Statistical Analysis Plan Addendum	
Drug Substance	K-877
Protocol Number	K-877-303
Edition Number	1.0
Date	21 October 2019

A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With a 40-Week, Active-Controlled, Open-Label 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 Mild or Moderate Renal Impairment

Investigational Product: K-877
Protocol Number: K-877-303
Original Protocol Version 1.0: 13 September 2016
Protocol Version 2.0: 25 August 2017

SAP Version: 1.0
SAP Date: 19 October 2016

SAP Version: 2.0
SAP Date: 21 June 2019

SAP Addendum Version: 1.0
SAP Addendum Date: 21 October 2019

SAP ADDENDUM SIGNATURE PAGE

A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With a 40-Week, Active-Controlled, Open-Label 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 Mild or Moderate Renal Impairment

We, the understood, have understood and approved the SAP Addendum

[redacted]

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1. INTRODUCTION

The statistical analysis plan, version 2.0, for study with protocol number K-877-303 was finalized on June 21, 2019. The study was finished with the database locked on August 23, 2019. The treatment code was unblinded on August 26, 2019. Due to issue in coding process for prior and concomitant medications coding and medical history coding in electronic data capture system, the database was corrected and locked again on September 11, 2019.

The study results were reviewed. After the systemic review, the decision was made to perform the post-lock data analysis change or clarification as described in this document.

Summary of changes:

- The primary imputation method in the SAP did not take into account the scenario of imputing missing data when observed data had a value of 0. We have specified all scenarios for the primary imputation method.
- The secondary efficacy endpoint, where data value of 0 is observed at baseline, will additionally include analysis for 'change from baseline to week 12' given percent change not being calculable for such lab parameters. However, for these lab parameters, analysis of percent change from baseline to week 12 will be performed using data where percent change from baseline is available.
- For parameters where post-baseline values are missing for a single patient whose ethnicity was listed as 'Unknown', multiple imputation will be performed by assigning the ethnicity of the single patient as 'Not Hispanic or Latino'.
- [redacted]

2. DATA ANALYSIS CHANGES

2.1 Imputation error due to lab parameters with value of 0

After database lock and unblinding, it was observed that some lab parameters had a value of 0 at baseline or at week 12 or both. With such values, the primary imputation, which includes log-transformation of lab values at baseline and week 12, returned an error. The following parameters from the K-877-303 study had a data value of 0 for lab parameters that resulted in an error for log transformation:

Lab Category	Parameter (Unit)	Number of subjects with value 0	
		Baseline	Week 12
Lipids	LDL-C (Ultracentrifugation): ApoB	1	0

Lipoprotein Fraction	HDL Particles-Large (umol/L)	30	20
Lipoprotein Fraction	HDL Particles-Medium (umol/L)	40	36
Lipoprotein Fraction	HDL Particles-Small (umol/L)	3	1
Lipoprotein Fraction	HDL cholesterol (total) (mg/dL)	0	1
Lipoprotein Fraction	IDL Particles (nmol/L)	19	10
Lipoprotein Fraction	LDL Particles-Large (nmol/L)	252	170
Lipoprotein Fraction	LDL Particles-Small (nmol/L)	7	0
Lipoprotein Fraction	VLDL & Chylomicron Particles-Large (nmol/L)	1	0
Lipoprotein Fraction	VLDL & Chylomicron Particles-Medium (nmol/L)	12	8
Lipoprotein Fraction	VLDL & Chylomicron Particles-Small (nmol/L)	55	30

It was decided post database lock that an extension to the existing pattern mixture model multiple imputation method with fully conditional specification methods will be applied to the above parameters to account for the observed data values of 0. This method is called the predictive mean matching method which uses a simulated regression model to impute values randomly from a set of observed values whose predicted values are close to the predicted value of the missing value..

2.2 Secondary efficacy endpoints for lab parameters with a baseline value of 0

The protocol defined one of the secondary endpoints as percent change from baseline to week 12 in lipoprotein fraction (nuclear magnetic resonance). Since a few lipoprotein parameters have one or multiple records with a baseline value of 0, the percent change cannot be determined for such records. In such cases, the secondary endpoints for the lipoprotein parameters will be evaluated additionally for change from baseline to week 12. Analysis for percent change from baseline will be performed for patients who do not have a value of 0 at baseline.

2.3 Multiple Imputation for one subject with unknown ethnicity

One of the covariates included in the multiple imputation model was ethnicity which was categorized into 'Hispanic or Latino', 'Not Hispanic or Latino', and 'Unknown' based on the values in the electronic data capture. In this study, out of 471 randomized patients, 19 patients were identified with 'Hispanic or Latino' ethnicity and 451 randomized patients were 'Not Hispanic or Latino'. One randomized patient had ethnicity listed as 'Unknown' and imputation of missing data of certain parameters for this patient resulted in a warning message observed due to unavailability of multiple patients with ethnicity listed as 'Unknown'. Following is the table of parameters, where the patient with unknown ethnicity had a missing value:

Lab Category	Parameter (Unit)
Biomarkers	Adiponectin (mg/L)
Ion Mobility	Diameter of the major LDL particle (Å)
Ion Mobility	High density lipoproteins 2b (nmol/L)
Ion Mobility	High density lipoproteins 3 and 2a (nmol/L)
Ion Mobility	Intermediate density lipoproteins 1 (nmol/L)
Ion Mobility	Intermediate density lipoproteins 2 (nmol/L)
Ion Mobility	Low density lipoproteins I (nmol/L)
Ion Mobility	Low density lipoproteins IIIa (nmol/L)
Ion Mobility	Low density lipoproteins IIIb (nmol/L)
Ion Mobility	Low density lipoproteins IIa (nmol/L)
Ion Mobility	Low density lipoproteins IIb (nmol/L)
Ion Mobility	Low density lipoproteins IVa (nmol/L)
Ion Mobility	Low density lipoproteins IVb (nmol/L)
Ion Mobility	Low density lipoproteins IVc (nmol/L)
Ion Mobility	VLDL Cholesterol-Intermediate (nmol/L)

Ion Mobility	VLDL Cholesterol-Large (nmol/L)
Ion Mobility	VLDL Cholesterol-Small (nmol/L)

It was decided post database lock that for the above parameters, where an imputation warning occurs due to ethnicity of a subject categorized as 'Unknown', the ethnicity value will be replaced as 'Not Hispanic or Latino' prior to imputation and analysis. Since a vast majority of the randomized population are identified as 'Not Hispanic or Latino', it would be appropriate to include the patient with 'Unknown' ethnicity in this category prior to imputation of the above parameters.

[redacted]

3. DATA ANLAYSIS CLARIFICATION

The changes in analysis described in sections 2.1 and 2.2 of this document were applied only to the lab parameters where lab value of 0 was observed at baseline or post-baseline.

Similarly, imputation issues resulting from missing data for one patient with unknown ethnicity will be resolved by assigning that patient under the ethnicity category of 'Not Hispanic or Latino'. This change will only be applied to the parameters listed in section 2.3 of this document.

The above mentioned changes as well as the change in section 2.4 of this document will not affect the imputation results for the primary endpoint as well as secondary endpoints that were tested in a hierarchical step-down manner

4. PRIMARY IMPUTATION METHOD

For the main analysis of the primary efficacy variable, missing Week 12 endpoint will be imputed using the pattern mixture model using the fully conditional specification method. This imputation method will include factors such as patient demographics, disease status, and baseline values. The imputation method was specified in the SAP Appendix 1, pages 25, 26 and 27.

It was found after database lock that there was an error imputing data with a value of 0 as the pattern mixture model using the fully conditional specification method utilized log transformation of the observed values. The parameters mentioned in section 2.1 of this document resulted in imputation error because of log transformation of 0 values. After reviewing the methodology in SAP, it was decided that this scenario would be handled using the predictive mean matching method as an extension to the pattern mixture model of imputation.

Below is a summary of description of the imputation using the predictive mean matching method:

In addition to following the same description of steps in Appendix 1 (in Pages 25-27) of the SAP version 2.0, any lab parameter with a 0 value at baseline or week 12 will utilize the following SAS code to include the predictive mean matching method to impute missing data.

Step II a.

```
PROC MI DATA= DATA21a OUT=IMOUT1a
        MINIMUM=0 SEED=68756 NIMPUTE=100 ROUND=1E-10;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN WEEK12; CLASS
SEX ETHNICITY COUNTRY STATIN;
FCS REGPMM; /* fully conditional specification method with predictive mean matching
method.*/
RUN;
```

Step II b.

```
PROC MI DATA=DATA22 OUT=IMOUT22
          MINIMUM=0 SEED=63546 NIMPUTE=100 ROUND=1E-10;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN BASE WEEK 4
        WEEK8 WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN;
FCS REGPMM; /*fully conditional specification method with predictive mean matching
method/*
RUN;
```

Step III.

```
PROC MI DATA= DATA21c OUT=IMOUT1c
          MINIMUM=0 SEED=745369 NIMPUTE=100 ROUND=1E-10;
BY TRT;
VAR AGE SEX ETHNICITY COUNTRY BMI SBP DBP EGFR STATIN BASE WEEK4
          WEEK8 WEEK12;
CLASS SEX ETHNICITY COUNTRY STATIN;
FCS REGPMM; /*fully conditional specification method with predictive mean matching
method*/
RUN;
```

5. REFERENCES

O'Kelly M, and Ratitch B (2014), *Clinical Trials with Missing Data: A Guide for Practitioners*, Willey, U.K.

Dmitrienko A, and Koch G.G. (2017), *Analysis of Clinical Trials Using SAS: A Practical Guide, Second Edition*, SAS Institute