' names, personal addresses, phone numbers, medical record, and accession numbers.

Once reported, automatic updates will be sent to the Sponsor and designated study staff. Initial reports will often not be complete. Central study staff will guide the site regarding the completion of an SAE form along with retrieval of the pertinent medical records for determination of a final diagnosis. Study site staff may contact participants directly to determine the resolution of AEs, if necessary.

In the event that the EDC is unavailable, and the 24-hour reporting timeline cannot be accommodated, such events will be reported by faxing the back-up paper SAE and/or pregnancy report form to [redacted] Lifecycle Safety using the provided fax cover sheet and the appropriate fax number provided for your country. Once the EDC system becomes available, the investigator will enter SAEs reported on the paper SAE and/or pregnancy report form into the EDC system as soon as possible.

Additionally, sites must follow the requirements of their institutional IRB/IEC/REC for reporting AEs.

12.3.3.2. Sponsor Responsibilities

Reporting of SAEs will be done by the Sponsor (or designee) in accordance with their safety management plan and regulatory requirements.

The PROMINENT DSMB will review AEs that occur in the conduct of PROMINENT, and may issue statements or guidance about the conduct of the study broadly or to individual sites. These statements will be reported by the Sponsor and sites as required. Refer to Section 12.4 for further details on the DSMB.

Additional SAE reporting for all participants will occur for central and/or local IRB/IEC/REC requirements, as relevant.

Primary endpoint events in this study will be waived from expedited reporting to health authorities, investigators, or IRBs/IECs/RECs; refer to Appendix B (Section 21.2) for a list of SMQ terms exempt from expedited reporting.

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse events.

12.4. Data Safety Monitoring Board (DSMB)

Due to the potential risks to study participants, the size and multicenter nature of the study, and the fact that this is a Phase 3 clinical study, the study will have a formal and independent DSMB. The DSMB will be established by the EC and will include, at a minimum, members with specific expertise in the management of CVD and diabetes and familiarity with clinical study conduct, and a biostatistician with specific expertise in the design, analysis, and safety monitoring of multicenter clinical studies. The DSMB will operate under a charter agreed to by the Sponsor and will have the responsibility of monitoring outcome measurements/endpoints, AEs, and SAEs, and recommending termination of the study if it appears at any point during the study that the participants (or a subgroup of participants) are being placed at undue risk as a result of their participation.

The DSMB will meet (face-to-face or by teleconference) semi-annually to review accumulated data on safety and efficacy, and if appropriate, conduct an interim analysis of the data. Blinded data reports will be prepared by the data coordinating center (DCC) and un-blinded reports, if needed, will be prepared by the un-blinded DCC statistician prior to each meeting of the DSMB. Reports to the DSMB will include comparisons of baseline characteristics between treatment groups, displays of cumulative recruitment by study time, comparisons of post-randomization laboratory values by treatment group, and rates of AEs by treatment group, both overall and within system organ class (SOC). The DSMB will also receive summaries of lipid levels and concomitant lipid therapy dosing changes by treatment arm throughout the study to monitor imbalance in use of statins or other LDL-C lowering therapies. Summary statistics of safety laboratory testing will also be reviewed by the DSMB in important subgroups such as participants requiring CYP3A and CYP2C8 inhibitors. Should these data demonstrate no adverse safety signal, the frequency of safety blood laboratory testing after year 1 will be reduced to once annually, ie, the chemistry panel testing at intervening in-person visits will be discontinued.

Interim analyses of rates of the primary outcome, as well as rates of the individual components of the composite endpoint, and the prespecified secondary endpoints will also be prepared for presentation to the DSMB. The reports will be reviewed initially with DSMB members blinded to treatment group assignments. If, however, aggregate data suggests a trend toward harm in 1 treatment group, or at the request of the Sponsor's safety group, an un-blinded interim analysis may be requested and reviewed by the DSMB. Refer to Section 14.7 for further details.

Guidelines for the possible early termination of the study will be formulated by the DSMB, with a formal charter agreed upon prior to study enrollment. The proceedings of each meeting of the DSMB will be recorded in minutes. Any participant-specific protected health information reviewed by the DSMB will be kept completely confidential. Access to the closed session minutes of the DSMB meetings by Executive/Operations Committee (OC) Members, clinical site investigators, or members of the DCC, will be prohibited until after the database for the study has been locked and the study has been unblinded. A formal report will be submitted by the DSMB to the EC, with a recommendation that the study be continued, modified in a manner to enhance participant safety, or terminated.

13. PATIENT REPORTED OUTCOMES

13.1. Quality of Life Assessment

Patient-reported quality of life assessments will be evaluated in this study using the following questionnaires:

- European Quality of Life – 5 Dimensions (EQ-5D-5L)

EQ-5D-5L will be completed at the Randomization Visit, annually thereafter, at the first in-person visit after a primary and secondary endpoint occurs, and at the CSED Visit. The data collected may be used in pharmacoeconomics assessment.

14. STATISTICS

14.1. Stratification and Randomization

Participants willing and eligible to be randomized will be stratified by the following: sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline, defined as those who are taking no statin at baseline or are statin intolerant compared to all others. Within each strata, participants will be randomized with equal probability to active K-877 or placebo.

14.2. Sample Size and Power

The study was designed using an event-driven approach where all participants are followed until a sufficient number of events have accrued. Regardless of the rate of major CV events in the placebo group, the study must accrue 1,071 adjudicated and confirmed major CV events (with a minimum of 200 events accrued in women) in order to have 90% power to detect a 18% reduction in the rate with pemafibrate, based on a 2-sided test with alpha=0.05. The sample size has been increased by 1.9% to maintain 90% power in the presence of interim monitoring. Consequently, we stipulate that the study will require accrual of 1,092 total primary events.

Using the approach of Lachin and Foulkes under the assumption of a uniform hazard we can estimate the duration of the study.[64] We will use the following assumptions:

1. The **recruitment will be uniform over a 30-month period**. Each randomized participant will be asked to continue blinded treatment until the study completion (when sufficient endpoints have been accrued).

2. Unless otherwise specified, **power is set at 90%** to detect the specified effect.

3. As these participants have strong affiliations with their treatment centers and will have been tested in a Placebo Run-In Period, low rates of loss to follow-up are anticipated. Power calculations assume a **1% loss to follow-up**.

4. Sample size is assumed to be **10,000 randomized participants** (5000 receiving pemafibrate and 5000 receiving placebo).

Based on previous studies, it is anticipated that **annual event rates will be between 3.5 and 4.5 per 100 person-years** in the placebo group. We expect a higher event rate in the secondary prevention cohort (~2/3 with prior CVD) than the primary prevention cohort (~1/3 with no prior CVD). For example, a total annual event rate in the placebo group of 4.5 per 100 person years could be achieved via an event rate of 5.2 per 100 person years in the secondary prevention group and 3 per 100 person years in the primary prevention group.

Under these assumptions, Lachin and Foulkes show that the power of the study with N total randomized participants in the pemafibrate and placebo groups combined is:

$$Power = \Phi^{-1}\left(\frac{\sqrt{N}|\lambda_e - \lambda_c| - 3.92\sqrt{\Psi(\bar{\lambda})}}{\sqrt{2\Psi(\lambda_e) + 2\Psi(\lambda_c)}}\right)$$

where Φ is the standard normal distribution function, and **ψ(λ)** is defined as follows:

$$\Psi(\lambda) = \lambda(\lambda + 0.05)/(1 - \frac{\left[\exp\left(-T_r(\lambda + 0.05)\right) - \exp\left(-T_f(\lambda + 0.05)\right)\right]}{2(\lambda + 0.05)})$$

λ_e is the incidence rate in the pemafibrate group,
λ_c is the incidence rate in the placebo group,
T_r is the recruitment duration (assumed to be 30 months), T_f is the follow-up duration, and

$$\bar{\lambda} = .5\lambda_e - .5\lambda_c$$

These power calculations are based on the Intent-to-Treat (ITT) population analyses. As such, they incorporate the effects of noncompliance. We estimate, based on experience observed in other studies that in addition to those who drop out, 10% of the pemafibrate group will discontinue active therapy, but that none of the placebo group will initiate pemafibrate therapy (drop-in). The impact of noncompliance on power can be evaluated from interpolation using Table 6. For example, if the true rate of major CV events in persons meeting eligibility criteria but not on pemafibrate is 3.5 per 100-person years, and fully compliant pemafibrate reduces this rate by 20%, we estimate a rate of the primary endpoint of 2.9 per 100 person-years in the pemafibrate group and 3.5 per 100 person-years in the placebo group. This would correspond to an observed 18% reduction in the active treatment group relative to placebo with the above noncompliance and drop-in rates. The proposed study would thus require 5 years of follow-up to have power above 90% to detect the anticipated effect on observed event rates and ITT analyses, as summarized in Table 6.

With respect to the above assumptions on accrual and drop out, and the range of event rates in the placebo group shown in Table 6, the proposed study with 10,000 randomized participants would be expected to require approximately 5 years of follow-up (approximate placebo event rate=3.7/100 person-years) under the assumption of a 18% reduction in hazard associated with pemafibrate.

Table 6: Number of Events and Estimated Study Duration in Years to Achieve 90% Power with 10,000 Randomized Participants

Relative Rate	Events (adjusted for Monitoring)	Rate of Major Cardiovascular Events in the Placebo Group (per 100 person-years)		
		3.5	4.0	4.5
0.85	1626	7.6 years	6.7 years	6.0 years
0.82	1092	5.2 years	4.7 years	4.3 years
0.80	865	4.3 years	3.9 years	3.6 years

14.3. Demographics and Baseline Characteristics

The randomized design and large sample size of 10,000 should provide a balanced distribution of demographic and baseline characteristics between the 2 treatment groups. Nonetheless, initial analyses will be conducted to identify any chance imbalances in the distribution of these characteristics. In particular, these analyses will form part of the routine monitoring of the study and will be regularly reported to the DSMB. For continuous and ordinal variables, including age and baseline levels of risk factors including lipid levels, blood pressure, BMI, duration of diabetes, and baseline HbA1c, comparisons between treatment groups will be made using the Wilcoxon rank-sum test. For categorical variables, including sex, race, current and former cigarette smoking, past history of CVD, congestive heart failure (CHF), atrial fibrillation, peripheral vascular disease, hypertension, and concomitant therapies, comparisons between treatment groups will be made using Chi-square tests. These hypothesis tests are intended for data monitoring and quality control, and not to determine which baseline covariates to include in efficacy analyses.

14.4. Primary Analyses

The primary endpoint of the study is the time from randomization to the first occurrence of any component of the clinical composite endpoint of nonfatal MI, nonfatal ischemic stroke, CV death, and hospitalization for unstable angina requiring urgent coronary revascularization. The primary analysis of the study will use a likelihood ratio test based on a proportional hazards model stratified on sex, prior history of CVD (primary vs. secondary prevention cohorts), and statin use at baseline, defined as those who are taking no statin at baseline or are statin intolerant compared to all others, to test the null hypothesis of no association between assignment to pemafibrate and the rate of the primary endpoint.

The ITT population will serve as the primary analysis population and will include all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment. Statistical significance will be based on a 2-sided test with level 0.05. The estimated relative hazard in the pemafibrate group compared to the placebo group with an accompanying 95% CI will quantify the treatment effect.[65] If this relative hazard is less than 1, then 100*(1-estimated relative hazard) will be defined as the percent reduction in hazard associated with pemafibrate treatment.

Rates of occurrence of the primary endpoint will be defined as the total number of participants who have this event in a treatment group per 100 person-years of follow-up, counting all time from randomization until the first of the event, death, end of trial, or withdrawal of consent, whichever comes first. Estimates of the probability of the primary endpoint by time after randomization within treatment groups will be based on the method of Kaplan and Meier.[66] We will also use the proportional hazards model to control for baseline factors that might influence the rate of the primary endpoint (eg, age, race, sex, baseline comorbidities, and concomitant medications), as control for these variables may yield more efficient estimates of relative treatment effects.[67] If Kaplan-Meier plots of event-free survival by study time, or related plots of log(-log)(survival), indicate violations of the proportional hazards assumption, or a formal test of trend in the scaled Schoenfeld residuals indicates such a violation, then weighted log-rank tests will be used according to strategies described by Pecková and Fleming.[68] However, even in the

presence of an apparent violation of the proportional hazards assumption, the primary analysis described above gives a valid (although perhaps not optimal) test of the main study hypothesis and will remain the primary analytic strategy, with these weighted log-rank tests serving as sensitivity analyses.

14.5. Secondary and Tertiary Analyses

In addition to the primary comparisons of pemafibrate treatment with placebo, prespecified secondary and tertiary endpoints will also be compared between the treatment groups. All secondary endpoints will only be evaluated if primary endpoint is positive. The total secondary endpoint alpha of 0.05 will be allocated between the secondary endpoint groups as specified in the Statistical Analysis Plan.

Additional analyses will separately evaluate whether the relative effects of pemafibrate versus placebo on primary and secondary endpoints is uniform over the follow-up period. These evaluations will be based on the tests for significant interactions between study time and treatments proposed by Cox,[65] as well as consideration of trends in scaled Schoenfeld residuals in the proportional hazards model. Specifically, residuals will be plotted and a significant rank correlation of residuals with time will be indicative of a changing effect.[71] In the presence of significant correlation, separate effects by time period will be reported. However, even with a significant correlation of residuals with time, the best overall estimate of the effect of treatment will be the estimate obtained from the proportional hazards model without the interaction.

To assess the effect of non-informative censoring on the primary outcome, analyses will be performed following the reference-based method outlined by Carpenter, Roger, and Kenward[69] and detailed in the Statistical Analysis Plan using the piece-wise exponential method described by Lipkovich at al.[70] For those participants who were lost-to-follow-up, event status after the time of last observation is imputed using the distribution of retrieved dropouts for each arm. Retrieved dropouts are defined as participants who are no longer taking study drug but have agreed to continue to be followed. Other imputation models for missing data will also be explored for their effect on the primary outcome, including models that use the entire placebo group as the reference.

Separate proportional hazards models will also be used to compare the effects of pemafibrate treatment on time to each of the individual components of the composite primary endpoint. Analyses will use methods of competing risks survival analysis and compare the relative effects of randomized treatments on the different components of the composite outcome.[72, 73] The approach of Lunn and McNeil[72] provides a readily accessible implementation of a classical approach to competing risk analysis developed by Kalbfleisch and Prentice.[74]

Secondary lipid efficacy endpoints will be analyzed using analysis of covariance (ANCOVA) with a retrieved dropout based pattern mixture model. Participants with missing data will be imputed using the distribution of retrieved dropouts for each arm, where retrieved dropouts are defined as participants who are no longer taking study drug but have agreed to continue to be followed. Imputed data will be analyzed using an ANCOVA model with baseline measurement as a covariate and the treatment arm and randomization strata as fixed effects.

While all primary analyses are on the ITT population, a Per-Protocol population will also be analyzed which will be limited to participants with no major protocol deviations. Sensitivity analyses for the primary efficacy endpoint will also be conducted examining the effect of compliance and escalation of other lipid-lowering medications. Longitudinal analyses will quantify the impact of pemafibrate on lipid levels, biomarkers of inflammation, and glycemic parameters and other pre-specified exploratory lipid and non-lipid biomarkers (Tertiary Endpoints: Section 5.3.1).

We will also assess whether any effects on these biomarkers mediate observed benefits or risks of pemafibrate on clinical outcomes in the study.

14.6. Subgroup Analyses

Additional planned exploratory analyses include evaluation of whether treatment effects vary across categories of baseline covariates. Key pre-specified subgroup analyses will examine treatment effect by sex, prior CVD, and baseline statin use. Other subgroups of interest include region, age, race, baseline lipid levels, and other baseline biomarker levels. Within each subgroup, we will use proportional hazards models to estimate the relative rate of the primary endpoint associated with active treatment versus placebo. Both crude analyses and models including limited baseline covariates will be fitted. To test for the significance of modification of treatment effects by a baseline characteristic, we will include interaction terms between this characteristic and treatment in the proportional hazards model, with statistical significance determined by a likelihood ratio test comparing models with and without the interaction terms between treatment and the categories of a specific covariate.

Subgroup analyses will be conducted regardless of whether or not the overall analyses of treatment effects are significant. Our approach to interpretation of subgroup analyses has always been very cautious and recognizes that, even in large studies, it is not likely to be possible to identify reliably subgroups of participants in whom treatment is especially effective or ineffective. In the absence of prior evidence for real heterogeneity, the overall study result may provide the best evidence for the presence of a benefit in a subgroup. Our approach thus corresponds to an informal empirical Bayes procedure in which effects in an outlying subgroup require interpretation in light of the overall treatment effect.

14.7. Planned Interim Analyses

While the frequency of meetings and the approach to interim monitoring will be the choice of the DSMB, we anticipate at least twice yearly meetings to monitor recruitment and retention, with quarterly safety reports. To preserve alpha and to minimize the likelihood of an inflated effect estimate associated with early stopping, preplanned efficacy analyses will occur at accrual of approximately 50% and 75% of the planned study primary endpoints. The design of the study, including evaluation of the implications of interim monitoring on study power, considered that stopping boundaries would be based on the Haybittle-Peto method. Under this approach, the Z-values for the boundary at the 50% and 75% information times would be ±3.29, corresponding to 2-sided p-values of 0.001. Additionally, the DSMB will also consider the direction of effect for each of the components of the primary endpoint as well as the sensitivity analysis for loss-to-follow-up, ensuring that the point estimate for each is consistent with the composite result and there is no concern for safety. The DSMB will also consider the direction of the effect in women,

again ensuring consistency with the overall result and no concern for safety. Specifically, in order for the study to be stopped early, the estimated HR for the pemafibrate group compared to placebo must be < 1 for each component of the primary endpoint as well as for the subgroup of women. Further, the HR of 1.36 seen in ACCORD[59] must not be in the 95% CI for the primary endpoint in the subgroup of women.

As a guideline for considering a recommendation to stop the study early because of convincing evidence of inefficacy (futility), preplanned inefficacy bounds will also be considered at accrual of approximately 30%, 50%, and 75% of planned study endpoints. Based upon the Linear 10% Inefficacy Boundary approach described by Freidlin, Korn, and Gray[75], the inefficacy boundary will be crossed if the observed relative hazard of the primary endpoint associated with pemafibrate assignment is greater than 1.000 at the first interim futility analysis, greater than 0.996 at the second interim futility analysis, or greater than 0.988 at the third interim futility analysis and the 95% CI excludes the expected effect. Simulations performed by Freidlin et al indicate that their Linear 10% Inefficacy Boundary approach is associated with a less than 1% loss of power due to inefficacy monitoring. Further, their approach is more conservative than a 10 or 30% conditional power approach in later follow-up (ie, after 70% of information is accrued). However, the Linear 10% Inefficacy Boundary approach is more aggressive than a 10% (or even a 20%) conditional power rule at earlier information accrual points, so a more conservative boundary may be preferred at the first interim futility analysis.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

PROMINENT will be coordinated through an academic-industry partnership between investigators in the CCVDP at the Brigham and Women's Hospital and Harvard Medical School (Boston, US) and Kowa Research Institute, Inc., or its designees. The study structure will include a Scientific Advisory Committee (SAC) with specific knowledge of PPAR-α biology and with responsibilities including the evaluation and amendment of the study design before launch; a study Steering Committee (SC) to include members from all participating countries; an EC with responsibilities for the overall enrollment, conduct, and completion of the study; an OC with responsibilities for daily management and interactions with the study Contract Research Organization (CRO), central laboratory, biorepository, and drug dispensary; a blinded CEC; a DCC; and a fully independent DSMB.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. It is understood that the monitor will contact and visit the investigator regularly and will be allowed, to inspect the various records of the study. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, accuracy and consistency of the data; and adherence to the ICH GCP and local regulations on the conduct of clinical research. The monitor should have access to laboratory reports, study medication, records associated with it, and other medical records needed to verify the entries on the eCRF.

15.1.1. Committees

Steering Committee

The SC will include the Principal Investigators and designated representatives from the investigative team (CCVDP) and the CRO ([redacted]), key representatives from the Study Sponsor (Kowa) as well as key representatives (including investigators) from each region that are deemed to have clinical and methodological expertise (national coordinators). The SC will meet as needed, with an estimated frequency of twice per year.

Executive Committee

The EC will include the Principal Investigators and a limited number of designated representatives from the investigative team (CCVDP), Sponsor, and key opinion leaders (KOLs). The EC will be responsible for evaluating overall execution of the study, review of recommendations from the DSMB, evaluation and approval of all proposed substudies, and will oversee study publications. The EC will meet, as required, through completion of the study, with an estimated frequency of 2 times per year.

Operations Committee

The OC will include the Principal Investigators and members of the investigative team including the project manager, senior research coordinators, senior database analysts, and research

assistants as well as designated members from the CRO and the Sponsor. The OC will be responsible for ensuring that study execution and management is of the highest quality, and will monitor recruitment, compliance, and the adjudication process and address the day-to-day issues arising in the study. This committee will meet by telephone and/or in person on a weekly basis, as needed, through completion of the study.

Clinical Endpoint Committee

The CEC will conduct a blinded review of all potential primary and secondary endpoint events to confirm that the data support the endpoint designation. The committee members who perform the review of the endpoint events will not be investigators in the study. Any differences between reviewer designations will be adjudicated in conference calls or regular meetings. A separate CEC Manual of Operations will fully describe the methods used by the CEC.

Scientific Advisory Committee

The SAC will be composed of the Principal Investigators and designated representatives from the investigative team (CCVDP), key representatives from the Study Sponsor, and KOLs determined by the Study Sponsor. The SAC will meet once every year and will provide scientific guidance to the SC.

15.1.2. Data Coordinating Center and Treatment Masking

The DCC will work with the CRO to oversee data collection, monitoring, and reporting to the study committees and DSMB. With the CRO, the DCC will provide reports to the EC as needed. Both the Progress Report and the Quality Control Report will pool participants across treatment groups to maintain the study blind.

15.1.3. Data and Safety Monitoring Board (DSMB)

Due to the potential risks to study participants, the size and multicenter nature of the study, and the fact that this is a Phase 3 clinical study, the study will have a formal and independent DSMB. The DSMB will be established by the EC and will include, at a minimum, members with specific expertise in the management of CVD and diabetes and familiarity with clinical study conduct, and a biostatistician with specific expertise in the design, analysis, and safety monitoring of multicenter clinical studies. The DSMB will operate under a charter agreed to by the Sponsor and will have the responsibility of monitoring outcome measurements/endpoints, AEs, SAEs, and lipid levels and concomitant lipid therapy dosing changes by treatment arm to monitor imbalance in use of statins or other LDL-C lowering therapies. Additionally, the DSMB will have the responsibility of recommending termination of the study if it appears at any point during the study that the participants (or a subgroup of participants) are being placed at undue risk as a result of their participation.

Refer to Section 12.4 for further details on the DSMB.

15.2. Audits and Inspections

Kowa and/or its authorized representatives, a regulatory authority, an IRB/IEC/REC may visit the sites to perform audits or inspections, including source-data verification. The purpose of an

audit or inspection includes, but is not limited to a systematic and independent examination of all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and applicable regulatory requirements. The investigator should contact Kowa immediately if contacted by a regulatory agency about an inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, Kowa, or their designee, may conduct quality assurance audits of the investigators and supporting vendors. Please see Section 15.2 for more details regarding the audit process.

Investigators who become aware of quality issues at their site, including misuse or abuse of medication by study participants, should record these in the EDC.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC/REC as appropriate, before being implemented by the investigator. The written approval/favorable opinion from the IRB/IEC/REC must be received by the investigator and the Sponsor before the investigator can enroll any participants into the study.

The Principal Investigator or the Sponsor is responsible for informing the IRB/IEC/REC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC/REC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB/IEC/REC upon receipt of amendments, and annually, as per local regulations.

As required by local regulation, the investigator or the Sponsor will report promptly to the IRB/IEC/REC, any new information that may adversely affect the safety of participants or the conduct of the study. Similarly, the investigator or the Sponsor will submit written summaries of the study status to the IRB/IEC/REC annually, or more frequently, if requested by the IRB/IEC/REC. Upon completion of the study, the investigator or the Sponsor will provide the IRB/IEC/REC with a brief report of the outcome of the study, if required.

The Sponsor or its representative will provide Regulatory Authorities, Ethics Committees, and investigators with safety updates/reports according to local regulations and guidelines, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

The Principal Investigator or the Sponsor is also responsible for providing the IRB/IEC/REC with reports of any serious adverse drug reactions from any other study conducted with the investigational product in accordance with local regulations. Kowa or [redacted] will provide the necessary adverse event drug reaction reports to the Principal Investigators for submission to the IRB/IEC/REC.

17.2. Ethical Conduct of the Study

Informed consent will be obtained from the study participants and the study will be conducted in accordance with the ethical principles in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October, 2013), the GCP guidelines (CPMP/ICH/135/95), and the applicable drug and data protection laws and regulations of the countries in which the study will be conducted.

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described herein and to adhere to the principles of GCP, which is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. This study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety, and wellbeing

of the study participants are protected, consistent with the ethical principles that have their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

Before any study-specific procedures or assessments are conducted, participants who have had the protocol fully explained by the responsible investigator and who are willing to participate in the study must read, sign, and date an ICF. The Principal Investigator(s) at each center will ensure that the participant is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant.

As described in the informed consent documents, participation in the genetic biobanking portions of the study will be on an "opt-out" basis and are not a requirement for participation in the main study.

The ICF will be used to explain the risks and benefits of study participation to the participant in simple terms before the participant will be entered into the study. The ICF contains a statement that the consent is freely given, that the participant is aware of the risks and benefits of entering the study, and that the participant is free to withdraw from the study at any time. The ICF will describe all levels of participation, including passive follow-up and contact of participants who stop attending study visits to confirm vital status and endpoint occurrence at study end. Written consent must be given by the participant and/or legal representative, after the receipt of detailed information on the study.

The investigator is responsible for ensuring that informed consent is obtained from each participant or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The investigator will provide each participant with a copy of the signed and dated consent form.

18. DATA HANDLING AND RECORDKEEPING

18.1. Electronic Data Capture

An EDC system will be developed and used to collect and transmit source data throughout the course of the study. This system will be compliant with 21 Code of Federal Regulations (CFR), Part 11 and will meet all relevant governmental regulations. The system will be maintained by [redacted] System functionality will be thoroughly tested and validated prior to implementation. Furthermore, to ensure compliance with standards of use of electronic study data, standard operating procedures will be maintained for the use of the system, an audit trail of data changes will ensure that there is no modification of entered data without documentation, and security systems will be maintained to protect against unauthorized access. Furthermore, adequate procedures will be used to back up the data and safeguard the blinding of the study.

The EDC system will be used in each of the following steps to create, modify, maintain, archive, retrieve, and/or transmit source data:

- Creation of eCRFs
- Resolution of data discrepancies through data queries and checks
- Monitoring of drug distribution
- Reporting of AEs and endpoints

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics Departments of [redacted]
All eCRF data will be entered into electronic forms at the study center. Data collection will be completed by authorized study-center staff designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study participants.

All data must be entered in English. The eCRFs should always reflect the latest observations on the participants in the study. **Therefore, the eCRFs are to be completed by the sites as soon as possible during or after the participant's visit to allow for site monitoring of the data.** To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

The [redacted] Monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no data discrepancies. All entries, corrections, and changes are to be made by the investigator or

his/her designee. The Monitor cannot enter data in the eCRFs. Once clinical data in the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible Monitor, Data Manager, or designee will raise a query in the EDC application. The appropriate study center staff will answer the query. The entire chain of events will be audit trailed by the EDC application, including the name of each person who makes entries into the system, along with the time and date stamp for each entry.

The eCRF is essentially considered a data entry form or copy and should not constitute the original (or source) medical records.

The investigator is responsible for maintaining source documents. These will be made available for review by the Study Monitor at each monitoring visit. The investigator must submit a completed eCRF for each participant screened for the study. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and participant number. Any personal information, including participant name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 18.1). Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO DD). Concomitant diseases/medical history will be coded using MedDRA, Version 18.1.

18.2. Source documents

As the eCRF serves as a data entry form, it does not constitute the original or source medical record of the participant. The data entered into the eCRF must be derived from source documents, which provide evidence for the existence of the participant and substantiate the integrity of the data collected and recorded in the eCRF. Source documents constitute all documents used by the investigator or hospital that relate to the participant's medical history, the participant's fulfillment of the inclusion and exclusion criteria, and all records covering the participant's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, participant files, etc. The investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each participant randomized into the study.

All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and participant number. Any personal information, including participant name, should be removed or rendered illegible to preserve individual confidentiality.

Source documents are filed at the study site. Data entered into the eCRFs that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. Current medical records on the participant must be available. The investigator may need to request previous medical records or transfer records.

18.3. Inspection of Records

Kowa, or its designee, will be allowed to conduct site visits for the purpose of monitoring any aspect of the study. The investigator agrees to allow the Monitor to inspect the drug storage area, study drug supply, drug accountability records, participant charts and study source documents, and other records relating to study conduct.

The investigator will allow the Sponsor, CRO, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual participant medical records, as appropriate.

18.4. Retention of Records

It is the investigator's responsibility to maintain essential study documents (ie, protocol and amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period if required by the applicable regulatory requirements, or the hospital, institution, or private practice in which the study is being conducted. Participant identification codes (ie, participant names and corresponding study numbers) should be retained for the same period of time. If acceptable to the Sponsor, these documents may be transferred to another responsible party, who must agree to abide by the retention policies. In such a case, written notification of transfer must be submitted to the Sponsor.

The investigator must contact the Sponsor prior to disposing of any study records. No records may be disposed of without the written approval of the Sponsor.

If it becomes necessary for Kowa or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

19. PUBLICATION POLICY

The EC is responsible for the reporting and publication of the study results. Kowa will be provided a reasonable opportunity to review such manuscripts prior to journal submission, as set forth in the Clinical Research Start-Up Activities Agreement between the Brigham and Women's Hospital, Inc. and Kowa Research Institute, Inc. effective August 1, 2014. The results of the study will be published, irrespective of whether the endpoints are met, or whether the results are regarded as positive or negative. For clarity and transparency, and as explicitly described in the EC Charter for the PROMINENT study, for any issues related to publication or presentation of the study results, the Sponsor will be free to make recommendations to the EC, but the voting academic members of the EC will make the final determination as to whether or not such recommendations will be implemented. As such, the academic members of the EC have final responsibility and decision making authority for all aspects of study presentation and publication.

Confidentiality, publication, and patent applications related to unpublished study-related information and unpublished information given to the site investigators by Kowa shall be handled as set forth in the Clinical Research Start Up Activities Agreement.

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21. APPENDICES

21.1. Appendix A: Schedule of Laboratory Testing

Visits	V1	V1.1	V2	V5	V6	V7	V9	V11	V13	V15	V17	V19	V21	V23	V25	V27	V29	V31	V33	CSED
Month	Screen	Retest	Rand	M4	M6	M8	M12	M16	M20	M24	M28	M32	M36	M40	M44	M48	M52	M56	M60	
Fasting (F)/Non-Fasting (N)	F	F	N	F	N	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
Chemistry (Total Cohort)																				
Chemistry Panel, includes K, Na, Cl, ALT, AST, Tbili, Dbili, BUN, Creatinine, calc eGFR, CK, total Protein, LDH, Uric Acid, γGTP, ALP	●		●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●
TSH, FT4	●						●			●			●			●			●	●
Hematology (Total Cohort)																				
Hematology Panel w/ Platelet and WBC differential)	●		●	●	●		●			●			●			●			●	●
Pregnancy Testing in WOCB																				
Beta-HCG (~10%)	●		●	●	●		●			●			●			●			●	●
Urine (Total Cohort)																				
Urine Microalbumin, Creatinine, Chem Panel			●	●			●			●			●			●			●	●
Core Lipid Parameters (Total Cohort)																				
Lipid Panel [TC, TG, HDL-C, calc non HDL-C, calc VLDL-C, calc LDL-C (Friedwald, Hopkins, Delong)]	●	●	●	●	●		●			●			●			●			●	●
Direct LDL-C, Apo B, remnant cholesterol	●*		●	●	●		●			●			●			●			●	●
Apo E	●*			●			●			●			●			●			●	●
Advanced Lipid Parameters (Total Cohort)																				
Apolipoprotein A1, C3, LDL particles (NMR)	●*			●			●			●¥			●¥			●¥			●¥	●¥
LDL-Cholesterol by PUC	●*			●			●			●§¥			●§¥			●§¥			●§¥	●§¥
LDL-TG by PUC, HDL-TG by PUC	●*			●																
Direct sdLDL-C and LDL-TG	●			●			●													
Inflammatory and Glycemic (Total Cohort)																				
HbA1c, glucose	●		●	●	●		●			●			●			●			●	●
C-reactive Protein, hsCRP	●*		●	●	●		●			●			●			●			●	●
FGF21	●*						●			●¥			●¥			●¥			●¥	●¥
Expanded Exploratory (Subcohort: US/Ca)																				
Apo A5, B48	●*			●			●													
ANGPTL 3, ANGPTL 4	●*			●			●													
PCSK9 Mass	●*			●			●													
CK-18	●*			●			●													
Type IV Collagen	●*			●			●													
BWH BIOREPOSITORY SPECIMEN	●*		●	●																
DNA EXTRACTION			●																	

●* Hold until randomized; § measured when TG > 400 mg/dL; ¥ After M12, all samples saved. For participants with an event, the sample immediately prior to event will be analyzed. For participants without an event, the CSED visit sample will be used.

BWH Biorepository Specimen Blood Volume – V1: 22mL (18 mL EDTA Plasma, 4 mL Serum Sample), **V2 and V5: 16 mL** (12 mL EDTA, 4 mL Serum Sample)

21.2. Appendix B: Serious Adverse Event Endpoints Exempted from Regulatory Reporting

SMQ Terms (PTs unless otherwise specified) for exemption from expedited reporting are as follows:

Myocardial Infarction

Diagnoses

Acute coronary syndrome

Acute myocardial infarction

Infarction

Myocardial infarction

Myocardial necrosis

Papillary muscle infarction

Post procedural myocardial infarction

Silent myocardial infarction

Lesions

Coronary artery embolism

Coronary artery occlusion

Coronary artery reocclusion

Coronary artery restenosis

Coronary artery stenosis

Coronary artery thrombosis

Coronary bypass thrombosis

Coronary vascular graft occlusion

In-stent coronary artery restenosis

Stent thrombosis

Unstable Angina

Acute coronary syndrome

Angina pectoris

Angina unstable

Anginal equivalent

Coronary artery insufficiency

Myocardial ischemia

Postinfarction angina

Subendocardial ischemia

Ischemic Stroke

Diagnoses

Basal ganglia infarction

Basal ganglia stroke

Brain stem infarction

Brain stem ischemia

Brain stem stroke

Cerebellar infarction

Cerebellar ischemia

Cerebral infarction

Cerebral ischemia

Cerebral thrombosis

Cerebrovascular accident

Cerebrovascular disorder

Cerebrovascular insufficiency

Embolic cerebral infarction

Embolic stroke

Infarction

Ischemic cerebral infarction

Ischemic stroke

Lacunar infarction

Lacunar stroke

Lateral medullary syndrome

Post procedural stroke

Stroke in evolution

Thalamic infarction

Thrombotic cerebral infarction

Thrombotic stroke

Reversible ischemic neurological deficit

Transient ischemic attack

Lesions

Basilar artery occlusion

Basilar artery stenosis

Basilar artery thrombosis

Brain stem embolism

Brain stem thrombosis

Carotid arterial embolus

Carotid artery insufficiency

Carotid artery occlusion

Carotid artery restenosis

Carotid artery stenosis

Carotid artery thrombosis

Cerebellar artery occlusion

Cerebellar artery thrombosis

Cerebellar embolism

Cerebral artery embolism

Cerebral artery occlusion

Cerebral artery restenosis

Cerebral artery stenosis

Cerebral artery thrombosis

Cerebral thrombosis

Cerebral vascular occlusion

Cerebrovascular stenosis

Carotid artery thrombosis

Precerebral artery occlusion

Precerebral artery thrombosis

CV Death

Cardiac death

Sudden cardiac death

Sudden death

LLTs under Death PT

Death occurring in less than 24 hours from onset of symptoms, not otherwise explained

Death unascertained

Death unattended

Death unexplained

Death unexplained (NOS)

Unattended death

Unknown cause of death