KOWA

RESEARCH INSTITUTE, INC.

A Multicenter, Randomized, Open-Label, 4-Week Study to Investigate the Efficacy and [redacted] of K-877-ER [redacted] Treatment (From [redacted] day to [redacted] day) Compared to K-877-IR [redacted] Treatment ([redacted] day) in Adult Patients With Fasting Triglyceride Levels ≥200 mg/dL and <500 mg/dL

NCT #: 04447820

Protocol Version Date: 28 January 2020

CONFIDENTIAL

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RESEARCH INSTITUTE, INC.

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Clinical Study Protocol

Drug Name:	K-877-ER
Study Number:	K-877-ER-201
U.S. IND Number:	109388
EudraCT Number:	2015-003511-37
Protocol Version Date:	28 January 2020
Version #:	1.0
Name of Sponsor:	**Kowa Research Institute, Inc.**
Address:	[redacted]
Managing Contract Research Organization:	[redacted]
Address:	[redacted]
Telephone:	
Fax:	

PROTOCOL SIGNATURE PAGE

STUDY TITLE: A Multicenter, Randomized, Open-Label, 4-Week Study to Investigate the Efficacy and [redacted] Profile of K-877-ER [redacted] Treatment (From [redacted]/day to [redacted]/day) Compared to K-877-IR [redacted] Treatment ([redacted]/day) in Adult Patients With Fasting Triglyceride Levels ≥200 mg/dL and <500 mg/dL

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

[redacted]

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Kowa Research Institute, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Kowa Research Institute, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Kowa Research Institute, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Multicenter, Randomized, Open-Label, 4-Week Study to Investigate the Efficacy and [redacted] of K-877-ER [redacted] Treatment (From [redacted] day to [redacted] day) Compared to K-877-IR [redacted] Treatment ([redacted] day) in Adult Patients With Fasting Triglyceride Levels ≥200 mg/dL and <500 mg/dL

PROTOCOL NUMBER: K-877-ER-201

INVESTIGATIONAL PRODUCT: K-877-ER

PHASE: 2

INDICATION: Dyslipidemia

OBJECTIVES:

The primary objective of this study is to demonstrate the efficacy of K-877-ER [redacted] compared to K-877-IR [redacted] from baseline to Day 28 in lowering fasting triglyceride (TG) levels in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL.

The secondary objectives of this study are the following:

- To demonstrate the efficacy of K-877-ER [redacted] compared to K-877-IR [redacted] from baseline to Day 28 in lowering fasting TG levels in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL;
- To evaluate the efficacy of K-877-ER [redacted] treatments (from [redacted] day to [redacted] day) from baseline to Day 28 in altering pharmacodynamic properties, including lipid parameters, in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL; and
- To evaluate the multiple-dose [redacted] properties at steady state of K-877-ER [redacted]

POPULATION:

Inclusion Criteria

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

1. Able to provide written informed consent before any study-specific evaluation is performed;
2. Aged ≥18 years;
3. [redacted]

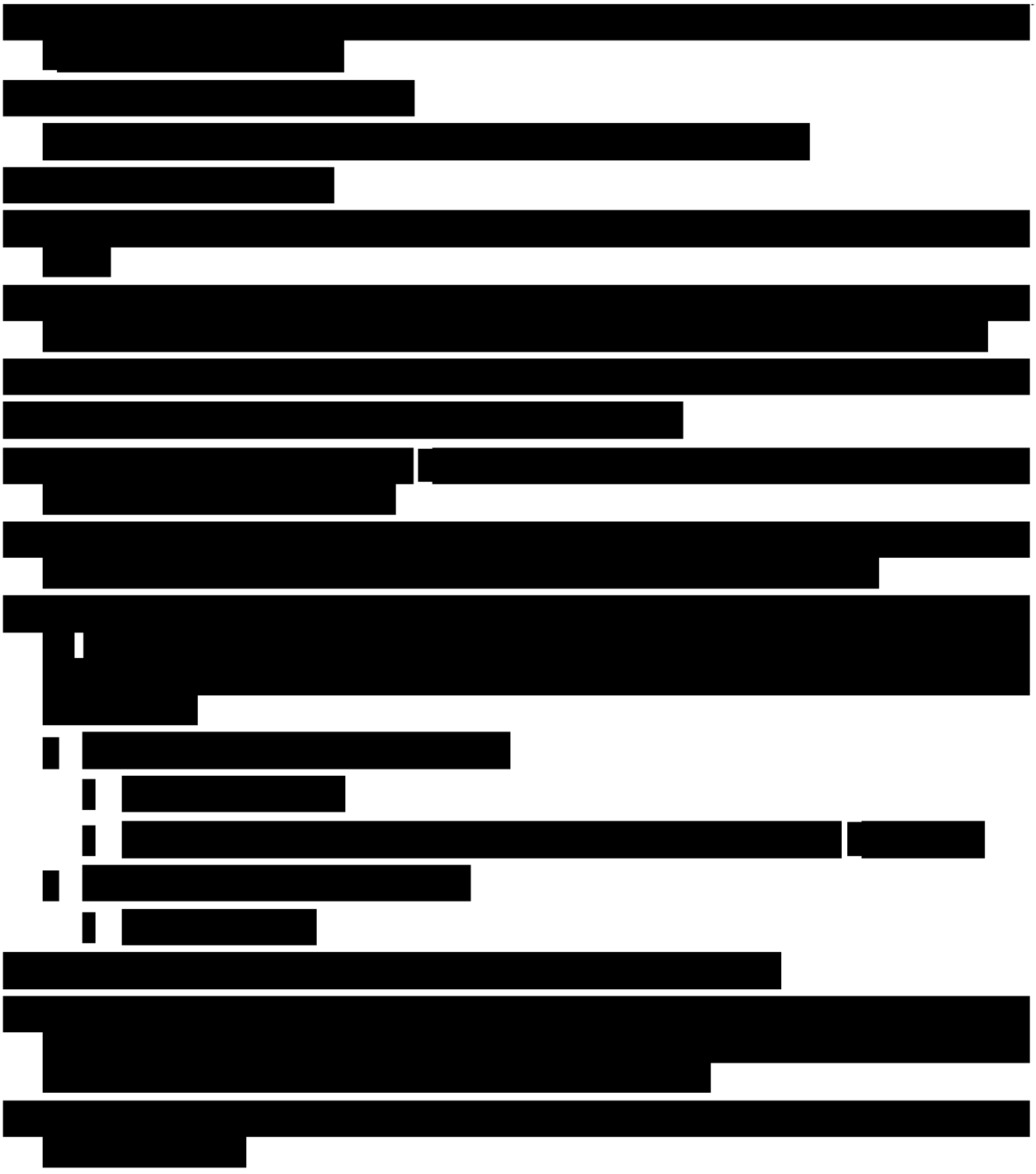
4. [redacted]
5. No clinically significant abnormal findings on hematology, serum chemistry, endocrinology, urinalysis, medical history, physical examination, vital signs, and 12-lead electrocardiogram (ECG), that would impair participation or safe conduction of the study as judged by the Investigator at screening;
6. Female patients of childbearing potential must not be breastfeeding and must have a negative serum pregnancy test at screening. Female patients of childbearing potential must use 1 of the following acceptable birth control methods, as specified, before enrollment and throughout the study (i.e., through discharge from the clinical site):
    - Surgical sterilization (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 6 months prior to the first dose of study drug;
    - Intrauterine device in place for at least 3 months prior to the first dose of study drug and throughout the study;
    - Barrier method (condom or diaphragm) with spermicide for at least 30 days prior to the first dose of study drug and throughout the study;
    - Surgical sterilization of the male partner (vasectomy at least 6 months prior to the first dose of study drug); or
    - Consistent hormonal contraceptives (oral, implantable, transdermal, ring, or injectable) use with a barrier method for at least 3 months prior to the first dose of study drug and throughout the study;
7. Female patients are not considered to be of childbearing potential if they meet at least 1 of the following 2 criteria as documented by the Investigator:
    - They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at a minimum of 1 menstrual cycle prior to signing the informed consent form (ICF); or
    - They are postmenopausal: for female patients ≥55 years of age, defined as ≥1 year since their last menstrual period, or for female patients <55 years of age, defined as ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in the central laboratory's normal range for postmenopausal phase;
8. Able and willing to comply with the protocol and study procedures;
9. Willing to abstain from alcohol and caffeine 24 hours prior to screening and 24 hours prior to each clinical site visit; and
10. For [redacted] patients: able and willing to abstain from grapefruit-containing foods or beverages, St. John's wort, and herbal supplements from 7 days before Day 1 to discharge on Day 2, and from 7 days before Day 28 to discharge on Day 29.

Exclusion Criteria

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

1. Require lipid-altering treatments other than study drugs, statins, ezetimibe, or PCSK9 inhibitors during the study. These include bile acid sequestrants, fibrates, niacin (>100 mg/day), omega-3 fatty acids (>1000 mg/day), or any supplements used to alter lipid metabolism including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols. These lipid-altering medications can be washed out, after informed consent, during a 6-week washout period prior to the Qualification Period;
2. Known hypersensitivity or intolerance to fibrates or peroxisome proliferator-activated receptor alpha agonists;
3. Body mass index >45 kg/m^2;
4. Type 1 diabetes mellitus;
5. Newly diagnosed (within 3 months prior to screening) or poorly controlled type 2 diabetes mellitus, defined by a hemoglobin A1c >9.5% at screening;

[redacted]



STUDY DESIGN AND DURATION:

Study K-877-ER-201 is a Phase 2, multicenter, randomized, open-label study investigating the efficacy and [redacted] profile of K-877-ER [redacted] treatment (from [redacted] day to [redacted] day) compared to K-877-IR [redacted] [redacted] treatment ([redacted] day) in adult patients with fasting TG levels ≥200 mg/dL and <500 mg/dL. The study consists of a Screening Period, of up to 10 weeks, and a 4-week

Treatment Period. During the Treatment Period, patients will receive K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted]

Approximately [redacted] patients who meet all the inclusion criteria and no exclusion criteria will be enrolled in the study. Of the approximately 90 patients enrolled, [redacted] patients will be enrolled as [redacted] patients, and will have blood samples for [redacted] assessments collected. [redacted] patients will not have blood samples for [redacted] assessments collected.

The Screening Period will occur no more than 70 days and no less than 7 days prior to the first dose of study drug (Day 1, Visit 4). The up to 10-week Screening Period will allow for a 6-week washout period, if needed, followed by up to a 4-week Qualification Period that will be used to assess patient eligibility. At the Screening Visit (Visit 1), a patient's individual TG level must be ≥180 mg/dL and <550 mg/dL.

Patients on non-permitted background lipid-altering therapy must complete a 6-week washout period prior to the first Qualification Period visit (Visit 2). If a patient does not require washout, the patient may start the Qualification Period (Visit 2) 24 hours after signing the ICF. Patients may continue through the Qualification Period provided that there are no prohibitive safety or eligibility results from the Screening Visit (Visit 1) laboratory tests.

[redacted]

Prior to treatment on Day 1, eligible patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups. Randomization will be stratified by sex (male or female), statin use (yes or no), and [redacted] (yes or no).

The Treatment Period will occur from Days 1 through 28. On Days 14 and 28, patients will return to the clinical site for efficacy and safety assessments. Patients enrolled as [redacted] patients will be admitted to the clinical site on Day -1 and confined until discharge on Day 2. [redacted]

Patients will participate in a Follow-Up Telephone Call 7 days (±2 days) following the last dose of study drug for safety monitoring.

All procedures to be conducted during the study, including timing of all procedures, are described in the Schedule of Procedures. Selected study procedures should be performed prior to administration of study drug, as applicable.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

On Day 1, prior to dosing, eligible patients will be randomized in a 1:1:1 ratio to 1 of the following treatment groups:

- K-877-ER [redacted] orally;
- K-877-ER [redacted] orally; or
- K-877-IR [redacted] orally.

Patients will receive oral doses of K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted] starting on Day 1 and concluding on Day 28 in the fed state. Patients in the K-877-IR [redacted] treatment group will receive only the morning dose on Day 28. Study drug will be administered in the fed state at 0 hour with 240 mL of room temperature tap water. Within 30 minutes prior to study drug administration on Days 1 and 28, [redacted] patients confined to the clinical site will be administered a meal containing 2300 to 2500 calories, less than 60% carbohydrates, and less than 25% fat. Patients in the K-877-IR [redacted] treatment group will receive an evening dose after a meal.

EFFICACY VARIABLES:

The primary efficacy endpoint is the percent change in fasting TG from baseline to Day 28. The baseline fasting TG level will be defined as the mean of 3 TG levels: 2 Qualification Period TG levels within the target range (≥200 mg/dL and <500 mg/dL) and the Day 1 (Visit 4) TG level.

The secondary efficacy endpoints include the percent change from baseline to Day 28 for the following:

- Total cholesterol (TC);
- Low-density lipoprotein cholesterol (LDL-C);
- High-density lipoprotein cholesterol (HDL-C);
- Remnant cholesterol (calculated as TC – LDL-C – HDL-C);
- Non-HDL-C; and
- Free fatty acids.

[redacted]

[redacted]

SAFETY VARIABLES:

Safety parameters will include all adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including lipid parameters], coagulation, and urinalysis), vital sign measurements, 12-lead ECG findings, and physical examination findings.

STATISTICAL ANALYSES:

Analysis Populations

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

The Per-Protocol Set will include all FAS patients without any major protocol deviations and who have baseline and Day 28 endpoint fasting serum TG measurements. Major protocol deviations will be confirmed prior to database lock. The Per-Protocol Set will be the primary analysis population.

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

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

Analysis of Efficacy

The primary efficacy analysis will compare 1 of the 2 K-877-ER treatments (test treatments) to the K-877-IR [redacted] treatment (reference treatment) in percent change in fasting TG from baseline to Day 28 with a mixed model for repeated measures based on the Per-Protocol Set population. The model will include Visit (Day 14 or 28), treatment (K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted] the interaction term between Visit and treatment, baseline value, sex (male or female), and statin use (yes or no) as fixed effects, and an unstructured covariance matrix will be utilized. If the model for the unstructured covariance matrix fails to converge, other covariance structure will be considered.

Point estimates and 2-sided 90% confidence intervals (CIs), as well as 95% CIs of the differences of least squares means between either of the test treatments and reference treatment will be calculated. A non-inferiority of tested treatments will be indicated if the upper limit of the 2-sided 90% CI is <15% in TG percent change from baseline.

The secondary efficacy analysis will compare 1 of the 2 K-877-ER treatments (test treatments) to the K-877-IR [redacted] treatment (reference treatment) in percent change from baseline to Day 28 for the secondary endpoints with a mixed model for repeated measures with the same model used for primary efficacy analysis. The secondary endpoints to be included are TC, LDL- C, HD-C, remnamt cholesterol (calculated as TC – LDL-C – HDL-C), non-HDL-C, and free fatty acids.

The same analyses will be repeated in the FAS population for both primary and secondary efficacy analyses.

Descriptive statistics (n, mean, standard deviation [SD], minimum, first quartile [Q1], median, third quartile [Q3], maximum, and 90% CI) for the primary endpoint (percent change from baseline in TG) and secondary endpoints will be summarized by treatment group at baseline and Days 14 and 28. Descriptive statistics for changes from baseline and for percent changes from baseline to each visit will also be summarized. Point estimates and 90% CIs of the differences between either of the test treatments and reference treatment will be calculated.

[redacted]

[redacted]

Analysis of Safety

Demographics and baseline characteristics will be listed and summarized. Data listings will be presented for all AEs, clinical laboratory tests (hematology, serum chemistry [including lipid parameters], coagulation, and urinalysis), vital sign measurements, 12-lead ECG findings, and physical examination findings.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. All treatment-emergent AEs (TEAEs) will be summarized by treatment. In addition, TEAEs will be summarized for each treatment by intensity and relationship to study drug. All TEAEs leading to withdrawal from study drug and serious AEs will also be summarized. All tables will be summarized by system organ class and preferred term, including counts of AEs and patients with AEs. All AEs will be listed by patient.

Clinical laboratory tests, vital sign measurements, and 12-lead ECG findings will be summarized by time point and change from baseline for each treatment. Laboratory values that are below the lower limit or above the upper limit of the reference range will be flagged and assessed for clinical significance by the Investigator.

SAMPLE SIZE DETERMINATION:

Assuming an effect size delta = 0, pooled SD = 21.38, an alpha = 0.05 (1-sided), and a non-inferiority limit of 15%, a sample size of 26 patients per treatment group provides a power of 0.80.

In the case that the actual effect size delta is 10%, the power is then 0.2. If the real effect is different, the result less likely shows non-inferiority.

To account for any potential drop off, a total of 90 patients, 30 patients in each treatment group, is planned to be randomized.

SITES: Approximately 12 sites in the United States

SPONSOR:

Kowa Research Institute, Inc.

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	[redacted]
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
[redacted]	[redacted]
CRA	Clinical Research Associate
[redacted]	[redacted]
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FT4	Free thyroxine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

Abbreviation	Definition
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	Interactive response technology
[redacted]	[redacted]
LDL-C	Low-density lipoprotein cholesterol
[redacted]	[redacted]
OATP	Organic anion-transporting polypeptide
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PPARα	Peroxisome proliferator-activated receptor alpha
Q1	First quartile
Q3	Third quartile
[redacted]	[redacted]
RNA	Ribonucleic acid
[redacted]	[redacted]
SAE	Serious adverse event
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
[redacted]	[redacted]
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
[redacted]	[redacted]

1 INTRODUCTION AND BACKGROUND INFORMATION

Pemafibrate (K-877) is a potent and selective peroxisome proliferator-activated receptor alpha (PPARα) modulator.[1] [redacted] K-877 is a selective PPARα modulator and in this manner activates PPARα. As a result, this process triggers a ligand-specific conformational change, regulating target gene expression, leading to improved lipid metabolism, especially decreased triglyceride (TG), but also decreased TG-rich lipoprotein, decreased apolipoprotein C3, and increased high-density lipoprotein cholesterol (HDL-C).[2]

Dyslipidemia is an important modifiable risk factor for the development of atherosclerosis and cardiovascular disease, and successful treatment is associated with improved patient outcomes and a reduction in morbidity and mortality.[3,4,5,6,7,8,9] While therapeutic lifestyle changes (i.e., smoking reduction/cessation, increased physical activity, dietary modifications, and weight control) remain essential to the management of dyslipidemia, many patients require concurrent pharmacotherapy to improve atherogenic dyslipidemia.[10,11] The currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), and selective cholesterol absorption inhibitors (e.g., ezetimibe).[11] In addition, recently approved lipid-lowering drugs include lomitapide (a microsomal TG transfer protein inhibitor) and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors.[2]

Fibrates improve TG and HDL-C by activating PPARα[12] and are labeled in the United States for the treatment of severe hypertriglyceridemia. In the United States, fenofibrate, fenofibric acid, and gemfibrozil are available.

Most fibrates are contraindicated or require careful administration in patients with renal dysfunction, partly because increased exposure may result in increased risk of adverse reactions in such a population. [redacted]

Total K-877 daily doses ranging from [redacted] to [redacted] administered [redacted] or divided into [redacted] doses, demonstrated an acceptable safety profile. [redacted]

1.1 Rationale

The present study is a Phase 2, multicenter, randomized, open-label study investigating the efficacy and [redacted] profile of K-877-ER [redacted] treatment (from [redacted] day to

[redacted] day) compared to K-877-IR [redacted] treatment ([redacted] day) in adult patients with fasting TG levels ≥200 mg/dL and <500 mg/dL.

[redacted]

K-877-ER tablets were designed to have a slower pemafibrate dissolution rate than that of K-877-IR tablets. The K-877-ER tablet is anticipated to provide extended K-877 plasma concentrations, which may provide a similar efficacy profile to K-877-IR tablets administered [redacted] K-877-ER tablets will be used for the same target indications as K-877-IR tablets, and are expected to contribute to better drug adherence and, therefore, better efficacy.[2]

The results of this study will provide a better understanding of the efficacy, [redacted] and pharmacodynamics (PD) associated with K-877-ER [redacted] treatments compared to K-877-IR [redacted] treatment.

1.2 Risk/Benefit

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of K-877-ER can be found in the Investigator Brochure (IB).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate the efficacy of K-877-ER [redacted] compared to K-877-IR [redacted] from baseline to Day 28 in lowering fasting TG levels in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To demonstrate the efficacy of K-877-ER [redacted] compared to K-877-IR [redacted] from baseline to Day 28 in lowering fasting TG levels in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL;
- To evaluate the efficacy of K-877-ER [redacted] treatments (from [redacted] day to [redacted] day) from baseline to Day 28 in altering PD properties, including lipid parameters, in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL; and
- To evaluate the multiple-dose [redacted] properties at steady state of K-877-ER [redacted]

3 STUDY DESCRIPTION

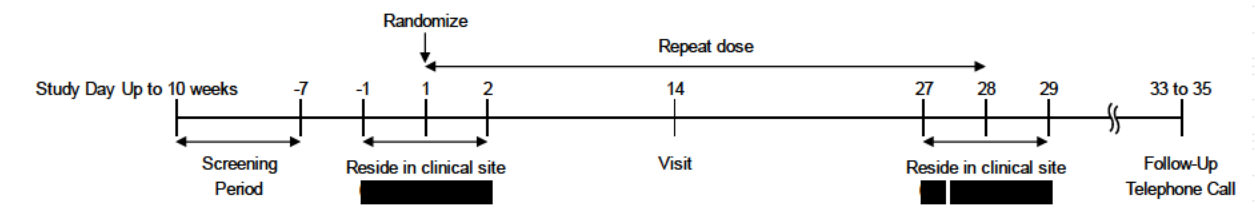
3.1 Summary of Study Design

Study K-877-ER-201 is a Phase 2, multicenter, randomized, open-label study investigating the efficacy and [redacted] profile of K-877-ER [redacted] treatment (from [redacted] day to [redacted] day) compared to K-877-IR [redacted] treatment ([redacted] day) in adult patients with fasting TG levels ≥200 mg/dL and <500 mg/dL. The study consists of a Screening Period, of up to 10 weeks, and a 4-week Treatment Period. During the Treatment Period, patients will receive K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted]

Approximately 90 patients who meet all the inclusion criteria and no exclusion criteria will be enrolled in the study. Of the approximately 90 patients enrolled, 24 patients will be enrolled as [redacted] see Section 7.3.

Figure 1 illustrates the study design for both [redacted]. All treatment groups and administration of study drug are described in Section 5.

Figure 1. Illustration of Study Design



[redacted] = [redacted]

The Screening Period will occur no more than 70 days and no less than 7 days prior to the first dose of study drug (Day 1, Visit 4). The up to 10-week Screening Period will allow for a 6-week washout period, if needed, followed by up to a 4-week Qualification Period that will be used to assess patient eligibility. At the Screening Visit (Visit 1), a patient's individual TG level must be ≥180 mg/dL and <550 mg/dL.

Patients on non-permitted background lipid-altering therapy, as outlined in Section 4.2, must complete a 6-week washout period prior to the first Qualification Period visit (Visit 2). If a patient does not require washout, the patient may start the Qualification Period (Visit 2) 24 hours after signing the informed consent form (ICF). Patients may continue through the Qualification Period provided that there are no prohibitive safety or eligibility results from the Screening Visit (Visit 1) laboratory tests.

[redacted]

[redacted]

Prior to treatment on Day 1, eligible patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups. Randomization will be stratified by sex (male or female), statin use (yes or no), and [redacted] (yes or no).

The Treatment Period will occur from Days 1 through 28. On Days 14 and 28, patients will return to the clinical site for efficacy and safety assessments. Patients enrolled as [redacted] patients will be admitted to the clinical site on Day -1 and confined until discharge on Day 2. On Day 27, [redacted] patients will be readmitted to the clinical site and confined until discharge on Day 29.

[redacted]

Patients will participate in a Follow-Up Telephone Call 7 days (±2 days) following the last dose of study drug for safety monitoring.

All procedures to be conducted during the study, including timing of all procedures, are described in the Schedule of Procedures in Appendix A. Selected study procedures should be performed prior to administration of study drug, as applicable. A complete list of laboratory analytes is provided in Appendix B.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Able to provide written informed consent before any study-specific evaluation is performed;
2. Aged ≥18 years;

5. No clinically significant abnormal findings on hematology, serum chemistry, endocrinology, urinalysis, medical history, physical examination, vital signs, and 12-lead electrocardiogram (ECG), that would impair participation or safe conduction of the study as judged by the Investigator at screening;
6. Female patients of childbearing potential must not be breastfeeding and must have a negative serum pregnancy test at screening. Female patients of childbearing potential must use 1 of the following acceptable birth control methods, as specified, before enrollment and throughout the study (i.e., through discharge from the clinical site):
    - Surgical sterilization (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 6 months prior to the first dose of study drug;
    - Intrauterine device in place for at least 3 months prior to the first dose of study drug and throughout the study;
    - Barrier method (condom or diaphragm) with spermicide for at least 30 days prior to the first dose of study drug and throughout the study;
    - Surgical sterilization of the male partner (vasectomy at least 6 months prior to the first dose of study drug); or
    - Consistent hormonal contraceptives (oral, implantable, transdermal, ring, or injectable) use with a barrier method for at least 3 months prior to the first dose of study drug and throughout the study;
7. Female patients are not considered to be of childbearing potential if they meet at least 1 of the following 2 criteria as documented by the Investigator:
    - They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at a minimum of 1 menstrual cycle prior to signing the ICF; or

- They are postmenopausal: for female patients ≥55 years of age, defined as ≥1 year since their last menstrual period, or for female patients <55 years of age, defined as ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in the central laboratory's normal range for postmenopausal phase;

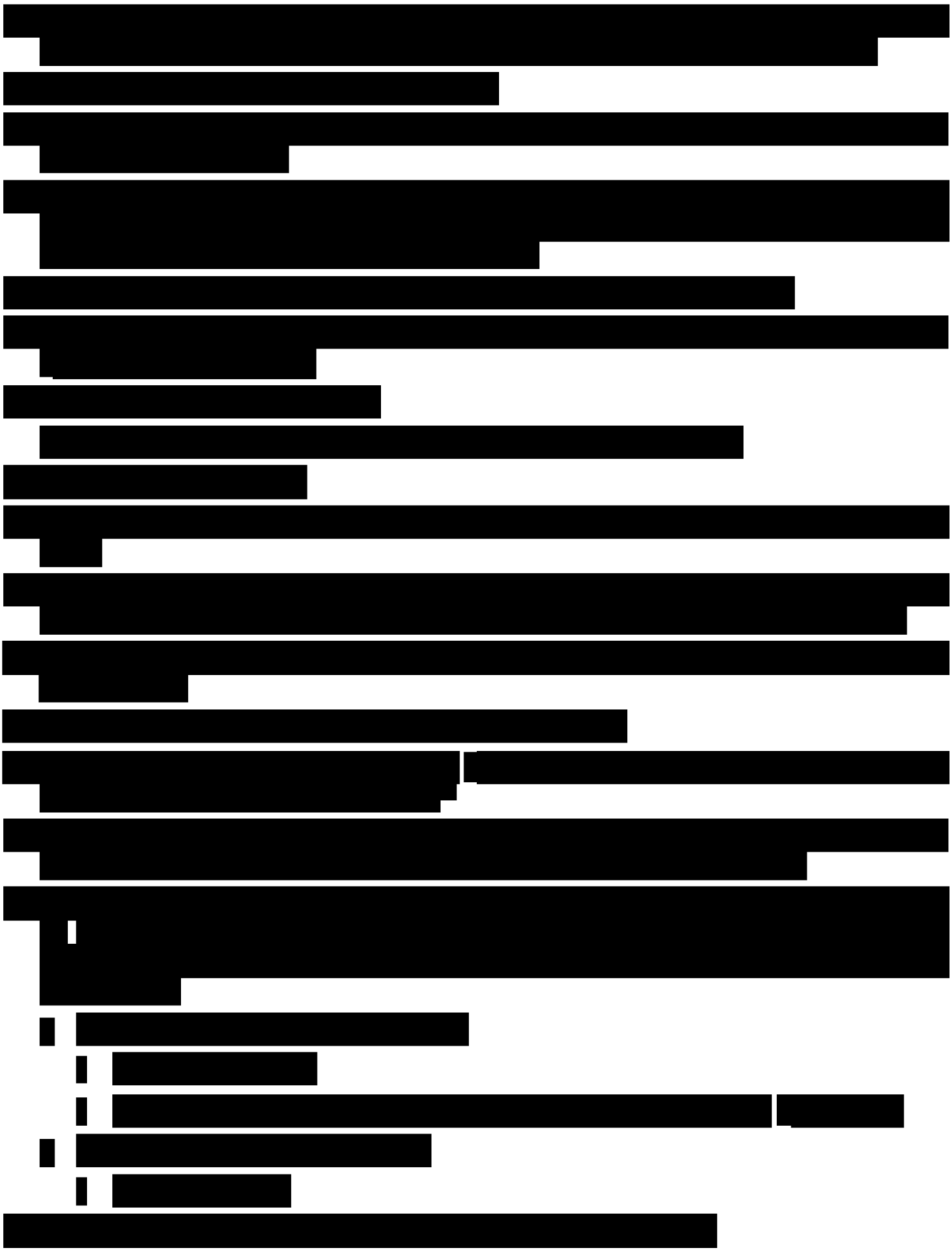
8. Able and willing to comply with the protocol and study procedures;
9. Willing to abstain from alcohol and caffeine 24 hours prior to screening and 24 hours prior to each clinical site visit; and
10. For [redacted] patients: able and willing to abstain from grapefruit-containing foods or beverages, St. John's wort, and herbal supplements from 7 days before Day 1 to discharge on Day 2, and from 7 days before Day 28 to discharge on Day 29.

4.2 Exclusion Criteria

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

1. Require lipid-altering treatments other than study drugs, statins, ezetimibe, or PCSK9 inhibitors during the study. These include bile acid sequestrants, fibrates, niacin (>100 mg/day), omega-3 fatty acids (>1000 mg/day), or any supplements used to alter lipid metabolism including, but not limited to, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols. These lipid-altering medications can be washed out, after informed consent, during a 6-week washout period prior to the Qualification Period;
2. Known hypersensitivity or intolerance to fibrates or PPARα agonists;
3. Body mass index (BMI) >45 kg/m^2;
4. Type 1 diabetes mellitus;
5. Newly diagnosed (within 3 months prior to screening) or poorly controlled type 2 diabetes mellitus, defined by a hemoglobin A1c (HbA1c) >9.5% at screening;

[redacted]



[redacted]

4.3 Study Drug Discontinuation Criteria

It will be necessary to make a distinction between patients who prematurely discontinue study drug treatment and those who withdraw from the study for any reason. If the patient discontinues study drug, the reason should be captured and could include the following:

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

During the 4-week Treatment Period, patients who discontinue study drug prematurely will remain in the study until Day 28 (Visit 6). If a patient who has discontinued study drug fails to attend any follow-up appointments, reasonable efforts (telephone calls to family members or friends, email contacts, etc.) will be made in order to encourage the patient to complete the study visits.

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

4.4 Withdrawal Criteria

The patient has the right to withdraw from the study at any time. Nevertheless, in this study, every attempt will be made to prevent missing data and to obtain complete follow-up of all patients.

Patients who meet study drug discontinuation criteria described in Sections 4.3 and 4.6 will be discontinued from study drug and may also be withdrawn from the study. However, patients who discontinue study drug are not required to withdraw from the study. As such, these patients will be encouraged to remain in the study and asked to attend all of the remaining study visits as outlined in the Schedule of Procedures in Appendix A. If a patient fails to actively maintain contact with the Investigator, reasonable efforts (telephone calls to family members or friends, email contacts, etc.) will be made in order to encourage the patient to complete the study visits.

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

1. The patient withdraws consent at any time or requests discontinuation from the study;
2. The patient fails to comply with protocol requirements or study-related procedures if, in the opinion of the Investigator or the Sponsor, the non-compliance will significantly compromise data interpretation or safety;
3. In the Investigator's judgment, it is in the patient's best interests;
4. Violation of the protocol inclusion and exclusion criteria is discovered, if, in the opinion of the Investigator or the Sponsor, the violation will significantly compromise data interpretation or safety; or
5. The Sponsor or the regulatory authority terminates the study.

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

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

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

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

4.5 Re-Screening of Screen Failures

Patients who are screen failures for a modifiable condition (such as elevated HbA1c or uncontrolled hypertension), other than failing the TG criteria, can be re-screened once, and enrolled in the study at a future date if they are then deemed eligible for study participation based on protocol entry criteria after having medications adjusted and stabilized. Before each patient is re-screened, the Investigator should discuss the case with the Medical Monitor.

4.6 Study Drug Discontinuation for Persistent Abnormal Clinical Laboratory Values

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

1. ALT or AST >8 × ULN, confirmed on repeat;
2. ALT or AST >3 × ULN and bilirubin >2 × ULN or international normalized ratio >1.5, confirmed on repeat (if patient has Gilbert's syndrome, bilirubin will require Medical Monitor review);

3. ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) confirmed on repeat;
4. ALT or AST >5 × ULN which persists for 2 weeks;
5. Unexplained CK >5 × ULN confirmed on repeat. For patients with CK ≥10 × ULN, Investigators should immediately interrupt study drug while awaiting re-evaluation;
6. Fasting TG levels >2000 mg/dL (22.60 mmol/L) with signs or symptoms of pancreatitis at any time during the study. For repeated or persistent elevations of TG >2000 mg/dL (22.60 mmol/L) that are not accompanied by signs or symptoms of pancreatitis, Investigators may discontinue study drug at their discretion; or
7. eGFR <30 mL/min/1.73 m^2 occurring on or after Day 14 (Visit 5), confirmed on repeat.

Note: Repeat testing should occur as soon as possible within 72 hours unless otherwise specified. If at any time during the study a patient develops elevations in ALT or AST >3 × ULN, CK >5 × ULN, TG >2000 mg/dL (>22.60 mmol/L), or a decrease in eGFR <30 mL/min/1.73 m^2 the study site will receive an alert from the central laboratory.

5 STUDY TREATMENTS

5.1 Treatment Groups

On Day 1, prior to dosing, eligible patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups. Patients will receive K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted] starting on Day 1 through 28. Treatment groups are detailed in Table 1.

Table 1. Treatment Groups

Treatment Group		
K-877-ER [redacted]	K-877-ER [redacted]	[redacted]
K-877-ER [redacted]	K-877-ER [redacted]	[redacted]
K-877-IR [redacted]	K-877-IR [redacted]	K-877-IR [redacted]
[redacted] = [redacted] = [redacted]		

5.2 Rationale for Dosing

A Phase 1 clinical study (K-877-101) conducted in healthy adults showed that the half-life of pemafibrate is relatively short (approximately 2 hours). A subsequent Phase 2 clinical study (K-877-201) conducted in patients with dyslipidemia showed that [redacted] administration of pemafibrate [redacted] tablet resulted in slightly higher efficacy in TG reduction than [redacted] administration of 2 pemafibrate [redacted] tablets (i.e., pemafibrate [redacted] As such, these results suggest that sustained pemafibrate plasma concentration, resulting from [redacted] administration, could contribute to higher pemafibrate efficacy in TG reduction. It is for this reason that the ongoing Phase 3 clinical studies are being conducted using [redacted] administration.

However, [redacted] formulations would be expected to contribute to better drug adherence and, therefore, better overall efficacy. Therefore, K-877-ER tablets were designed to have a slower pemafibrate dissolution rate than that of K-877-IR tablets, and as a result, are anticipated to provide extended K-877 plasma concentrations. This may, therefore, result in a similar efficacy profile to K-877-IR tablets administered [redacted] for the same target indications.

5.3 Randomization and Blinding

On Day 1, prior to dosing, eligible patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups. Randomization will be stratified by sex (male or female), statin use (yes or no), and [redacted] (yes or no). The Investigator or designee will access interactive response technology (IRT) and enter the patient identification number. The IRT system will record the randomized treatment assignment for the patient and assign the appropriate study drug kit.

5.4 Breaking the Blind

This is an open-label study.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The K-877-ER [redacted] tablet is a round, 7.6 mm diameter, white, film-coated tablet for oral administration, containing [redacted] pemafibrate.

The K-877-ER tablet contains the following excipients: [redacted]

The K-877-IR [redacted] tablet is a round, 7.1 mm diameter, white, film-coated tablet for oral administration, containing [redacted] pemafibrate.

K-877-IR [redacted] tablet contains the following excipients: [redacted]

Drug packaging will be completed by an [redacted] Investigational product will be distributed to sites by [redacted].

Study drugs will be packaged in clear polyvinylidene chloride/aluminum foil blisters within a child-resistant card. Patients will receive a complete supply of study drug on Day 1.

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

- Name and address of Sponsor (i.e., KRI);
- A study reference code (e.g., protocol number) allowing identification of the investigational site and Investigator;
- Route of administration, quantity of dosage units, and pharmacological form as appropriate;
- Lot number;
- Directions for use;
- The statement "Caution - New Drug - Limited by Federal (United States) Law to Investigational Use";
- The statement "Keep out of reach of children"; and
- The storage conditions.

5.5.2 Study Drug Preparation and Dispensing

Study drug, for entire treatment period, will be dispensed to eligible patients beginning on Day 1 (Visit 4), after randomization, via the IRT system.

5.5.3 Study Drug Administration

Patients will receive oral doses of K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted] starting on Day 1 and concluding on Day 28 in the fed state. Patients in the K-877-IR [redacted] treatment group will receive only the morning dose on Day 28. Study drug will be administered in the fed state at 0 hour with 240 mL of room temperature tap water. Within 30 minutes prior to study drug administration on Days 1 and 28, [redacted] patients confined to the clinical site will be administered a meal containing 2300 to 2500 calories, less than 60% carbohydrates, and less than 25% fat. On Days 1 and 28, [redacted] patients will remain fasted for at least 4 hours after

morning dose. [redacted] patients will not receive any oral fluids other than those used to administer the dose for 1 hour before and 1 hour after dosing on Days 1 and 28.

[redacted] patients will remain standing or sitting upright for 4 hours after dosing, except as required by any study procedure. Patients in the K-877-IR [redacted] treatment group will receive an evening dose after a meal.

Diet and dosing time should remain consistent for all doses throughout the study. Patients will be instructed by the site to follow dosing instructions on the drug packaging and to return all used, partially used, and unused study drug materials on Day 28.

5.5.4 Treatment Compliance

Study drug will be dispensed in excess of the amount required for the study. Patients will be instructed to bring all unused study drug to each visit. At both visits, Days 14 and 28, the patient will be asked whether there have been any problems with taking the medication, and the Investigator will record any significant departure from the dosing instructions (e.g., misuse or overdose) as a protocol deviation. A Special Situations Report may need to be completed (see Section 8.6 for additional details about Special Situation Reports). A record of the number of tablets dispensed, taken, and returned for each patient must be documented on the Drug Accountability Log and eCRF. Compliance will be assessed from information recorded in the eCRF, including study drug count and the start and end date of study drug. Patients will be considered compliant if they have taken between 80% and 120% of the intended regimen.

During the treatment period, if compliance is not between 80% and 120%, inclusive, the patient will be counseled about the importance of compliance with the regimen. See Section 5.5.3 for study drug administration information.

5.5.5 Storage and Accountability

K-877-ER [redacted] tablets and K-877-IR [redacted] tablets must be stored at controlled room temperatures of 20°C to 25°C (68°F to 77°F) in a secured area with access limited to the Investigator and the site staff. The permitted excursion temperature range is 15°C to 30°C (59°F to 86°F).

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

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

[redacted]

Use of any systemic corticosteroids is prohibited.

[redacted]

5.6.2 Restricted Medications and/or Procedures

Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless those medications are specifically excluded in the protocol. Patients taking concomitant medications should be on stable doses for ≥4 weeks prior to screening and should remain at a stable dose throughout the study, unless changes need to be made for an AE or for appropriate medical management.

5.6.3 Allowed Medications and/or Procedures

[redacted]

5.6.4 Documentation of Prior and Concomitant Medication Use

All concomitant medication as well as dietary supplements taken during the study must be recorded on the concomitant medication eCRF at each study visit as indicated in the Schedule of Procedures in Appendix A. The medication name, dose, frequency, route of administration, date(s) of administration, and reason for administration must be recorded. The use of permitted dietary supplements should remain unchanged throughout the study. Changes in any medications must also be noted on the eCRF.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises for an AE or for appropriate medical management, the Investigator should base decisions on the patient and clinical factors. Any additional medication, whether prescription or over-the-counter, used at screening and/or during the study must be documented with the start and stop dates on the concomitant medications eCRF.

6 STUDY PROCEDURES

All study procedures are detailed in the Schedule of Procedures in Appendix A.

6.1 Informed Consent

Written consent will be obtained from the patient prior to any study-specific procedure or investigation, including the washout period when applicable.

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

Participating patients will be asked to sign and date an ICF. The ICF will contain the option to participate in the study as a [redacted] patient. The original signed ICF will be kept by the Investigator. A copy of the signed ICF will be given to the patient. A record will be made in the source document that the patient voluntarily agreed to participate in the study.

6.2 Screening Period

6.2.1 Screening Visit

The Screening Visit will occur no more than 70 days and no less than 29 days prior to the first dose of study drug (Day 1, Visit 4). Screening Visit procedures are outlined in the Schedule of Procedures in Appendix A.

6.2.2 Qualification Period

During the Qualification Period only samples to measure fasting TG levels will be collected. Patients will fast for a minimum of 8 hours prior to collection of TG samples. [redacted]

6.3 Randomization

Randomization will take place on Day 1 prior to treatment via IRT.

6.4 Treatment Period

Following randomization, assigned study drug will be dispensed to patients. Details of initial visit along with subsequent visits are detailed in the Schedule of Procedures in Appendix A. The Treatment Period begins on Day 1 and concludes on Day 28. [redacted] patients will be required to return to the clinical site on Day 14 (±3 days) and Day 28 (±3 days) for efficacy and safety assessments.

[redacted] patients will be admitted to the clinical site on Day -1 and will remain until discharged from the clinical site on Day 2. [redacted] patients will return to the clinical site on Day 14 (±3 days) for efficacy and safety assessments. On Day 27, [redacted] patients will be readmitted to the clinical site and will remain until discharged from the clinical site on Day 29.

6.5 Follow-Up Telephone Call

Patients will participate in a Follow-Up Telephone Call 7 days (±2 days) following the last dose of study drug.

6.6 Early Termination Visit and Withdrawal Procedures

The end of treatment for patients completing the study is Day 28. For patients who are withdrawn from the study prior to completion, all Day 28 procedures will be performed at an ET Visit. These procedures are outlined in the Schedule of Procedures in Appendix A.

7 EFFICACY AND [redacted] ASSESSMENTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in fasting TG from baseline to Day 28. The baseline fasting TG level will be defined as the mean of 3 TG levels: 2 Qualification Period TG levels within the target range (≥200 mg/dL and <500 mg/dL) and the Day 1 (Visit 4) TG level.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the percent change from baseline to Day 28 for the following:

- Total cholesterol (TC);
- Low-density lipoprotein cholesterol (LDL-C);
- HDL-C;
- Remnant cholesterol (calculated as TC – LDL-C – HDL-C);
- Non-HDL-C; and
- Free fatty acids.

[redacted]

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the Follow-Up Telephone Call. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning from the time of informed consent, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the Screening Visit should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at the Screening Visit and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment

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

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event must occur after the study drug is given. The length of time from study drug exposure to the event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- [redacted]

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death;

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations;

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; and/or
- An important medical event;

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to [redacted] within 24 hours of the

knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to the [redacted] or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or call the [redacted] SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible of the system becoming available.

Follow-Up Reports

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

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant from the time of initiation of study drug through the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug immediately and the patient should be withdrawn from the study. ET procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] within 24 hours of knowledge of the event. [redacted] will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted] within 24 hours of completion.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted] If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA) and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

8.7 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted according to the Schedule of Procedures in Appendix A. See Appendix B for a complete list of laboratory analytes.

8.8 Vital Signs

Vital signs, systolic and diastolic BP, pulse, respiratory rate, and body temperature will be measured (sitting) after resting for a minimum of 5 minutes at the times indicated in the Schedule of Procedures in Appendix A. Patients should avoid smoking, caffeine, or exercise within 30 minutes prior to BP measurement. On Days 1, 14, and 28, BP and pulse must be measured prior to administration of study drug and again approximately 1 hour post-administration.

Additional measurements of vital signs may be performed at the discretion of the Investigator.

8.9 Electrocardiograms

For each patient, a 12-lead digital ECG will be collected locally according to the Schedule of Procedures in Appendix A. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs will be interpreted locally by a qualified physician as soon after the time of ECG collection as possible and, ideally, while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified. The qualified physician must document his/her review of the ECG at the time of evaluation.

The ECGs will be maintained at the site and made available to the Sponsor as requested.

8.10 Physical Examinations

For each patient, one complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at the Screening Visit. This examination will determine whether the patient meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for treatment-emergent adverse event (TEAE) assessment. All other physical examinations throughout the study are indicated in the Schedule of Procedures in Appendix A and must include a symptom-directed physical evaluation, as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Full Analysis Set

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

9.1.2 Per-Protocol Set

The Per-Protocol Set will include all FAS patients without any major protocol deviations and who have baseline and Day 28 endpoint fasting serum TG measurements. Major protocol deviations will be confirmed prior to database lock. The following criteria will be used to determine major protocol deviations prior to unblinding of treatment allocation:

- No violations of eligibility criteria;
- No discontinuation of study drug;
- Patients did not take any prohibited concomitant medications during the study;
- Study drug compliance within 80% to 120%; and
- No other substantial protocol deviations.

The Per-Protocol Set will be the primary analysis population.

[redacted]

9.1.4 Safety Analysis Set

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

9.2 Statistical Methods

The efficacy and [redacted] data will be analyzed and reported separately. [redacted] Patient characteristics will include age, gender, ethnicity, BMI and country. [redacted]

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

The primary efficacy analysis will compare 1 of the 2 K-877-ER treatments (test treatments) to the K-877-IR [redacted] treatment (reference treatment) in percent change in fasting TG from baseline to Day 28 with a mixed model for repeated measures based on the Per-Protocol Set population. The model will include Visit (Day 14 or 28), treatment (K-877-ER [redacted] K-877-ER [redacted] or K-877-IR [redacted] the interaction term between Visit and treatment, baseline value, sex (male or female), and statin use (yes or no) as fixed effects, and an unstructured covariance matrix will be utilized. If the model for the unstructured covariance matrix fails to converge, other covariance structure will be considered.

Point estimates and 2-sided 90% confidence intervals (CIs), as well as 95% CIs of the differences of least squares means between either of the test treatments and reference treatment will be calculated. A non-inferiority of tested treatments will be indicated if the upper limit of the 2-sided 90% CI is <15% in TG percent change from baseline.

9.2.1.2 Secondary efficacy analysis

The secondary efficacy analysis will compare 1 of the 2 K-877-ER treatments (test treatments) to the K-877-IR [redacted] treatment (reference treatment) in percent change from baseline to Day 28 for the secondary endpoints with a mixed model for repeated measures with the same model used for primary efficacy analysis. The secondary endpoints to be included are TC, LDL-C, HDL-C, remnamt cholesterol (calculated as TC – LDL-C – HDL-C), non-HDL-C, and free fatty acids.

The same analyses will be repeated in the FAS population for both primary and secondary efficacy analyses.

Descriptive statistics (n, mean, standard deviation [SD], minimum, first quartile [Q1], median, third quartile [Q3], maximum, and 90% CI) for the primary endpoint (percent change from baseline in TG) and secondary endpoints will be summarized by treatment group at baseline and Days 14 and 28. Descriptive statistics for changes from baseline and for percent changes from baseline to each visit will also be summarized. Point estimates and 90% CIs of the differences between either of the test treatments and reference treatment will be calculated.

[redacted]

[redacted]

9.2.3 Analysis of Safety

Demographics and baseline characteristics will be listed and summarized. Data listings will be presented for all AEs, clinical laboratory tests (hematology, serum chemistry [including lipid parameters], coagulation, and urinalysis), vital sign measurements, 12-lead ECG findings, and physical examination findings.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. All TEAEs will be summarized by treatment. In addition, TEAEs will be summarized for each treatment by intensity and relationship to study drug. All TEAEs leading to withdrawal from study drug and SAEs will also be summarized. All tables will be summarized by system organ class and preferred term, including counts of AEs and patients with AEs. All AEs will be listed by patient.

Clinical laboratory tests, vital sign measurements, and 12-lead ECG findings will be summarized by time point and change from baseline for each treatment. Laboratory values that are below the lower limit or above the upper limit of the reference range will be flagged and assessed for clinical significance by the Investigator.

9.2.4 Interim Analysis

No interim analysis is planned for this study.

9.2.5 Sample Size Determination

Assuming an effect size delta = 0, pooled SD = 21.38, an alpha = 0.05 (1-sided), and a non-inferiority limit of 15%, a sample size of 26 patients per treatment group provides a power of 0.80.

In the case that the actual effect size delta is 10%, the power is then 0.2. If the real effect is different, the result less likely shows non-inferiority.

To account for any potential drop off, a total of 90 patients, 30 patients in each treatment group, is planned to be randomized.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associates (CRAs) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) GCP Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the clinical site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all FDA regulations/ICH GCP guidelines, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and must document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, FDA/ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the

Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records must be retained by the Investigator according to specifications in the FDA regulations/ICH GCP guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor must be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB and the Sponsor within 5 working days.

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 2. Schedule of Procedures [redacted] Patients)

	Screening Period				Treatment Period			Follow-Up Telephone Call[f]
	Screening Visit[a,b]	Qualification Period[c]						
Visit Name	**Visit 1**	**Visit 2[b]**	**Visit 3[d]**	**Visit 3.1[d,e]**	**Visit 4[d]**	**Visit 5**	**Visit 6/ET**	
Study Day	**-70 to -29**	**-28 to -21**	**-21 to -14**	**-14 to -7**	**1**	**14**	**28**	**35**
Visit Window (days)		**±3**	**±3**	**±3**		**±3**	**±3**	**±2**
Assessment								
Informed consent[g]	X							
Inclusion/exclusion criteria	X	X	X	X	X			
Fasting TG level		X[h]	X[h]	X[h]				
[redacted]								
Serum FSH[i]	X							
Pregnancy test[j]	X				X[k]		X[k]	
Height, body weight, and BMI	X						X[k,l]	
Demographic/medical history	X							
Urine drug screen[m]	X							
Prior/concomitant medication	X	X	X	X	X	X	X	X
TSH, FT4, and HbA1c	X							
Randomization					X[k]			
Physical examination[n]	X				X[k]	X[k]	X[k]	
Clinical laboratory tests[o]	X				X[k]	X[k]	X[k]	
Vital signs[p]	X				X	X	X	
12-lead ECG[q]	X				X		X	
PD sample[r]	X				X[k]	X[k]	X[k]	
Dispense study drug[s]					X			
Dosing[t]					←	X	→	
AEs	←			X			→	
Study drug compliance check						X	X	

a. Patients who are screen failures for a modifiable condition, other than failing the TG criteria, can be re-screened once. Before each patient is re-screened, the Investigator should discuss the case with the Medical Monitor.

b. At the Screening Visit (Visit 1), patients not needing a washout period may start the Qualification Period (Visit 2) 24 hours after signing the informed consent form. Patients may continue through the Qualification Period provided that there are no prohibitive safety or eligibility results from the Screening Visit (Visit 1) laboratory tests.

c. All Qualification Period visits will occur 7 days (±3 days) apart.

d. The last fasting TG Qualification Period visit (Visit 3 or 3.1) should occur ≥1 week prior to Day 1 (Visit 4).
e. Visit 3.1 is only needed if 1 Qualification Period TG level from Visit 2 or 3 is within 10% of the target range (≥180 mg/dL and <550 mg/dL) and 1 Qualification Period TG level from Visit 2 or 3 is within the target range (≥200 mg/dL and <500 mg/dL).
f. A Follow-Up Telephone Call will be performed 7 days (±2 days) following the last dose of study drug.
g. Written consent must be obtained from the patient prior to any study-specific procedure or investigation, including the washout period when applicable.
[redacted]
i. FSH is to be obtained in women <55 years of age who have not had a menstrual period for ≥1 year. Female patients will be considered postmenopausal if the FSH level is in the central laboratory's normal range for postmenopausal phase.
j. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1), a negative urine pregnancy test at Visit 4 and Visit 6, and must agree to use effective methods of contraception.
k. Assessments will be performed prior to dosing.
l. Only body weight will be measured at Visit 6 prior to dosing.
m. A urine drug screen will be performed at the discretion of the Investigator.
n. At the Screening Visit, a complete physical examination excludes pelvic, rectal, and breast examinations. All other physical examinations throughout the study must include a symptom-directed physical examination, as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.
o. Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.
p. Vital signs include systolic and diastolic BP, pulse, respiratory rate, and body temperature and will be measured (sitting) after resting for a minimum of 5 minutes. Patients should avoid smoking, caffeine, or exercise within 30 minutes prior to BP measurement. On Days 1, 14, and 28, BP and pulse must be measured prior to administration of study drug and again approximately 1 hour post-administration.
q. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
r. PD assessments will be performed under fasting conditions (≥8 hours) and include TG, TC, LDL-C, HDL-C, remnant cholesterol (calculated as TC – LDL-C – HDL-C), non-HDL-C, FFA.
s. Study drug, for entire treatment period, will be dispensed to eligible patients on Day 1 (Visit 4), after randomization, via the IRT system.
t. Daily oral dose will be administered by the patient and taken according to treatment group starting on Day 1 (Visit 4) and concluding on Day 28 (Visit 6) (28 dosing days). Patients in the K-877-IR[redacted] treatment group will receive only the morning dose on Day 28. Study drug will be administered in the fed state at 0 hour with 240 mL of room temperature tap water.

AE = adverse event; [redacted] = [redacted] BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; ET = Early Termination; FFA = free fatty acid; FSH = follicle-stimulating hormone; FT4 = free thyroxine; HbA1c = hemoglobin A1c; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IRT = interactive response technology; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone.

Table 3. Schedule of Procedures ([redacted]

	Screening Period					Treatment Period						Follow-Up
	Screening Visit[a,b]	Qualification Period[c]			Check-In 1	Visit 4[d]	Discharge 1	Visit 5	Check-In 2	Visit 6/ET	Discharge 2	Telephone Call[f]
Visit Name	**Visit 1**	**Visit 2[b]**	**Visit 3[d]**	**Visit 3.1[d,e]**								
Study Day	**-70 to -29**	**-28 to -21**	**-21 to -14**	**-14 to -7**	**-1**	**1**	**2**	**14**	**27**	**28**	**29**	**35**
Visit Window (days)		**±3**	**±3**	**±3**				**±3**		**±3**		**±2**
Assessment												
Informed consent[g]	X											
Inclusion/exclusion criteria	X	X	X	X	X	X						
Fasting TG level		X[h]	X[h]	X[h]								
[redacted]												
Serum FSH[i]	X											
Pregnancy test[j]	X				X				X			
Height, body weight, and BMI	X									X[k]		
Demographic/medical history	X											
Urine drug screen[l]	X											
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
TSH, FT4, and HbA1c	X											
Randomization						X[m]						
Physical examination[n]	X					X[m]		X[m]		X[m]		
Clinical laboratory tests[o]	X					X[m,p]		X[m]		X[m,p]		
Vital signs[q]	X					X		X		X		
12-lead ECG[r]	X					X				X		
PD sample[s]	X					X[i]		X[m]		X[m]		
[redacted]												
Admission to clinical site					X				X			

Table 3. Schedule of Procedures ([redacted] Patients) (Continued)

	Screening Period					Treatment Period						Follow-Up
	Screening Visit[a,b]	Qualification Period[c]										
Visit Name	Visit 1	Visit 2[b]	Visit 3[d]	Visit 3.1[d,e]	Check-In 1	Visit 4[d]	Discharge 1	Visit 5	Check-In 2	Visit 6/ET	Discharge 2	Telephone Call[f]
Study Day	-70 to -29	-28 to 21	-21 to -14	-14 to -7	-1	1	2	14	27	28	29	35
Visit Window (days)		±3	±3	±3				±3		±3		±2
Assessment												
Discharge from clinical site							X				X	
Dispense study drug[v]						X						
Dosing[w]						←	—	X	—	→		
AEs	←						X					→
Study drug compliance check								X		X		

a. Patients who are screen failures for a modifiable condition, other than failing the TG criteria, can be re-screened once. Before each patient is re-screened the Investigator should discuss the case with the Medical Monitor.
b. At the Screening Visit (Visit 1), patients not needing a washout period may start the Qualification Period (Visit 2) 24 hours after signing the informed consent form. Patients may continue through the Qualification Period provided that there are no prohibitive safety or eligibility results from the Screening Visit (Visit 1) laboratory tests.
c. All Qualification Period visits will occur 7 days (±3 days) apart.
d. The last fasting TG Qualification Period visit (Visit 3 or 3.1) should occur ≥1 week prior to Day 1 (Visit 4).
e. Visit 3.1 is only needed if 1 Qualification Period TG level from Visit 2 or 3 is within 10% of the target range (≥180 mg/dL and <550 mg/dL) and 1 Qualification Period TG level from Visit 2 or 3 is within the target range (≥200 mg/dL and <500 mg/dL).
f. A Follow-Up Telephone Call will be performed 7 days (±2 days) following the last dose of study drug.
g. Written informed consent must be obtained from the patient prior to any study-specific procedure or investigation, including the washout period when applicable.
[redacted]
i. FSH is to be obtained in women <55 years of age who have not had a menstrual period for ≥1 year. Female patients will be considered postmenopausal if the FSH level is in the central laboratory's normal range for postmenopausal phase.
j. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit (Visit 1), a negative urine pregnancy test at Check-Ins 1 and 2, and must agree to use effective methods of contraception.
k. Only body weight will be measured at Visit 6 prior to dosing.
l. A urine drug screen will be performed at the discretion of the Investigator.
m. Assessments will be performed prior to dosing.

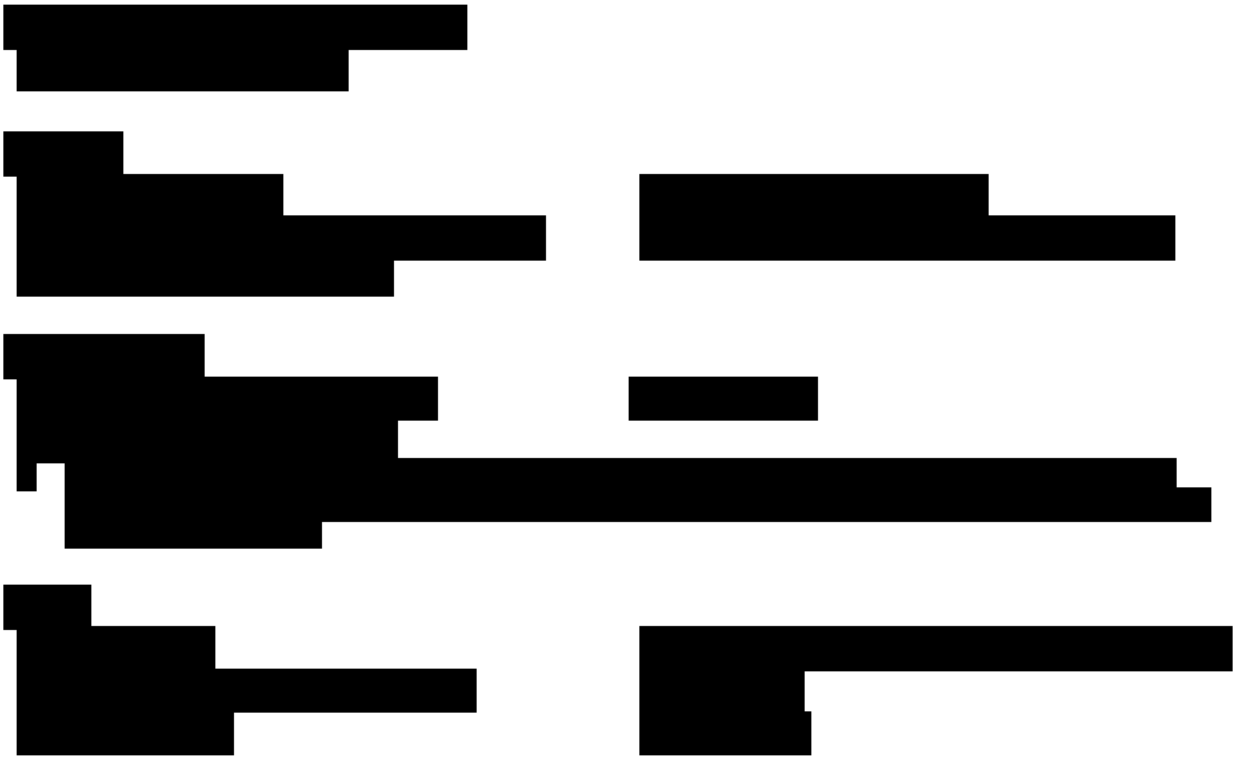
n. At the Screening Visit, a complete physical examination excludes pelvic, rectal, and breast examinations. All other physical examinations throughout the study must include a symptom-directed physical examination, as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.
o. Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.
p. No urinalysis needed on Days 1 (Visit 4) and 28 (Visit 6).
q. Vital signs include systolic and diastolic BP, pulse, respiratory rate, and body temperature and will be measured (sitting) after resting for a minimum of 5 minutes. Patients should avoid smoking, caffeine, or exercise within 30 minutes prior to BP measurement. On Days 1, 14, and 28, BP and pulse must be measured prior to administration of study drug and again approximately 1 hour post-administration.
r. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
s. PD assessments will be performed under fasting conditions (≥8 hours) and include TG, TC, LDL-C, HDL-C, remnant cholesterol (calculated as TC – LDL-C – HDL-C), non-HDL-C, FFA
[redacted]
v. Study drug, for entire treatment period, will be dispensed to eligible patients on Day 1 (Visit 4), after randomization via the IRT system.
w. Daily oral dose will be administered by the patient and taken according to treatment group starting on Day 1 (Visit 4) and concluding on Day 28 (Visit 6) (28 dosing days). Patients in the K-877-IR [redacted] treatment group will receive only the morning dose on Day 28. Study drug will be administered in the fed state at 0 hour with 240 mL of room temperature tap water.

AE = adverse event; [redacted] = [redacted] BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; ET = Early Termination; FFA = free fatty acid; FSH = follicle-stimulating hormone; FT4 = free thyroxine; HbA1c = hemoglobin A1c; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IRT = interactive response technology; LDL-C = low-density lipoprotein cholesterol; [redacted] PD = pharmacodynamic(s); TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase
Albumin
Alkaline phosphatase
Amylase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatine kinase
Creatinine
Direct bilirubin
Estimated glomerular filtration rate
Gamma-glutamyl transferase
Glucose
Inorganic phosphorus
Lactate dehydrogenase
Lipase
Potassium
Sodium
Total bilirubin
Total protein
Uric acid



[redacted]

[redacted]