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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

SAP Version/Date: Version 1.0, 21 August 2020

STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Number:	K-877-ER-201
Protocol Version/Date:	Version 1.0, 28 January 2020
Investigational Product:	K-877-ER
Sponsor:	Kowa Research Institute, Inc. [redacted]
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CONFIDENTIAL

SIGNATURE PAGE

Protocol 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

Protocol Number: K-877-ER-201

SAP Version/Date: Version 1.0, 21 August 2020

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	21AUG2020	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alanine Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BLQ	Below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatinine Kinase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
[redacted]	[redacted]
CRF	Case report form
CSR	Clinical Study Report
eGFR	Estimated Glomerular Filtration Rate
ECG	12-lead Electrocardiogram
FAS	Full Analysis Set
IRT	Interactive Response Technology
[redacted]	[redacted]
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PPS	Per-Protocol Set
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TG	Triglyceride
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number K-877-ER-201. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 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 triglyceride (TG) levels in patients with fasting TG levels ≥200 mg/dL and <500 mg/dL.

2.1.2 Secondary Objectives

The secondary objectives of this study are as follows:

- 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.
- To evaluate the multiple-dose [redacted] properties [redacted] of K-877-ER [redacted]

2.2 Study Design

2.2.1 Overview

This 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 (from 12 sites in the United States) 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] patients, and will have blood samples for [redacted] assessments collected. Non-[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 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 one of three treatment groups. Randomization will be stratified by sex (male or female), statin use (yes or no), and [redacted] assessment (yes or no).

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.

Selected study procedures will be performed prior to administration of study drug, as applicable.

The schedule of procedures for [redacted] and [redacted] procedures can be found below in Tables 1 and 2 respectively.

Table 1. Schedule of Procedures [redacted]

	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]**	**Visit 4[d]**	**Visit 5**	**Visit 6/ET**	**Telephone Call[f]**
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 2. Schedule of Procedures ([redacted]

	Screening Period					Treatment Period						
Visit Name	**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**	**Follow-Up Telephone Call[f]**
	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		

Table 2. Schedule of Procedures ([redacted] patients) (Continued)

	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												
PD sample[s]	X					X[i]		X[m]		X[m]		
[redacted]												
Admission to clinical site					X				X			
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 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]

[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. Urinalysis is 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] 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] s); PD = pharmacodynamic(s); TC = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone

2.2.2 Randomization and Blinding

2.2.2.1 Randomization

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 3.

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.

2.2.2.2 Blinding

This study is open-label.

2.2.3 Study Drug

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

Patients will receive oral doses of K-877-ER [redacted] (one [redacted] tablet every morning), K-877-ER [redacted] (two [redacted] tablets every morning), or K-877-IR [redacted] (one [redacted] the morning and one [redacted] tablet in the evening) 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.

Table 3. [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
K-877-ER [redacted]	K-877-ER [redacted]	[redacted]	[redacted]
K-877-ER [redacted]	K-877-ER [redacted]	[redacted]	[redacted]
K-877-IR [redacted]	K-877-IR [redacted]	K-877-IR [redacted]	[redacted]

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 approximately 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.

2.2.4 Sample Size Determination

Approximately 90 patients will be enrolled.

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% (effect of tested regimen 10% less than the reference regimen), the power is then 0.2. If the real effect is different, the result less likely shows non-inferiority.

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

2.3 Efficacy and [redacted] Endpoints

2.3.1 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.

2.3.2 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)
- High-density lipoprotein cholesterol (HDL-C)
- Remnant cholesterol (calculated as TC – LDL-C – HDL-C)
- Non-HDL-C
- Free fatty acids

2.3.3 [redacted]

[redacted]

- [redacted]

[redacted]

2.4 Safety Endpoints

Safety assessments include analysis of adverse events (AEs), clinical laboratory evaluations (serum chemistry, hematology, coagulation, and urinalysis), vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead electrocardiogram (ECG), and physical examinations.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of randomization. The day of randomization will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

The study consists of a 28-day treatment period where study visits will occur at Day 1, Day 14, and Day 28. Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). Unscheduled and early termination visits will be analyzed at the next available visit within the 28-day treatment period. Where multiple measurements for a parameter appear within an analysis visit, the scheduled visit will be used. If there is no scheduled visit and multiple unscheduled visits and/or early termination visits exist within an analysis visit, the later result will be used for the summary measure.

Analysis visits to be assigned are Baseline, Day 14, and Day 28.

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

3.1.3 Definition of Baseline

Baseline for TG will be defined as the mean of 3 TG levels: 2 TG levels within the target range (≥200 mg/dL and <500 mg/dL) and the Day 1 (Visit 4) TG level. If any of the 3 TG levels are missing, the average of non-missing TG levels will be used to calculate baseline.

Baseline for all other efficacy and safety variables will be defined as the Visit 4 (Day 1) measurement. If the measurement at this visit is missing, the last measurement prior to the first dose of study drug will be used as baseline.

3.1.4 Summary Statistics

All study-collected data will be summarized by treatment group for the appropriate analysis population, using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include n (number of non-missing values), mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum, and maximum. Analysis of categorical variables will include frequency and percentage.

3.1.5 Handling of Dropouts and Missing Data

Missing data will be imputed only in the context of sensitivity analysis as described in section 3.4.1.

3.2 Analysis Populations

3.2.1 Full Analysis Set (FAS)

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

3.2.2 Per-Protocol Set (PPS)

The Per-Protocol Set (PPS) 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. Major protocol deviations that may impact the primary efficacy assessment may include but are not limited to:

- Failed to meet eligibility criteria
- Discontinued study drug
- Had study drug compliance <80% or >120%
- Took a restricted concomitant medication

A list of patients with major protocol deviations leading to exclusion from the PPS will be finalized prior to database lock.

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

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 [redacted]

[redacted]

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened patients. Primary reasons for screen failure will also be summarized. Patients whose primary reason for screen failure was due to Coronavirus Disease 2019 (COVID-19) will also be summarized.

Counts and percentages of patients who were randomized, treated, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized patients. Primary reasons for early discontinuation will also be summarized. Patients whose primary reason for early discontinuation was due to COVID-19 will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations are defined in the Protocol Deviation Plan and classified as CSR reportable or CSR non-reportable. All CSR-reportable protocol deviations will be listed.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on all randomized patients.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex (Male or Female)
- Age categories by sex (Age categories include <12 years, 12 - <18 years, 18 - <65 years, and ≥ 65 years).
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Statin Use (Yes, No)
- [redacted]

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment and in total for all randomized patients and each defined analysis population.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Dictionary updates will be applied at the time of database lock to the latest version available. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized patients.

3.3.6 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary Global B3, September 2019. Dictionary updates will be applied at the time of database lock to the latest version available. For summary purposes, medications will be considered prior medications if they were stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Analysis Set.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a patient was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment based on the Safety Analysis Set with descriptive statistics.

Percent compliance to the study drug regimen will be calculated as follows:

For patients randomized to the K-877-ER [redacted] arm, compliance will be calculated as:

$$\frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{Date\ of\ last\ visit - Date\ of\ randomization + 1}\ x\ 100$$

For patients randomized to the K-877-ER [redacted] arm, compliance will be calculated as:

$$\frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{2 * (Date\ of\ last\ visit - Date\ of\ randomization + 1)}\ x\ 100$$

For patients randomized to the K-877-IR [redacted] arm and completed the 28-day treatment period, compliance will be calculated as:

$$\frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{\big(2 * (Date\ of\ last\ visit - Date\ of\ randomization + 1)\big) - 1}\ x\ 100$$

For patients randomized to the K-877-IR [redacted] arm and discontinued prior Day 28, compliance will be calculated as:

$$\frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{2 * (Date\ of\ last\ visit - Date\ of\ randomization + 1)}\ x\ 100$$

If study drug is not returned, the number of tablets returned will be considered 0 for the compliance calculation.

Percent compliance to the study drug will be summarized by treatment based on the Safety Analysis Set with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

- <80%
- 80-120%
- >120%

3.4 Efficacy Assessment

Efficacy data will be summarized by randomized treatment based on the PPS. The primary and secondary efficacy endpoints will also be summarized based on the FAS. Descriptive statistics (n, mean, standard deviation [SD], first quartile [Q1], median, third quartile [Q3], minimum, maximum, and 90% CI) for the primary endpoint 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.

All available and derived data for the primary and secondary endpoints will be listed for the randomized patients.

Spaghetti plots of individual patient data by treatment and box plots of the percent change from baseline to each post-baseline visit by treatment will be generated for the primary and secondary efficacy endpoints based on the PPS and FAS. Mean ± SD of percent change from baseline to each post-baseline visit by treatment will also be generated for the primary and secondary efficacy endpoints based on the PPS and FAS.

3.4.1 Primary Efficacy Endpoint

Primary Analysis

The primary analysis variable is the percent change in fasting TG from baseline to Day 28.

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 from baseline to Day 28 and will be carried out using mixed model for repeated measures (MMRM) based on the PPS. The MMRM model will include percent change from baseline value as the dependent or response variable. Variables for 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 TG value, sex (male or female), and statin use (yes or no) will be used as fixed effects.

An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The analysis will be performed based on all observed post-baseline scores without any imputation of missing data. In the case when the MMRM fails to converge using an unstructured covariance matrix in any stage, a less stringent covariance matrix (e.g., autoregressive 1) will be used.

The sample SAS code for primary efficacy analysis can be found below:

```
*****************************************************************
* PCHG = Percent change in TG
* VISIT = Visit
* TRT = Treatment group
* TRT*VISIT = Treatment group by visit interaction
* BASE = Baseline value
* SEX = Gender (Male or Female)
* STATIN = Statin Use (Yes or No)
* USUBJID = Unique subject identifier
*****************************************************************;
PROC MIXED DATA=efficacy METHOD=REML COVTEST;
 CLASS USUBJID VISIT TRT SEX STATIN;
 MODEL PCHG = VISIT TRTA TRT*VISIT BASE SEX STATIN/DDFM=KENWARDROGER;
 REPEATED / TYPE=UN SUBJECT=USUBJID;

 LSMEANS TRT / DIFF CL ALPHA = 0.10;

 LSMESTIMATE TRT 'ER0.4MG - IR0.2MG' 1 0 -1 / ALPHA = 0.05 CL;
 LSMESTIMATE TRT 'ER0.8MG - IR0.2MG' 0 1 -1 / ALPHA = 0.05 CL;

 ODS OUTPUT TESTS3= TESTS3 LSMESTIMATES=LSMESTIMATES LSMEANS=LSMEAN DIFFS=D;
run;
```

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.

Secondary Analyses

As a secondary analysis, the primary analysis described above will be repeated in the FAS.

3.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarized and analyzed in the same manner as the primary analysis (Section 3.4.1). Each secondary endpoint will be evaluated using the MMRM model in the PPS where percent change from baseline variable will be used as the dependent or response variable.

The following secondary endpoints will be analyzed:

- TC
- LDL-C
- HDL-C
- Remnant cholesterol (calculated as TC – LDL-C – HDL-C)
- Non-HDL-C
- Free fatty acids

Analysis of the above secondary efficacy endpoints will also be repeated in the FAS.

[redacted]

[redacted]

3.6 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Analysis Set.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 23.0.

Treatment-emergent adverse events (TEAEs) are defined as AEs that occurred for the first time after the first dose of study drug or existed prior to the first dose and worsened during the treatment period. AE worsening applies to severity, or relationship to study drug.

An overview of AEs will be provided including counts and percentages of patients and event counts with the following:

- Any TEAEs (overall, by maximum severity, and by relationship to study drug)
- Any study drug related TEAEs (overall and by maximum severity)
- [redacted]
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any study drug related TESAEs
- Any AEs and TEAEs leading to death
- Any TEAEs leading to study drug discontinuation
- Any TEAEs leading to study discontinuation
- Any TESAEs leading to study drug discontinuation
- Any study drug related TEAEs leading to study drug discontinuation

Counts and percentages of patients and event counts will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

3.6.2 Clinical Laboratory Tests

Descriptive statistics for chemistry and hematology parameters will be presented at baseline and each post-baseline visit. At each post-baseline visit, change from baseline will also be summarized.

Incidence of lab abnormalities indicated as ‘below the lower limit of normal (LLN) range’ and ‘above the upper limit of normal (ULN) range’ at each visit will be summarized for chemistry and hematology parameters with counts and percentages of patients.

Post-baseline changes of lab tests abnormalities for alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), total bilirubin, alkaline phosphatase (ALP), and estimated Glomerular Filtration Rate (eGFR) will be summarized by presenting a shift table with

number and percentage of patients in each treatment group with worst post-baseline value satisfying each of the criteria in the table below.

Parameter	**Categories**						
ALT	<Normal	Normal	>1xULN to ≤3xULN	>3xULN to ≤5xULN	>5xULN to ≤10xULN	>10xULN to ≤20xULN	>20x ULN
AST	<Normal	Normal	>1xULN to ≤3xULN	>3xULN to ≤5xULN	>5xULN to ≤10xULN	>10xULN to ≤20xULN	>20x ULN
ALP	<Normal	Normal	>1xULN to ≤ 1.5xULN	>1.5xULN			
CK	<Normal	Normal	>1xULN to ≤5xULN	>5xULN to ≤10xULN	>10xULN		
Total Bilirubin	<Normal	Normal	>1xULN to ≤1.5xULN	>1.5xULN to ≤2xULN	>2xULN		
Total Bilirubin accompanied 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 patient data over time and boxplots of the values at baseline and each post-baseline visit will be presented by treatment for ALP, ALT, AST, CK, and total bilirubin. Normal ranges will be displayed on these plots for reference.

Counts and percentages of patients who meet ALT or AST >3xULN, ALP < 2xULN, 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 data for ALT, AST, ALP and total bilirubin for these patients 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 lower left quadrant, and Hy's law cases (ALT3×ULN and total bilirubin>2×ULN) can be found in the upper right quadrant. Patients with Gilbert's syndrome or cholestasis are typically found in the upper left quadrant, and patients 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.

Other clinical laboratory tests categories include Serology, Endocrinology, Coagulation, and Urinalysis. Continuous parameters for these categories will be summarized using descriptive statistics at baseline and each post-baseline visit along with change from baseline at each visit, and categorical parameters will be presented with counts and percentages of patients at each scheduled visit.

All laboratory measurements will be listed.

A list of laboratory tests to be performed is included in Appendix B of the protocol.

3.6.3 Vital Signs

Vital signs to be assessed are height, weight, body mass index, temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate. Vital signs will be summarized at Baseline, Day 14, and Day 28 using descriptive statistics for the Safety Analysis Set.

At Baseline, Day 14, and Day 28, blood pressure (systolic and diastolic) and heart rate will be taken prior to dosing and one hour after dosing.

Change from baseline at Day 14 and Day 28 will also be summarized. All vital signs measurements will also be listed.

3.6.4 Electrocardiograms

ECG overall interpretation findings will be summarized for the Safety Analysis Set. Continuous parameters will be summarized descriptively at each visit.

3.6.5 Physical Examinations

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

4 ANALYSIS TIMING

4.1 Draft Analysis/Blinded Data Reviews

Draft analysis tables, figures, and listings (TFLs) for data reviews will be provided approximately 1 month prior to the scheduled database lock for final review.

4.2 Interim Analysis

No interim analysis is planned.

4.3 Pre-Final Analysis

After data entry process is completed, exclusions from analysis populations will be finalized prior to database lock and the pre-final analysis will be generated after database lock. Topline tables will be provided one week after final database lock. All pre-final TFLs will be provided approximately 3 weeks after database lock.

4.4 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final

analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, Standard Data Tabulation Model (SDTM) data and Analysis Data Model (ADaM) data along with associated files will be provided. Associated files may include: annotated CRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There are no changes form protocol specified statistical analyses.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using controlled clinical trials to learn more about acute drug-induced liver injury. *Hepatology*. 2008;48(5):1680-1689. doi:10.1002/hep.22633

FDA Guidance for Industry, Drug-induced liver injury: Premarketing Clinical Evaluation. Jul2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Little R. (1993) Pattern-Mixture Models for Multivariate Incomplete Data. Journal of the American Statistical Association. Vol. 88, No. 421 (Mar, 1993), pp. 125-134

Ratitch B, O'Kelly M and Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics 2013; 12 337-347