CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

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

Drug Name:	**K-877**
Study Number:	**K-877-301**
EudraCT Number:	**2015-003511-37**
US IND Number	**109388**
Sponsor:	**Kowa Research Institute, Inc.**
Address:	430 Davis Drive, Suite 200 Morrisville, NC 27560 United States of America
Protocol Version/Date:	**V1.0, 13 September 2016**
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SAP Date:	**21 June 2019**

VERSION	DATE	DESCRIPTION OF CHANGES
1.0	19 OCTOBER 2016	Final document
2.0	21 JUNE 2019	Updates made to existing primary analysis imputation method when sufficient data is not available for imputation in Section (3.7.3 and Section 7: Appendix A1, Part II a and b, and additional method added after Part III) of the SAP. Updates made to section 3.7.4 of SAP to include additional method for secondary endpoint analysis. One column added in table under section 3.8.2, subsection 3.8.2.1.

[redacted]

STUDY TITLE: **A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With a 40-Week, Active-Controlled, Double-Blind Extension to Evaluate the Efficacy and Safety of K-877 in Adult Patients With Fasting Triglyceride Levels ≥500 mg/dL and <2000 mg/dL and Normal Renal Function**

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
CK	Creatine kinase
ECG	Electrocardiogram
FAS	Full Analysis Set
FFA	Free fatty acid
FGF21	Fibroblast growth factor 21
[redacted]	[redacted]
γ-GTP	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HOMA-β	Homeostatic model assessment for beta-cell function
HOMA-IR	Homeostatic model assessment for insulin resistance
hsCRP	High-sensitivity C-reactive protein
IND	Investigational New Drug
IQR	Inter-quartile range
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MMRM	Mixed-effect model repeat measurement
NMR	Nuclear magnetic resonance
QUICKI	Quantitative insulin sensitivity check index
Q1	25^{th} percentile
Q3	75^{th} percentile
SAE	Serious adverse event
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
[redacted]	[redacted]
ULN	Upper limit of normal

1. INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the study with protocol number K-877-301, version V1.0, 13 September 2016. Any deviations from this Statistical Analysis Plan (SAP) will be documented in the final clinical study report.

2. STUDY OBJECTIVES AND STUDY DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives of the study are the following:

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

2.1.3 Exploratory Objective

[redacted]

2.2 Study Design

This is a Phase 3, multi-center, randomized, double-blind study to confirm the efficacy and safety of K-877 0.2 mg twice daily compared to matching placebo (in the 12-week Efficacy Period) and an active comparator, fenofibrate (in the 40-week Extension Period), in patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) and normal renal function.

Eligible patients will enter a 4- to 6-week lifestyle stabilization period (4-week stabilization for patients not requiring washout and 6-week washout and stabilization for patients on lipid-altering therapy other than statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors). The stabilization period will be followed by a 2-week TG qualifying period (Visits 2 [Week -2] and 3 [Week -1]), and patient eligibility will be assessed based on the mean TG value from these 2 visits. If the patient's mean TG level

during the TG qualifying period is ≥450 mg/dL (5.09 mmol/L) and <500 mg/dL (5.65 mmol/L), an additional TG measurement can be taken 1 week later at Visit 3.1. The mean of all 3 TG measurements will be used to determine eligibility for the study. After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind Efficacy Period. At Visit 4 (Day 1), patients will be randomly assigned in a 2:1 ratio to K-877 0.2 mg twice daily or identical matching placebo tablets twice daily. During the 12-week Efficacy Period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who successfully complete the 12-week Efficacy Period are eligible to continue in a 40-week, double-blind, active-controlled Extension Period after completing the Visit 7 (Week 12) procedures. Patients randomized to receive K-877 0.2 mg twice daily in the 12-week Efficacy Period will continue to receive K-877 0.2 mg twice daily, as well as placebo matching fenofibrate 145 mg once daily, in the 40-week Extension Period. Patients randomized to receive placebo matching K-877 0.2 mg twice daily in the 12-week Efficacy Period will receive fenofibrate 145 mg once daily and placebo matching K-877 0.2 mg twice daily in the 40-week Extension Period.

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

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

Table 1: Clinical Evaluation Schedule

ASSESSMENTS PERFORMED	STUDY PERIOD										
	Screening Period			Treatment Period							
	Lifestyle Stabilization/ Washout Period	Triglyceride Qualifying Period [1]		12-Week Efficacy Period				40-Week Extension Period			
Time	Week -8 or -6	Week -2 ±3 days	Week -1 ±3 days	Day 1	Week 4 ±3 days	Week 8 ±3 days	Week 12 ±3 days	Week 16 ±3 days	Week 28 ±7 days	Week 40 ±7 days	Week 52 ±7 days or ET
Visit Number	1 [2]	2	3 [1]	4	5	6	7	8	9	10	11
Informed consent	X										
Medical, surgical, and family history, and demographics	X										
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X	X	X							
Vital signs (heart rate, respiratory rate, and blood pressure)	X	X	X	X	X	X	X	X	X	X	X
Height [3], weight, and waist circumference	X			X			X				X
Register screening number with IRT	X										
Urine drug and blood alcohol screen [4]	X										
[redacted]											
Amylase and lipase	X			X							
HbA1c	X			X			X		X	X	X
Insulin, glycated albumin, HOMA-IR, HOMA-β, and QUICKI				X			X		X	X	X
Serum pregnancy test for WOCBP	X										
Urine pregnancy test for WOCBP				X			X		X		X
Chemistry, hematology, coagulation, and urinalysis	X			X	X		X	X	X	X	X
Plasma Population PK sampling [7]	[redacted]										
PK/PD sampling [8]											
TG, TC, HDL-C, non-HDL-C, LDL-C, and remnant cholesterol [9]	X	X	X	X	X	X	X	X	X	X	X

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ASSESSMENTS PERFORMED	STUDY PERIOD	
	Screening Period	Treatment Period

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

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

[redacted]

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[redacted]

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

[redacted]

12. TLC counseling can be provided by the Investigator or designee (see Section **Error! Reference source not found.**).

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

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

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

2.3.2 Secondary Efficacy Endpoints

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

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

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

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

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

[redacted]

2.3.3 Exploratory Efficacy Endpoints

[redacted]

2.3.4 Safety Endpoints

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

2.3.5 Pharmacokinetic/Pharmacodynamic Endpoints

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

3. STATISTICAL METHODOLOGY

3.1 Baseline, Endpoint, and Other Statistical Considerations

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

[redacted]

Post-baseline lipid assessments will be assigned a visit number based on the date of assessment relative to the first dose of the double-blind study drug. Visit windows will be defined as the scheduled time from dosing date with a 7-day window (±7 days). Within a visit window, if a scheduled visit occurs, then the measurement from this scheduled visit will be used as the measurement for this visit window. If no scheduled visit occurs within a visit window, the last unscheduled measurement within the window will be used. If no visits occur within a visit window, the measurement of this visit will be treated as missing.

Any lipid measurements that have resulted from a non-fasting sample will be considered invalid and will not be used in the derivation of an efficacy endpoint.

Descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum, 25th (Q1) percentile and 75th (Q3) percentile) will be used to summarize the continuous data. Discrete measures will be summarized using counts and percentages.

3.2 Analysis Sets

3.2.1 Full Analysis Set

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

3.2.2 Per-Protocol Set

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

- No eligibility criterion violations,
- Did not discontinue study drug,
- Study medication compliance within 80-120%,
- Not taken any prohibited concomitant medication,
- Not unblinded during the 12-week double-blind treatment period, and
- No other substantial protocol violations.

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

3.2.3 Safety Analysis Set

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

3.2.4 Pharmacokinetic Analysis Set

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

3.3 Patient Disposition

The reason given for each screen failure will be summarized and listed. Patient disposition will be provided for all randomized patients. The number and percentage of patients in each of the following disposition categories will be presented:

- Patients who are randomized,
- Patients who start study drug,
- Patients who complete the 12-week Efficacy Period on study drug,
- Patients who complete the 12-week Efficacy Period but stopped study drug during the 12-week Efficacy Period,
- Patients who withdraw from the study during the 12-week Efficacy Period,
- Patients who enter the 40-week Extension Period,
- Patients who complete the 40-week Extension Period,

- Patients who withdraw from the study during the 40-week Extension Period.

For randomized patients who withdraw from the study, the primary reason for the withdrawal will be listed and summarized.

The number of patients included in each analysis set will be summarized.

3.4 Demographics and Baseline Characteristics

Demographics (age, sex, race, and ethnicity), body weight, height, and BMI will be summarized by randomized treatment using descriptive statistics for the randomized patients and the Full Analysis Set. Age group (<65 years versus ≥65 years and 18-64 years, 65-84 years, and ≥85 years) and current statin therapy use (not on statin therapy versus currently receiving statin therapy), ezetimibe use (yes/no), PCSK9 inhibitor use (yes/no), any lipid-altering medications use including statins, ezetimibe and/or PCSK9 inhibitor (yes/no) will also be summarized.

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

[redacted]

Patient medical history will be summarized by randomized treatment using descriptive statistics for the randomized patients and the Full Analysis Sets

3.5 Prior/Concomitant Medications

The use of any prior medication and concomitant or post-treatment medication will be listed for the Safety Analysis Set with an indication of whether the medication was prior or concomitant during the 12-week Efficacy Period, or concomitant during the 40-week Extension Period.

The number and percentage of patients taking each concomitant medication will be summarized by preferred term within Anatomical Therapeutic Chemical (ATC) classification and by treatment group for the Safety Analysis Set.

Statins, ezetimibe and PCSK9 inhibitors will be summarized by preferred term and dose at baseline for each treatment group for the Safety Analysis Set during the 12-week Efficacy Period and 40-week Extension Period.

Lipid medications including statin that are added or changed during the 12-week Efficacy Period and 40-week Extension Period will be summarized for the Safety Analysis Set.

3.6 Study medication Exposure and Compliance

Days of exposure to study medication will be summarized by treatment group for the Safety Analysis Set using descriptive statistics. Exposure in days is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1. In addition, a contingency table will be provided to display the number and percentage of patients with exposure in the following categories:

For K-877

- 1 to ≤4 weeks (1-28 days)
- >4 to ≤8 weeks (29-56 days)
- >8 to ≤12 weeks (57-84 days)
- >12 to ≤16 weeks (85-112 days)
- >16 to ≤28 weeks (113-196 days)
- >28 to ≤40 weeks (197-280 days)
- >40 to ≤52 weeks (281-364 days)
- >52 weeks (≥365 days)

For placebo

- 1 to ≤4 weeks (1-28 days)
- >4 to ≤8 weeks (29-56 days)
- >8 to ≤12 weeks (57-84 days)
- >12 weeks (≥85 days)

For fenofibrate

- 1 to ≤4 weeks (1-28 days)
- >4 to ≤16 weeks (29-112 days)
- >16 to ≤28 weeks (113-196 days)
- >28 to ≤40 weeks (196-280 days)
- >40 weeks (≥281 days)

Percent compliance with the study medication at the 12-week Efficacy Period and during the 40-week Extension Period will be summarized by treatment group for the Safety Analysis Set using descriptive statistics. Additionally the number and percentage of patients within each treatment group with overall compliance in the following categories: <80%, 80% to 120%, and >120%, will be provided.

3.7 Analysis of Efficacy

3.7.1 Descriptive Statistics

All available original and derived lipid data will be listed for the randomized patients. Descriptive statistics of the baseline, change from baseline and percent change from baseline to each post-baseline value will be presented by treatment group for each measured lipid level and derived ratio for the Full Analysis Set and the Per-Protocol Set.

Spaghetti plots of the individual patient data over time by treatment for lipid parameters will be provided for the Full Analysis Set. Boxplots of the percent change in lipid parameters from baseline to each post-baseline visit by treatment will also be produced.

3.7.2 Hypothesis Testing Procedure

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

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

3.7.3 Primary Endpoint Analyses

Several analyses (the primary analysis, and sensitivity analyses) will be carried out on the primary endpoint (the percent change in fasting TG from baseline to Week 12).

3.7.3.1 Statistical Analyses of Primary Efficacy Endpoint

Hodges-Lehmann Estimator with A Pattern Mixture Model Imputation

Due to the known distribution of TG and percent change from TG, normality assumption is usually difficult to satisfy. Also from historical data, the variances of percent change from baseline in TG are significantly unequal between K-877 0.2 mg and placebo. A nonparametric approach will be used as the primary analysis for the primary efficacy endpoint. As an extension to the Wilcoxon rank-sum test, the Hodges-Lehmann method will be used to estimate the median difference and its corresponding 95% CI for percent changes between K-877 0.2 mg and placebo.

The SAS code for Hodges-Lehmann estimates is listed below:

```
proc npar1way hl alpha=.05;
     class TRT01PN;
     var PCHG;
  run;
```

For this study, during the 12-week Efficacy Period, patients who discontinue study drug prematurely will remain in the study until Visit 7 (Week 12). If a patient who has discontinued study drug fails to attend any follow-up appointments, reasonable efforts (telephone calls to family members or friends, e-mail contacts, etc.) will be made in order to encourage the patient to complete the study visits.

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

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

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

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

    - For the placebo arm, missing Week 12 TG values will be imputed assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data from the placebo arm including patients who completed the efficacy period and have a valid Week 12 TG value.

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

Details of the primary imputation method is described in **Appendix 1**.

The multiple imputation procedure in the pattern mixture model will be conducted by two parts: PROC MI and PROC MIANALYZE. The first procedure will generate 100 multiple samples and then perform the Hodges-Lehmann analysis for each sample. The SAS procedure (PROC NPAR1WAY) specified above will generate two statistics in the output:

- Hodges-Lehmann Estimation
- Asymptotic Standard Error

These two statistics can be read into PROC MIANALYZE to get the overall estimate of location difference (treatment difference), as well as the confidence interval and p-value.

The primary efficacy analysis will be performed on the FAS population.

[redacted]

3.7.4 Secondary Endpoint Analyses

Secondary efficacy endpoints included in the hierarchical step-down testing procedure include percent change from baseline to Week 12 in a fixed sequence of (1) remnant cholesterol, (2) HDL-C, (3) Apo A1, and (4) non-HDL-C. These secondary efficacy endpoints will be analyzed using the same statistical method used for the primary analysis which is Hodges-Lehmann Estimation including the same multiple imputation procedure for the FAS population. The endpoints will be tested at a level of 0.05 in order if the previous one is statistically significant. Additionally, the endpoints will be analyzed using the ANCOVA model stated in the next paragraph as supplementary analyses.

The other secondary and exploratory efficacy endpoints during the 12-week Efficacy Period will be analyzed using an ANCOVA model with the same imputation method used for the primary analysis. The ANCOVA model will include country, current statin therapy use (not on statin therapy versus currently receiving statin therapy), and treatment as factors; baseline value as a covariate. Estimates for treatment difference, p-values and 95% confidence intervals will be provided. If normality assumption is not met, Hodges-Lehmann estimator with the same imputation method used for the primary analysis will be used.

The secondary efficacy endpoint of percent change from baseline to Week 52 in fasting TG will be summarized descriptively by treatment on the FAS. [redacted] Other efficacy endpoints during the Extension Period will be summarized descriptively in the same manner. No hypothesis testing will be performed for the percent change or change from baseline to Week 52 endpoints. 95% confidence interval will be presented for percent change or change from baseline within each treatment group.

[redacted]

3.8 Analysis of Safety

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

3.8.1 Adverse Events

A Treatment-Emergent Adverse Event (TEAE) is defined as any AE that occurred for the first time after the first dose of double-blind study drug or existed prior to the first dose and worsened during the post dosing period. AE worsening applies to severity, or relationship to study drug.

A summary overview of TEAEs will be provided, which presents the number and percentage of patients in each treatment group from the Safety Analysis Set for the 12-week Efficacy Period and the 40-week Extension Period and overall period satisfying each of the following categories:

- Any TEAEs,
- Maximum severity of TEAEs,
- Study drug-related TEAEs,
- Maximum severity of study drug-related TEAEs,
- All TE-SAEs,
- All study drug-related TE-SAEs,
- TEAEs leading to death,
- TEAEs leading to interruption/study drug discontinuation, and
- Study drug-related TEAEs leading to interruption/study drug discontinuation.

The number and percentage of patients with TEAEs will be summarized by their MedDRA preferred term within system organ class and by treatment. AEs will be counted by number of events as well as the number of patients. For event count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) and onset date and time from the same patient will only be counted once. For patient count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) from the same patient will only be counted once. Whether the AE belongs to the 12-week Efficacy Period and the 40-week Extension Period will be determined by the AE onset date.

The number and percentage of patients with TEAEs will be summarized by reported maximum severity within each MedDRA preferred term within system organ class and by treatment.

The number and percentage of patients with any drug-related TEAEs, drug-related TE-SAEs, and TEAEs and TE-SAEs that lead to study drug discontinuation will be summarized by preferred term within system organ class and by treatment. In these summaries, any patients reporting multiple episodes of the same TEAE (i.e., same preferred term and system organ class), will be counted once.

All SAEs will be listed with an indication of whether the SAE was treatment emergent or started prior to treatment.

All TEAEs that are reported as having led to a withdrawal of study drug will be listed.

The number of events and number of patients with TEAEs by each 12 weeks of treatment (0-12, 12-24, 24-36, 36-48, 48-52 and >52 weeks) will also be summarized for each MedDRA preferred term, system organ class, and treatment.

3.8.2 Clinical Laboratory Assessments

3.8.2.1 Chemistry and Hematology

Descriptive statistics of each chemistry and hematology parameter will be presented for baseline, 'Time point', and Change from Baseline to each 'Time point'; where 'Time point' is each post-baseline assessment. These will be presented by treatment group for each parameter using the Safety Analysis Set.

Counts and percentages of patients with any post-baseline observation that is below the lower limit of normal (<LLN) or above the upper limit of normal (>ULN) will be summarized for each chemistry and hematology parameter by treatment group and overall.

Post-baseline changes of specified lab tests (ALT, AST, CK, serum creatinine, total bilirubin, alkaline phosphatase) abnormalities will be summarized by presenting the number and percentage of patients in each treatment group whose worst post-baseline value satisfies each of the following criteria in the table below and shift tables will be produced during the 12-week Efficacy Period and during the 40-week Extension Period and overall period.

Parameter	**Categories**						
ALT	<Normal	Normal	>1xULN to ≤3xULN	>3xULN to ≤5xULN	>5xULN to ≤10x ULN	>10xULN to ≤20x ULN	> 20x ULN
AST	<Normal	Normal	>1xULN to ≤3xULN	>3xULN to ≤5xULN	>5xULN to ≤10x ULN	>10xULN to ≤20x ULN	> 20x ULN
CK	<Normal	Normal	>1xULN to ≤5xULN	>5xULN to ≤10xULN	>10xULN		
Serum Creatinine	<Normal	Normal	>1xULN to ≤1.5xULN	>1.5xULN to ≤2xULN	>2xULN		
Serum Creatinine	≥2xbaseline						
ALP	<Normal	Normal	>1xULN to ≤1.5xULN	>1.5xULN			
Total Bilirubin	<Normal	Normal	>1xULN to ≤1.5xULN	>1.5xULN to ≤2xULN	>2xULN		
Total Bilirubin accompany by ALT or AST>3xULN	<Normal	Normal	>1xULN to ≤1.5xULN	>1.5xULN to ≤2xULN	>2xULN		
eGFR	≥90 mL/min/1.73m^2	≥60 to <90 mL/min/1.73m^2	≥30 to <60 mL/min/1.73m^2	<30 mL/min/1.73m^2			

Spaghetti plots of the individual patient data over time and boxplots of the values at baseline and each post-baseline visit will be presented by treatment for ALT, AST, CK, serum creatinine, total bilirubin, and alkaline phosphatase. Normal reference ranges will be plotted on these plots.

The number and percentage of patients who meet ALT or AST >3xULN and total bilirubin >2xULN at any time after the first dose of the study drug are identified as potential Hy's Law cases and will be summarized and these patients' ALT, AST, ALP and total bilirubin data will be listed. To assess cases meeting requirements for Hy's Law, an eDISH (evaluation of drug-induced serious hepatotoxicity) figure plotting peak ALT vs. peak total bilirubin (both on a logarithmic scale xULN) will be produced as recommended by Watkins et al (2008), so that values within the normal reference range (<ULN) for ALT and total bilirubin are found in the left lower quadrant and Hy's Law case candidates are in the upper right quadrant (ALT>3×ULN and total bilirubin>2×ULN). Subjects with Gilbert's syndrome or cholestasis are typically found in the upper left quadrant, and subjects with ALT elevations without significant hepatic impairment (i.e., without increased total bilirubin) are found in the lower right quadrant. This plot will also be plotted for peak AST by peak total bilirubin.

3.8.3 12-Lead Electrocardiogram

ECG overall interpretation findings will be summarized by randomized treatment using descriptive statistics for the Safety Analysis Set.

3.8.4 Physical Examination

The number and percentage of patients with physical examination findings will be presented for the Safety Analysis Set.

3.8.5 Vital Signs, Weight, Height, BMI

Vital signs parameters will be summarized using descriptive statistics for the Safety Analysis Set. The change from baseline will also be presented.

3.8.6 Other Safety Parameters

Other safety data will be listed.

3.9 Analysis of Pharmacokinetic/Pharmacodynamic Data

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

[redacted]

3.10 Interim Analysis

No interim analysis was planned for this study.

4. SAMPLE SIZE DETERMINATION

Approximately 630 patients with fasting TG levels ≥500 mg/dL (5.65 mmol/L) and <2000 mg/dL (22.60 mmol/L) will be randomized in a 2:1 ratio into one of the following treatment groups: K-877 0.2 mg twice daily or identical matching placebo twice daily.

[redacted]

5. PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.3 or above. All available data will be presented in subject data listings, which will be sorted by site number, unique subject identifier and where appropriate, visit number and visit/assessment date.

The programming specification, including the mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specification, will be prepared in stand-alone documents. The programming specification document will be finalized prior to the database lock and unblinding the treatment code.

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7. APPENDIX

Appendix 1 Primary Analysis Imputation Method for Missing Week 12 Efficacy Data – A Pattern Mixture Model

Pattern mixture model was first introduced by Glynn et al (1986) and Little (1993). Later Little and Yau (1993) suggested control based pattern mixture models, which assume that after discontinuation, subjects on the experimental treatment who withdraw will tend to have efficacy close to subjects on the control treatment. The imputation model for this study will impute missing Week 12 fasting TG measurements as follows:

I. For patients who do not adhere to therapy and who do not have Week 12 fasting TG measurements, the missing data imputation method will use patients in the same treatment arm who do not adhere to therapy and have Week 12 fasting TG measurements.

   Patients without Week 12 fasting TG measurements and patients with Week 12 fasting TG measurements but discontinue treatment prior to Week 12 will be selected.

```
DATA DATAIN1;
SET ALLTG;
IF TRTCOMPL='N' THEN OUTPUT DATAIN1; /*output patients who did not complete 12-week
treatment and have Week-12 TG and those missing Week 12*/
RUN;
```

   Missing Week 12 TG data will be imputed using PROC MI procedure with a multivariate imputation by fully conditional specification methods to create 100 datasets. In the imputation model, patient demographics (age, sex, ethnicity, country, and baseline BMI), current statin therapy use (not on statin therapy versus currently receiving statin therapy), disease status (baseline systolic and diastolic blood pressures, baseline eGFR), and baseline TG. The FCS statement will be used. This statements calls a multivariate imputation by fully conditional specification methods.

```
PROC MI DATA=DATAIN1 OUT=IMOUT1 MINIMUM=0 SEED=98547 NIMPUTE=100;
BY TRT;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN BASE WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN;
FCS; /* fully conditional specification method*/
TRANSFORM LOG(BASE) LOG(WEEK12);
RUN;
```

II. If there are no or very few patients in the same treatment arm who do not adhere to therapy and have Week 12 TG measurements, missing Week 12 TG measurements will be imputed as follows:

   a. For the K-877 arm, the treatment effect is considered washed out and baseline TG measurements of all K-877 patients will be used to impute the

Week 12 TG measurements. Missing Week 12 TG values will be imputed by using the method which was proposed by Ratitch et al (2013).

```
DATA DATA21;
SET ALLTG;
IF TRT='K-877';  /*Select patients from the K-877 arm*/
RUN;

DATA DATA21a;
LENGTH SUBJID2 $8 ;
SET DATA21(RENAME=(WEEK12=WEEK12A));
SUBJID2 ="ORI";
WEEK12 = BASE;
OUTPUT;
IF WEEK12A =. THEN DO  ;
SUBJID2 ="IMP";
WEEK12 = .;
IF TRTCOMPFL= 'Y' and SUBJID2 = 'IMP' then delete; /*These will be imputed in step III*/
OUTPUT;
END;
RUN;

PROC MI DATA= DATA21a OUT=IMOUT1a MINIMUM=0 SEED=68756 NIMPUTE=100;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN TRTCOMPFL
WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN TRTCOMPFL;
FCS; /* fully conditional specification method*/
TRANSFORM LOG(WEEK12);
RUN;

DATA IMOUT1a;
SET IMOUT1a;
IF WEEK12A^=. THEN WEEK12=WEEK12A; /*set Week12 back to use the observed Week 12
values for those not missing Week 12*/
IF TRTCOMPFL = "N"
IF SUBJID2= "IMP" or (SUBJID2= "ORI" and WEEK12A^=.); /*keep imputed records of only
for K-877 subjects who did not complete the treatment period*/
RUN;
```

b. For the placebo arm, missing Week 12 TG values will be imputed assuming missing at random, including patient demographics, disease status, and baseline and post-baseline efficacy data from the placebo arm including patients who completed the efficacy period and have a valid Week 12 TG value.

```
DATA DATA22;
SET ALLTG;
IF TRT="PLACEBO"; /*select patients from the Placebo arm*/
IF TRTCOMPL='N' OR (TRTCOMPL='Y' AND WEEK12 ^= .); /*Include Placebo patients who
                    did not adhere to therapy as well as patients who adhered to therapy and have
                    a non-missing Week 12 TG value */
RUN;

PROC MI DATA=DATA22 OUT=IMOUT22 MINIMUM=0 SEED=63546 NIMPUTE=100;
```

```
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN BASE WEEK 4 WEEK8
WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN;
FCS;/* fully conditional specification method*/
TRANSFORM LOG(BASE) LOG(WEEK4) LOG(WEEK8) LOG(WEEK12);
RUN;
```

III. For patients who adhere to therapy (complete the 12 week efficacy treatment) and who do not have Week 12 fasting TG measurements, the missing data imputation method will use patients in the same treatment arm who adhere to therapy and have Week 12 fasting TG measurements. i.e. Missing at random assumption will be used.

```
DATA DATA21c;
SET ALLTG;
IF (WEEK12=. & TRTCOMPL='Y') | (WEEK12^=. & TRTCOMPL='Y');
RUN;

PROC MI DATA= DATA21c OUT=IMOUT1c MINIMUM=0 SEED=745369 NIMPUTE=100;
BY TRT;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN BASE WEEK4 WEEK8
WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN;
FCS; /* fully conditional specification method*/
TRANSFORM LOG(BASE) LOG(WEEK4) LOG(WEEK8) LOG(WEEK12);
RUN;
```

If there are no patients who adhere to therapy and miss Week 12 fasting TG measurement in DATA21c, 100 datasets will be created from DATA21c in order to merge with the 100 imputed datasets from the others.

If there are not enough observations to fit regression models for missing Week 12 values with a FCS regression method specified in steps II (a and b) and III, a correlation test between baseline TG measurements and the covariates will be performed based on the Full Analysis Set. The covariate with the lowest absolute value of Spearman correlation coefficient will be removed from the model in step II, while on the other hand, the one with the largest absolute value of that will be removed from the model in step III. And then the analysis will be performed. If the model still does not fit, the variable with the next lowest value of Spearman correlation coefficient will be removed. This process will be repeated until the regression model fits successfully.

After imputation step, percentage change in TG will be calculated and each of the 100 multiply imputed datasets for FAS patients will be analyzed by either PROC NPAR1WAY procedure or PROC MIXED procedure. The estimate and standard error for treatment effect from the analysis will be analyzed by PROC MIANALYZE to obtain the overall estimate of treatment difference, as well as the confidence interval and p-value.

For example, the primary analysis method will output the Hodges-Lehmann estimation and asymptotic standard error from PROC NPAR1WAY procedure.

```
PROC MIANALYZE DATA=DIFF;
```

```
MODELEFFECTS ESTIMATE;
STDERR STDERR;
 RUN;
```

The SAP could be updated as a result of a blind review of the data and will be finalized before breaking the blind. Final imputed values will be saved in analysis database when the SAP is finalized as well as when the blind is subsequently broken.

Appendix 2 Sensitivity Imputation Method: Probabilities of Missing Estimated by Logistic Regressions

Below is a summary of steps/description of the imputation with probabilities of missing estimated by logistic regressions with the imputation forward for an early withdrew subject *i*:

Step 1: To calculate the probabilities for missing data for Visit 5, a logit model is performed with treatment, baseline TG value, country, and baseline current statin therapy use (not on statin therapy versus currently receiving statin therapy) in the model. Percent change in TG at Visit 5 is calculated based on the formula below.

$PCHG5_i = (1 - P5_i)$ x (the median PCHG from the control group at Visit 5).

$TG5_i = BTG_i + (PCHG5_i /100) \times BTG_i$

Step 2: Imputed Percent change in TG at Visit 5 is put into the data for those with missing Visit 5 to calculate the probabilities for missing data for Visit 6 using the same logit model with treatment, baseline value, country, and baseline current statin therapy use and Visit 5 TG as covariates.

$PCHG6_i = (1 - P6_i) \times PCHG5_i$.

$TG6_i = BTG_i + (PCHG6_i /100) \times BTG_i$;

Step 3: Imputed Percent change in TG at Visit 6 is put into the data for those with missing Visit 7 to calculate the probabilities for missing data for Visit 7 using the same logit model with treatment, baseline value, country, and baseline current statin therapy use and Visit 6 TG as covariates.

$PCHG7_i = (1 - P7_i) \times PCHG6_i$.

$TG7_i = BTG_i + (PCHG7_i /100) \times BTG_i$;

Where for subject *i*,

$PCHG5_i$ $PCHG6_i$ $PCHG7_i$ = percent change in TG at Visit 5(Week 4), Visit 6(Week 8), Visit 7(Week 12) respectively,

$TG5_i$ $TG6_i$ $TG7_i$ = TG at Visit 5(Week 4), Visit 6(Week 8), Visit 7(Week 12) respectively,

BTGi =baseline TG

$P5_i$ $P6_i$ $P7_i$ = probability of missing estimated from the logistic regression respectively,

Firth's penalized likelihood approach will be used to address any issues of separability.