NCT03071692

STATISTICAL ANALYSIS PLAN

PHASE III

VERSION: 1.0
DATE OF PLAN:

OCTOBER 24, 2022

BASED ON:

Protocol Version 2 dated March 04, 2020

STUDY DRUG:

K-877 (PEMAFIBRATE)

PROTOCOL NUMBER:

K-877-302

STUDY TITLE:

PROMINENT
Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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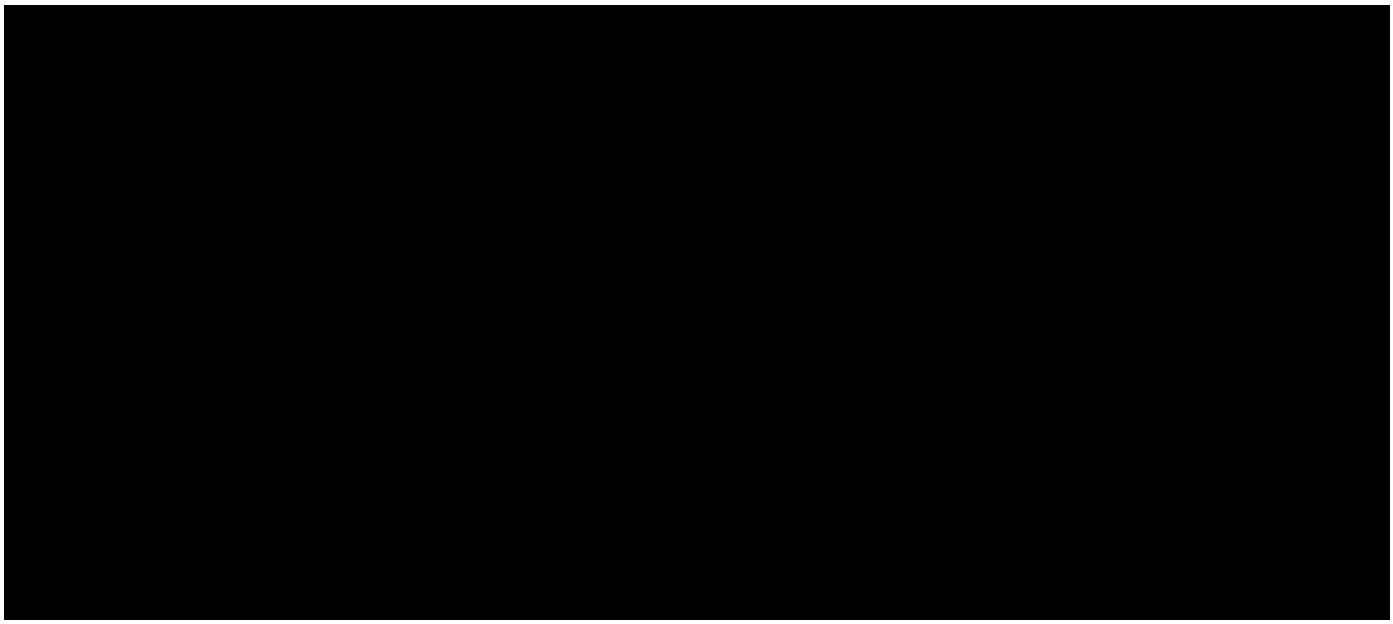

This document has been reviewed and accepted by:

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company **Kowa Company Limited**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: **K-877 (pemafibrate)**	**Page:**	
Name of Active Ingredient: **K-877 (pemafibrate)**		
Title Of Study: Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes (PROMINENT)		
Investigators: Study Center(s): This study will be conducted at approximately **750** investigational centers in 20 to 25 countries (exact locations to be decided)		
Studied period (years): Estimated date first patient enrolled: Q2/2017 Estimated date last patient completed: Q2/2022		**Phase of development:** Phase 3

Objectives:

Primary:

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, coronary 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;
- 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 (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.

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, coronary revascularization, or CV death. The study is event-driven such that after 1,304 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 16.6% 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 10 (Visit 8), 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, except for the Month 2 visit, 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 2, 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 (except no urine samples at the Month 2 visit) will be collected for safety and efficacy assessments. Based on Data Safety Monitoring Board (DSMB) review of blood safety data which took place on November 11, 2019, effective from global protocol amendment 2, the frequency of safety blood laboratory testing after Year 1 (Month 12) will be reduced to once annually, ie, the chemistry panel testing at intervening in-person visits will be discontinued. 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 potential primary or secondary 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, 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, PCSK9 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 Subjects (planned and analyzed):

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 (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.

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, glitazones 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) ≤ the lower limit of normal] 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 IQVIA 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:

Primary Efficacy Endpoint:

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

1. Nonfatal MI
2. Nonfatal ischemic stroke
3. Coronary revascularization
4. Cardiovascular death

Secondary Clinical Efficacy Endpoints:

- The group A (clinical) endpoints are time to first occurrence of:
  - The 4-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or cardiovascular death

- Any component of the 3-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, or cardiovascular death
- Any component of the primary endpoint or hospitalization for HF
- Any component of the primary endpoint or all-cause mortality
- 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)

- Time of first occurrence of individual endpoints and an analysis of total events (evaluating time to occurrence of the first and all recurrent non-fatal MI, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death).

- Additionally, as a prespecified secondary analysis, evidence of any genetic effect modification that may relate to pemafibrate and incident cardiovascular events will be evaluated. In particular, whether the effect of pemafibrate as compared with placebo on cardiovascular events differs according to known genetic polymorphisms in the PPAR-α gene (such as, but not limited to rs6008845), will be assessed.

- 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 16.6% reduction in the rate of the primary endpoint in the pemafibrate arm compared to placebo, at least 1,304 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 (KM) 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[11]. 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.

In addition to the above, an analysis of time to first occurrence of individual endpoints and an analysis of total events (evaluating time to occurrence of the first and all recurrent non-fatal MI, nonfatal ischemic stroke, coronary revascularization, or CV death) will be performed.

Additionally, as a prespecified secondary analysis, evidence of any genetic effect modification that may relate to pemafibrate and incident CV events will be evaluated. In particular, whether the effect of pemafibrate as compared with placebo on CV events differs according to known genetic polymorphisms in the PPAR-α gene (such as, but not limited to rs6008845) will be assessed.

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.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANGPTL	Angiopoietin-like
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BID	Twice a Day
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
CEC	Clinical Endpoint Committee
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-18	Cytokeratin-18
C_{max}	Maximum plasma concentration
CSED	Common Study End Date
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life–5 Dimensions 5 Level Questionnaire

Abbreviation	Explanation
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
HIV	Human immunodeficiency virus
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDL-TG	Low-density lipoprotein associated triglycerides
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MMRM	Multilevel Modeling for Repeated Measures
NMR	nuclear magnetic resonance
OATP	Organic anion transporting polypeptides
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PP	Per Protocol
PPAR	Peroxisome proliferator alpha receptor
PROMINENT	Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes

Abbreviation	Explanation
PT	Preferred Term
PUC	Preparative ultracentrifugation
RBC	Red blood cell
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sdLDL-C	Small dense low-density lipoprotein cholesterol
SOC	System organ class
SPPARM-α	selective peroxisome proliferator alpha receptor modulator
TC	Total cholesterol
TEAE	Treatment Emergent Adverse Event
T2D	Type 2 diabetes
T4	Thyroxin
TG	Triglyceride(s)
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
ULQ	Upper Limit of Quantitation
VLDL-C	Very low-density lipoprotein cholesterol
WHO DD	World Health Organization Drug Dictionary
WOCP	Women of childbearing potential

2. INTRODUCTION

The statistical analysis plan (SAP) is based on:

- Protocol No. K-877-302
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)
- Discussions with the Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA)

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data Study Protocol No. K-877-302.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. 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, coronary revascularization, and CV death in participants with T2D who have elevated TGs and low 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
- 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 (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.

3.1.2. Secondary Objectives

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.

3.1.3. Tertiary Objectives

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

3.2. Study Endpoints

3.2.1. 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
- Coronary revascularization
- Cardiovascular death

All events will be adjudicated following processes outlined in the Clinical Endpoint Committee (CEC) charter.

3.2.2. Secondary Endpoints

3.2.2.1. Group A: Clinical Endpoints

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

1. The 4-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or cardiovascular death
2. Any component of the 3-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, or cardiovascular death
3. Any component of the primary endpoint or hospitalization for heart failure (HF)
4. Any component of the primary endpoint or all-cause mortality
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 ≤ 0.90 or other diagnostic testing (eg, toe-brachial index, angiogram, or other imaging study)

6. Time to first occurrence of individual endpoints and an analysis of total events (evaluating time to occurrence of the first and all recurrent non-fatal MI, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death).
7. Additionally, as a prespecified secondary analysis, evidence of any genetic effect modification that may relate to pemafibrate and incident cardiovascular events will be evaluated. In particular, whether the effect of pemafibrate as compared with placebo on cardiovascular events differs according to known genetic polymorphisms in the PPAR-α gene (such as, but not limited to rs6008845) will be assessed.

3.2.2.2. Group B: Lipid Endpoints

The Group B lipid efficacy endpoints are:

1. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for TG
2. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for VLDL-C (calculated). VLDL-C is calculated as TC minus HDL-C minus LDL-C, where LDL-C is measured by a direct homogenous method.
3. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for ApoC3
4. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for ApoE
5. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for HDL-C
6. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for non-HDL-C (calculated)
7. The percent change from Randomization Visit (Visit 2) to Month 6 Visit (Visit 6) for non-fasting remnant cholesterol
8. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for TC
9. The percent change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for ApoA1

3.2.3. 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.

4. STUDY DESIGN

4.1. Summary of 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, coronary revascularization, or CV death. The study is event-driven such that after 1,304 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 16.6% 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 10 (Visit 8), 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, except for the Month 2 visit, 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 2, 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 (except no urine samples at the Month 2 visit) will be collected for safety and efficacy assessments. Based on Data Safety Monitoring Board (DSMB) review of blood safety data which took place on November 11, 2019, effective from global protocol amendment 2, the frequency of safety blood laboratory testing after Year 1 (Month 12) will be reduced to once annually, ie, the chemistry panel testing at intervening in-person visits will be discontinued. 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 potential primary or secondary endpoint occurs, and at the CSED Visit.

Lipid parameters, as outlined in the protocol 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 the protocol 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 the protocol 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.

4.2. Definition of Study Drugs

Product Name:	Pemafibrate	Placebo
Dosage Form:	Tablet	Tablet
Unit Dose	0.2 mg	0 mg
Daily Intake	BID	BID
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

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

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 1,304 adjudicated and confirmed major CV events (with a minimum of 200 events accrued in women) in order to have 90% power to detect a 16.6% 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 1,304 total primary events.

Using the approach of Lachin and Foulkes[1] under the assumption of a uniform hazard we can estimate the duration of the study. 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:

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

where Φ is the standard normal distribution function, and $\boldsymbol{\psi(\lambda)}$ is defined as follows:

$$\Psi(\lambda) = \lambda^2\left\{\frac{\lambda}{(\eta+\lambda)}\left[1 - \frac{\left[e^{(-(T_f - T_r)(\eta+\lambda)} - e^{(-T_f(\eta+\lambda)}\right]}{T_r(\eta+\lambda)}\right]\right\}^{-1}$$

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

λ_e is the incidence rate in the pemafibrate group,

Qe is the proportion of the total participants in the pemafibrate group,

λ_c is the incidence rate in the placebo group,

Qc is the proportion of the total participants in the placebo group,

η is the loss to follow up rate,

T_r is the recruitment duration,

T_f is the follow-up duration (also equal to the length of the study),

Z_α is the standard normal deviate at level α, and

$$\bar{\lambda} = Q_e\lambda_e + Q_c\lambda_c = .5\lambda_e + .5\lambda_c$$

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 2. 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 3.8 per 100 person-years in the pemafibrate group and 4.5 per 100 person-years in the placebo group. This would correspond to an observed 16.6% 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 2.

With respect to the above assumptions on accrual and drop out, and the range of event rates in the placebo group shown in Table 2, the proposed study with 10,000 randomized participants would be expected to require approximately 5 years of follow-up (approximate placebo event rate=4.5/100 person-years) under the assumption of a 16.6% reduction in hazard associated with pemafibrate.

Table 2: 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
0.834	1304	6.1 years	5.4 years	4.9 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

4.3.2. Sample Size Re-estimation

Sample size re-estimation is not currently anticipated. The change to the primary endpoint led to the re-estimation of the number of events required but not to the re-estimation of the sample size (Appendix 1, Amendment 2).

4.4. 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.

4.5. Clinical Assessments

The schedule of clinical assessments is as follows:

		Placebo Run-In Period[a]			Treatment Period										
Visit	**Pre-screen**	**Screening/ Enrollment**	**Retest**	**Random -ization**	**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**		**X [c]**	**X [c]**	**X**	
Telephone Visit[d]					**X[e]**						**X**				**X**
Assessment															
Informed consent	X														
Demographic Data and Medical History[f]	X	X		X											
Medical records submission[f]	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	

		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)**		
Week (W) or Month (M)	**-6W**	**-3W**		**0**	**2W**	**M2**	**M4**	**M6**	**M8**	**M12**				**CSED Visit[b]**	**Post-Study Safety Call[c]**
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**		**X [e]**	**X [e]**	**X**	
Telephone Visit[d]					**X[e]**						**X**				**X**
Assessment															
EQ-5D-5L Questionnaire[g]				X[g]						X[g]		X[g]	X[g]	X[g]	
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			X[l]	X	
Urine sample				X			X			X			X[l]	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)**		
Week (W) or Month (M)	**-6W**	**-3W**		**0**	**2W**	**M2**	**M4**	**M6**	**M8**	**M12**				**CSED Visit[b]**	**Post-Study Safety Call[c]**
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**		**X [e]**	**X [e]**	**X**	
Telephone Visit[d]					**X[e]**						**X**				**X**
Assessment															
Pregnancy test in WOCP[m]		X		X		X	X	X		X			X	X	
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 4 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 protocol 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 protocol 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). Effective from global protocol amendment 2, frequency of these additional blood safety measurements will be reduced to once annually based upon 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 protocol Section 11.1 and Section 11.2 for definitions of efficacy events).

5. PLANNED ANALYSES

5.1. Data and Safety Monitoring Board (DSMB)

The details regarding the DSMB processes and procedures will be outlined in the DSMB Charter. The DSMB Charter will specify the analyses to be included in the regular reviews of cumulative safety data. The DSMB will also be responsible for assessing whether results from the interim analyses justify stopping the trial early for futility. The analyses planned will be a subset of the analyses described in this SAP for the final analyses.

5.2. Interim Analyses

Three interim analyses will take place for this study. The analysis methodology for the interim analyses will be consistent with the final analysis described in the main body of this SAP. The one difference is that censoring at the interim analysis will utilize the interim analysis data cut-off date instead of the end of study date. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analyses.

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 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[3], 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.

5.3. Final Analyses

This trial is endpoint driven. When the appropriate number of major cardiovascular events have occurred, a close out procedure will be initiated. The close out procedure will end at the date of the last visit of the last patient, which will be the analysis cutoff date. Information will continue to be collected after the final visits, including endpoint adjudication, and follow-up of patients who withdrew consent or did not attend their final visit. Database lock will occur after data cleaning and adjudication of all endpoints.

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this statistical analysis plan, database lock, and unblinding of treatment.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

In general, summary tables will be organized with respect to treatment group (K-877 followed by placebo). When deemed appropriate, tables will display sub-group differences by treatment group.

Summary tables for medications, medical conditions, and adverse events are coded according to standard dictionaries including the WHO Drug standard dictionary and the MedDRA dictionary.

Supportive individual Subject Data Listings, as a minimum, are sorted and presented by treatment group (group) and investigational site (center). Listings will also include subject number, visit number, visit date, and days relative to the initiation of double-blind treatment, if applicable.

6.2. Software Version

Derived data sets will be analyzed and summary data tables generated using SAS version 9.4 or higher.

6.3. Data Presentation Conventions

Continuous variables (eg, age) will be summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), median, and minimum and maximum). Categorical variables (eg, race) will be summarized using counts and percentages. Percentages will be calculated using the total subjects per treatment group.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables will be formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal aligned.
- P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

6.4. Analysis Populations and Overall Study Period

6.4.1. Screen Failures

Subjects are considered a screen failure if they are not found to be eligible for randomization under the eligibility criteria specified in the protocol. Once they are randomized and receive study drug (even if mis-randomized) they are included in one or more analysis sets below.

6.4.2. Safety Population

The safety population includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to their randomized treatment group, unless a subject inadvertently receives the incorrect drug during the entire study, in which case, the subject will be grouped according to the treatment actually received.

6.4.3. Intent-To-Treat (ITT) Population

The Intention-To-Treat population will serve as the primary analysis population and will include all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed according to their randomized treatment group regardless of whether they adhere to their assigned treatment.

6.4.4. Per-Protocol (PP) Population

The Per-Protocol population will include all subjects in the ITT analysis set who have been identified by having efficacy affected through violations on the CTMS log or compliance. The reason for exclusion was identified with CTMS external data source and an external compliance data source. Subjects will be analyzed according to their randomized treatment group regardless of whether they adhere to their assigned treatment.

6.4.5. Overall Study Period

Overall Study Period is defined as the time from the date of first study treatment to the Common Study End Date (CSED).

6.5. Baseline Definition

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). In the case where the last non-missing measurement and the first dose date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the first dose date will be considered post-baseline.

6.6. Derived and Transformed Data

6.6.1. Baseline Age

Subjects' age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR((date of informed consent – date of birth)/365.25)

where FLOOR( ) function returns the integer part of the result. If any component of the date of birth is unknown, the subject's baseline age will be taken directly from the eCRF.

6.6.2. Study Day

If the date of interest (i.e., event date, assessment date, etc.) occurs on or after the date of first dose of study treatment then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the date of first dose of study treatment then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

6.6.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as ((change from baseline/baseline result) * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.6.4. Visit Windows

No visit windowing will be applied to this study. For by-visit summaries, data recorded at the nominal visit will be presented. If multiple assessments occur within a visit, the result closest to the protocol defined visit will be used for the by-visit summaries.

Unscheduled measurements will not be included in by-visit summaries, but would be included in time to event analyses.

6.7. Handling of Missing Data

Every effort will be made to minimize missing data throughout the trial, from the design phase through follow-up.

Right censoring will apply for any time to event analyses.

For select continuous measures, missing data will be addressed using Mixed-Effect Model Repeated Measure (MMRM) methods.

6.7.1. Missing Endpoint Dates

For time to event analyses, only observed events will be used and censoring will be assumed to be non-informative for the main analyses. Partially missing endpoint event dates will be imputed using the start date and end date of the Overall Study Period after due diligence to obtain accurate information has failed. A conservative imputation approach will be implemented such that more events will be included in the analyses. If the known components of the endpoint date indicate the event occurred in the same month as the start of the Overall Study period, the event day will be imputed using the Overall Study period start day. If the known components show the event occurred in the same year as the start of the Overall Study period, the event month and day will be imputed using the Overall Study period start day and month. Similarly, if the known components of the endpoint date indicate the event occurred in the same month as the end of the Overall Study period, the event day will be imputed using the Overall Study period end day. If the known components show the event occurred in the same year as the end of the Overall Study

period, the event month and day will be imputed using the Overall Study period end day and month. For missing date components falling outside the assumptions outlined previously, a conservative imputation approach will be implemented in regards to time to event. If only the year is known, the event day and month will be assigned to January 1st. If the month and year are known, the event day will be assigned to the first day of the month.

6.7.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Imputation of partially missing dates would follow the conservative imputation approach as defined in section 6.7.1. When needed for summary tables of analysis, imputation for missing prior and concomitant medication use would be done using the rules below.

Start Date	Stop Date	Prior	Concomitant
Missing	Missing	Yes	Yes
Missing	Before First Dose	Yes	No
Before First Dose	Missing	Yes	Yes
Missing	After First Dose	Yes	Yes
After First Dose	Missing	No	Yes

6.7.3. Missing Start and Stop Dates for Adverse Events

Completely missing or partially missing AE onset dates will be imputed as follows after due diligence to obtain accurate AE information has failed. If the event date is completely missing and could have occurred after the start of therapy, the date will be set to the start date of therapy. Partially missing event dates will be imputed using the start date and end date of the Overall Study Period. A conservative imputation approach will be implemented such that more events will be considered treatment emergent.

7. STUDY POPULATION

7.1. Subjects Disposition

The number of patients in each population will be presented overall and by region and site for all randomized subjects.

Subject disposition and withdrawals will be presented by treatment group and overall. This summary includes total number of subjects completing the study and total number of subjects discontinuing from the study and reasons for discontinuation. Patients who withdrew from the study will be presented in a listing.

Descriptive statistics of the number of days in trial will also be summarized. Number of days on trial will be calculated as: date of end of participation (from EOS form) – date of randomization +1.

Additional replicate tables may also be generated presenting the same accounting and disposition data for important sub-sets of the study, including by region or country. Graphical summaries including Kaplan-Meier plots of the dropout patterns will also be provided so that it can be clearly seen if there is a differential dropout pattern between the treatment groups. The number and percent of subjects who completed follow-up will be summarized by treatment group. A subject will be counted as 'completed follow-up' if the subject is known to be dead or has completed an assessment visit at the end of the study. Otherwise, a subject will be counted as 'incomplete follow-up'.

7.2. Screen Failures

The demographic profile of subjects who terminate the trial as screen failures will be summarized and presented in a listing or a submitted dataset.

7.3. Protocol Deviations

Deviations from the protocol which, based on clinical input, may have an impact on the efficacy analyses will be presented. These are related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment. The number of patients with ITT population and protocol deviation type will be presented. Protocol deviations identified by type will also be presented in a listing.

Prior to database lock and unblinding, subjects and the protocol deviation type will be given to bios to present the reason.

7.4. Demographic and Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the ITT population. Statistical testing will be carried out for baseline characteristics for descriptive purposes only. Chi-square tests will be performed on categorical results and Wilcoxon rank-sum tests will be performed on continuous and ordinal results.

The following demographic and other baseline characteristics will be reported for this study:

Demographics

- Age (years)
- Age categorized (<55, >=55)
- Sex
- Race
- Ethnicity
- Region

Baseline Characteristics

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
    - BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- BMI categorized (<30, >=30 kg/m^2)
- Waist circumference (cm)

Cardiovascular Diseases and Risk factors

- Smoking Status (Current Smoker, Past Smoker, Never Smoked)
- Statin Use (defined hierarchically by the following categories: 1) moderate/high intensity statin, 2) Statin intolerance, 3) LDL-C $\leq$ 70 mg/dL (1.81 mmol/L))
- Congestive Heart Failure (Yes/No)
- Prior MI (Yes/No)
- Prior Coronary Revascularization (Yes/No)
- Peripheral Artery Disease (Yes/No)
- HbA_{1C} (% and mmol/mol)
- HbA_{1C} categorized ($\leq$8.5%; >8.5%)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse (beats/min)
- HDL-C (mg/dL)
- LDL-C (mg/dL)
- Apo B

- Remnant-C (mg/dL)
- Apo C-III (mg/dL)
- Fasting TG (mg/dL)
- Non-fasting TG (mg/dL)
- Diabetes duration (years)
- Hypertension (Yes/No)
- eGFR
- eGFR categorized (≤53 mL/min/1.73m^2; >53 mL/min/1.73m^2)

7.5. Listing of Subject Inclusion and Exclusion Criteria

Although compliance with subject selection criteria is not routinely summarized in table format, these data will be listed on an individual subject basis as needed for all randomized subjects.

7.6. Medical History and Medical Conditions Present at Entry

Past medical history and medical conditions present at entry will be described separately for the ITT population. A medical condition will be considered present at entry if the stop date is unknown or the condition is reported as ongoing at the time the medical history was obtained.

Conditions will be coded according to MedDRA dictionaries where information is available and summarized by System Organ Class (SOC) and Preferred Term (PT).

7.7. Prior Medication History

Prior medication history will be described separately for the ITT population. A medication will be considered prior medication history if the medication start and stop dates are prior to first dose of study treatment. Missing dates will be imputed according to the method outlined in section 6.7.2.

All medications will be coded using the WHO dictionary and summarized by preferred term and drug classes (level 3 – therapeutic class). Anatomic-Therapeutic Class (ATC) coding will be used to define diagnosis-related drugs.

7.7.1. Non-Diagnosis Related Prior Medication History

This supportive listing, limited to non-diagnosis related medications, will include the unique data associated with medication start and stop dates, dose, frequency of administration, route of administration, trade name, generic name, and why it was prescribed.Non-Diagnosis related medications will be identified as drugs used in diabetes and not related as in section 7.7.2 Diagnosis related prior medication history.

7.7.2. Diagnosis Related Prior Medication History

Similar listings as described in Section 7.7.1 will be provided for diagnosis related prior medications. Diagnosis related medications will be identified by ATC coding level 2 equal to "DRUGS USED IN DIABETES".

8. EFFICACY

8.1. General Considerations

The following will be applied to all efficacy analyses where applicable.

The ITT population will be used in the analysis of efficacy endpoints. Endpoints will be summarized by treatment group unless otherwise stated. Results will be presented by region and center where appropriate. Extreme results by region or center will be noted.

The summary statistics for the efficacy endpoints and their individual components will be provided. These statistics include the number of first events (i.e. the number of subjects with the event), the total exposure to first event or censoring time, the annualized event rate, and the Kaplan Meier estimates, when applicable. The annualized event rate will be calculated as the number of subject with events divided by the total time at risk (years) to the subjects' first event or censoring time. The hazard ratio of the exposure group versus placebo with 95% CIs will be provided using the Cox proportional hazards model including treatment. The model will be stratified by the three stratification variables, sex, prior history of CVD, and baseline statin use, under the assumption of differing baseline hazards.

8.2. Statement of the Null and Alternate Hypotheses

The primary statistical null and alternative hypotheses are:

H_O: The hazard rate of first occurrence of any component of the clinical composite endpoint of nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death in the K-877 treatment group is equal to the hazard rate in the placebo group

H_1: The hazard rate of first occurrence of any component of the clinical composite endpoint of nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death in the K-877 treatment group is not equal to the hazard rate in the placebo group

8.3. Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint and each individual component as well as other endpoints as needed. Where applicable, each subgroup will be analyzed using a Cox proportional hazard model including treatment and the two stratification variables: sex and prior history of CVD. Due to the low level of statin intolerance at baseline, primary subgroup analyses will not stratify on statin use at baseline. The descriptive summaries and the two sided 95% CIs for the hazard ratio will be provided. Likelihood tests for treatment by subgroup interaction comparing models with and without interaction terms between treatment and categories will also be assessed. While a formal test for heterogeneity of treatment effect by country or center has not been prespecified, center level deviations will be monitored across multiple operational quality measures such as rate of discontinuation of study drug to ensure there are no systematic differences introduced during the study.

The subgroups may be based on characteristics including but not limited to the list below.

Variable	**Categories**
Baseline Subgroups	
Sex	Men, Women
Established Cardiovascular Disease	Yes, No
Statin Use	Defined as those who are taking no statin at baseline or are statin intolerant compared to all others.
Region	Africa, Asia (comprising Japan, Israel and India), Eastern Europe, Latin America, US/Canada, Western Europe
Age	<65, >=65
BMI (kg/m^2)	<30, 30-34, >=35
Race	Asian, Black or African American, White, Other (including, Other, Multiracial and Not Reported)
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Unknown/Not Reported
Duration of Diabetes	<10 years,

	>=10 years
Hypertension	Yes, No
HDL	Above/below median at baseline (screening value)
LDL	Above/below median at baseline (screening value)
Fasting TG	Above/below median at baseline (screening value)
Non-Fasting TG	Above/below median at baseline (randomization value)
Non-HDL Cholesterol	Above/below median at baseline (screening value)
ApoB	Above/below median at baseline (screening value)
Non-fasting Remnant Cholesterol	Above/below median at baseline (randomization visit)
HbA1c	Above/below median at baseline (screening value)
hsCRP	Above/below median at baseline (screening value)
CYP3A4 or CYP2C8 Inhibitor Use	Yes, No
Ezetimibe Use	Yes, No
PPAR-α rs6008845 genotype	TT variant, TC variant, CC variant
On-Treatment Subgroups	
On-Treatment Fasting TG	Above/below the median of the on-treatment values in the pemafibrate group at a fasting 4 Month visit.

On-Treatment Non-Fasting TG	Above/below the median of the on-treatment values in the pemafibrate group at a non-fasting 6 Month visit.
On-Treatment Non-HDL Cholesterol	Above/below the median of the on-treatment values in the pemafibrate group at 4 Month visit.
On-Treatment ApoB	Above/below the median of the on-treatment values in the pemafibrate group at 4 Month visit.
On-Treatment Non-Fasting Remnant Cholesterol	Above/below the median of the on-treatment values in the pemafibrate group at 6 Month visit.
On-Treatment hsCRP	Above/below the median of the on-treatment values in the pemafibrate group at 4 Month visit.

Subgroup analyses may also be added to safety presentations as needed.

Forest plots will be generated for the subgroup analyses.

8.4. Analysis of the Primary Efficacy Endpoint

8.4.1. Primary Efficacy Analysis

The primary endpoint of the trial is the time from randomization to the first occurrence of any component of the clinical composite endpoint of nonfatal myocardial infarction, nonfatal ischemic stroke, cardiovascular death, and coronary revascularization.

Patients who do not have an event will be censored at withdrawal of consent, end of study, or death. The censor date will be the date of withdrawal of consent for follow-up, CSED or the subject's last assessment, or death, whichever comes first. The time to event/censoring in days will be derived as (Date of First Occurrence of Event/Censoring – Date of First Dose) +1.
The primary analysis of the trial will use a likelihood ratio test based on a proportional hazards model stratified on sex, prior history of CVD, and statin use at baseline to test the null hypothesis of no association between assignment to active K-877 and the rate of the primary endpoint. All analyses will classify patients according to their randomized treatment assignment, i.e. according to the intention to treat principle, and will base evaluation of statistical significance on a two-sided test with level 0.05. The estimated relative hazard in the K-877 group compared to the placebo group with an accompanying 95% confidence interval will quantify the treatment effect[9]. 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 K-877 treatment. Rates of occurrence of the primary endpoint will be defined as the total number of subjects who have this event in a treatment group per 100 person-years of follow-up. 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.

Analysis will be implemented using the SAS® procedure PHREG as follows:

```
PROC PHREG DATA = …;
     CLASS TREATMENT (ref='2');
     MODEL AVAL*CNSR(1) = TREATMENT;
     STRATA SEX CVD STATIN;
     HAZARDRATIO TREATMENT / ALPHA=0.05;
RUN;
```

where AVAL = time to event
TREATMENT = Randomized treatment group (pemafibrate and placebo)
CNSR = Censoring variable – 0 = Event, 1 = Censored
SEX = sex
CVD = prior history of CVD
STATIN = statin use at baseline

Additional analyses will separately evaluate whether the relative effects of K-877 versus placebo 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 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. 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.

8.4.2. Sensitivity Analyses of the Primary Efficacy Results

Two main types of sensitivity analyses will be done for the primary efficacy results. One sensitivity analysis will be to repeat the primary analysis on the Per-Protocol population. The other includes post-randomization changes in other lipid-lowering therapies.

Sensitivity of the results to post-randomization changes in other lipid-lowering therapies will be assessed using a combination of strategies. As noted in the subgroup analyses, the results will be stratified by baseline statin use. Additionally, an inverse probability treatment weighted approach as developed by Robins and Hernan[8] will be used to account for time varying changes in lipid-lowering therapy and to obtain an adjusted treatment effect estimate.

Additional analysis to clearly explore the efficacy over time will be performed as follows:

Primary endpoint as well as every component of the primary endpoint will be summarized by treatment and by within year from randomization (first year from randomization, second year from randomization, third year from randomization, fourth year from randomization, and greater than 4 years from randomization).

Secondary endpoints will also by summarized similar to the primary endpoint by within year from randomization.

8.5. Analysis of the Secondary and Tertiary Efficacy Endpoints

In addition to the primary comparisons of K-877 treatment with placebo, prespecified secondary efficacy endpoints will also be compared between treatment groups.

A sequential gate-keeping procedure will be used for the secondary endpoint testing to control for the overall type I error at the 0.05 significance level. The primary endpoint will be tested first at the 0.05 significance level, secondary endpoints will only be evaluated if primary endpoint is positive. The total secondary endpoint alpha of 0.05 will be allocated between the two secondary endpoints groups. Group A will be allocated an alpha of 0.049 and Group B will be allocated 0.001. Within each secondary endpoint group, a hierarchical testing structure will be followed, if the testing is found to be statistically significant then proceed to the next endpoint testing at the significance level of the group, otherwise stop testing. The hierarchical testing will be based on the order of endpoints defined in Sections 3.2.2.1 and 3.2.2.2.

The order of Group A secondary endpoints is as follows:

1. The 4-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or cardiovascular death

2. Any component of the 3-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, or cardiovascular death

3. Any component of the primary endpoint or hospitalization HF

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

5. Any new or worsening PAD

6. Individual endpoints and an analysis of total events (first and all recurrent non-fatal MI, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death)

7. Heterogeneity of effect by PPAR-α genetic polymorphisms, in particular but not limited to rs6008845.

Analysis of time to event Group A secondary endpoints 1-5 and individual endpoints analysis (first part of endpoint 6) will mirror the primary analysis. Specifically, analyses of these secondary endpoints will use a likelihood ratio test based on a proportional hazards model stratified on sex, prior history of CVD, and statin use at baseline to test the null hypothesis of no association between assignment to active K-877 and the rate of a specific secondary endpoint.

The total events analysis (second part of endpoint 6) will use negative binomial regression, with outcome being the total number of such events, a log link function, and a subject's total follow-up time as an offset. The independent variable will be randomized treatment assignment, and the

model will consider the following variables as fixed effects: sex, prior history of CVD, and statin use at baseline.

The analysis of heterogeneity of treatment effect by PPAR-α genetic polymorphisms will use a Cox proportional hazards model including two stratification variables: sex and prior history of CVD. This is due to both the low level of statin intolerance at baseline and concern that some of the genetic subgroups may be sparse.

In addition to the separate analyses of each component of the primary endpoint, possible heterogeneity in their effects across components will be evaluated. 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[4, 5]. The approach of Fine and Gray provides a readily accessible implementation of a classical approach to competing risk analysis developed by Kalbfleisch and Prentice[6].

In addition to the individual components of the composite primary endpoint, other CVD endpoints will be evaluated for treatment effect, including time to all-cause mortality, time to first MI, time to first stroke, time to first ischemic stroke, and time to first hemorrhagic stroke. Analyses will consider both fatal and non-fatal events where appropriate.

Secondary Group B lipid efficacy endpoints will be analyzed using analysis of covariance (ANCOVA) with a retrieved dropout based pattern mixture model. Subjects 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.

Analysis using an ANCOVA model will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
     CLASS TREATMENT SEX CVD STATIN;
     MODEL PCHG = BASELINE TREATMENT SEX CVD STATIN;
     LSMEANS TREATMENT / DIFF CL;
RUN;
```

where `PCHG` = percent change from baseline
`TREATMENT` = Randomized treatment group (pemafibrate and placebo)
`BASELINE` = baseline value
`SEX` = sex
`CVD` = prior history of CVD
`STATIN` = statin use at baseline

The time to event microvascular tertiary endpoints will be analyzed as outlined for the primary analysis. The other tertiary endpoints will be analyzed using MMRM method. Each model will include the endpoint result change from baseline at each study visit as the response variable and

study visit, randomization strata, baseline endpoint result, baseline result-by-study visit interaction, treatment, and treatment-by-study visit interaction.

Analysis using MMRM method will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
     CLASS VISIT SEX CVD STATIN TREATMENT SUBJID;
     MODEL CHG = VISIT SEX CVD STATIN BASELINE BASELINE*VISIT
     TREATMENT TREATMENT*VISIT / DDFM=KR;
     REPEATED VISIT / SUBJECT = SUBJID TYPE=UN;
     LSMEANS TREATMENT*VISIT / DIFF CL;
RUN;
```

where `CHG` = change from baseline at each study visit
`TREATMENT` = randomized treatment group (pemafibrate and placebo)
`BASELINE` = baseline value
`SEX` = sex
`CVD` = prior history of CVD
`STATIN` = statin use at baseline
`VISIT` = study visit
`SUBJID` = subject ID

If the MMRM model using an unstructured covariance matrix fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm will be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yields convergence, a structured covariance, such as heterogeneous Toeplitz and Toeplitz structures, will be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance-covariance estimator is asymptotically consistent.

8.6. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

Any subjects excluded from the per-protocol population (PP) will be summarized by treatment group and supported by an individual subject data listing providing the reason each subject was made unevaluable.

9. QUALITY OF LIFE ANALYSES

9.1. Summary of European Quality of Life–5 Dimensions 5 Level Questionnaire

For assessment of health related quality of life, the EQ-5D-5L will be used to generate summary indices. These will be analyzed using an MMRM that will include the EQ-5D-5L VAS Score change from baseline at each study visit as the response variable and study visit, randomization strata, baseline result, baseline result-by-study visit interaction, treatment, and treatment-by-study visit interaction..

The same SAS® procedure MIXED as stated in Section 8.5 for the analysis of the tertiary lipid endpoints will be used.

10. SAFETY AND TOLERABILITY

The safety analyses will be summarized for all subjects included in the Safety population by treatment group.

10.1. Overall Summary of Adverse Events

Any AE that occurs during the study is a study AE. Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and prior to the last date of study medication + 30 days (inclusive). The overall incidence summary of all AEs will include the following:

- Number and percent of subjects with at least one TEAE;
- Number and percent of subjects with at least one TESAE;
- Number and percent of subjects with at least one severe TEAE;
- Number and percent of subjects with at least one drug related TEAE;
- Number and percent of subjects with at least one drug related TESAE;
- Number and percent of subjects with at least one TEAE leading to death;
- Number and percent of subjects with at least one TEAE leading to study drug interruption/discontinuation;

The information presented in this table is derived from the adverse event record and these results may differ from summaries that use the end of study record as the data source (e.g., subject accounting and disposition). This can occur when counting the number of discontinuations due to AE using data in the end of study record compared to the outcome in the AE record.

10.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.0 or higher.

10.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

Incidence of TEAEs will be presented by SOC and PT. Subjects will be counted only once at the SOC level and will be counted once for each applicable PT; multiple occurrences of the same preferred term for a subject will be counted only once. Subjects who experience more than one event within the same SOC are counted once at each preferred term level.

Supplementary tables will summarize the events with respect to the maximum severity observed for each preferred term and relationship to study medication.

10.2.2. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

Adverse event incidence rates, by SOC and PT, will be summarized for subjects who report a non-fatal serious adverse event, discontinue treatment prematurely due to an adverse event, and

deaths. A listing will also be generated of premature discontinuations due to all causality. Individual data listings will support these tables in two forms:

1. Sorted by subject and all events at the preferred term level.
2. Sorted by preferred term and listing all subjects.

10.3. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, Compliance, and Study Drug Exposure

The duration of treatment will be summarized as a continuous measure and in a frequency distribution. The average daily dose, maximum daily dose attained at any time during the study, the final daily dose taken just prior to study termination, and compliance will also be summarized.

Subject months of drug exposure will be presented as cumulative summary statistics. The total number of days of treatment will be determined for each subject and then summed over all subjects. This total is divided by 30 days to estimate the months.

10.4. Concomitant and Other Medications

Concomitant medications, prescribed and over the counter, that the subject takes or continues to take after baseline will be summarized. Medications with missing dates will be imputed according to section 6.7.2. The same summary format applies here as it was described for the medication history in section 7.7 with respect to major drug class, minor drug class, and generic name. The same subject counting procedures will also apply (eg, major class frequencies will represent subjects only once even though the same subject can be counted for multiple minor sub-classes and generic names).

10.5. Routine Laboratory Data

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. Presentations will use SI units. Tryglicerides and Glucose will be split by fasting status. An additional by visit Lipid table will be presented using conventional units along with the reference ranges and change from baseline.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries.

Actual and change from baseline by visit will be summarized for quantitative measurements. The within-group p-value from the paired t-test on the mean change from baseline and the 95% confidence interval limits for the mean change from baseline are also included with the change descriptive statistics. For select quantitative laboratory data, assessments will also be presented graphically to show the change from baseline as a function of the baseline value.

Shift tables (in categories of low, normal, and high) from baseline to each post-baseline scheduled visit will be provided by treatment group for selected laboratory parameters. Also, the number and percentage of subjects with clinically relevant abnormal laboratory values will be

calculated for each treatment group for selected laboratory parameters. Percentages for these summaries will be based on the available data, rather than the total number of subjects.

10.6. Vital Signs

Actual and change from baseline vital signs will be summarized by visit for systolic and diastolic blood pressures (mmHg), heart rate (bpm), waist circumference (cm), weight (kg) and BMI (kg/m^2). The organization of the results is the same as described for the laboratory data.

The incidence rates of significant vital sign changes, including the criteria for clinically notable, will be summarized. Clinically notable will be identified as the following criteria:

- Systolic BP
    - <=90 Low
    - 90-160 Normal
    - >=160 High
- Diastolic BP
    - <=60 Low
    - 60-100 Normal
    - >=100 High
- Heart Rate (HR)
    - <55 Low
    - Greater than or equal to 55 and less than or equal to 130 Normal
    - >130 High

11. REFERENCES

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APPENDIX 1: SUMMARY OF CHANGES TO THE CLINICAL TRIAL PROTOCOL

Amendment 1. On March 27, 2017, the clinical trial protocol was amended to incorporate the following changes:

1. The telephone visit at Month 2 was converted to an in-person visit with fasting blood samples for safety laboratory assessment and pregnancy testing.

2. A second criterion was added to Section 8.2.3 (Rescue Therapy for Persistently Elevated TG During the Study). Specifically, an alert to Investigators was added when fasting TG levels exceed 650 mg/dL (7.34 mmol/L) with a concurrent 60% increase from fasting baseline value. This was added to clarify alerts for both fasting and non-fasting TG values.

3. Clarification was made that study drug compliance would be assessed at in-person dispensing visits.

4. Clarification was made that unblinded participants must continue to be followed for study visits.

5. Urine sample collection was removed from the Screening and Enrollment Visit.

6. A typographical error in the Lachin and Foulkes power formula was corrected.

7. Alpha allocation was specified for Group A and Group B secondary endpoints.

8. A sentence indicating that while a formal test for heterogeneity of treatment effect by country or center is not pre-specified, center level deviations across multiple operational quality measures will be monitored.

9. Other minor changes including a) typographical error pertaining to free T4 levels, Section 7.2 exclusion criterion 6, b) insertion of ‘low’ prior to HDL-C levels, Section 5.1, and c) removal of ‘time to first occurrence of’ for Group B lipid endpoints, section 5.2.2.

Amendment 2. On March 18, 2020, the clinical trial protocol was amended to incorporate the following changes:

1. The primary endpoint was modified. “Hospitalization for unstable angina requiring unplanned coronary revascularization” was replace with “coronary revascularization.

2. The change in detectable risk reduction was changed from 18% to 16.6%.

3. It was clarified that the study must accrue 1279 (previously mentioned as 1071) adjudicated and confirmed events in order to achieve 90% power for the 16.6% risk reduction and that this number was increased by 1.9% to account for interim monitoring, bringing the final targeted number of events to 1304.

4. The target number of events was changed throughout the document from 1092 to 1304.

5. Associated tables and entries which describe event rates (Table 2 in this document) were updated accordingly to reflect the new risk reduction, target number of events adjusted for interim analyses, and placebo event rates.

6. The secondary endpoints (Group A Clinical) were updated to reflect the corresponding changes in the primary endpoints. Specifically, the original primary endpoint was made the first Group A endpoint.

7. Time to event analyses of individual endpoints and total events were added as part of the secondary analysis.

8. An additional secondary analysis was added to investigate evidence of any genetic effect modification that may relate to pemafibrate and incident cardiovascular events. In particular, the investigation of the effect of pemafibrate as compared to placebo on cardiovascular events according to known genetic polymorphisms in the PPAR-α gene, (such as, but not limited to rs6008845) is now pre-specified.

9. Text was added to clarify the difference between study drug discontinuation (temporary) and permanent discontinuation (through written withdrawal of consent from the study).

10. A statement was added to clarify that for subjects who withdraw from the study but do not revoke consent, contact methods in the original consent form may be used to ascertain health status.

11. A definition of coronary revascularization was added to support the update to the primary endpoint.

12. To enhance compliance among subjects who have discontinued study medication, an option to restart study medication at once daily dosing has been added with a goal to achieve targeted twice daily dosing.

13. The frequency of safety laboratory tests was decreased to annual after month 12 to limit unnecessary blood draws.

14. Other minor changes include clarification regarding timing of the Quality of Life questionnaire, deletion of mention of thyroid studies from month 2, 4, and 6 visits to align with the protocol text and lab schedule, and administrative changes (e.g. Quintiles changed to IQVIA throughout).

15. All countries where subjects are participating in the trial were sent Protocol Amendment 2 for consideration. The only country that objected to the proposed changes was India. The Subject Expert Committee (SEC) representing the Indian Regulatory Authority (DCGI)

denied acceptance of the changes. Submission of study data to the Indian Regulatory Authority will be addressed at the end of the trial based upon future discussions with India.